FUNCTIONALIZATION OF TERMINAL OLEFINS USING CATIONIC PALLADIUM CATALYSTS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

During the past decade, palladium-catalyzed alkene functionalization reactions that intercept the Pd-alkyl intermediate for further functionalization has attracted significant interest because of its ability to generate diverse C-O, C-N and C-C bond connections. However, developments of these reactions are considered to be challenging due to the propensity of the Pd-alkyl intermediate for β-hydride elimination. The Sigman group has been involved in developing methods to stabilize the Pd-alkyl intermediate that is formed at the benzylic or allylic positions to generate interesting product. Herein, we describe the discovery of new efficient methods to stabilize these intermediates to achieve difunctionalization and hydrofunctionalization products.

First, a highly cationic Pd^{II}-catalyzed alkene difunctionalization of terminal olefins using organostannanes is developed in which a conjugated alkene can lead to a 1,2-addition product. However, electron withdrawing styrenes gave a mixture of 1,2- and 1,1-addition products. Based on an observed linear free energy relationship, it was found that electronic nature of the styrene determines the ratio of the 1,2- vs 1,1-diarylation product. This study ultimately lead us to develop a 1,1-diarylartion reaction using simple olefins. The mechanistic experiments suggested that the electrophilic nature of the palladium catalyst is necessary to stabilize the resultant π-benzyl species, that yields the alkene difunctionalization product.

Based on the mechanistic insight that was observed on the oxidative cationic Pd^{II}-catalyzed diarylation reaction, a new method was developed using a Pd^{0}-catalyst for the coupling of vinyl triflates, aryl stannanes, and terminal alkenes in a single step. In this reaction, the electrophilc Pd-alkenyl species is generated in situ from the oxidative addition of a vinyl triflate, that is proposed to be the key intermediate for the success of this three component coupling reaction.

Finally, a system for the Pd-catalyzed hydroalkylation of styrenes was developed based on an initial lead observed in the oxidative diarylation reaction using tetra-butylstannane instead of an aryl-tributylstannane. In this reaction, the propensity of an unstabilized Pd-alkyl intermediate to undergo β-hydride elimination has been utilized to generate the Pd-hydride species, which is used for the generation of Pd-alkyl intermediate that can be stabilized by a π-benzyl species.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

3ÅMS	3 Å molecular sieves
APCI	Atmospheric pressure chemical ionization
atm	Atmosphere
bc	Bathocuproine
bs	Broad singlet
d	Doublet
dd	Doublet of doublets
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
E.I.	Electron impact ionization
ER	Estrogen receptor
ESI	Electrospray ionization
Et_2O	Diethyl ether

EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
h	Hour
HOTf	Trifluoromethanesulfonic acid (triflic acid)
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
I*i*Pr	1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazole
IMes	1,3-dimesityl-2,3-dihydro-1H-imidazole
IP	Intraperitoneal
m	Multiplet
m/z	Mass to charge
MeCN	Acetonitrile
MeOH	Methanol
min	minute
MS	Mass spectrometry
MTS	[(3 - (4,5 - dimethylthiazol – 2 - yl) - 5- (3 - carboxymethoxyphenyl) – 2 - (4 - sulfophenyl) - 2H -tetrazolium, inner salt)]
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
KIE	Kinetic isotope effect
OAc	Acetate
OTf	Trifluoromethanesulfonate (triflate)

q	Quartet
R_f	Response factor
s	Singlet
sec	seconds
t	Triplet
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TOF	Time of flight mass spectrometry
UV	Ultraviolet

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I owe my deepest gratitude to my parents, brothers and my wife, Pranjali, for providing immense support and inspiring me to make it here and beyond.

CHAPTER 1

RECENT DEVELOPMENTS IN PALLADIUM-CATALYZED INTERCEPTION OF Pd^{II}-ALKYL SPECIES

Introduction

Palladium-catalyzed reactions for generating new carbon-carbon bonds[1] have significantly impacted the approach to natural product synthesis,[2,3] pharmaceuticals,[4] and materials. Over the past several decades, numerous Pd-catalyzed transformations have been developed utilizing Pd^{II}-alkenyl or alkynyl species as catalytic intermediates to generate carbon-carbon bonds.[1] In contrast, the use of Pd^{II}-alkyl species for further functionalization has been studied to a lesser extent.[5,6] For example, cross-coupling reactions that have focused on the functionalization of Pd^{II}-alkyl species with an organometallic reagent have resulted in inefficient conversion and issues with side reactions, particularly through β-hydride elimination from the reactive alkyl metal species.[1] The β-hydride elimination process is believed to operate via the pathways in Figure 1.1.[7] The saturated Pd^{II}-alkyl intermediate **A** is proposed to undergo initial ligand dissociation to form a coordinatively unsaturated species **B**. The vacant coordinate site is then filled by an agostic interaction from a C-H bond on the alkyl group that is β to the

alkyl-metal bond that ultimately undergoes β-hydride elimination. The resultant species **C** is prone to dissociate to form a metal hydride **D** and the olefin product. Recently, several research groups, including Sigman lab, have developed methods that can successfully control β-hydride elimination to achieve further functionalization of the Pd-alkyl to yield novel products.[8] This chapter focuses on specific case studies that showcase the recent advancements in palladium-catalyzed reactions that couple carbon-carbon sp^3 centers. Additionally, these studies will also highlight some of the challenges associated with the control of β-hydride elimination and the efforts that result in the further functionalization of the Pd^{II}-alkyl species.

Background

The ability to utilize the Pd^{II}-alkyl intermediate **A** for further functionalization has dramatically expanded the scope of Pd-catalyzed reactions in the past decades. Approaches to this functionalization of the Pd^{II}-alkyl intermediate can be divided into three general categories: (1) utilization of ligands to decrease the rate of β-hydride elimination,[9,10] (2) rapid oxidation of Pd^{II}-alkyl species before β-hydride elimination can occur,[8] or (3) incorporation of a functional group in the substrate to stabilize the Pd^{II}-alkyl intermediate. This section outlines the key issues associated with the generation of the Pd^{II}-alkyl intermediate and the approaches used to control β-hydride elimination to achieve interesting chemical transformations, supported by some key mechanistic studies.

Ligand mediated control of β-hydride elimination

A traditional method to generate Pd^{II}-alkyl species is by oxidative addition of alkyl electrophiles, such as alkyl halides or pseudohalides in cross-coupling reactions.[1] The mechanism is proposed to proceed with the initial oxidative addition of alkyl halides to generate intermediate **B**, followed by the transmetallation step to yield **D**. Finally, reductive elimination from the Pd^{II} species results in the alkyl-R coupled product **E** and the active catalyst **A** (Figure 1.2). The comparative lack of success in the utilization of Pd^{II}-alkyl species through this cross-coupling reaction is often attributed to two problematic steps in the catalytic cycle (Figure 1.2). First, oxidative addition of alkyl electrophiles to a low valent metal-complex is generally believed to be slower than the addition of aryl or alkenyl electrophiles, due to the highly electron-rich character of the alkyl halides or pseudohalides. Second, if oxidative addition does indeed occur, the alkyl-metal intermediate may undergo unimolecular β-hydride elimination to form product **C** more rapidly than bimolecular transmetallation. Moreover, the reductive elimination from this electron-rich system is also sluggish. However, during the past two decades, important advances have been made demonstrating that the aforementioned obstacles can be overcome and that the development of efficient catalysts for the coupling of a general class of alkyl electrophiles is possible.[9]

The first example of a Pd-catalyzed reaction that involves Pd^{II}-alkyl intermediates was reported by Suzuki and coworkers.[11-13] Specifically, they established that $Pd(PPh_3)_4$ catalyzes cross-coupling of β-hydrogen-containing primary alkyl iodides with alkyl-, alkenyl, and aryl-9-BBN reagents in the presence of base (Figure 1.3A). The success of the reaction is attributed to the use of monodentate ligand. It was proposed that these liga-

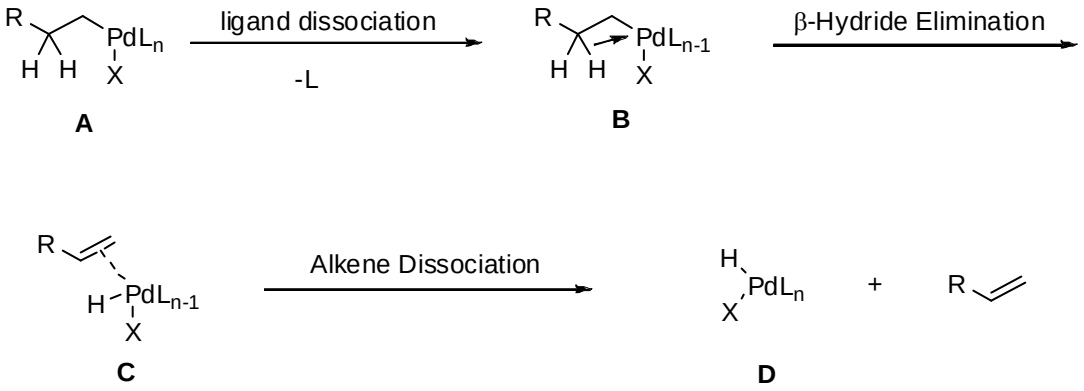


Figure 1.1. Proposed mechanism for the β-hydride elimination from the Pd(II)-alkyl intermediate to yield olefin and a Pd-hydride complex.

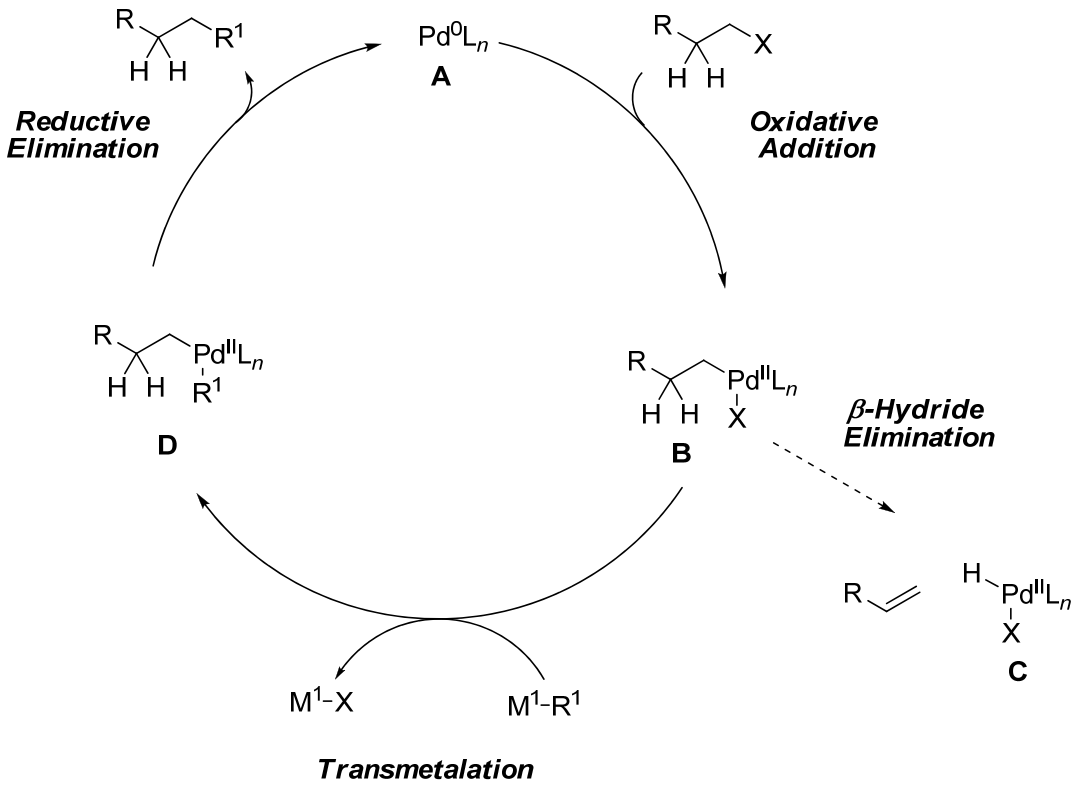
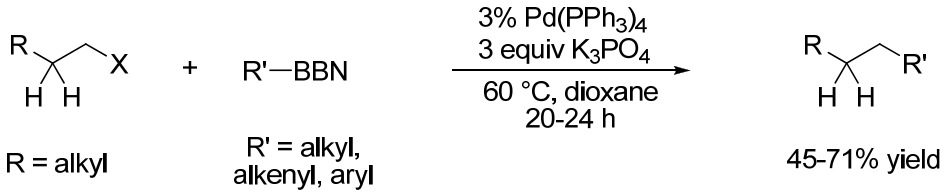


Figure 1.2. General mechanism for the cross-coupling reaction that initiates with oxidative addition followed by transmetallation and further reductive elimination to generate the alkyl-alkyl bond formation and the side reaction that leads to β-hydride elimination.

nds adopt a trans-configuration that prevents the open coordination site needed for β-hydride elimination to occur.[9] The reaction was able to generate Csp^3-Csp^3 coordination site needed for β-hydride elimination to occur.[9] Although, the reaction was able to generate Csp^3-Csp^3bonds, only alkyl-iodides and alkyl-9-BBN's should be employed in the cross-coupling reaction (Figure 1.3 B). Thus, there is still a need to develop more efficient reaction conditions that would include general classes of alkyl electrophiles, as well as organometallic reagents in palladium catalysis.

Pioneering work has been performed by Fu and coworkers in the field of cross-coupling involving alkyl-alkyl bond formation, through which they discovered that electron rich and bulky $P(alkyl)_3$ ligands are uniquely effective in overcoming the issue of sp^3-sp^3 carbon-carbon bond formation.[9] Because of their electron-rich properties, these ligands can promote oxidative addition of various alkyl electrophiles such as alkyl chlorides, alkyl bromides, alkyl tosylates, etc. Moreover, the steric nature of these ligands can be used for the control of β-hydride elimination. Subsequently, they reported an alkyl-alkyl coupling reaction in the presence of $Pd(OAc)_2/PCy_3$ as the catalyst system and $K_3PO_4•H_2O$ as base (Figure 1.4).[14] When different phosphine ligands were tested under identical conditions, it was observed that PCy_3 with a cone angle 170º gave the best results, whereas no cross-coupling was observed in the presence of triarylphosphines with larger and smaller cone angles. For example, electron-rich phospine such as $P(t\text{-}Bu)_3$ with a greater cone angle of 182˚, and less bulky $P(n\text{-}Bu)_3$ with cone angle 132˚, afford little or no product. Based on these results, they concluded that the size of the alkyl phosphine ligand is crucial for the control of β-hydride elimination in these reactions. Further, they extended their studies to understand the mechanistic details related to the Pd

Suzuki cross-coupling reaction



Mechanistic hypothesis

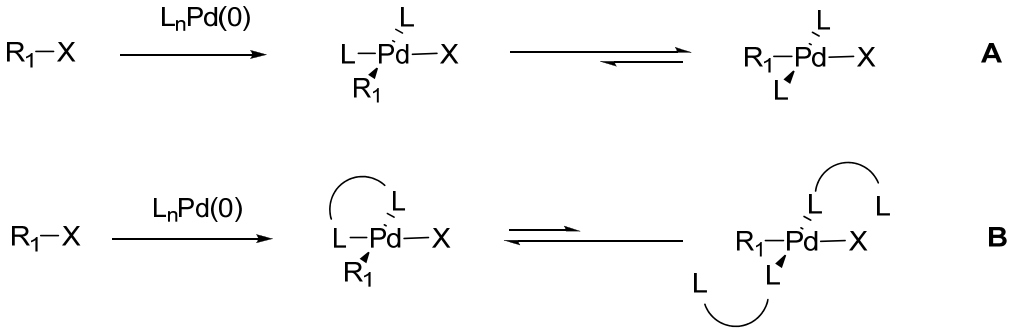


Figure 1.3. The first reported Suzuki cross-coupling reaction to generate alkyl-alkyl bonds and mechanistic hypothesis for the utilization of mono and bidentate ligands.

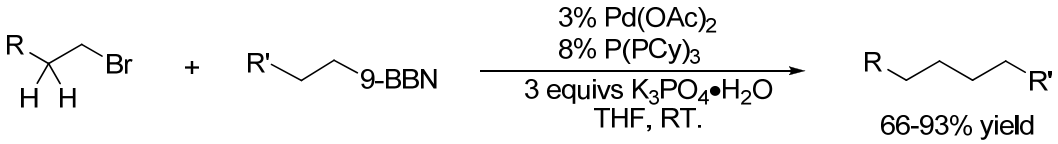


Figure 1.4. Fu and coworkers Suzuki cross-coupling reaction that illustrates the use of monodentate alkyl phospine to generate alkyl-alkyl bond formation in good yield.

/P*t*Bu$_2$Me based system. Particularly, focusing on the cross-coupling reaction involving alkyl tosylates and alkyl BBN reagents to determine the stereochemistry of oxidative addition mechanism (i.e., inversion or retention) (Figure 1.5).[14] They treated diastereomerically pure tosylate **1** with Pd/P*t*Bu$_2$Me in the absence of an organoborane and NaOH; the olefins that resulted from oxidative addition and subsequently followed β-hydride elimination were examined. Based on ^{1}H-NMR analysis, they determined that oxidative addition occurs predominantly with inversion of configuration,[15] pointing towards an S_N2 type mechanism.

Subsequently, they explored the stereochemical outcome of a Pd/P*t*Bu$_2$Me catalyzed cross-coupling of tosylate **1** with an organoborane **2** after reductive elimination (Figure 1.6).[14] Based on the ^{1}H-NMR analysis of the cross-coupled products, the Suzuki reaction provides cross-coupling product predominantly with inversion of configuration. Since, oxidative addition is associated with inversion of configuration, reductive elimination occurs through retention of configuration. Apart from phosphine ligands, N-heterocyclic carbene ligands have also been used successfully in alkyl-alkyl cross-coupling reactions with alkyl boranes as the transmetallating reagent.[16,17] Cloke and coworkers obtained the products of the palladium-catalyzed reactions of primary alkyl bromides **3** with hexyl-9-BBN **4** in the presence of I*i*PrHCl as the ligand precursor in 80% yields (Figure 1.7).[18]

Although there has been success utilizing Pd in coupling primary-primary sp^3-carbon bonds, the potential of these catalyzed cross-coupling processes will only be realized when secondary electrophiles can also be employed. Limited examples of the Pd-catalyzed reactions involving secondary alkyl electrophiles illustrate that with more hi

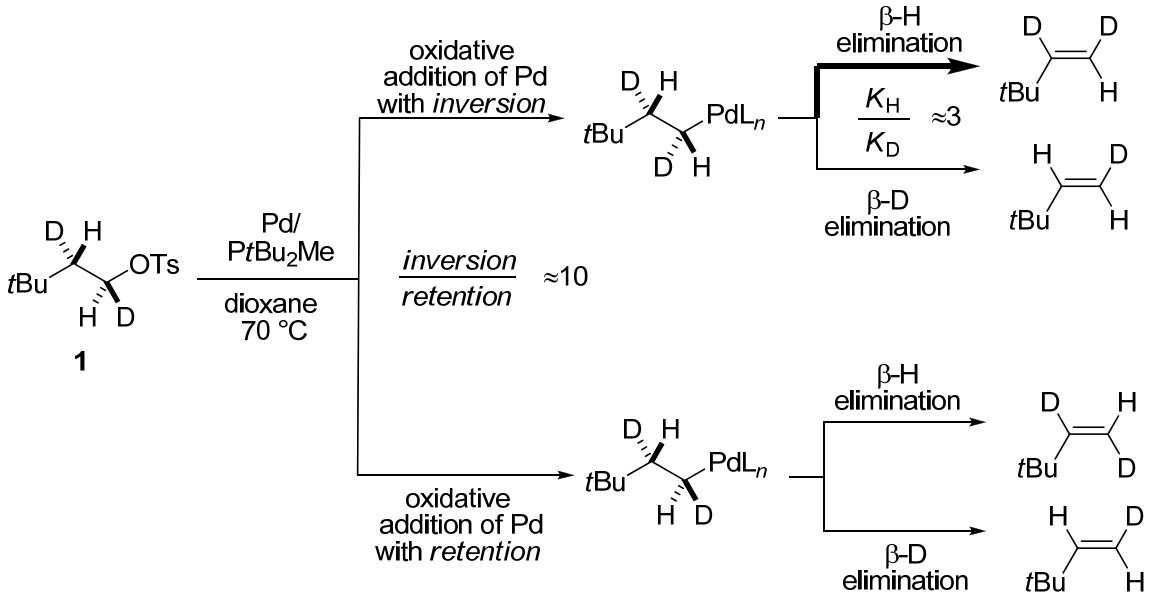


Figure 1.5. Fu and Netherton's mechanistic studies that describe the determination of the stereochemistry in the oxidative addition step of an alkyl tosylate.

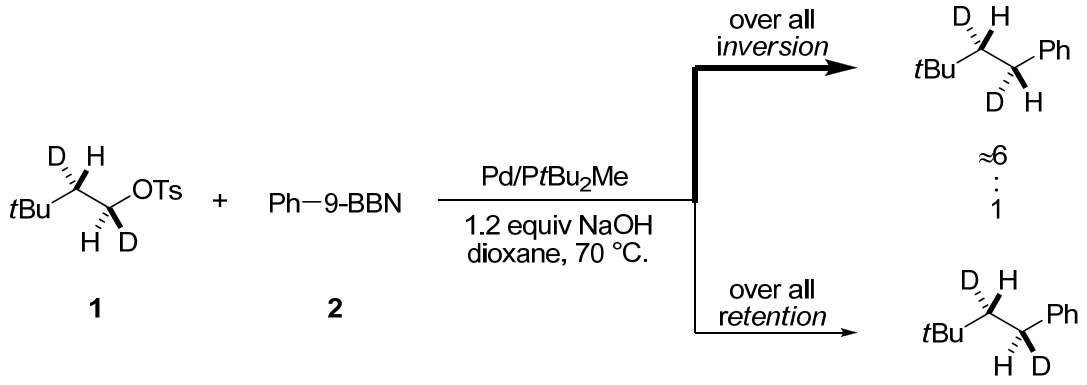


Figure 1.6. Fu and Netherton's mechanistic studies that describe the examination of the stereochemistry of a Pd/PtBu$_2$Me-catalyzed Suzuki cross-coupling of an alkyl tosylate.

-ndered electrophiles the problems of oxidative addition and β-hydride elimination are probably exacerbated. Nevertheless, there has been a dramatic rise in the development of cross-coupling reactions involving secondary alkyl halides, particularly in the last five years.[6,19] Nickel has been found to be the most versatile metal for the cross-coupling reactions of alkyl halides due to the observations that Ni alkyl complexes are intrinsically less prone to undergo β-hydride elimination as compared to the Pd alkyl complexes.[20] Through computational studies of a Pd-complex and an analogous Ni-complex, Morokuma demonstrated that Ni^{II} vacant d-orbitals have higher energy levels than their Pd counterparts, that will result in a weaker agnostic interaction with β-hydrogen atoms. Over the past decade many Nickel based catalysts have emerged as capable systems for circumventing β-hydride elimination to achieve alkyl-alkyl cross-coupling reactions.[21]

Knochel and coworkers discovered that $Ni(acac)_2$/LiI serves as an efficient catalyst for the coupling of primary alkyl halides with primary as well as secondary alkyl transmetallating agents to generate Csp^3-Csp^3 centers (Figure 1.8). It was proposed that the tethered alkene, which acts as π-acceptor is required to facilitate reductive elimination and also to accelerate catalysis.

In subsequent papers, Knochel established that instead of having a tethered alkene as a part of the molecule to activate the catalyst, an electron-poor arene such as 3-trifluorostyrene **A** can be used as an external additive that could act as a π-acceptor to facilitate reductive elimination. Using this concept, they were able to couple a primary electrophiles **9** and secondary organometallic reagent **10** to give high yield of the cross-coupling product (Figure 1.9).

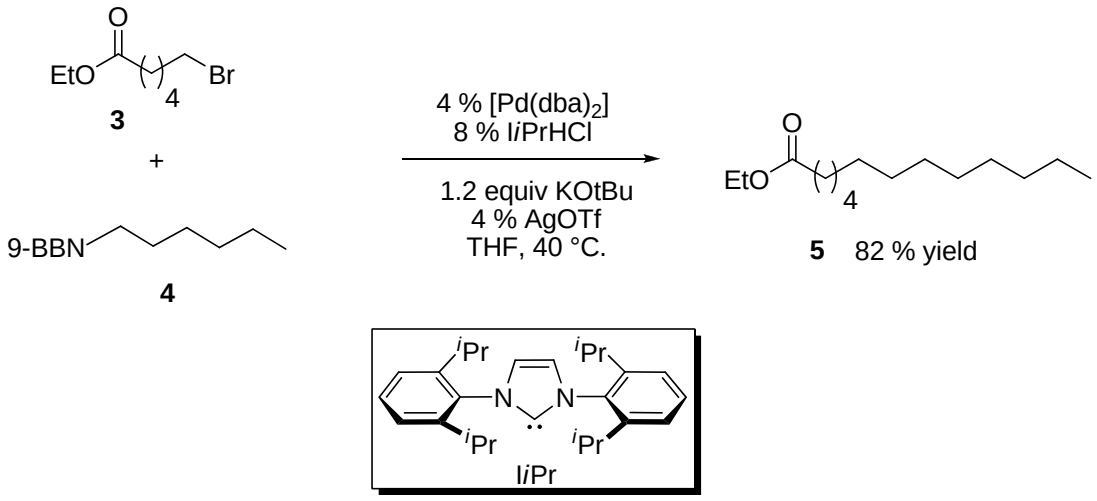


Figure 1.7. Cloke and coworkers Pd-catalyzed cross-coupling reaction that generates alkyl-alkyl bond by utilizing NHC ligands.

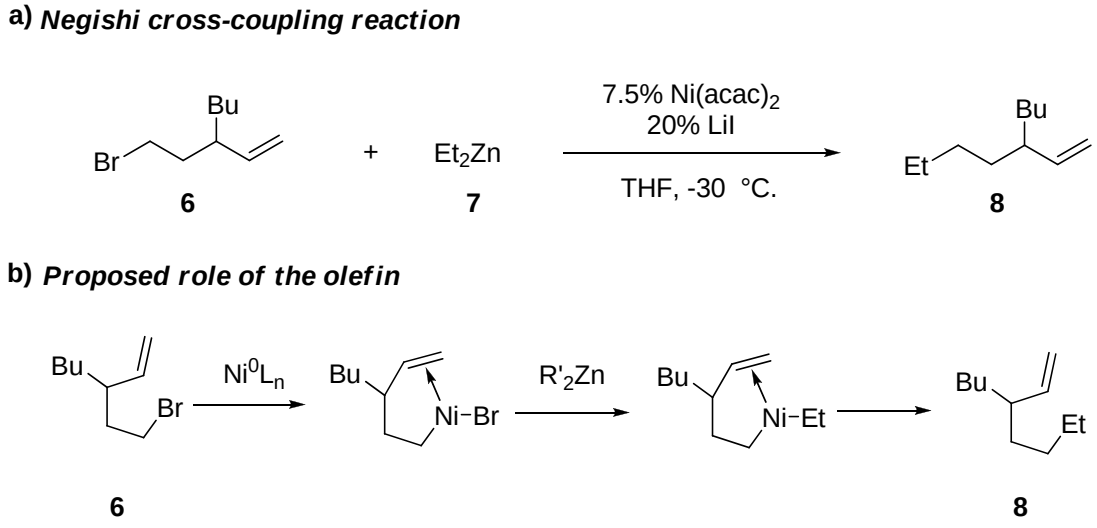


Figure 1.8. Knochel and coworkers nickel catalyzed coupling Csp^3-Csp^3 utilizing tethered olefins a) Negishi cross-coupling to generate alkyl-alkyl bond and b) the role of the olefin in Knochel and coworkers nickel-catalyzed reaction.

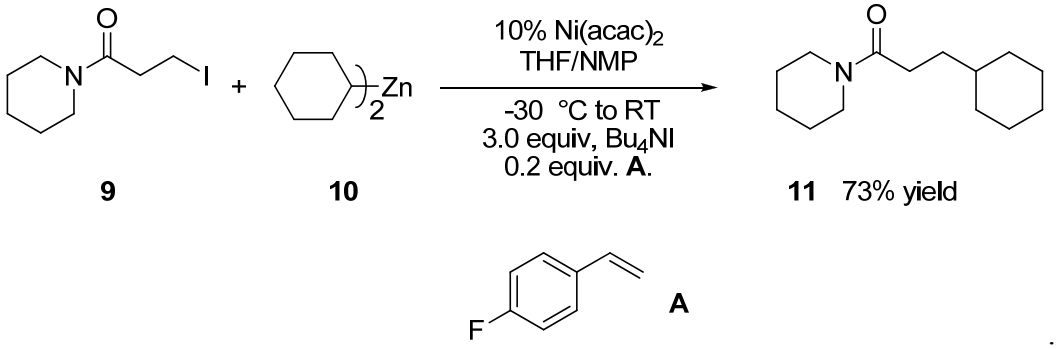


Figure 1.9. Nickel-catalyzed Negishi cross-coupling to generate primary alkyl-secondary alkyl bond described by Knochel and coworkers.

The utilization of a secondary electrophile is useful as this methodology can be expanded to asymmetric cross-coupling synthesis. Recently, Fu and coworkers reported a series of cross-coupling reactions for the formation of primary-secondary and secondary-secondary Csp^3-Csp^3 bonds are utilizing nickel catalysis. In 2005, they reported the first enantioselective cross-coupling of racemic secondary benzylic halides with an organozinc reagent in very good enantiomeric excess (Figure 1.10 A).[22] Next with a similar nickel-catalyst and a chiral diamine ligand, Fu and Saito reported the enantioselective coupling of unactivated secondary electrophile with alkyl-9-BBN reagent (Figure 1.10 B).[23] Following that, alkyl-alkyl Suzuki reactions of unactivated secondary alkyl electrophiles were developed using alkyl 9-BBN and proceed with good ee (Figure 1.10 C).[19] Fu and Smith also published the nickel-catalyzed cross-coupling of secondary alkyl electrophiles with secondary organometallic nucleophiles. In contrast to Pd-catalysis, the nickel-catalyzed alkyl-alkyl coupling mechanism is not well understood. However, there have been some experimental details and evidence for the possible pathways that will be discussed in this section.

The Vicic lab proposed a mechanistic hypothesis for the nickel catalyzed alkyl-alkyl cross-coupling reactions based on stoichiometric control experiments (Figure 1.11).[24-26] While working on synthetic methods to prepare Ni-dialkyl complexes in order to determine what factors favor reductive elimination over β-hydride elimination, they found that when using terpyridine based ligands, monomethyl complex **C** was generated**.** Based on this result, they hypothesized that the active catalyst was an alkyl Ni(I) species.

Vicic and coworkers further proposed that catalysis proceeds through a Ni(I)/Ni(III) cycle, wherein the final C-C bond is produced through a reductive eliminate

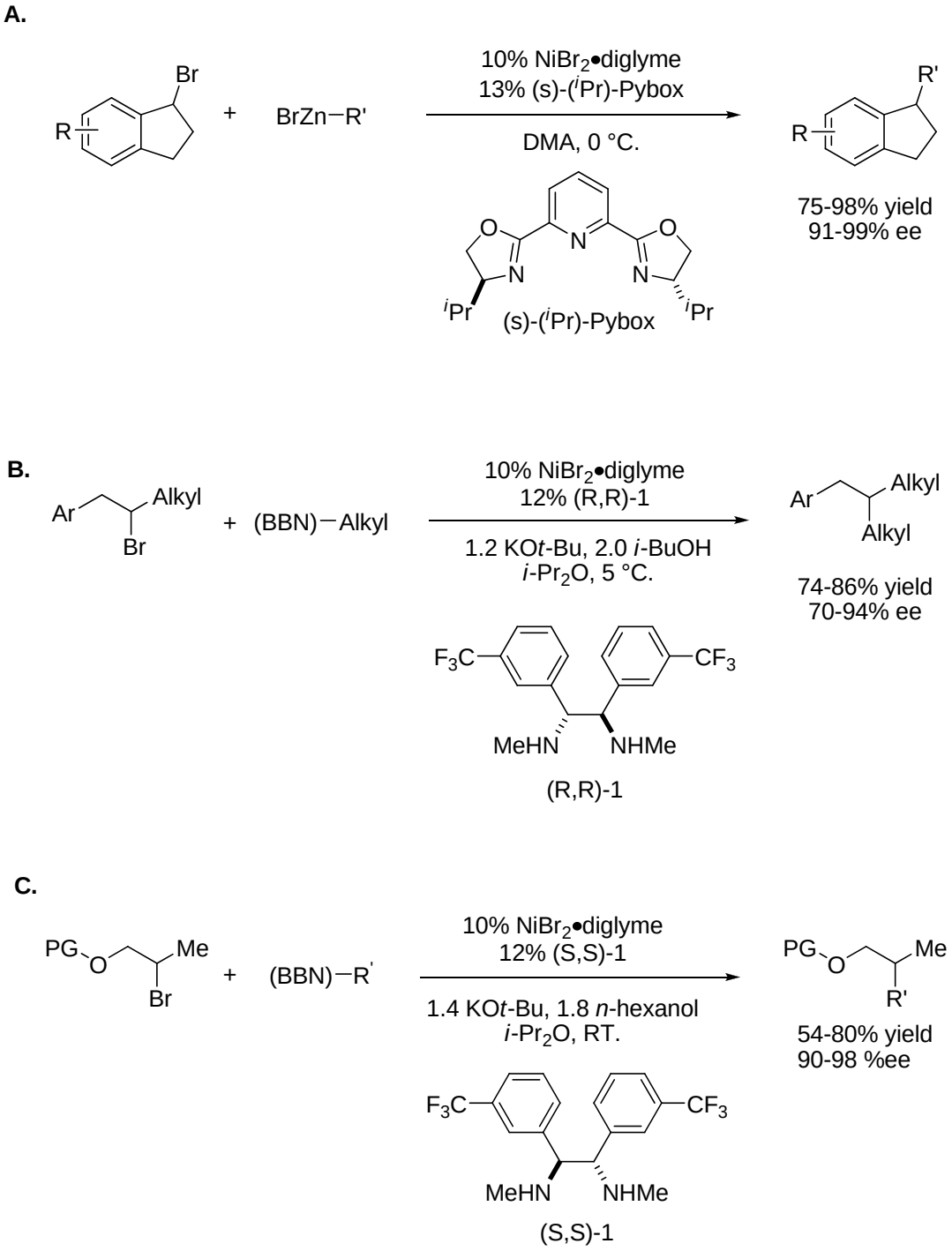


Figure 1.10. Fu and coworkers nickel-catalyzed cross-coupling reaction that couples secondary electrophiles and primary alkyl organometallic reagents.

from the Ni(III) intermediate **C** (Figure 1.12). This Ni(I)/ Ni(III) cycle was evaluated computationally and the mechanism was believe to be possible for primary alkyl halides, but less likely for secondary alkyl halides, due to an unfavorable reductive elimination step.[27]

Moreover, evidence suggests that oxidative addition proceeds first through radical formation at the formerly halogenated carbon and then results in combination of the alkyl radical and metal center, to generate the Ni-C bond. This is notable in that it provides a rationale for stereoconvergence, i.e, a free alkyl radical, having a rapidly interconverting geometry, could lose its stereochemical information during the oxidative addition step. In 2003, Fu and coworkers obtained further evidence supporting the possibility of an alkyl radical intermediate (Figure 1.13). In two nickel-based systems for Suzuki coupling of arylboronic acids and alkyl electrophiles, they observed that endo- and exo-2-bromonorborane both convert to the same exo-cross-coupling product, each in greater than 20:1 selectivity over the endo-product.[28]

Additionally, in a study of the nickel/bipyridine-mediated Stille coupling reactions of secondary alkylbromides, they observed formation of the corresponding 5-exo-trig cyclization product with high stereoselectivity of >20:1. This cis/trans ratio of cross-coupling products correlates with the ratios of previous radical cyclization studies of this substrate,[28-30] which is consistent with the possibility that an initially formed secondary alkyl radical cyclizes before reacting with nickel (Figure 1.14).[8,31]

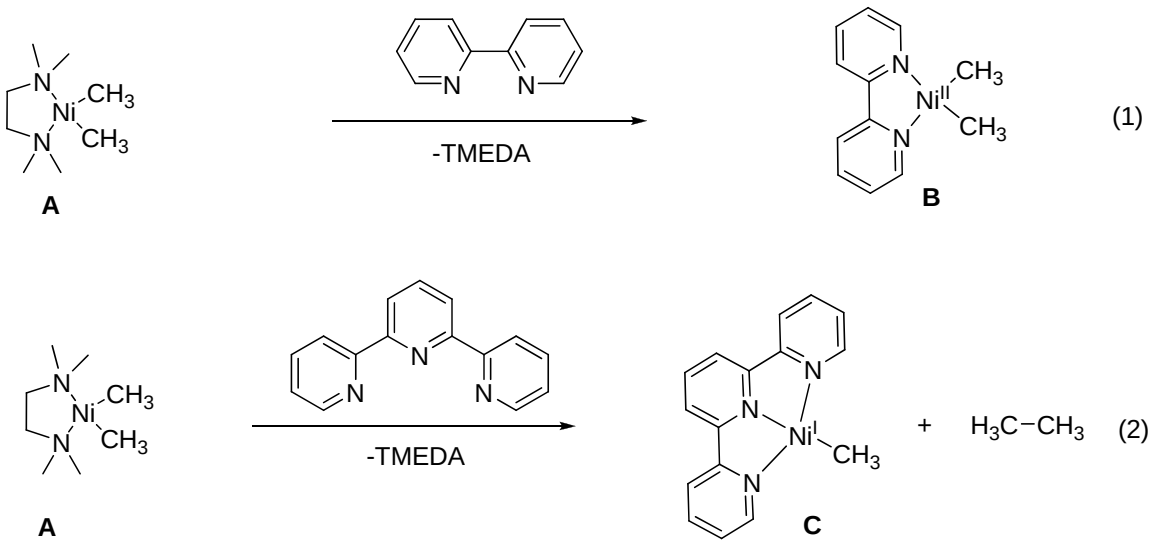


Figure 1.11. Evidence of isolated example of Ni(I) active species in the stoichiometric experiment that was performed by Vicic and coworkers.

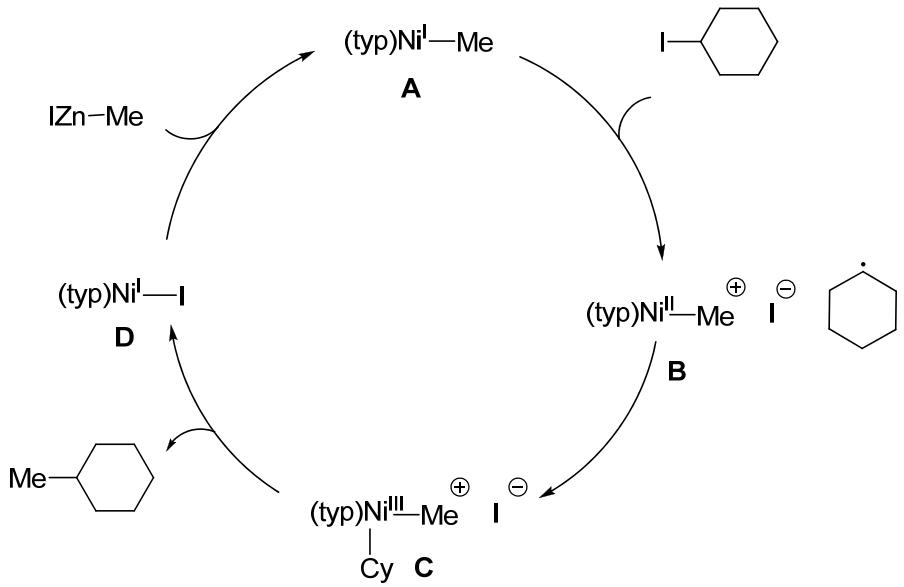


Figure 1.12. Proposed mechanism for the nickel-catalyzed cross-coupling reaction for the alkyl-alkyl bond formation that utilizes a Ni(I)/Ni(III) cycle.

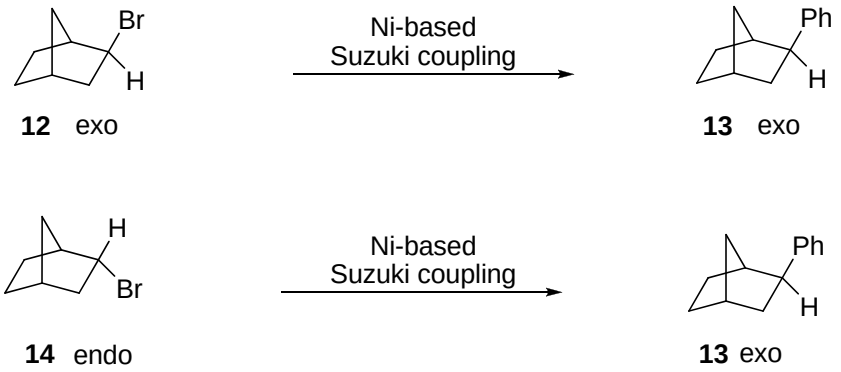


Figure 1.13. Nickel-catalysis for the Suzuki coupling of arylboronic acids and alkyl electrophiles to generate the exo cross-coupling product.

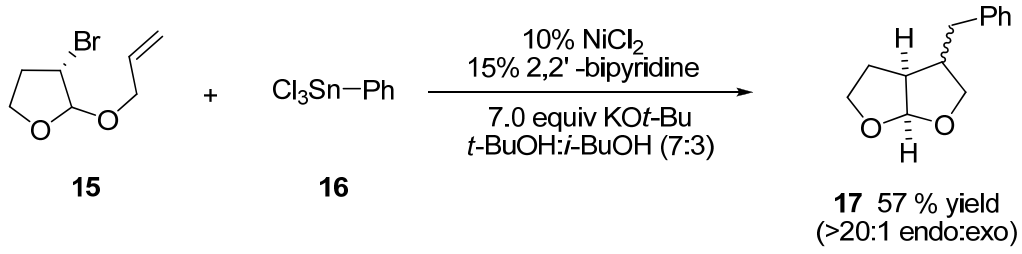


Figure 1.14. Nickel-catalysis for Suzuki coupling of arylboronic acids and alkyl electrophiles.

Rapid oxidation of Pd^{II}-alkyl species to control β-hydride elimination

An interesting strategy for the interception of the Pd^{II}-alkyl intermediate **A** that is receiving growing attention is to rapidly oxidize the Pd^{II}-alkyl **A** to Pd^{IV} **B** species before β-hydride elimination can occur.[32] During the past decade, this methodology has provided access to novel organic products that are highly complementary to those obtained in conventional Pd^0 and oxidative Pd^{II} chemistry.

Moreover, it has been established that Pd^{IV} complexes are often resistant to β-hydride elimination processes due to the nonavailability of an open coordination site, thereby allowing diverse functionalization of the Pd^{II}-σ-alkyl intermediate.[33-35] The proposed mechanism begins with alkene coordination, followed by nucleopalladation or by insertion into Pd^{II}-aryl bond to generate the intermediate **A**. The Pd^{II}-alkyl intermediate formed is oxidized with a suitable oxidant before β-hydride elimination can occur to generate a Pd^{IV} species. Then it undergoes reductive elimination to afford novel difunctionalized products (Figure 1.15). Sanford and coworkers have reported the cascade cyclization of enyne derivatives mediated by this type of $Pd^{II/IV}$ catalysis.[36] In this transformation, initial trans- acetoxypalladation of the alkyne generates the Pd^{II}-alkenyl intermediate **A**, followed by intramolecular olefin insertion to afford Pd^{II}-alkyl intermediates **B**, subsequent bond rotation and oxidation with $PhI(OAc)_2$ prior to β-hydride elimination would generate the Pd^{IV} intermediate **C**, so that further functionalization via S_N2-type attack on Pd^{IV} can be achieved to generate the cyclopropane product (Figure 1.16).

In the following report involving $Pd^{II/IV}$ catalysis manifolds, Sanford and Desai di-

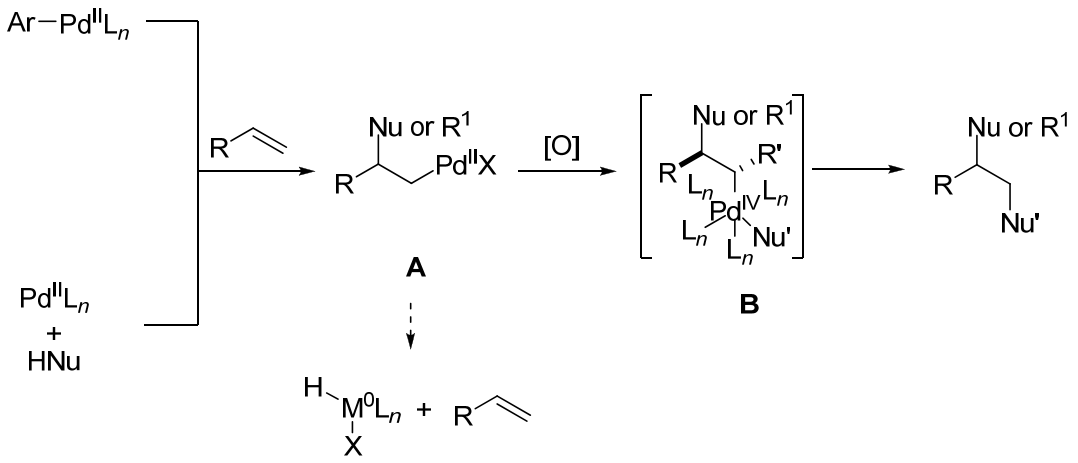


Figure 1.15. Pd-catalyzed alkene difunctionalization reaction that proceed via Pd(IV) chemistry and the competitive β-hydride elimination reactions.

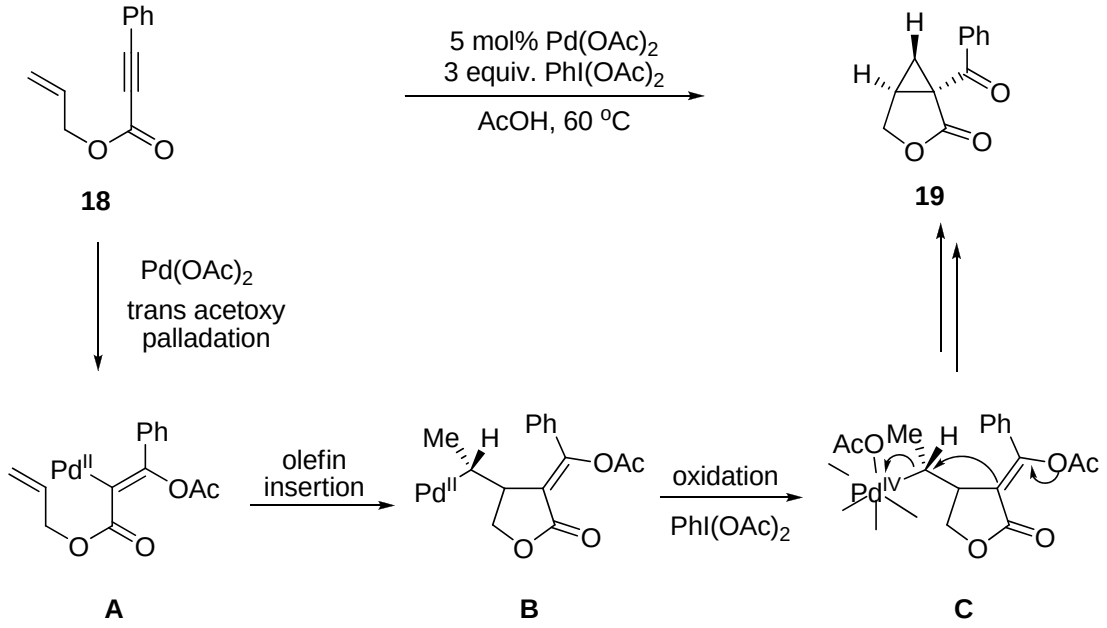


Figure 1.16. Pd(II/IV)-catalyzed cyclization of enyne to generate cyclopropane derivatives developed by Sanford and coworkers.

sclosed the aminooxygenation of alkenes.[35] This reaction uses $PhI(OAc)_2$ as an oxidant to oxidize Pd^{II} to Pd^{IV}, thereby promoting the reductive elimination pathway and allowing for functionalization at the Pd^{II}-alkyl intermediate **B** (Figure 1.17).

Further advances of this methodology include the 1,1- and 1,2-arylhalogenation of a terminal alkene (Figure 1.18).[37] This transformation proceeds with insertion of the alkene into the Pd^{II}-aryl bond to generate a Pd^{II}-alkyl bond. This intermediate is trapped by $PhICl_2$ or $CuCl_2$ oxidant and undergoes subsequent reductive elimination from a Pd^{IV} intermediate to yield the desired product. It was proposed that with the strong oxidant $PhICl_2$, the oxidative halogenations of the Heck intermediate **A** is significantly faster than competing β-hydride elimination, providing the 1,2-isomer **22** as the predominant product.

In contrast, with less electrophilic oxidants, such as $CuCl_2$, the rate of β-hydride elimination is faster than that of oxidative functionalization, allowing rapid equilibration between **A** and **D**. This allows for the selective oxidation of the benzylic Pd^{II}-alkyl intermediate, yielding the 1,1-isomer **23** as the predominant product.

Liu and coworkers published a report of alkene aminofluorination of substrates of type **24,** that contain a tethered *N*-tosylate, which can act as a nucleophile to yield heterocyclic products **25** (Figure 1.19).[38,39] The authors have demonstrated that after nucleopalladation, the Pd-alkyl intermediate formed can be oxidized by an I(III) oxidant to control β-hydride elimination. In the presence of AgF, they can successfully form the aminofluorination product using this method. In attempts to gain mechanistic insight into the aminofluorination process, a deuterium-labeled alkene was subjected to the standard reaction conditions and a successful aminofluorination afforded a mixture of trans and cis

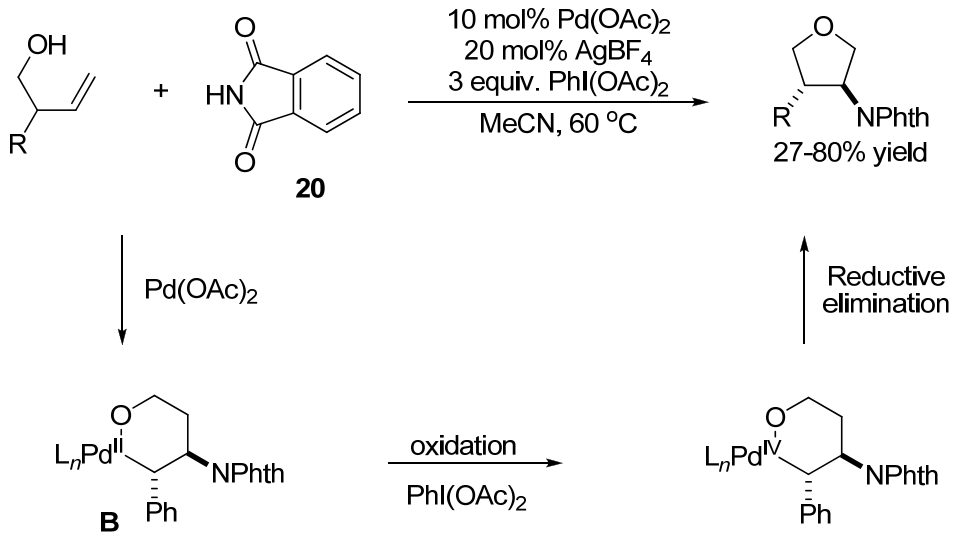
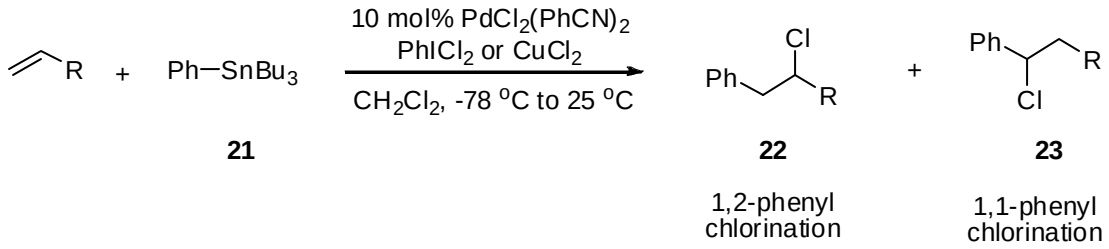


Figure 1.17. Sanford and Desai's Pd(II/IV)-catalyzed aminooxygenation of alkenes.

1,2- and 1,1-arylhalogenation of alkenes



Proposed Mechanism

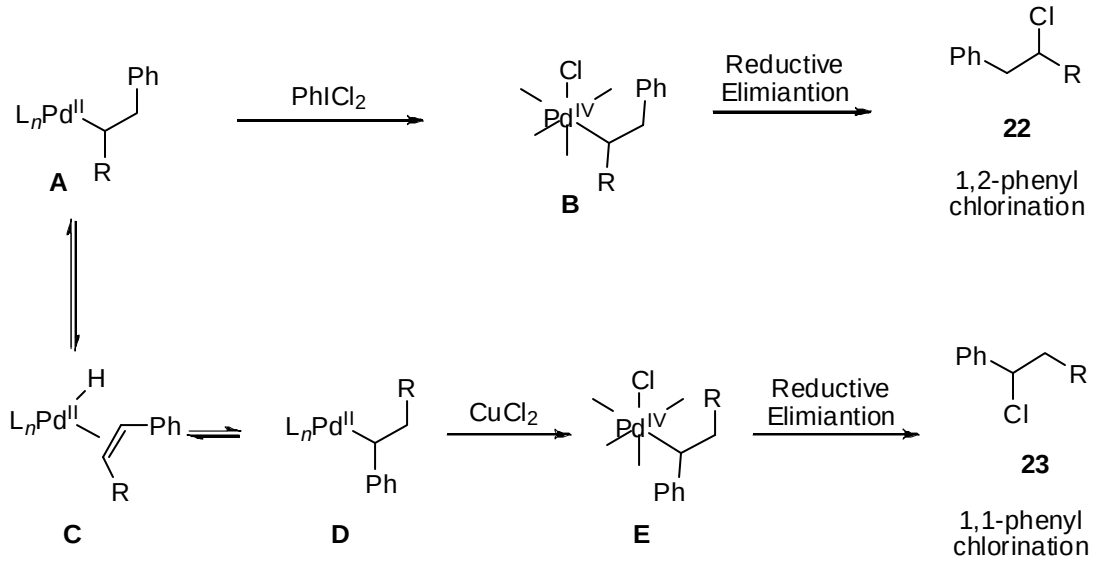


Figure 1.18. Sanford and coworkers Pd(II/IV)- catalyzed 1,2- and 1,1-arylhalogenation of alkenes.

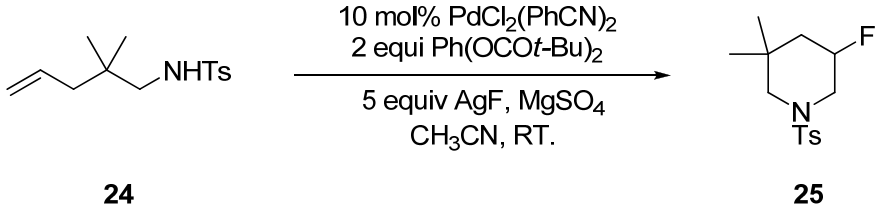


Figure 1.19. Pd(II/IV)-catalyzed aminofluorination of olefin tethered *N*-tosyl developed by Liu and coworkers.

isomers in 79% yield with a 72:28 ratio. It was proposed that Pd^{II}-mediated trans aminopalladation of the alkene with the attack at the terminal position of the alkene generates a Pd^{II}-alkyl intermediate that undergoes oxidation by $PhI(Opiv)_2$/AgF. This suggests that reductive elimination from Pd^{IV} intermediate is favored over an S_N2 type nucleophilic attack by fluoride (Figure 1.20).

Functional group in the substrate to stabilize the Pd^{II}-alkyl intermediate

An alternative approach to intercept the Pd^{II}-alkyl species is by using conjugated alkenes such as a diene or styrene. In this case, the second olefin coordinates to palladium, forming a π-allyl or π-benzyl complexes, thus preventing β-hydride elimination (Figure 1.21).[40-42] However, in order to achieve functionalization at the σ-alkyl-Pd^{II} species, it is necessary to develop conditions for which the rate of the second functionalization step should compete with β-hydride elimination. This section will focus on the substrate-controlled stabilization of σ-alkyl-Pd^{II} species to avoid β-hydride and to achieve further functionalization.

π-Allyl intermediate to control β-hydride elimination

Several interesting reactions have been developed based on the stabilization of the Pd^{II}-alkyl intermediate. In 1980s and 1990s, Bäckvall and coworkers developed several reactions based on this concept. One example is the formation of an aminochlorination product of a 1,3-diene, coordination of Pd^{II} followed by anti aminopalladiation utilizing

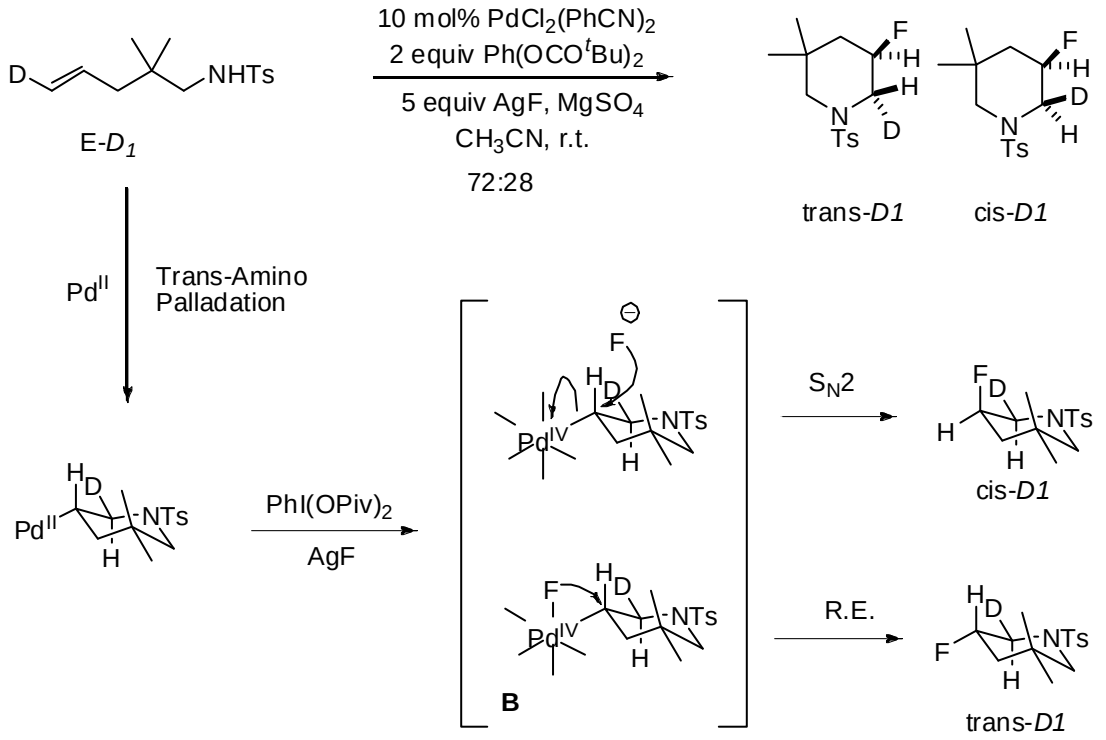


Figure 1.20. Proposed mechanism for the Pd(IV)-catalyzed aminofluorination of alkenes, that can proceed either via SN2 attack by fluoride or by reductive elimination from Pd(IV)-F intermediate.

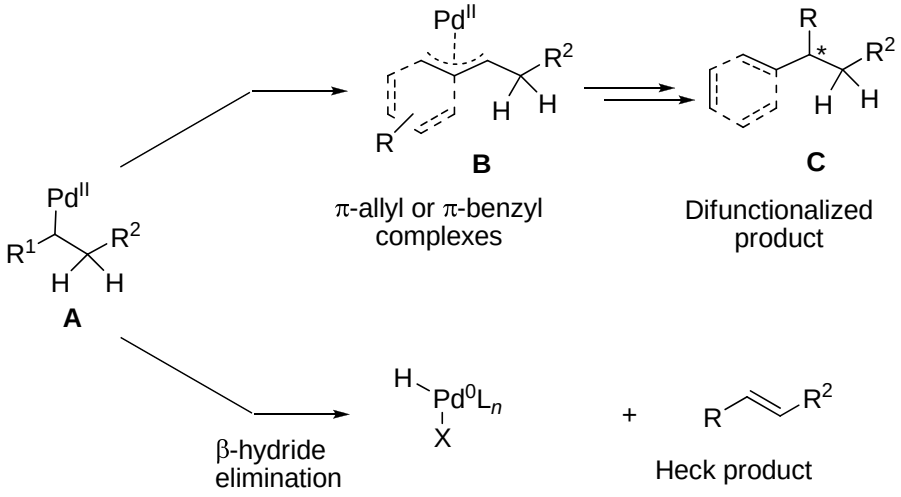


Figure 1.21. Pd-catalyzed reaction that involves a Pd-alkyl intermediate that can stabilize as a π-allyl or π-benzyl complexe to achieve functionalization and the competitive β-hydride elimination.

N-Ts as a intramolecular nucleophile resulted in the formation of Pd^{II}-alkyl bond, which is proposed to be stabilized by a π-allyl intermediate, to allow for a second functionalization via nucleophilic attack of a chloride group on the π-allyl complex (Figure 1.22).Following this transformation, numerous examples have been reported in the past two decades. For example, Lloyd-Jones and Booker-Milburn have also reported palladium-catalyzed diamination of dienes which utilizes palladium π-allyl complexes to achieve difunctionalized products (Figure 1.23).[43] In these reactions N,N'-diethyl urea **28** is used as a nucleophile to undergo diamination of the terminal alkene, which is proposed to proceed through palladium-π-allyl intermediate **A**, followed by subsequent intramolecular attack by the tethered second nucleophile.

Another interesting method for diene diamination has been reported by Shi and coworkers. This reaction is proposed to be initiated by oxidative addition of the di-*tert*-butyldiaziridinone **29** with Pd^0. The resulting palladacycle **A** undergoes alkene insertion to generate the palladium π-allyl intermediate **B**, which undergoes reductive elimination followed by β-hydride elimination to generated the difunctionalization product. The use of phosphoamide ligand **30** results in high levels of enantioselectivity (Figure 1.24).

Over the past decade, Pd-catalyzed ligand-directed C-H functionalizations have been extensively exploited to convert C-H bond into C-heteroatom and C-C bonds. Utilizing this methodology, Milburn and coworkers reported Pd-catalyzed C-H activation, followed by insertion into a diene.[44] In such cases, the Pd^{II}-alkyl intermediate generated is stabilized by a palladium π-allyl complex to yield 1,2-carboamination of the dienes. The proposed reaction proceeds via coordination of oxygen to Pd^{II}, followed by C-H insertion, leading to intermediate **A.** The Pd^{II}-aryl intermediate inserts into a diene

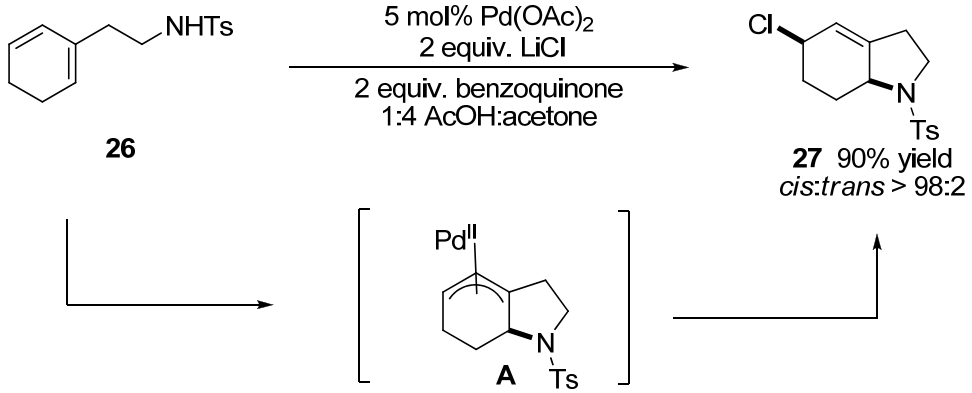


Figure 1.22. Pd-catalyzed intramolecular aminochlorination of diene substrate reported by Bäckvall and coworkers.

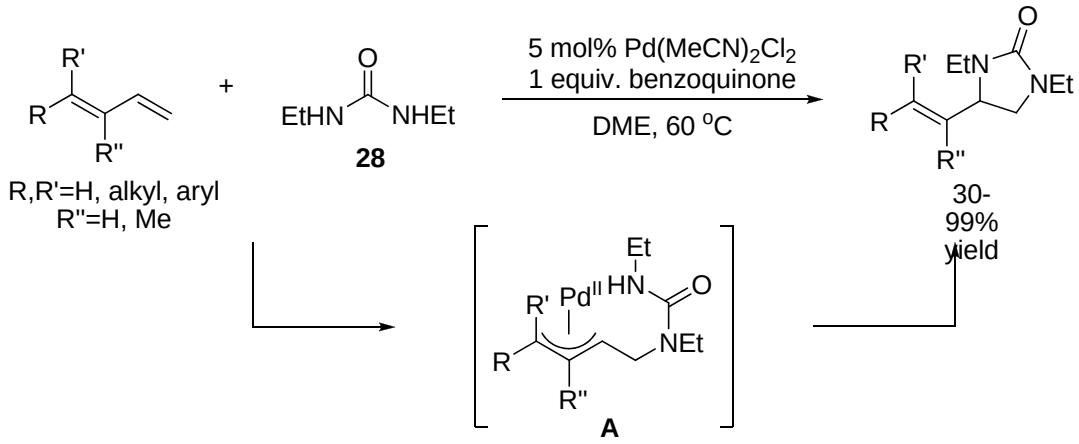


Figure 1.23. Lloyd-Jones and Booker-Milburn's Pd-catalyzed diamination of dienes that is proposed to proceed via π-ally intermediate.

which results in the formation of stable Pd^{II} π-allyl intermediate **B**. Nucleophilic attack of the urea nitrogen on the π-allyl species yields the desired product (Figure 1.25).

π-Benzyl species to control β-hydride elimination

Similar to π-allyl stabilization, π-benzyl complexes have been invoked in Pd-catalysis. However, reactions involving π-benzyl complexes have not been explored to the same extent as compared to π-allyl species, primarily due to the lack of optimized conditions that could effectively stabilize the π-benzyl species. The benzylic position is more prone to undergo β-hydride elimination as compared to π-allyl species due to potential loss of aromaticity as a π-benzyl species. Recently, Hartwig and Nettekoven have reported hydroamination of styrene derivatives, which proceeds through a π-benzyl species to control β-hydride elimination.[45,46] They described that a cationic Pd-π-benzyl complex is effective in stabilizing these intermediates to achieve functionalization at the benzylic position. During the catalyst initiation phase, attack of aniline on a coordinated styrene likely produces a palladium hydride and imine. This is based on the observation that 1 equiv. of imine per catalyst has been produced during catalytic reactions. Insertion of the olefin into this palladium hydride would lead to a η^3-phenethyl complex that reacts with an amine by an external attack. Final release of the product and proton transfer would regenerate the palladium hydride (Figure 1.26).

Sigman lab is also involved in utilizing Pd π-benzyl intermediates to achieve functionalization of olefins.[47-50] We have reported the hydroarylation of styrenes using organostannanes following that we also reported the similar reaction with organoboronic

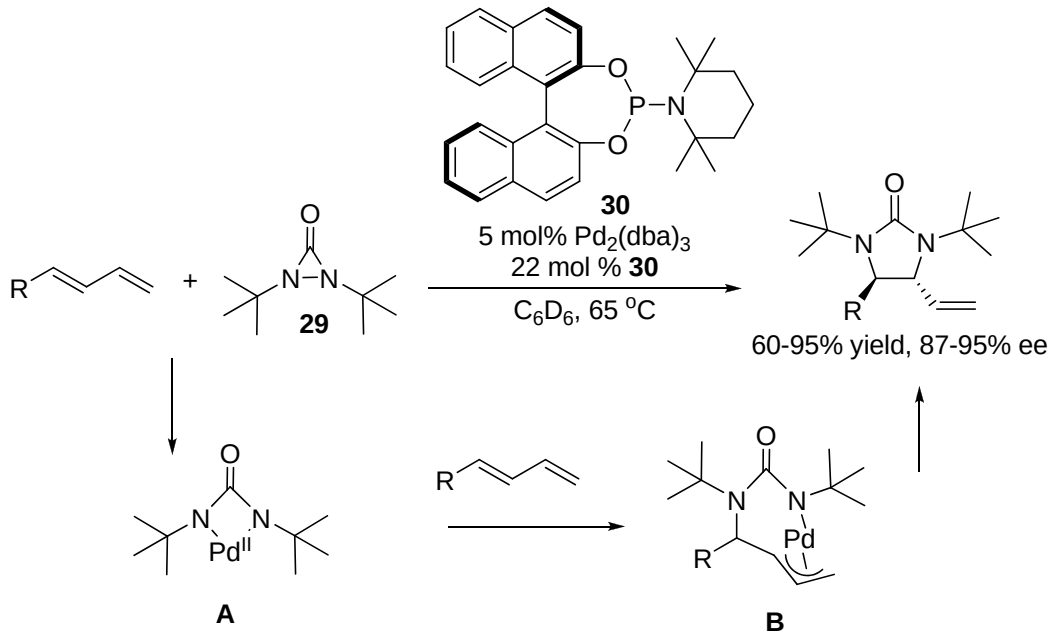


Figure 1.24. Pd-catalyzed diamination of diene reported by Shi and coworkers.

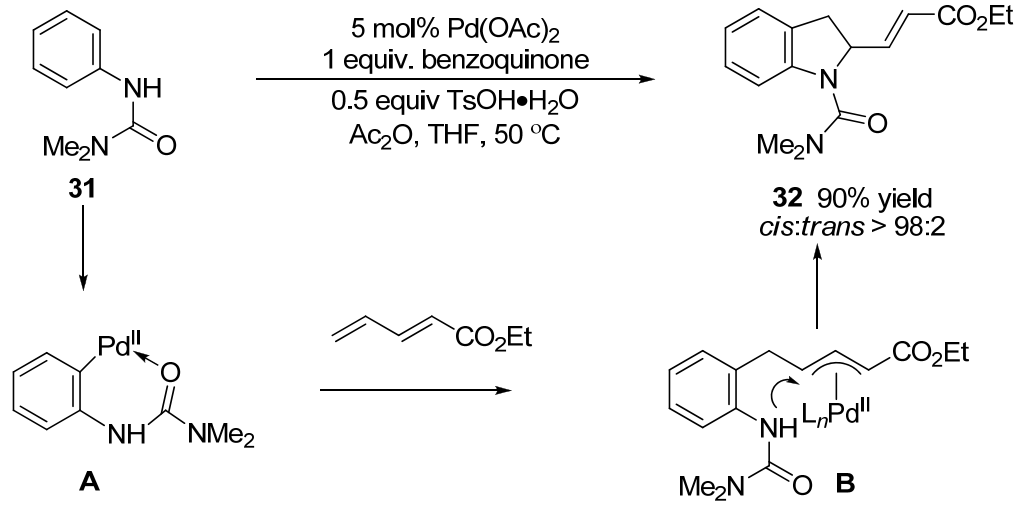


Figure 1.25. Pd-catalyzed intramolecular 1,2-carboamination of diene developed by Milburn and coworkers**.**

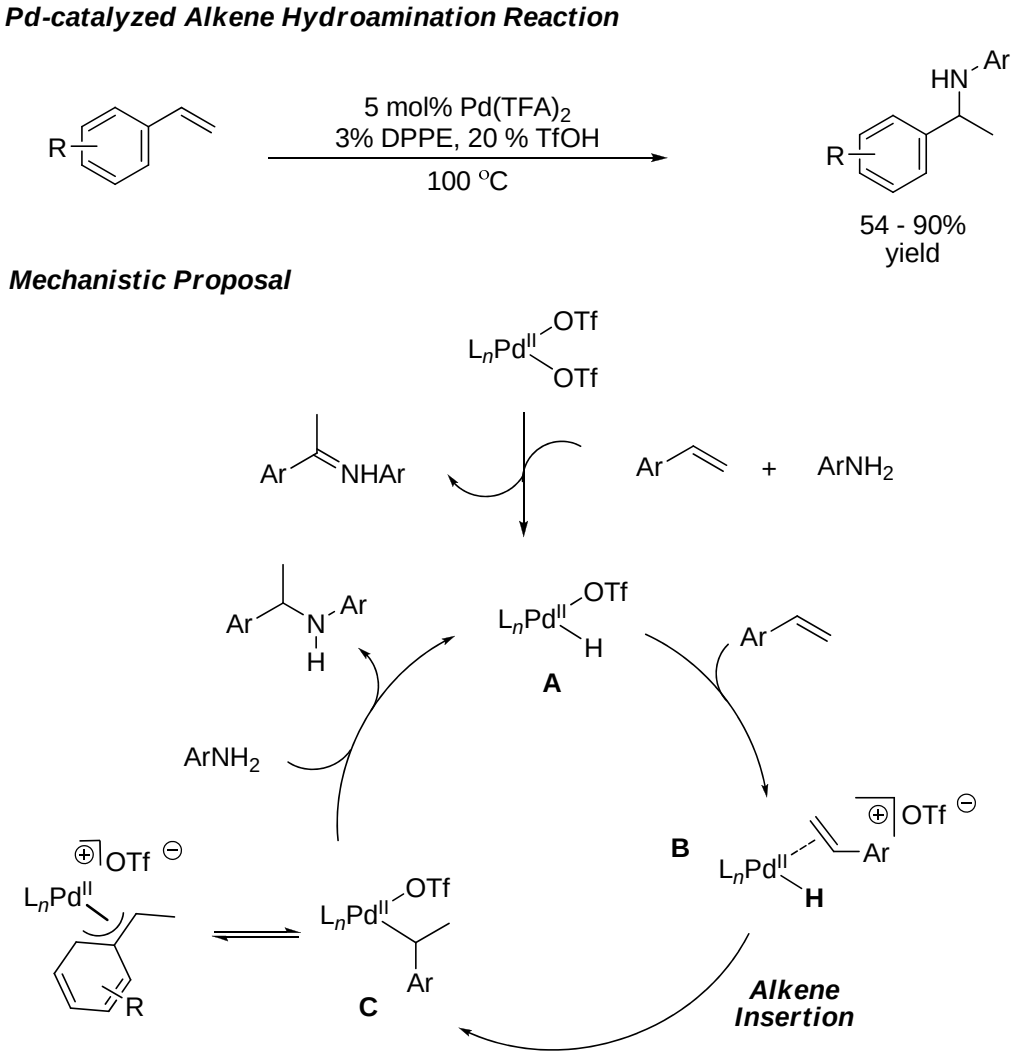


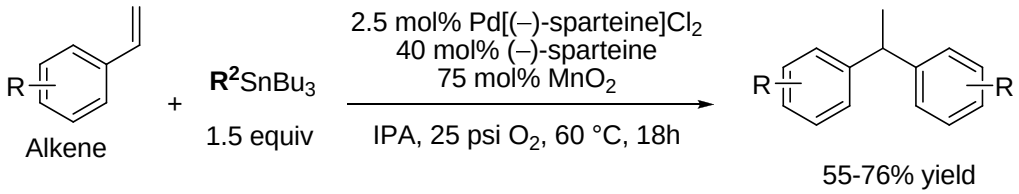
Figure 1.26. The proposed mechanism of Hartwig and coworkers Pd-catalyzed hydroamination of vinylarenes.

ester as a transmetallation agent. The proposed mechanism starts with oxidation of the alcoholic solvent with a Pd^{II} catalyst **A** to form the formation of Pd^{II}-hydride species, **B**. Coordination and insertion of the alkene into the Pd^{II}-hydride yields the Pd^{II}-alkyl intermediate **C** (or **C'**). Transmetallation forms **D** and subsequent reductive elimination generates the reductive coupling product as well as the reduced catalyst **E**. Aerobic oxidation of Pd^{0} to Pd^{II} completes the catalytic cycle.[51,52] In the overall reaction, the sp^2hybridized carbon atoms of the alkene will be transformed to sp^3 atoms.

Quinone methide formation to avoid formation of β-hydride elimination

In addition to the substrates containing conjugated alkenes in palladium catalyzed reactions, substrates containing alternative reactivity have also been used to control β-hydride elimination.[53-55] For example, a palladium-catalyzed dialkoxylation of propenylphenols has been developed by Dr. Mitch Schultz in Sigman lab utilizing quinone methide formation to avoid β-hydride elimination (Figure 1.27).[53] The Pd^{II}-alkyl intermediate is capable of forming a quinone methide intermediate **B** with simultaneous reduction to Pd^{0}, which is reoxidized to Pd^{II} using molecular oxygen (Figure 1.28). Dr. Katrina Jensen and Tejas Pathak have expanded this methodology wherein two distinct nucleophiles were added across the double bond (Figure 1.29). [55]

Reductive cross-coupling reaction



Mechansitic proposal

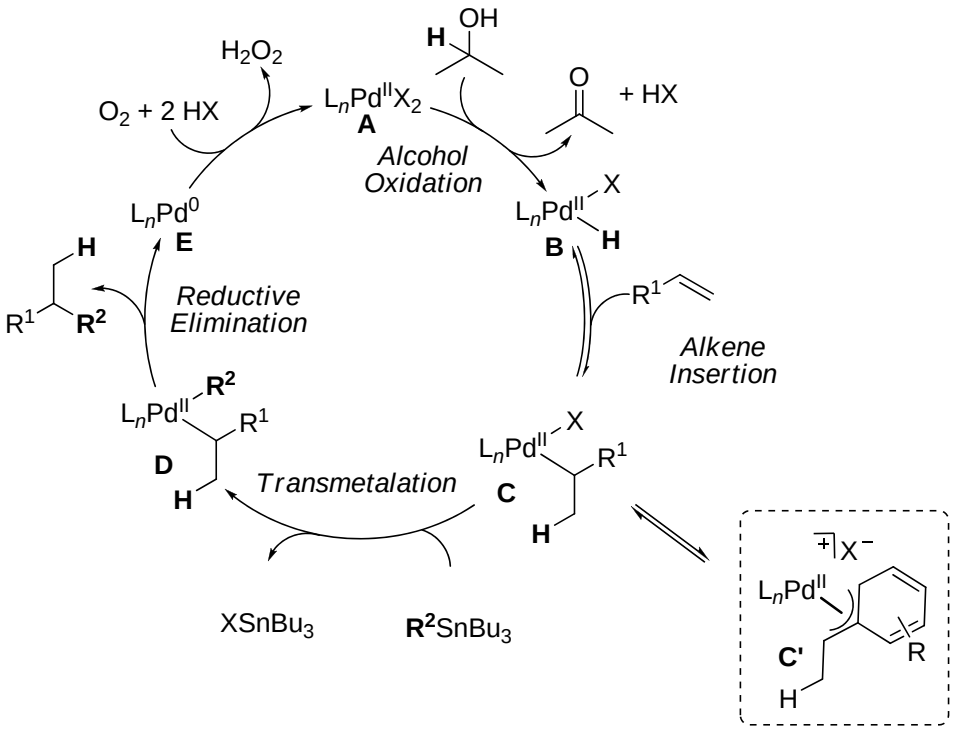


Figure 1.27. The proposed mechanism for Pd-catalyzed reductive cross-coupling of alkene and an organometal.

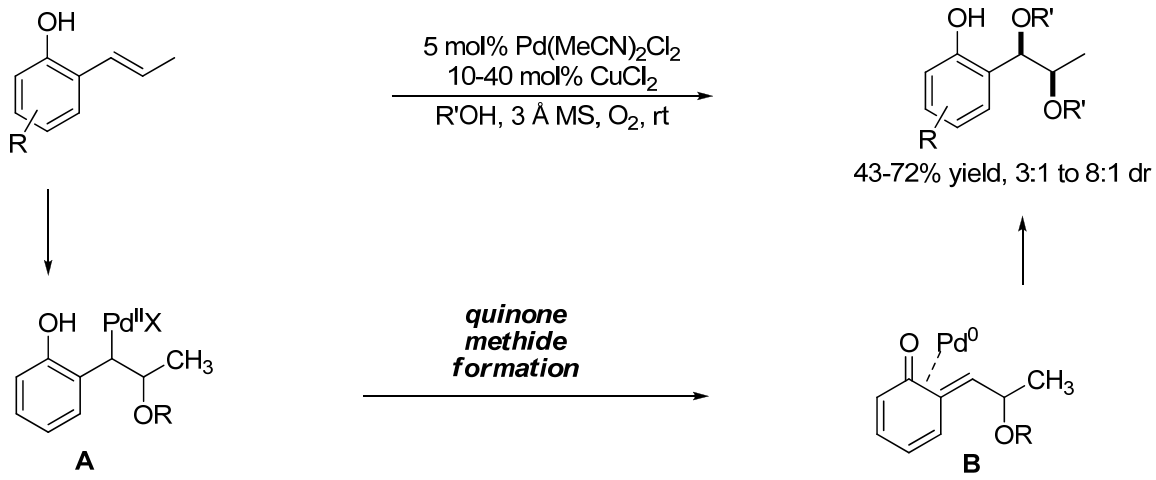


Figure 1.28. Pd-catalyzed alkene dialkoxylation of vinyl phenol that is proposed to proceed via quinone methide formation**.**

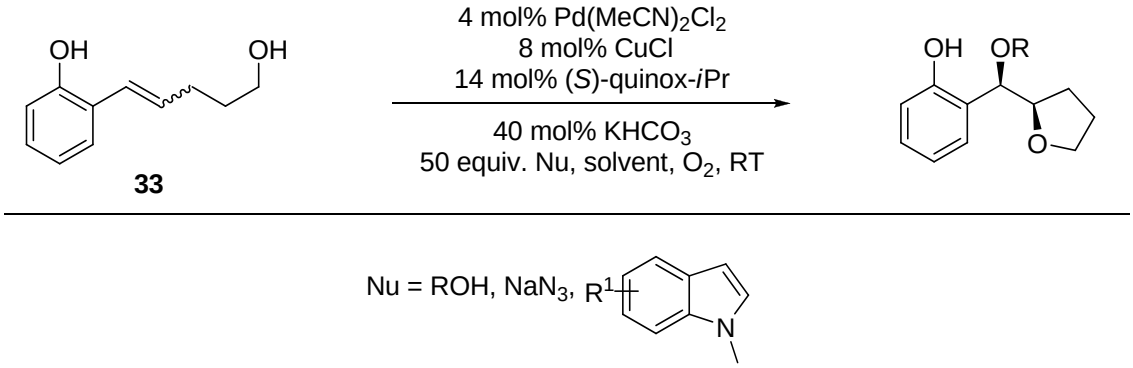


Figure 1.29. Pd-catalyzed alkene dialkoxylation reaction with two distinct nucleophiles**.**

Conclusion

In this chapter, methods based on the interception of Pd-alkyl intermediates for further functionalization have been presented. The main challenge associated with these transformations is the propensity of the Pd-alkyl intermediates to undergo β-hydride elimination. Depending upon the nature of the Pd-alkyl intermediate, different approaches have been adopted to control β-hydride elimination to accomplish further functionalization.

Sigman lab has developed several methods for hydro- and di- functionalization of olefins based on the stabilization of formal Pd π-benzyl or π-allyl complexes. In the following chapter, the utilization of an electrophilic Pd^{II}-complex for the development of 1,2- and 1,1-diarylations of terminal olefins via π-benzyl or π-allyl stabilization will be described. The stability of Pd π-allyl species was also utilized to achieve a 1,1-arylvinylation of olefins, which is discussed in the third chapter. Finally, as outlined in the fourth chapter, the propensity of unstabilized Pd-alkyl intermediates to undergo β-hydride elimination was exploited to generate a Pd-hydride, which is added across a styrene to generate a Pd π-benzyl complex. This complex is then alkylated for an over-all hydroalkylation.

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CHAPTER 2

PALLADIUM-CATALYZED INTERMOLECULAR DIFUNCTIONALIZATION OF TERMINAL ALKENES USING ORGANOSTANNANES

Introduction

The development of Pd-catalyzed reactions that generate carbon-carbon bonds has significantly contributed to organic synthesis.[1] These transformations are proposed to employ Pd^{II} as an active catalyst for the generation of the bond during the reaction; however, in the reaction, Pd^{0} is routinely generated and for effective catalysis, it is essential to regenerate Pd^{II} from Pd^{0} during the catalytic cycle.[1] A variety of reagents have been utilized to regenerate the active Pd^{II} species from Pd^{0}. The common methods for reoxidation is to employ an organic oxidant, such as organic halides or pseudohalide, wherein the oxidant can ultimately become incorporated into the products that are termed as Pd^{0}-catalyzed cross-coupling.[1] Over the past several decades this method has resulted in a wide variety of useful transformations. However, this process is limited by the types of substrate that can be used in the reactions. Alternatively, a terminal oxidant can be utilized, which is not involved in the transformation, but used for the generation of the

active Pd^{II} catalytic species from Pd^{0}.These transformations are termed as oxidative palladium catalysis or oxidase catalysis.[2,3] This type of reaction has recently received more attention because they can provide access to novel organic products that are complementary to those obtained in traditional Pd^{0}-catalyzed cross coupling chemistry. The Sigman laboratory has been involved in developing methodology based on oxidative palladium catalysis.[4,5] Particularly, our lab uses molecular oxygen as a terminal oxidant because of its versatility, low cost, and the non-toxicity of its byproducts.[6] As described in this chapter, our group has been involved in developing Pd-catalyzed alkene functionalization reactions that utilize oxidative Pd-catalysis. Moreover, as mentioned in the Chapter 1, the focus of our group is mainly on the development of reactions that avoid products derived from β-hydride elimination.[7]

In this regard, a former graduate student, Dr. Keith Gligorich, in our laboratory developed a Pd-catalyzed aerobic hydroarylation of alkenes reaction that generates a sp^3-sp^2 carbon-carbon bond (Figure 2.1). This reaction utilizes a Pd^{II}-alkyl intermediate for further functionalization. The proposed σ-alkyl Pd^{II}-intermediate is thought to be stabilized by the formation of a π-benzyl complex **B**, which undergoes transmetallation. During the optimization of the alkene hydroarylation, a new reaction class was discovered, namely the diarylation of styrenes (Figure 2.2). This chapter will focus on the optimization and the development of this difunctionalization reaction, which generates two new carbon-carbon bonds in a single step.[8,9] This transformation will also highlight key challenges that are associated with the β-hydride elimination step and will also explore the mechanistic details that help in controlling β-hydride elimination.[10-13]

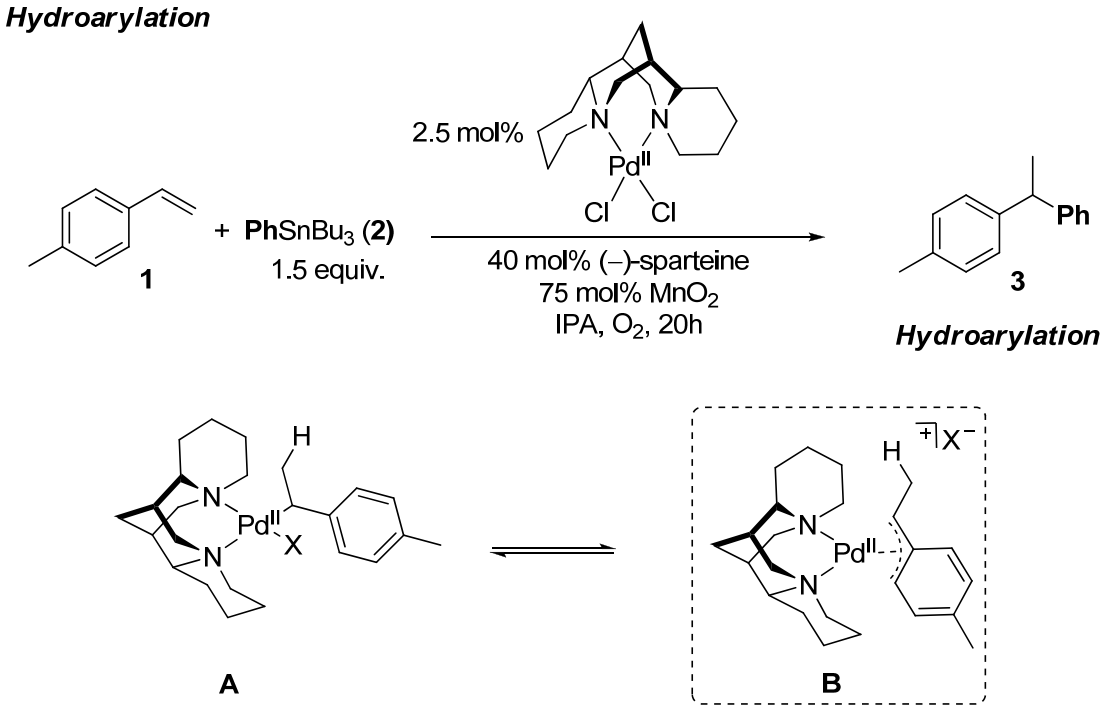


Figure 2.1. Pd-catalyzed reductive coupling of 4-methylstyrene and phenyltributylstannane and the proposed β-benzyl intermediate for the out of the regio-isomer.

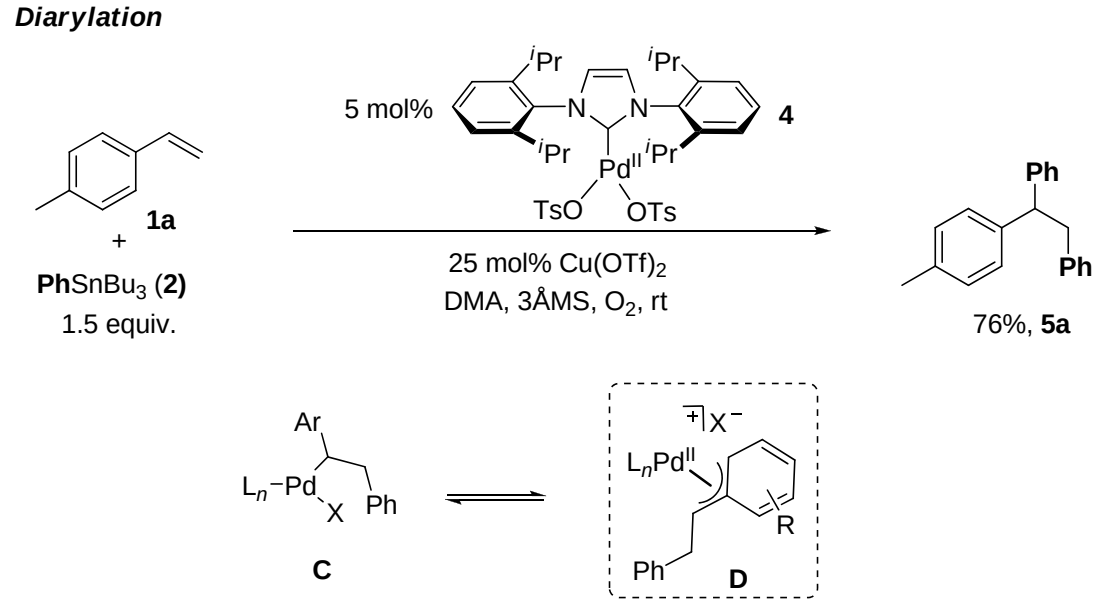


Figure 2.2. Pd-catalyzed coupling of 4-methylstyrene and phenylstannane to generate the diarylation product and the proposed π-benzyl stabilization to avoid β-hydride elimination.

Background and mechanism for oxidative catalysis

In order to develop an oxidative palladium catalyzed reaction, it is essential to understand the mechanistic details involved in the catalytic cycle (Figure 2.3). The transformation involving Pd^{II}/Pd^{0} catalysis can be broken down into two distinct half reactions.[6,14] The first half involves substrate oxidation which varies mechanistically depending on the type of transformation. The second half involves the oxidation of Pd^{0} to Pd^{II}, which is a significant step in most oxidase reactions. Importantly, the rate of formation of Pd^{0} after the substrate oxidation should match the rate of oxidation of Pd^{0} to Pd^{II} or the buildup of Pd^{0} species can lead to aggregation of the catalyst, which causes precipitation to an inactive metallic Pd^{0}. This has been one of the most challenging problems to overcome when developing new palladium oxidation type reactions that utilize O_2 as the sole stoichiometric oxidant. Recently, ligands have been used to stabilize the Pd^{0} intermediate to prevent catalyst aggregation. Oxidatively stable mono- and bidentate nitrogen-containing ligands and N-heterocyclic carbene (NHC) ligands are generally employed for oxidative catalysis because air-sensitive phosphine based ligands are incompatible (Figure 2.4).

Results and discussion

As described, the Sigman laboratory is interested in developing new Pd-catalyzed oxidative reactions. Recently, Dr. Keith Gligorich developed a hydroarylation of styrene derivatives using an organostannane as the transmetallating reagent (Figure 2.5).[23] In this reaction, the proposed σ-alkyl Pd^{II}-intermediate **C** is accessed by insertion of a Pd^{II}-

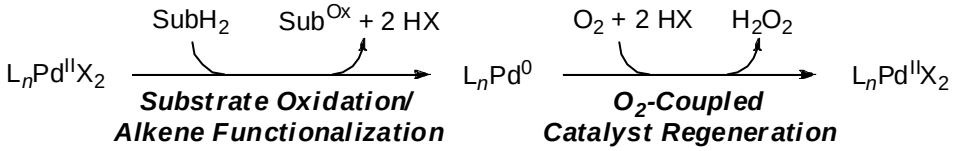


Figure 2.3. Palladium oxidase catalysis can be separated into two distinct half reactions: (1) substrate oxidation and (2) O_2-coupled catalyst regeneration.[2,6]

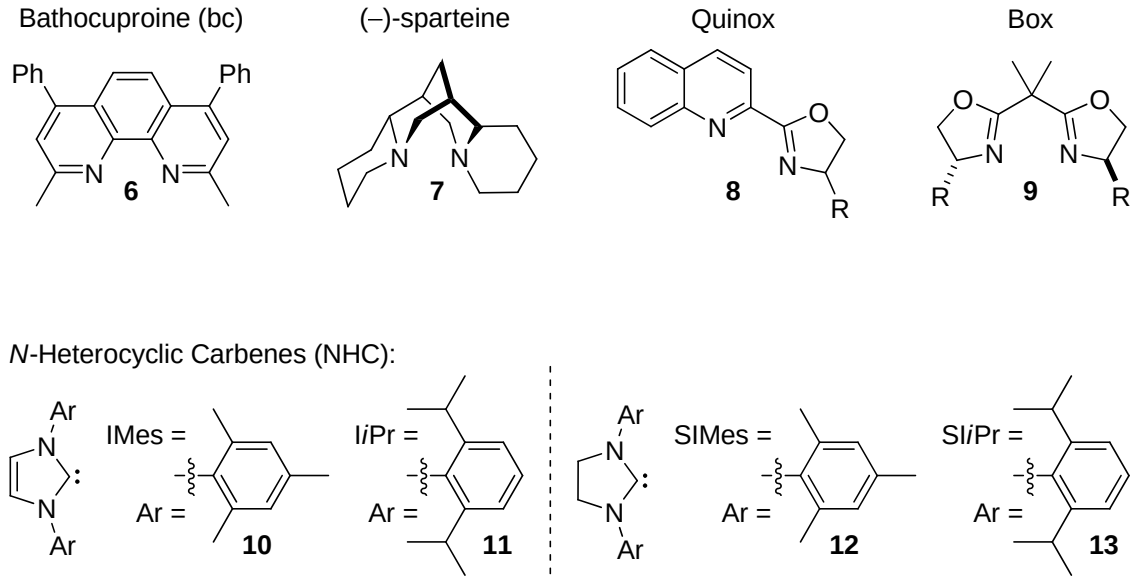


Figure 2.4. Examples of oxidatively stable mono- and bidentate nitrogen containing ligands and *N*-heterocyclic carbene ligands commonly used in Pd-oxidase catalysis.[2,15-22]

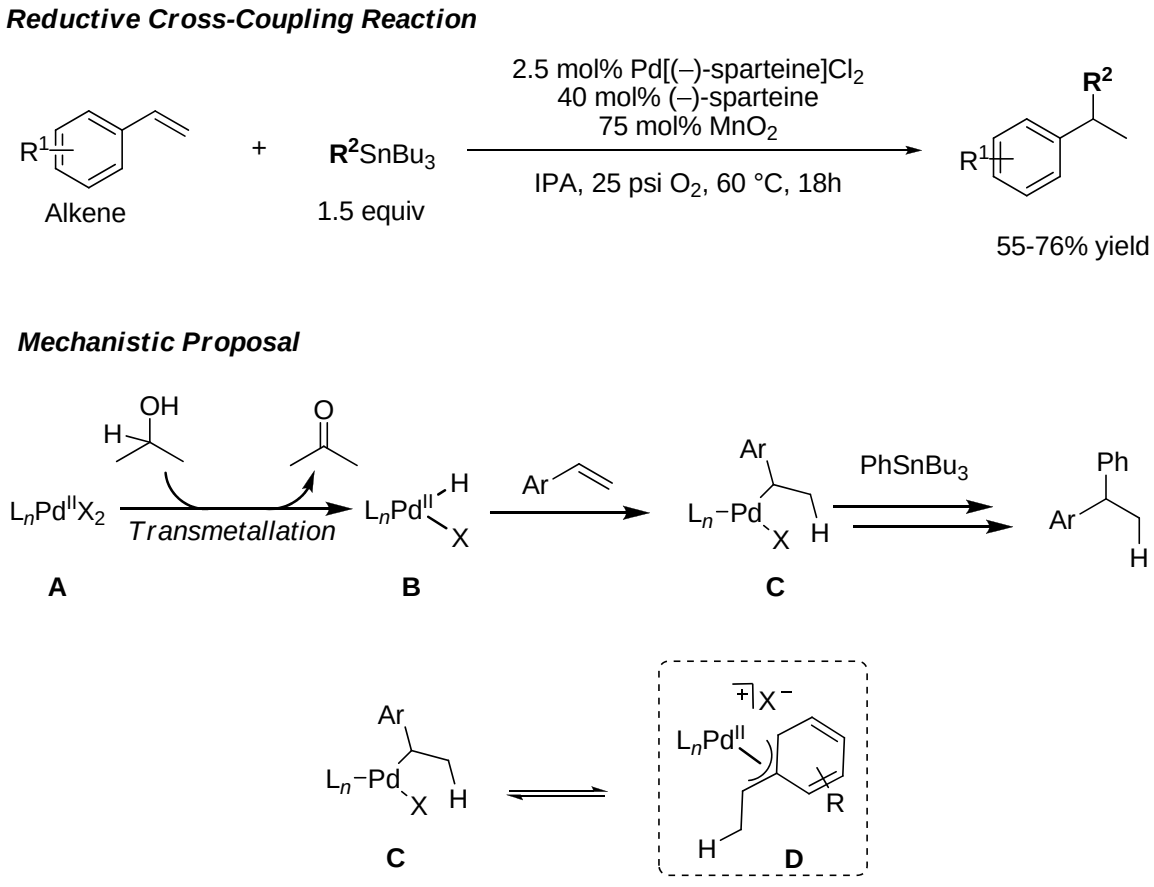


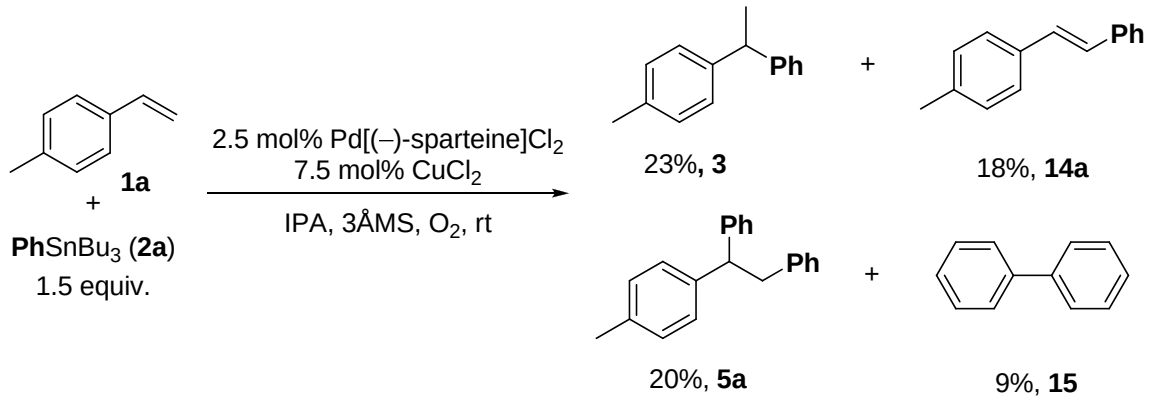
Figure 2.5. Envisioned reductive cross-coupling reaction that is proposed to initiate via alcohol oxidation and the Pd(II)-alkyl intermediate is stabilized by a π-benzyl species to avoid β-hydride elimination.

hydride into styrene (which is formed by the oxidation of the isopropanol solvent), this intermediate being thought to be stabilized by the formation of π-benzyl complex **D**, which undergoes transmetallation followed by reductive elimination to generate the hydroarylation product. As discussed in Chapter 1, in this case, the Pd^{II}-alkyl intermediate formed is stabilized using the substrate to achieve functionalization of the σ-alkyl Pd^{II}-intermediate.

During the course of reaction optimization Dr. Keith Gligorich discovered that the diarylation of styrene leads to a major byproduct along with the hydroarylation product (Figure 2.6). Mechanistically, this reaction is proposed to proceed with initial transmetallation to generate Pd^{II}-aryl intermediate **B,** which reacts with the alkene by a Heck insertion to yield Pd^{II}-alkyl **C**. Subsequent transmetallation forms **D** and reductive elimination yields the diarylation product and Pd^0, which is oxidized by O_2 to regeneratethe active catalyst **A**. Similar to hydroarylation, this reaction is also proposed to be dependent on a π-benzyl stabilization to avoid β-hydride elimination.

Initially, we were excited to observe the diarylation product because previously Pd-catalyzed difunctionalization reactions forming two C-C bonds in a single step on alkene substrates were known only when the substrates were norbornene type olefins or the olefins that form Pd-alkyl intermediates that do not contain β-hydrogens (Figure 2.7).[24-26] The successes for these norbornene difunctionalization reactions arose because the Pd-alkyl intermediate generated from norbornene could not undergo β-hydride elimination due to the absence of *cis* β–hydrogen. In this regard, expanding this reaction type to other alkene substrates will certainly expand the scope of oxidative Pd-catalysis. Therefore, we were interested in developing an alkene difunctionalization of substrates

Diarylation of Styrene Derivatives



Mechanistic Proposal

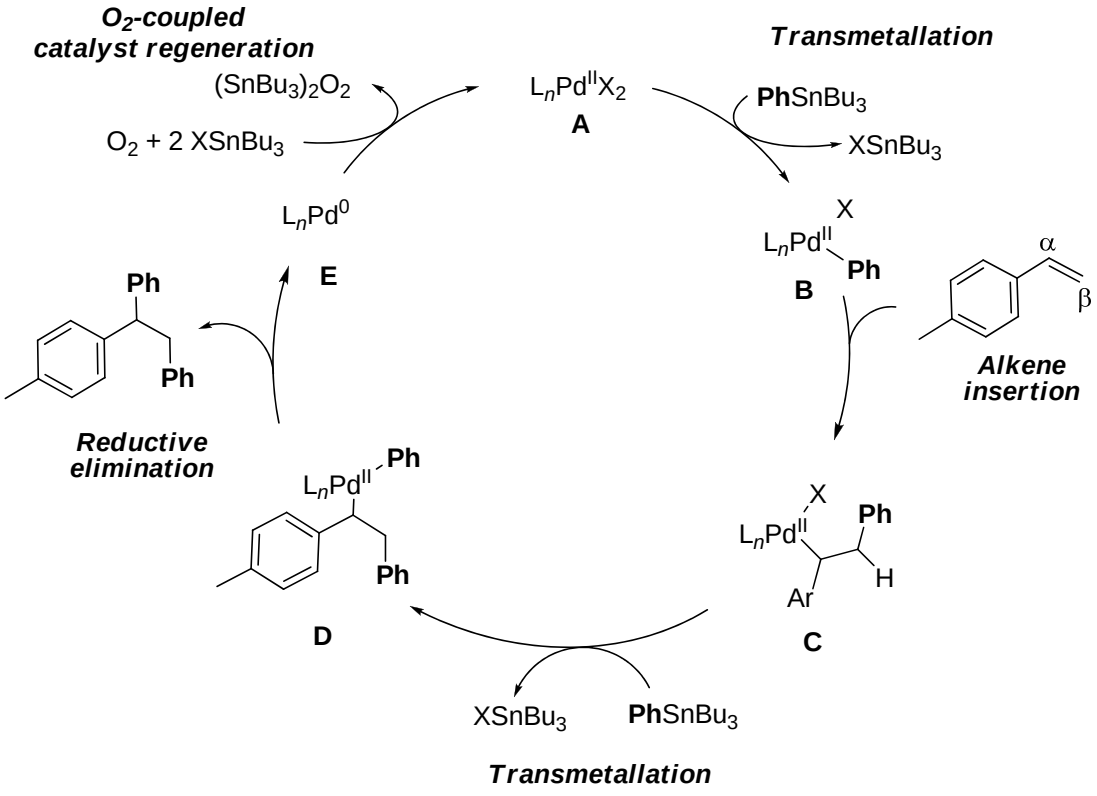


Figure 2.6. Palladium oxidative catalyzed diarylation of styrene reaction that is proposed to initiate via transmetallation and the Pd-alkyl intermediate is stabilized by π-benzyl intermediate to avoid β-hydride elimination

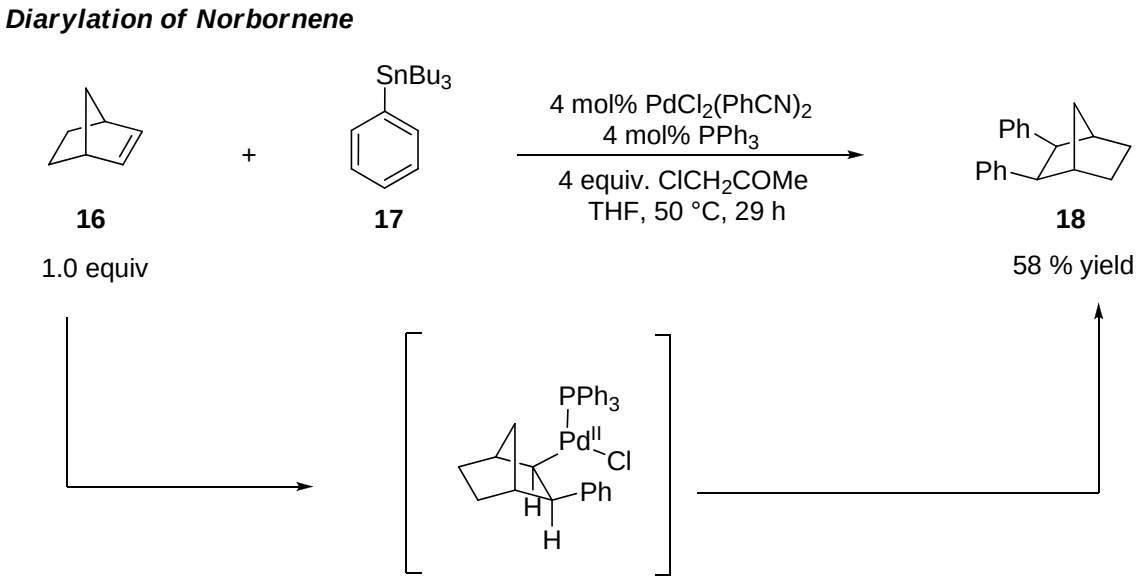


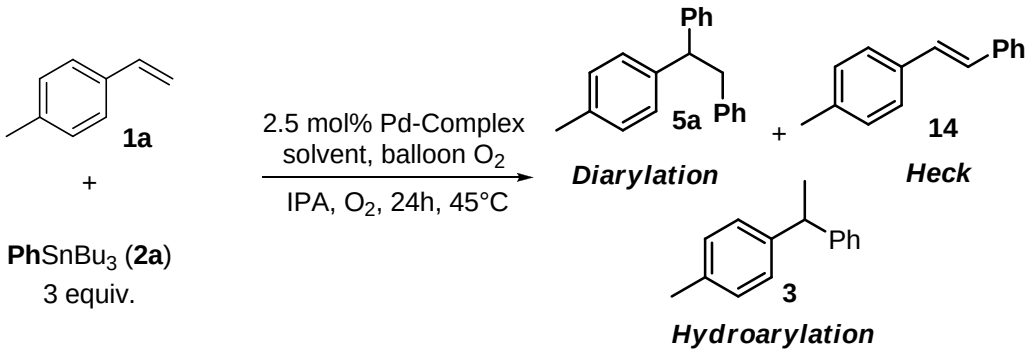
Figure 2.7. Kosugi and coworkers Pd-catalyzed oxidative diarylation of norbornene using an organostannane reagent.

other than norborene types. Based on the previous success of the hydroarylation reaction, we were encouraged to utilize styrene as the substrate to control β-hydride elimination via the stabilization of the resultant π-benzyl complex[27] to allow for alkene difunctionalization.

With the initial result of alkene diarylation observed when using Pd[(-)sparteine]Cl_2 as the catalyst, we initiated the optimization with the evaluation of different ligands (Table 2.1, Entries 1). Surprisingly, most of the amine based bidendate ligands gave low yields of the diarylation product, and interestingly, carbene based monodendate ligands gave an increase in yield of the product. Previously, our laboratory has found that *N*-heterocyclic carbene ligands were effective ligands for various Pd-catalyzed oxidative type reactions.[28,29] Moreover, Pd^{II}-NHC complexes were shown in our laboratory to be robust catalysts for various aerobic oxidation reactions and by others in cross-coupling reactions.[30-32] Therefore, we choose *N*-heterocyclic carbene ligands for further evaluation in this reaction. After testing several Pd-NHC complexes such as $[Pd(I\textit{i}Pr)(OAc)_2]$, $[Pd(S\textit{i}Pr)(OAc)_2]_2$, $[Pd(IMes)(OAc)_2]_2$ and $Pd(I\textit{i}Pr)(OAc)_2$, it was found that $Pd(I\textit{i}Pr)(OAc)_2$ resulted in an improved yield of the diarylation product (Table 2.1, Entries 2-5).

A number of byproducts were initially anticipated, such as oxidative Heck products,[33-35] hydroarylation,[23,29] and oxidative homocoupling of the transmetallating reagent.[36-38] The Heck product is proposed to be generated from transmetallation of the Pd(II)-catalyst **A** followed by coordination and insertion of olefin to yield intermediate **C**. Subsequent β-hydride elimination liberates the Heck product and the Pd-hydride. It was proposed that the Pd-alkyl intermediate **C** could be stabilized by a π-benzyl species to

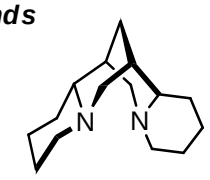
Table 2.1. Initial optimization for the diarylation product **5a**: discovery suitable ligand for the diarylation reaction.



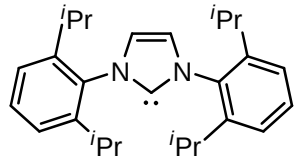
Entry[a]	Pd-Complex	Solvent	Conv. (%)[b]	**5a** (%)[c]	**5a** : **14** : **3**[d]
1[e]	Pd(**sp**)Cl_2	IPA	90	32	1.6 : 0.8 : 1
2	$[Pd(I\textit{i}Pr)(Cl)_2]_2$	IPA	27	10	5.0 : 1.5 : 1
3	Pd(S*i*Pr)$(OAc)_2$	IPA	90	33	2.3 : 1.7 : 1
4	Pd(I*i*Pr)$(OAc)_2$	IPA	99	41	8.2 : 8.6 : 1
5	Pd(IMes)$(OAc)_2$	IPA	76	31	2.3 : 0.9 : 1

[a]Reaction performed on a 0.2 mmol scale. [b]Percent conversion measured by GC using an internal standard. [c]GC yield. [d]Ratio of GC yields. [e]$CuCl_2$ (7.5 mol%) was used and reaction performed at RT.

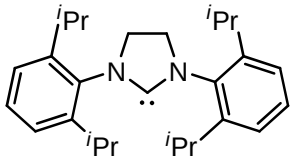
Ligands



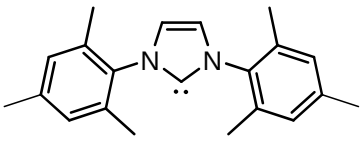
(–)-sparteine (**sp**)



I*i*Pr



S*i*Pr



IMes

allow for another transmetallation and reductive elimination to yield the diarylation product. Alternatively, intermediate **B** can also undergo a second transmetallation before alkene insertion, which leads to the homocoupled product

Analysis of different pathways leading to possible side products suggested that for a successful diarylation reaction, proper tuning of the reaction pathways is essential. Taking into account all the possible pathways, two important issues must be addressed. In order to avoid the homocoupling reaction, the rate of coordination and alkene insertion has to be greater than the rate of the second transmetallation. Second, to avoid the Heck product, the rate of β-hydride elimination has to be slowed to allow for the second transmetallation (Figure 2.8).

We hypothesized that an electrophilic palladium center might be suitable for this transformation, because after the formation of the Pd^{II}-aryl intermediate **B** (Figure 2.9), this electrophilic Pd center would increase the rate of coordination to the olefin over the second transmetallation to generate the Pd^{II}-alkyl intermediate **C**. Moreover, the Pd^{II}-alkyl intermediate formed is prone to undergo β-hydride elimination. However, we hypothesized that effective stabilization of the π-benzyl intermediate could allow for further transmetallation. Based on literature precedent, Pd with a triflate counterion is known to stabilize the π-benzyl species and examples of the isolated Pd- π-benzyl species are also known with the electrophile Pd-complexes (Figure 2.10).[39,40] Therefore, it was thought that the electrophilic palladium is suitable for stabilization of the resultant π-benzyl complex **C'**, and this would presumably slow the rate of β-hydride elimination and potentially allow for the second transmetallation with subsequent reductive elimination generating the diarylation product.

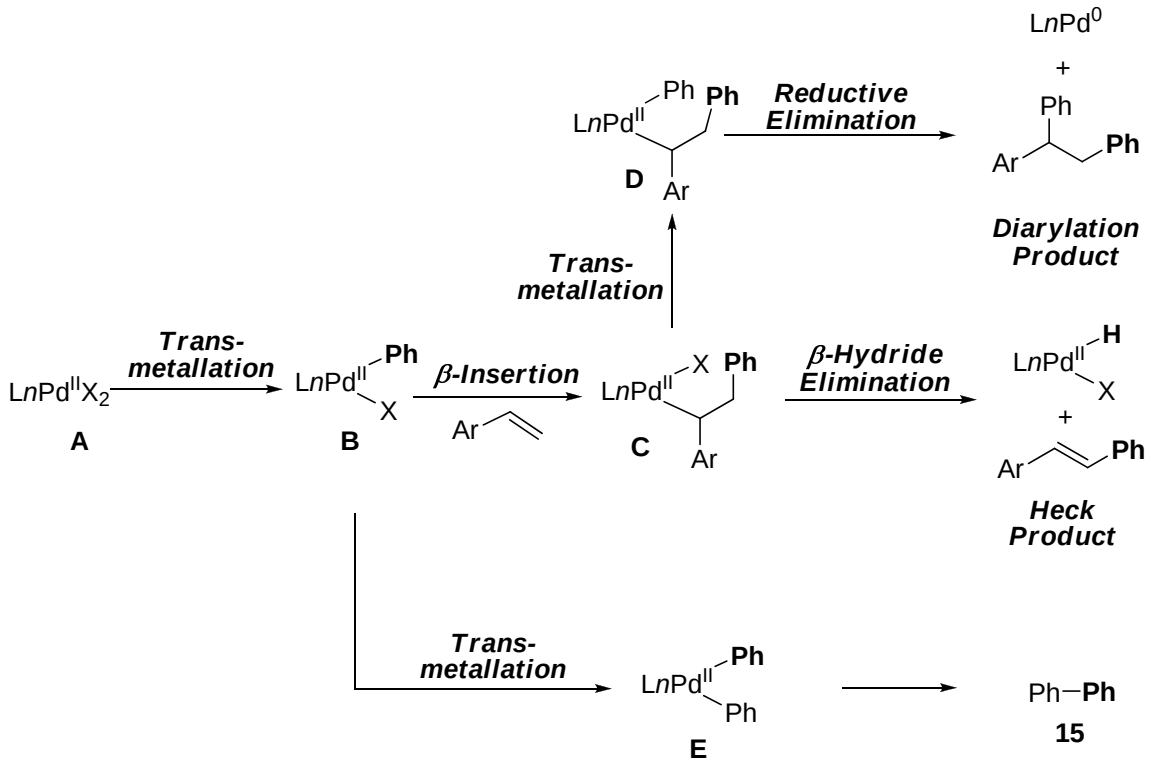


Figure 2.8. Proposed competitive pathways for the Pd-catalyzed alkene diarylation that lead to homocoupling, oxidative Heck reaction and diarylation products.

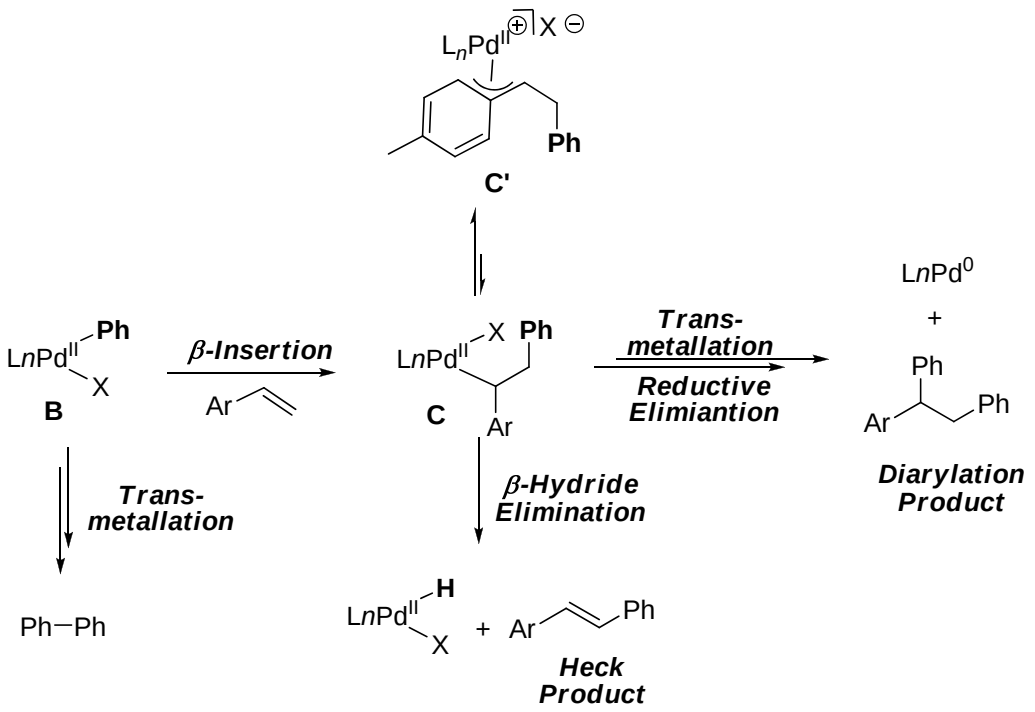


Figure 2.9. Approaches utilizing an electrophilic Pd-catalysis to avoid oxidative Heck reaction and oxidative homocoupling pathway.

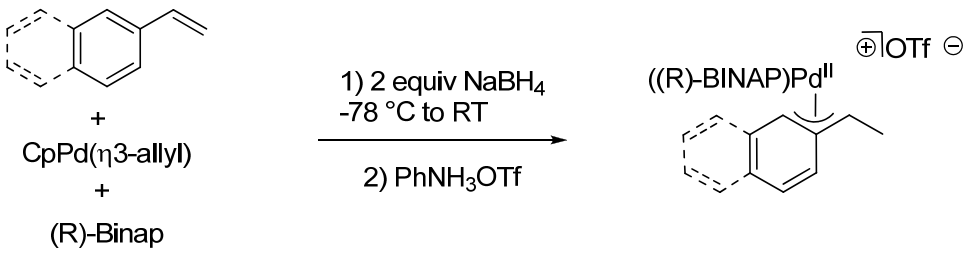
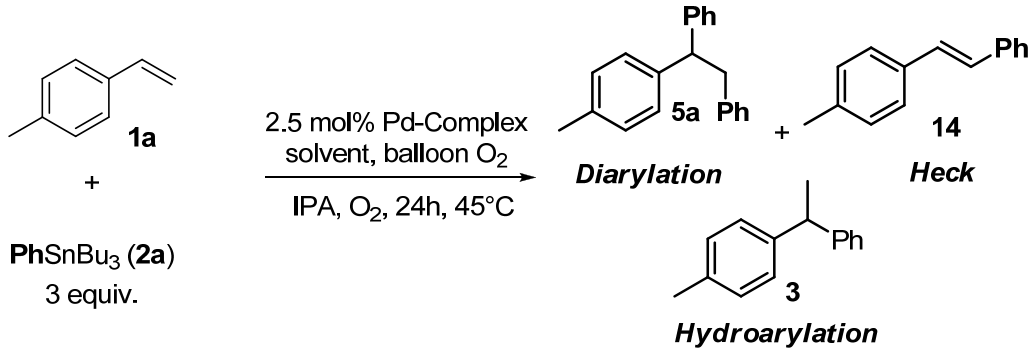


Figure 2.10. Examples of isolated complexes of electrophilic Pd-π-benzyl species that are stabilized by the aromatic electrons.

Based on this hypothesis, the electrophilic nature of the palladium was increased by changing the acetate counter ion to trifluoroacetate (Table 2.1, Entry 1). Interestingly, an increase in the product yield was observed along with improved selectivity for diarylation over the Heck and homocoupled products. Based on this finding, we were encouraged to further increase the electrophilic nature of the Pd-complex by replacing the counter ion with OTs, OTf, and BF_4, unfortunately decomposition of the catalyst was observed in all cases (Table 2.2, Entries 2-4). Though, the catalyst was decomposed over a period of time, in case of OTs as the counterion (Table 2.2, Entry 2), considerable conversion and yield of the diarylation product was observed along with the excellent selectivity, which suggested that our hypothesis of utilizing electrophillic palladium was correct. Furthermore, changing the solvent from IPA to DCE, dioxane, or N,N-dimethylacetamide (DMA) (Table 2.2, Entries 5-8) under the same reaction conditions resulted in an improved catalytic system with an increase in conversion and yield. At this stage, the major concern was the formation of the Heck product, and it was thought that a change in temperature would have an effect on the stabilization of π-benzyl species and in the rate of β-hydride elimination. Therefore, the reaction was tested at a different temperature, and interestingly, a decrease to room temperature gave excellent selectivity with a decrease in the yield of the product (Table 2.3, Entry 1). However, an increase in catalyst loading led to higher yield (Table 2.3, Entry 2). Next, substrate conversion was the main problem, with one of the possibilities being catalyst decomposition. In oxidative palladium catalysis, the rate of formation of Pd^0 after the substrate oxidation should match the rate of oxidation of Pd^0 to Pd^{II} or the build-up of Pd^0 species could lead to aggregation of the catalyst, which causes precipitation of metallic Pd^0.[14] Molecular sieves

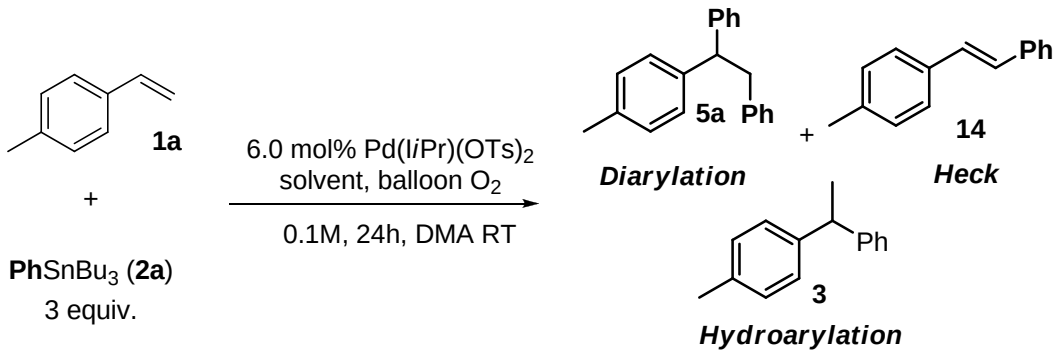
Table 2.2. Initial optimization for the diarylation product **5a,** and evaluating the electronic nature of counter ions and the affect of the solvent.



Entry[a]	Pd-Complex	Solvent	Conv. (%)[b]	**5a** (%)[c]	**5a** : **14** : **3**[d]
1	Pd(I*i*Pr)$(OCOCF_3)_2$	IPA	90	55	4.2 : 0.9 : 1
2	Pd(I*i*Pr)$(OTs)_2$	IPA	30	26	26 : 2.0 : 1
3	Pd(I*i*Pr)$(BF_4)_2$	IPA	22	15	15 : 1.3 : 1
4	Pd(I*i*Pr)$(OTf)_2$	IPA	24	17	14.1 : 1.2 : 1
5	Pd(I*i*Pr)$(OTs)_2$	DME	90	55	3.0 : 0.3 : 1
6	Pd(I*i*Pr)$(OTs)_2$	Dioxane	99	58	4.1 : 0.6 : 1
7	Pd(I*i*Pr)$(OTs)_2$	DMA	99	60	7.0 : 2.4 : 1
8	Pd(I*i*Pr)$(OTs)_2$	DMF	26	18	6.4 : 1.6 : 1

[a]Reaction performed on a 0.2 mmol scale. [b]Percent conversion measured by GC using an internal standard. [c]GC yield. [d]Ratio of GC yields.

Table 2.3. Final optimization for the diarylation product **5a** with the screening of suitable additives.



Entry[a]	mol% $CuOTf_2$	Conv. (%)[b]	**5a** (%)[c]	**5a** : **14** : **3**[d]
1[e]	0	46	36	20 : 4.5 : 1
2	0	78	50	17 : 5.3 :1
3[f]	0	91	63	16 : 0. 3 : 1
4[f]	5	>99	90	22 : 2.3 : 1
5[f]	15	>99	92	31 : 1.3 : 1
6[f]	25	>99	97	42 : 1.5 : 1
7[f]	35	>99	88	17 : 1.2 : 1

[a]Reaction performed on a 0.2 mmol scale. [b]Percent conversion measured by GC using an internal standard. [c]GC yield. [d]Ratio of GC yields. [e]2.5 mol% Pd(I*i*Pr)$(OTs)_2$ was used. [f]Activated molecular sieves (3 Å, 100mg) were used.

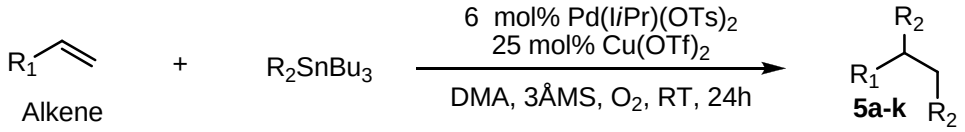
have been shown to decrease the aggregation of Pd^0.[41]

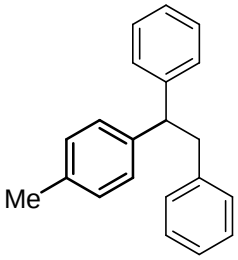
When we tested different amounts of molecular sieves, we observed an increase in product formation (Table 2.3, Entry 3). Finally, Cu-salts have seen use as co-oxidants with molecular oxygen to oxidize Pd^0 to Pd^{II}. Therefore, several Cu-salts were evaluated and when using $Cu(OTf)_2$, a significant rate enhancement and improved catalyst stability was observed.[42,43] Further, systematic screening of $Cu(OTf)_2$ concentration resulted in the use of 25 mol% (Table 2.3, Entries 4-7).

After suitable catalytic conditions were identified, the substrate scope of the styrene diarylation reaction was evaluated (Figure 2.11). Initially, electronically diverse organostannanes were tested and had minimal effect on the diarylation reaction. Electron rich styrenes, including those with *ortho* substitution, were found to undergo the reaction successfully with $PhSnBu_3$ in good yield. A cyclic enol ether derived organostannane performs well in this reaction indicating that a wide scope of alternative organostannanes can be anticipated **27** (Table 2.4). Terminal 1,3-dienes were evaluated wherein a π-allyl species can be formed rather than a π-benzyl stabilized intermediate (Table 2.5).[44] To our delight, the 1,2-diarylation of 1,3-dienes yielded the desired product as a single isomer. Finally, the difunctionalization of a 1,3-diene with a non-aryl derived organostannane was successful albeit in a modest yield.

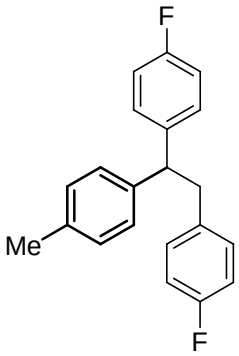
Based on the success of this reaction, other potential substrates for this catalyst system were explored. When disubstituted styrenes such as β- and α-methyl styrene were evaluated only a 14% GC yield of the product was observed with β-methyl styrene **32** and no product was detected on GC when using α-methyl styrene **34**, however, an increase in yield of the homocoupling side product was observed. These data suggest that

Table 2.4. Substrate scope of the Pd-catalyzed 1,2 diarylation reaction of styrenes with organostannanes.

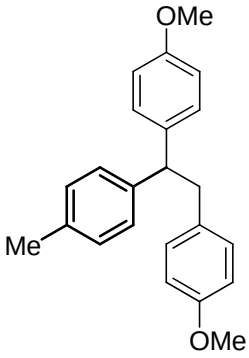




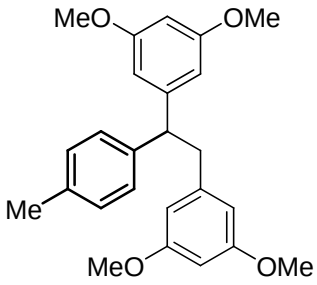
19
78% yield



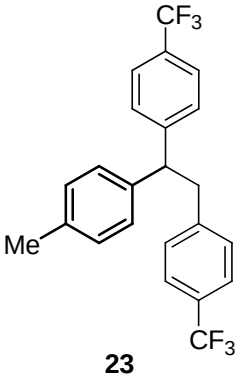
20
64% yield



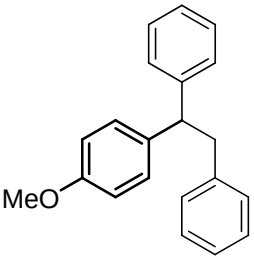
21
65% yield



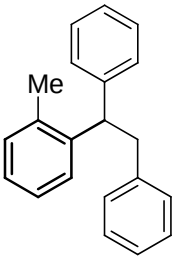
22
68% yield



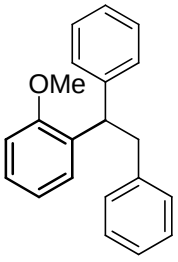
23
60% yield



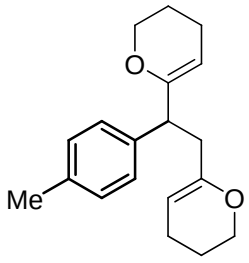
24
51% yield



25
64% yield



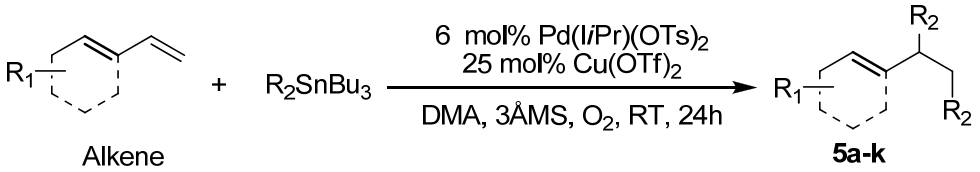
26
55% yield

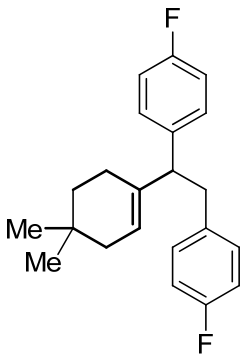


27
57% yield

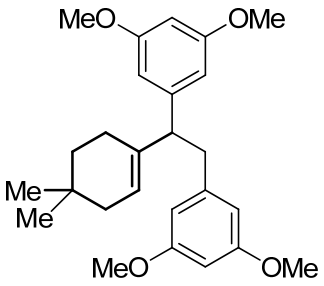
Average isolated yield of two experiments performed on 0.50 mmol scale.

Table 2.5. Substrate scope of the Pd-catalyzed 1,2 diarylation reaction of 1,3 dienes with organostannanes

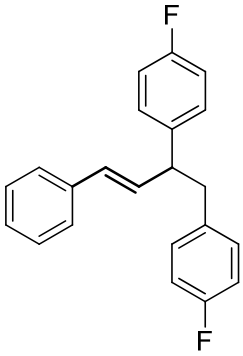




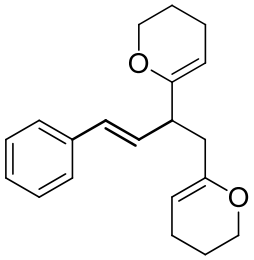
28
59% yield



29
55% yield



30
62% yield



31
37% yield

Average isolated yield of two experiments performed on 0.50 mmol scale.

a small increase in the steric bulk on the alkene substrate can alter the rate of homocoupling over the alkene coordination that leads to oxidative homocoupling products.

When the optimized conditions were applied to electron deficient styrene substrates such as *para*-trifluorostyrenes, an isomer was observed along with the expected 1,2-diarylation products (Figure 2.12). It was proposed to be the 1,1-diarylation product. It was hypothesized that the Pd^{II}-alkyl intermediate **A** formed at the electron withdrawing benzylic position would not be effectively stabilized. Therefore, the Pd-alkyl intermediate can more readily undergo β-hydride elimination, forming the other π-benzyl intermediate **C** through β-hydride elimination and reinsertion processes. Subsequent transmetallation and reductive elimination should generate the 1,1-diarylation products.

Furthermore, an interesting trend was discovered from a systematic examination of the effect of the electron-withdrawing group on the styrene and on the ratio of 1,1- and 1,2-diarylation (Table 2.6). These observations supported the hypothesis that strong electron withdrawing groups destabilized the electrophilic π-benzyl Pd-complex, which were in equilibrium with the σ-alkyl intermediate and leading to β-hydride elimination. Interestingly, when a Hammett plot was constructed by plotting Hammett σ values versus log(1,2/1,1), a linear free energy relationship was observed with a ρ value of -0.88 (Figure 2.13). Based on these findings we turned towards simple alkene substrates such as vinylbutylether and methylvinylketone (Figure 2.14). In this case, the Pd-alkyl intermediate **A** formed is prone to undergo β-hydride elimination, therefore we hypothesized that the rate of β-hydride elimination should be faster than the second trans-

Attempted Addition of disubstituted styrene

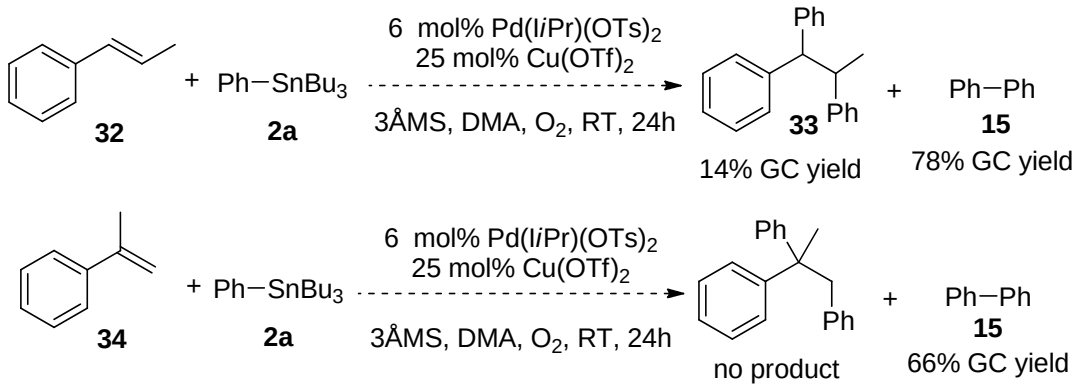


Figure 2.11. Evaluation of potential substrates that can be used in diarylation catalyst system, however none of the substrates gave expected results.

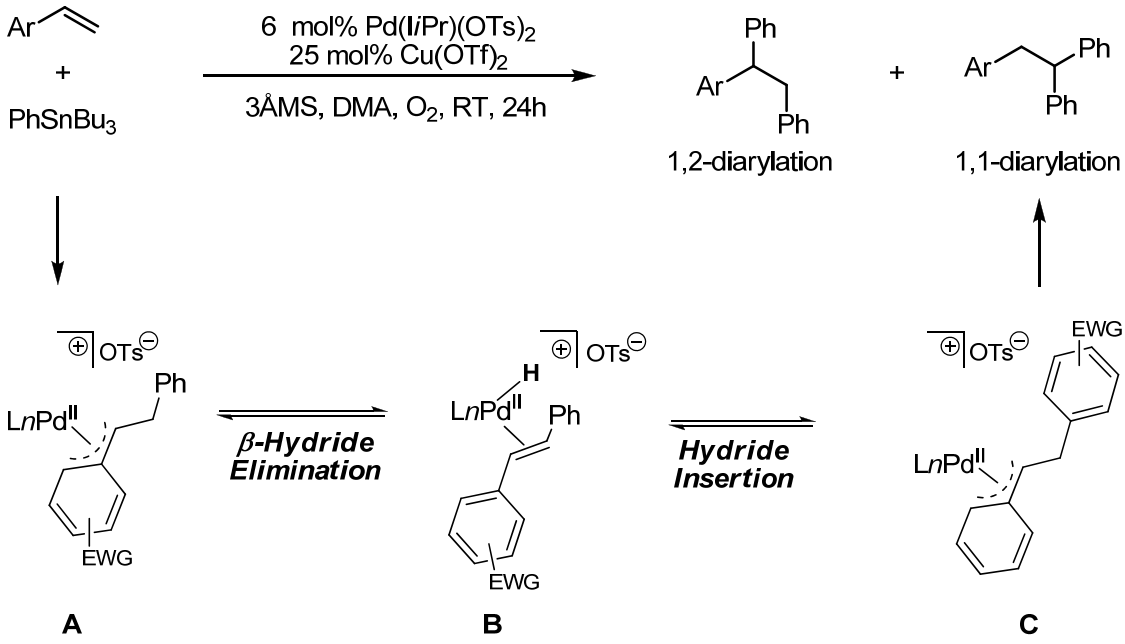
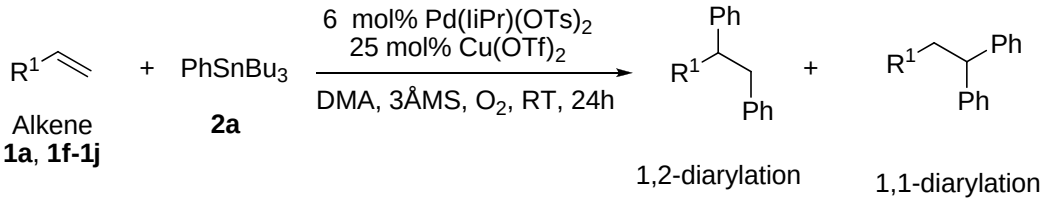
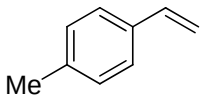
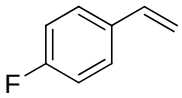
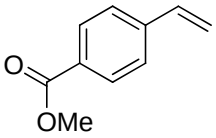
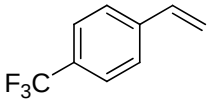
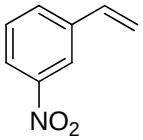


Figure 2.12. Electron withdrawing styrene lead to mixture of 1,2- and 1,1-diarylation product and the proposed pathways for the 1,1-diarylation product.

Table 2.6. Substrate scope of the alkene diarylation that utilizes electron withdrawing styrene substrate.



Alkene **1a**, **1f-1j** | **2a** | 1,2-diarylation | 1,1-diarylation

Entry	Alkene	Product	Yield(%)[a]	ratio(1,2/1,1)
1	**1a** 	**5a**	75	13.6
2	**1f** 	**5f**	65	8.5
3	**1g** 	**5g**	62	5.2
4	**1h** 	**5h**	64	3.7
5	**1j** 	**5j**	68	2.4

[a]Average isolated yield of two experiments performed on 0.5 mmol scale and the yield are reported as mixture of 1,2- and 1,1-diarylation.

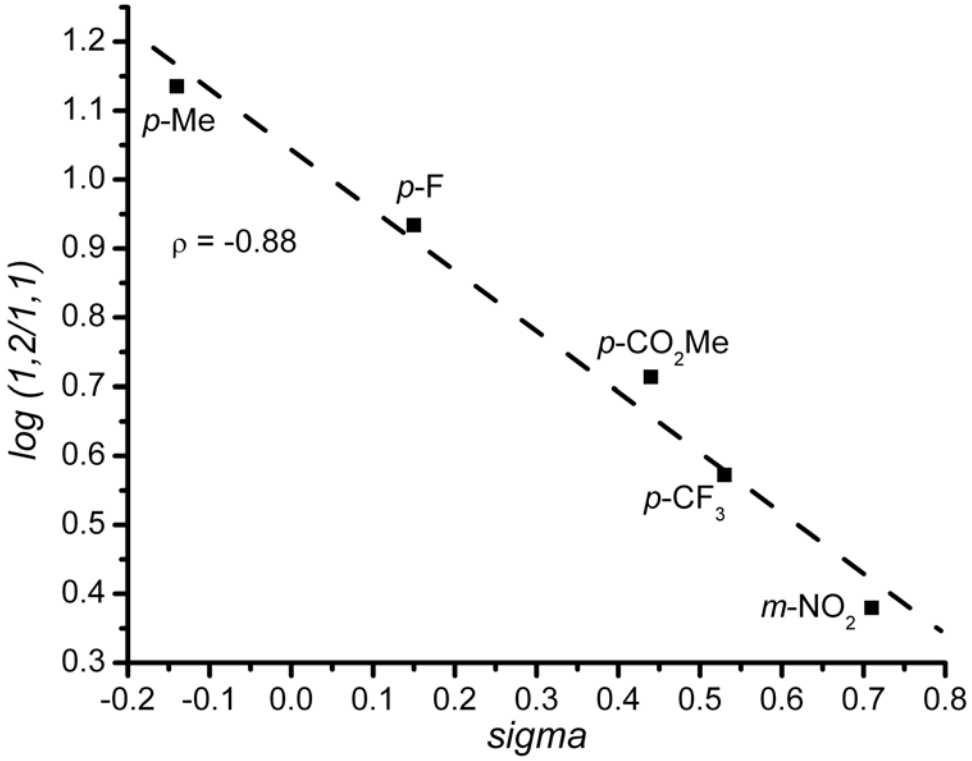


Figure 2.13. The ratio of 1,2-diarylation and 1,1-diarylation was compared by plotting Hammett σ values against log(1,2/1,1) and a linear free energy relationship was observed with a ρ value of -0.88.

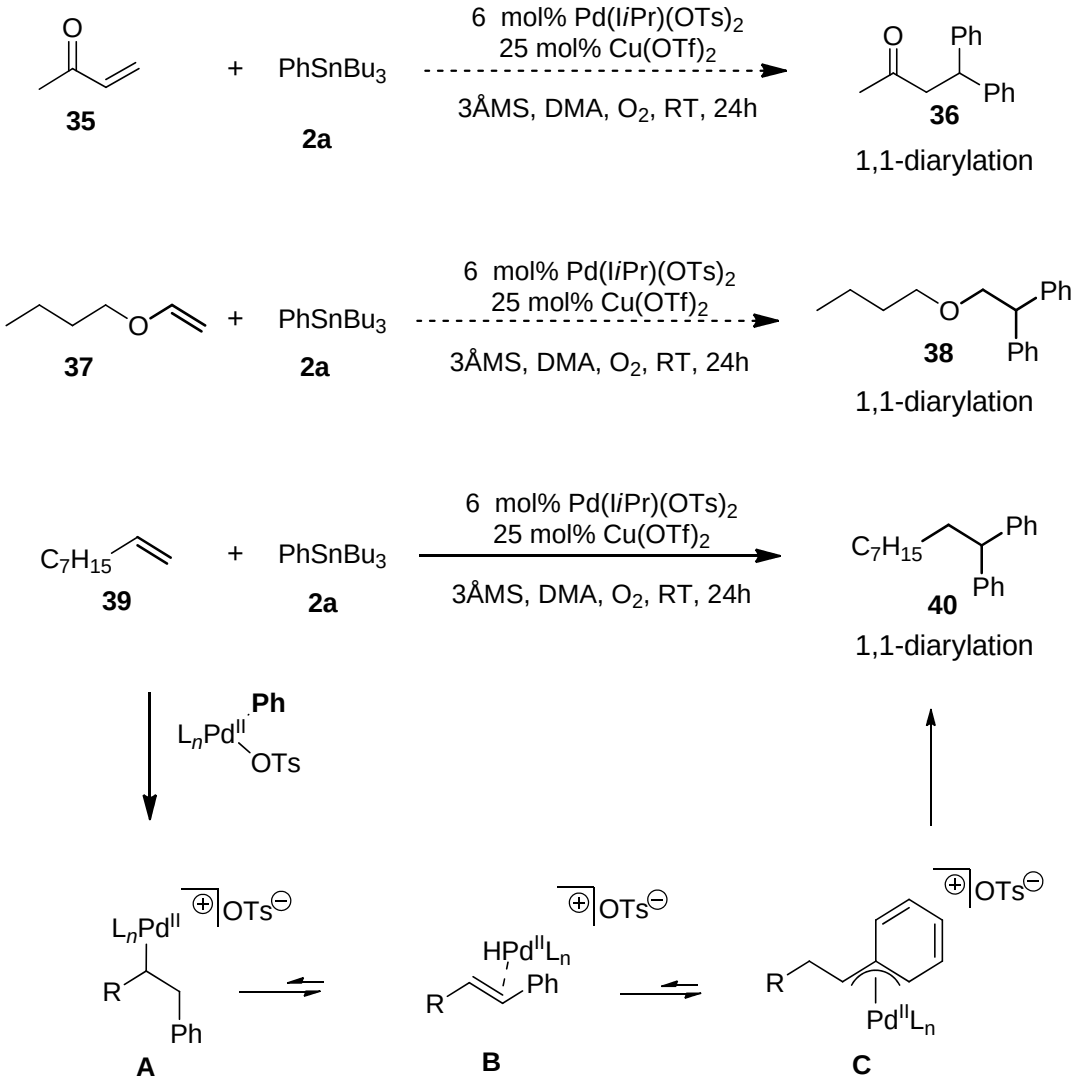


Figure 2.14: Evaluation of the simple alkene substrate with the optimized catalyzed system for the diaryltion product and the proposed hypothesis for the formation of 1,1-diarylation for the straight chain terminal alkenes.

metallation, hence this should rearrange via the β-hydride elimination/reinsertion process to ultimately form a stable π-benzyl intermediate **C**. The π-benzyl intermediate **C** could undergo a second transmetallation followed by reductive elimination to yield the 1,1-diarylation products as observed with the electron withdrawing styrenes. In order to test our hypothesis, we evaluated methylvinylketone **35** and vinylbutylether **41** under the standard diarylation condition; unfortunately, we did not observe any desired products. However, when 1-nonene **39** was subjected to the standard conditions, we were excited to observe the exclusive formation of the 1,1-diarylation product **40** by gas chromatography. With this result, the substrate scope for the 1,1-diarylation utilizing simple alkenes was explored. When using *para*-fluorophenylstannane **2b** and 3,5-dimethoxyphenylstannane **2d** as the transmetallating agent with 1-nonene **39** the desired 1,1-product was isolated in good yield (Figure 2.15). Further, the substrate scope for this 1,1-diarylation was extensively investigated by another graduate student Erik Werner.[45]

After exploring the scope of the diarylation reaction, we were interested in elucidating the mechanistic features of the catalysis. Specifically, in order to probe the source of incorporation of the proton at the β-position of 1-nonene, 1-nonene-(1,1-d_2) **39-*d*$_2$** was synthesized and was subjected to the same conditions. As expected, the 1,1-diarylation product **41-*d*$_2$** is formed with more than 93% incorporation of deuterium in the product (Figure 2.16).

Based on the mechanism, it can be proposed that the Pd-hydride that is coordinated to the olefin may dissociate and react with another alkene. In order to test the possibility of olefin dissociation, we also performed a crossover experiment, for this 1-nonene-(1,1-d_2) **39-*d*$_2$** and 1- undecene **43** were chosen and were subjected to the

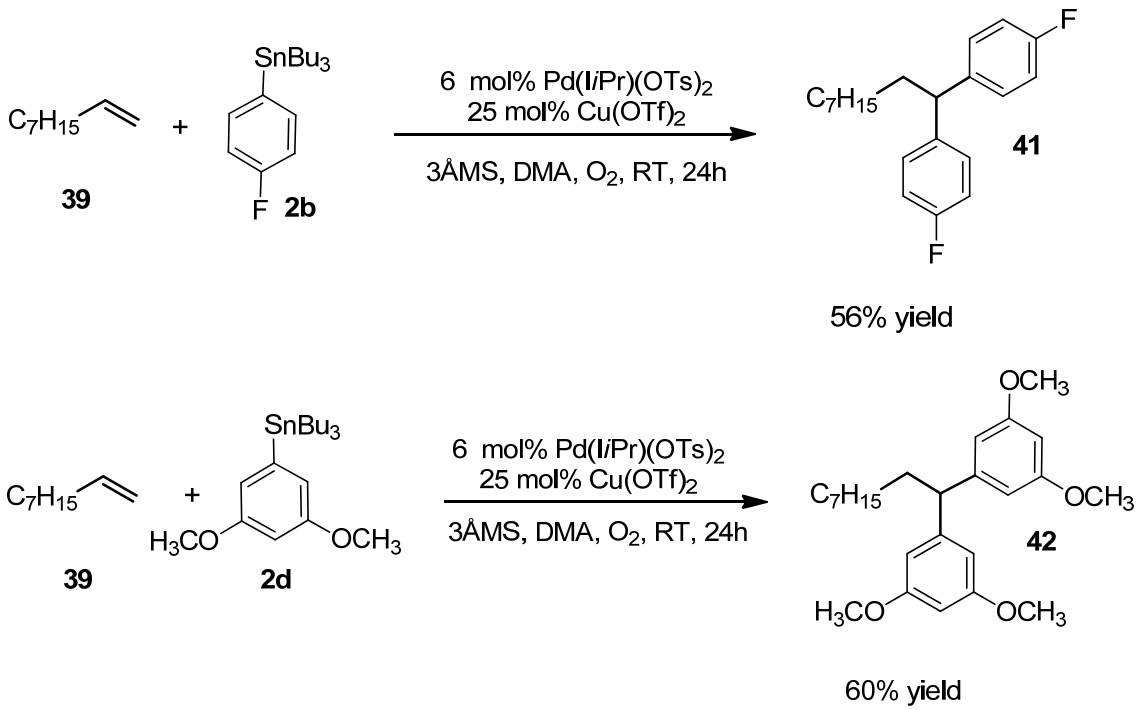
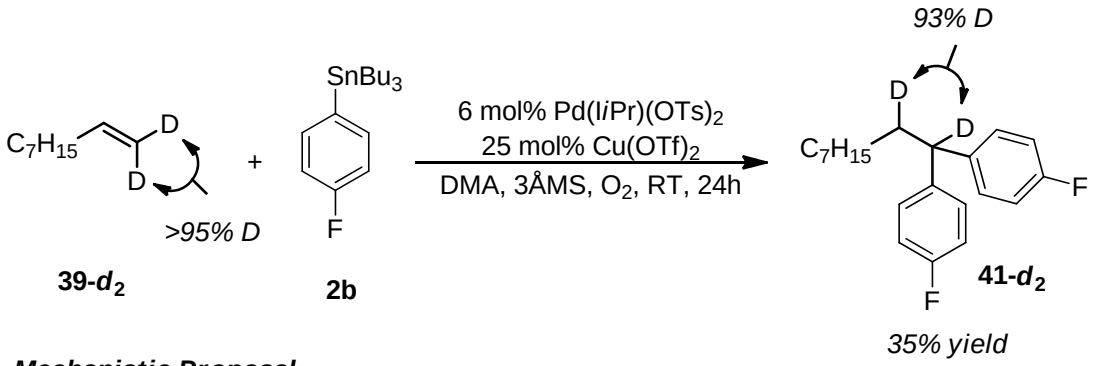


Figure 2.15. Substrate scope 1,2 versus 1,1-diarylation of styrenes and resulting correlation.

Deutrium Labelling Experiment



Mechanistic Proposal

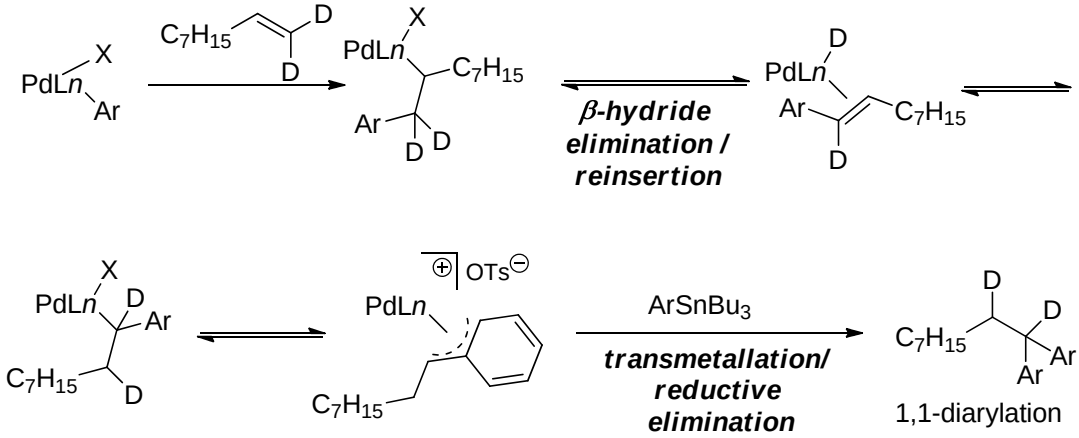


Figure 2.16. Deuterium labeling experiment with nonene-(1,1-d_2) leads to the product with migration of one deuterium, that was measured based on NMR mechanistic studies with 1-nonene-(1,1-d_2)

diarylation reaction conditions and interestingly, no crossover was observed, suggesting that the coordinated alkene does not dissociate prior to formation of the 1,1-diarylation product (Figure 2.17).

Summary

In summary, we have disclosed a unique difunctionalization reaction of terminal alkenes in which conjugated alkenes undergo 1,2-addition and simple terminal alkenes undergo 1,1-addition of organostannanes. Two carbon-carbon bonds are formed in this transformation, which provides facile access to diaryl methine compounds, a common pharmacophore.[46-48] The mechanism is proposed to proceed via Pd-alkyl intermediates, which are stabilized as π-benzyl species. Additionally, it was hypothesized that the electrophilic nature of the palladium has a positive effect on the stabilization of the π-benzyl species. Although this reaction generates two carbon-carbon bonds in a single step, these reactions are limited to installation of identical groups onto the double bonds. However, the information gained from this study has guided the development of a Pd-catalyzed three component reaction, installing two different groups on the alkene, which will be discussed in the next chapter.

Experimentals

General considerations

Two-propanol was dried by refluxing over calcium oxide for 12 h followed by fractional distillation. Dry DMA was purchased from Aldrich, THF was dried by distilling from

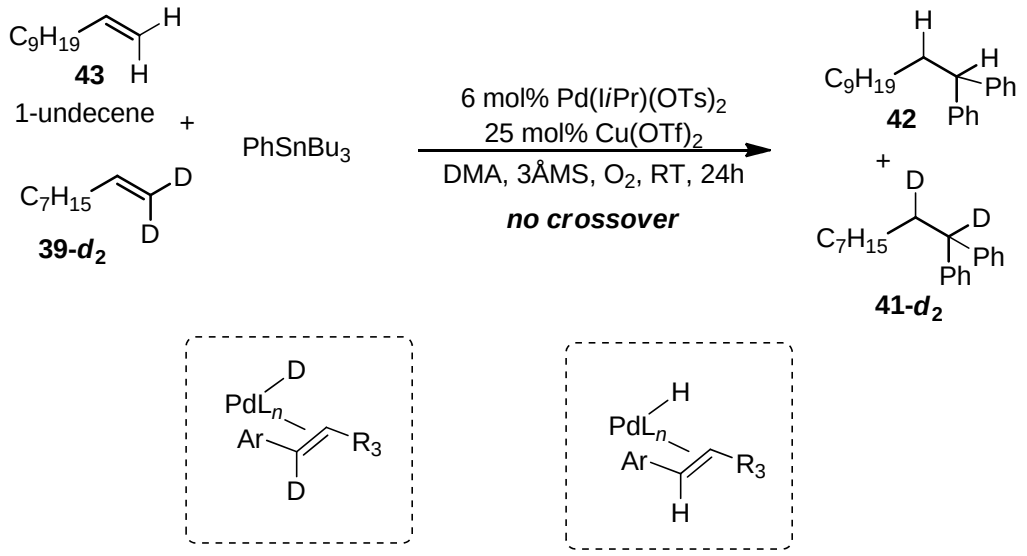


Figure 2.17. Crossover experiment with the 1:1 mixture of 1-undecene and 1-nonene-(1,1-d_2), performed to check the scrambling of deuterium between the alkene substrate by using GC-MS method

sodium benzophenone ketyl. CH_2Cl_2 and triethylamine (TEA) were dried by distilling from calcium hydride. The 3Å molecular sieves (3ÅMS) were powdered and activated by heating with a Bunsen burner while under vacuum. All styrenes are purchased from Aldrich or Acros. Styrenes were purified by passing through a small plug of activated alumina. Bu_3SnCl and $PhSnBu_3$ were purchased from Gelest Inc. Palladium(II) chloride was purchased from Pressure Chemicals. Pd[(–)-sparteine]Cl_2 was synthesized according to a previously reported procedure.[1] (–)-Sparteine was prepared from (–)-sparteine sulfate pentahydrate (purchased from Acros) according to a previously reported procedure.[2] $[Pd(allyl)Cl]_2$, Pd(I*i*Pr)$(OAc)_2(H_2O)$[3], and $[Pd(IiPr)Cl_2]_2$[4] were synthesized according to literature procedures. ^{1}H-NMR spectra were obtained at 400 MHz or 300 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.27 ppm and CH_2Cl_2 at 5.30 ppm. ^{13}C-NMR spectra were obtained at 100 MHz or 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.3 ppm. Flash chromatography was performed either using EM reagent silica 60 (230-400 mesh) or GFS Chemicals activated alumina Brockmann 1. All melting points are uncorrected and were recorded on an electrothermal melting point brand apparatus. IR spectra were recorded using a FTIR brand instrument and GC/MS were obtained with a HP 5890 (EI) 50:1 split using a DB-5 column. HRMS were obtained with either an ESI or APCI source with an Waters LCT Premier XE. GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 25:1 split. [Caution should be taken when heating flammable solvents in the presence of O_2.]

Optimization of the Pd-catalyzed oxidative difunctionalization

product (Table 2.1)

Entry 1. To an oven dried 10 mL sidearm flask equipped with a stir bar, was added 2.1 mg of Pd[(–)-sparteine]Cl_2 (0.0050 mmol, 0.025 equiv.), 1.3 mg of $CuCl_2$ (0.010 mmol, 0.050 equiv.), 900 μL of 2-propanol and 100 μL of a 2.00 M solution of 4-methylstyrene (**1a**) (0.200 mmol, 1.00 equiv.) in 2-propanol, which contained ca. 1% undecane as an internal standard. The flask was installed on a four-neck cow equipped with condensers (repeated three more times to perform four reactions at once) and a three-way joint fitted with a balloon of O_2 was installed on the top of the four-neck cow. The flasks were evacuated via water aspiration and refilled with oxygen three times, and the mixture was stirred vigorously for ca. 20 min at room temperature under O_2. Finally, 200 μL of $PhSnBu_3$ (0.600 mmol, 3.00 equiv.) was added dropwise to the reaction vessel. The reaction mixture was stirred **vigorously** under a balloon of O_2 at ambient temperature for 24 h. A small aliquot of the 2.00 M solution of **1a** with undecane as the internal standard was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 μL aliquot of the reaction mixture was removed and filtered through a small plug of silica, using elution with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using response factors (^{1}H-NMR was used to measure the response factors to account for varying detector response).

Entry 2. To an oven dried 10 mL sidearm flask equipped with a stir bar and was added 3.2 mg of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ (0.0050 mmol, 0.025 equiv.), 900 μmol of 2-propanol and 100 μmol of a 2.00 M solution of 4-methylstyrene (**1a**) (0.200 mmol, 1.00 equiv.) in

2-propanol, which contained ca. 1% undecane as an internal standard. The flask was installed on a four-neck cow equipped with condensers (repeated three more times to perform four reactions at once) and a three-way joint fitted with a balloon of O_2 was installed on the top of the four-neck flask. The flask was evacuated via water aspiration and refilled with oxygen three times and the mixture was stirred vigorously for ca. 20 min at room temperature under O_2. Finally 200 µL of $PhSnBu_3$ (0.6 mmol, 3.00 equiv.) were added dropwise to the reaction vessel. The reaction mixture was stirred vigorously under a balloon of O_2 at 45 °C for 18 h. A small aliquot of the 2.00 M solution of **1a** with undecane as the internal standard, was analyzed by GC and used to calculate the conversion of the substrate. After 18 h, a 50 µL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using correction factors (^{1}H-NMR was used to measure the response factor to account for varying detector response).

Entry 3. The same procedure as described for entry 2 was used except Pd(S*i*Pr)(OAc)$_2$ was added instead of [Pd(I*i*Pr)(Cl)$_2$]$_2$.

Entry 4. The same procedure as described for entry 2 was used except Pd(I*i*Pr)(OAc)$_2$ was added instead of [Pd(I*i*Pr)(Cl)$_2$]$_2$.

Entry 5. The same procedure as described for entry 2 was used except Pd(I*Mes*)(OAc)$_2$ was added instead of [Pd(I*i*Pr)(Cl)$_2$]$_2$.

Optimization of the Pd-catalyzed oxidative difunctionalization

product (Table 2.2)

Entry 1. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OCOCF_3)_2$ was added instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$.

Entry 2. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTs)_2$ was added instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$.

Entry 3. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(BF_4)_2$ was added instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$.

Entry 4. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTf)_2$ was added instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$.

Entry 5. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTs)_2$ instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ and dimethylether solvent instead of isoproponal were added.

Entry 6. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTs)_2$ instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ and dioxane solvent instead of isoproponal were added.

Entry 7. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTs)_2$ instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ and dimethylacetamide solvent instead of isoproponal were added.

Entry 8. The same procedure as described for Table 2.1 entry 2 was used except $Pd(I\textit{i}Pr)(OTs)_2$ instead of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ and dimethylformamide solvent instead of isoproponal were added.

Optimization of the Pd-catalyzed oxidative difunctionalization

product (Table 2.3)

Entry 1. To an oven dried 10 mL sidearm flask equipped with a stir bar, was added 3.2 mg of $[Pd(I\textit{i}Pr)(Cl)_2]_2$ (0.0050 mmol, 0.025 equiv.), 900 μmol of DMA and 100 μmol of a 2.00 M solution of 4-methylstyrene (**1a**) (0.200 mmol, 1.00 equiv.) in DMA, which contained ca. 1% undecane as an internal standard. The flask was installed on a four-neck cow equipped with condensers (repeated three more times to perform four reactions at once) and a three-way joint fitted with a balloon of O_2 was installed on the top of the 4-neck flask. The flask was evacuated via water aspiration and refilled with oxygen three times and the mixture was stirred **vigorously** for ca. 20 min at room temperature under O_2. Finally 200 μL of $PhSnBu_3$ (0.6 mmol, 3.00 equiv.) was added dropwise to the reaction vessel. The reaction mixture was stirred **vigorously** under a balloon of O_2 at RT for 24 h. A small aliquot of the 2.00 M solution of **1a** with undecane as the internal standard, was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 μL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using correction factors (^{1}H-NMR was used to measure the response factor to account for varying detector response).

Entry 2. The same procedure was used as described for entry 1, except 6 mol% $Pd(I\textit{i}Pr)(OTs)_2$ catalyst was added.

Entry 3. The same procedure was used as entry 1, except 6 mol% $Pd(I\textit{i}Pr)(OTs)_2$ catalyst was used, and 100 mg of activated molecular sieves were added.

Entry 4. The same procedure as entry 10 was used except 1.80 mg of $Cu(OTf)_2$ (0.0500 mmol, 0.250 equiv.) was added.

Entry 5. The same procedure as entry 10 was used except 5.40 mg of $Cu(OTf)_2$ (0.0500 mmol, 0.250 equiv.) was added.

Entry 6. The same procedure as entry 10 was used except 9.04 mg of $Cu(OTf)_2$ (0.0500 mmol, 0.250 equiv.) was added.

Entry 7. The same procedure as entry 10 was used except 12.6 mg of $Cu(OTf)_2$ (0.0500 mmol, 0.250 equiv.) was added.

Preparation of 4,4-dimethyl-1-vinylcyclohex-1-ene

4,4-dimethylcyclohexanone (3)j. Palladium on carbon (10%, 100 mg) was added to a solution of 6.23 g 4,4-dimethylcyclohexene-1-one (50 mmol, 1 equiv.) in petroleum ether (30 ml) and hydrogenated at atmospheric pressure for 20 h. After filtration, the solvent was removed *in vacuo* to afford 4,4-dimethylcyclohexanone. Yield 92% (5.8 g, 6.1 g). The 1H-NMR spectrum was compared to the previously reported spectrum.[5]

4,4-dimethyl-1-vinylcyclohexanol (4j). To an oven dried 100 mL round bottom flask equipped with a stir bar and was added 2.1g (15.9 mmol, 1.00 equiv.) 4,4-dimethyl cyclohexanone and 16 mL THF under a N_2 atmosphere. The solution was cooled to -78 ^oC, and a solution of 25 mL of a 1.00 M vinyl magnesium bromide solution in THF (25 mmol, 1.6 equiv.) was added drop wise. The reaction was slowly warmed to room temperature and stirred for another 12h. The reaction was quenched with aqueous HCl (1.00 M). The mixture was extracted with 50 mL Et_2O, and washed twice with 50 mL of

brine. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified with flash column chromatography eluting with 20% EtOAc/hexanes gave 4,4-dimethyl-1-vinylcyclohexanol as a colorless oil. Yield 67%. IR (neat) 3364, 2930, 2851, 1451, 1363, 1175, 1051, 918, 893, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 3H), 0.96 (s, 3H), 1.20-1.1.30 (m, 3H), 1.42-1.73(m, 6H), 5.05 (d, *J* = 10.7 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 5.05 (d,d *J* = 17.4 Hz, 10.7 Hz, 1H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 25.6, 29.8, 30.6, 31.4, 33.9, 34.9, 71.8, 111.9, 125.2, 146.3; MS (ESI/APCI) m/z $(M+H)^+$ calcd.: 117.1255 obsd.: 177.1250.

4,4-dimethyl-1-vinylcyclohex-1-ene (1j), To an oven dried 100 mL round bottom flask equipped with a stir bar and was added 2.34 g (15.2 mmol, 1.00 equiv) 4,4-dimethyl-1-vinylcyclohexanol, 25 mL pentane, 576 mg (3.03 mmol, 0.2 equiv) PTSA and 2.36 g 3Å M.S. under a N_2 atmosphere. Then a water condenser was installed and the reaction was heated to reflux overnight. The reaction was then filtered and washed with pentane, concentrated *in vacuo*. Distillation gave **1j** as colorless oil. Yield: 57% (1.23 g, 1.15g); Clear oil; IR (neat) 3003, 2950, 2915, 2865, 1644, 1383, 1009, 886, 832, 817 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 6H), 1.44 (t, *J* = 6.5 Hz, 2H), 1.92 (m, 2H), 2.15 (m, 2H), 4.91 (d, *J* = 10.7 Hz, 1H), 5.07 (d, *J* = 17.4 Hz, 1H), 5.69 (m, 1H), 6.38 (dd, *J* = 10.7 Hz, 17.4 Hz, 1H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 21.9, 22.0, 28.5, 29.3, 29.4, 35.5, 36.9, 40.1, 110.0, 129.2, 135.1, 140.2; MS (ESI/APCI) m/z $(M+H)^+$ calcd.: 136.1252 obsd.: 136.12.

Preparation of (E)-Buta-1,3-dienylbenzene

(E)-buta-1,3-dienylbenzene (1l). To an oven dried 100 round bottom flask equipped with a stir bar was added 1.45 g (3.9 mmol, 1.3 equiv.) methyltriphenylphosphonium bromide and 13 mL of THF under a N_2 atmosphere. To the cloudy mixture 1 mL of a 4.0 M THF solution of *t*-BuOK was added. The reaction mixture was stirred at room temperature for 10 min, to give an orange color. The reaction was cooled to -78 °C and 0.55 mL of cinnamaldehyde (3.00 mmol, 1.00 equiv.) was added dropwise. The mixture was allowed to slowly warm to room temperature, and stirred for 15.0 h. To the red mixture was added 20 mL of hexanes. The cloudy mixture was filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified via flash column chromatography eluting with pentane and isolated as colorless oil. Yield 64 %. R_f = 0.28 w/ 1% EtOAc:Hexanes(silica), PMA stain. IR (neat) 3080, 3026, 2969, 1601, 1493, 1448, 1028, 999, 946, 896, 752, 689 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.22 (d, *J* = 10 Hz, 1H), 5.41 (d, *J* = 17 Hz, 1H), 6.52-6.65 (m, 2H), 6.81 (dd, *J* = 10, 10 Hz 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 8 Hz, 2H), 7.45 (d, *J* = 7.7, 2H); ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 117.9, 126.7, 127.9, 128.9, 129.9, 133.2, 137.4, 137.5; MS (ESI/APCI) m/z $(M-H)^+$ calcd.: 129.0783 obsd.: 129. 1.

Preparation of 1-Nonene-d2

To an oven dried 100 mL round botton flask equipped with stir bar was added 1.6 g (3.9 mmol, 1.0 equiv) of methyl-d_3-triphenylphosphonium iodide and 15.0 mL of THF under N_2 atmosphere. The solution was cooled down to -78 °C and then was added 1.6

mL (3.9 mmol, 1.0 equiv) of *n*-butyllithium in hexanes by syringe. After 15 min, the reaction mixture was allowed to come to room temperature. After an additional 10.0 min, the mixture was again cooled to -78.0 °C, at which point 500 mg (3.9 mmol, 1.0 equiv) of 1-nonanal was added dropwise by syringe to the suspension. After 15 min at -78 °C, the reaction mixture was allowed to come to room temperature and was stirred for 1 hr. The suspension was filtered and 1 g of silica gel was added to the filtrate. The solvent was evaporated in *vacuo*, and the residue was slurried in 50 mL of hexane and filtered again. The solvent was removed in *vacuo* to give 400 mg crude mixture. The product was purified via flash column chromatography eluting with hexanes. Yield: 70% (350 mg and 360 mg); IR (neat) 2956, 2923, 2854, 2157, 1972, 1466, 1378, 931, 724 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.8-0.95 (m, 5H), 1.20-1.4 (m, 13H), 2.0-2.15(m, 2H), 7.81 (s, 1H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 14.4, 22.7, 23.0, 29.3, 29.4, 29.5, 31.9, 32.1, 34.0, 139.4

Synthesis of organostannane reagents

Tributyl(4-methoxyphenyl)stannane (9b). To a flame dried 100 mL Schlenk flask equipped with a stirbar and a dried water condenser under a N_2 atmosphere was added 25.0 mL of THF and 585 mg of magnesium turnings (24.0 mmol, 1.6 equiv.), which were activated by crushing with a mortar and pestle. To the stirred mixture four drops of 1,2-dibromoethane was added and 1.9 mL of 1-bromo-4-methoxybenzene (Aldrich) (15.0 mmol, 1.00 equiv.), which was added drop wise over 5 min. The mixture slowly turned dark brown and the stirred mixture was heated to reflux overnight. The reaction

mixture was cooled to room temperature and was cannulated into a dried 100 mL Schlenk flask equipped with a stirbar and condenser under a N_2 atmosphere. To the stirred mixture, was added 4.88 mL of Bu_3SnCl (18.0 mmol, 1.20 equiv.) dropwise over 5 min. The stirred mixture was heated to reflux for 4 h and was cooled to room temperature. To the stirred mixture was added ca. 20 mL of aqueous 1.00 M NaOH. After 1 h, the mixture was transferred to a separatory funnel and the aqueous layer was extracted three times with 20 mL of Et_2O. The organic extracts were collected and washed with 60 mL of brine, dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield clear oil. The product was purified by silica gel flash chromatography eluting with 2% Et_2O/hexanes. The product was obtained as a clear oil in 87% yield and the ^1H NMR spectrum was compared to a previously reported spectrum.

Tributyl(4-(trifluoromethyl)phenyl)stannane (9c). The same procedure used for the synthesis of **9b** was used except 2.4 mL of 1-bromo-4-(trifluoromethyl)benzene (Acros) (15.0 mmol, 1.0 equiv.) was used and the product was purified by silica gel flash chromatography eluting with pentane. The product was obtained as clear oil in 60% yield and the ^1H NMR spectrum was compared to a previously reported spectrum.

*Tributyl(o-tolyl)stannane (9d).*The same procedure used for the synthesis of **9b** was used except 1.78 mL of 2-bromotoluene (Aldrich) (15.0 mmol, 1.00 equiv.) was used and the product was purified by silica gel flash chromatography eluting with hexanes. Yield: 97% (5.56 g); R_f = 0.62 w/ Hexanes (silica); Clear oil; IR (neat) 3053, 2958, 2853, 1563, 1421, 1340, 1073, 869, 741, 688, 594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.3 Hz, 9H), 1.04-1.10 (m, 6H), 1.26-1.30 (m, 6H), 1.47-1.57 (m, 6H), 2.39 (s, 3H), 7.10-7.25 (bm, 3H), 7.38 (dd, *J* = 1.5 Hz, 7.0 Hz, 1H); ^{13}C NMR {^1H} (100 MHz,

$CDCl_3$): δ 10.3, 13.9, 25.2, 27.7, 29.4, 125.1, 128.5, 129.1, 136.8, 142.1, 144.8; MS (APCI) m/z $(MH)^+$ calcd.: 383.2 obsd.: 383.8. (the intensity of the $(M+H)^+$ peak was very small).

Tributyl(3,5-dimethoxyphenyl)stannane (9e). The same procedure used for the synthesis of **9b** was used except 2.59 g of 1-chloro-3,5-dimethoxybenzene (TCI America) (15.0 mmol, 1.00 equiv.) was used and the product was purified by silica gel flash chromatography eluting with 5% Et_2O/hexanes. Yield: 65% (4.18 g); R_f = 0.65 w/ 10% Et_2O/Hexanes (silica); Clear oil; IR (neat) 2956, 2926, 2851, 1560, 1461, 1378, 1246, 1156, 1063, 860, 734, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.3 Hz, 9H), 1.03-1.07 (m, 6H), 1.29-1.39 (m, 6H), 1.51-1.59 (m, 6H), 3.81 (s, 6H), 6.41 (dd, *J* = 2.3 Hz, 2.3 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$): δ 9.8, 13.8, 27.6, 29.3, 55.1, 99.9, 114.0, 144.1, 160.4; MS (ESI/APCI) m/z $(M+H)^+$ calcd.: 429.1816 obsd.: 429.1815.

Tributyl(3,4-dihydro-2H-pyran-6-yl)stannane (9f). Stannane **9f** was synthesized according to a previously reported procedure and the ^1H NMR spectrum was compared to the previously reported spectrum.

Tributyl(1-ethoxyprop-1-enyl)stannane (9g). Stannane **9g** was synthesized according to a previously reported procedure and the ^1H NMR spectrum was compared to the previously reported spectrum.

Tributyl(2-methylprop-1-enyl)stannane (9h). Stannane **9g** was synthesized according to a previously reported procedure from (2-methylprop-1-enyl)magnesium bromide (Aldrich) and the ^1H NMR spectrum was compared to the previously reported spectrum.

General oxidative difunctionalization reaction procedure

(1-(4-methylphenyl)ethane-1,2-diyl)dibenzene (19). To a flame-dried 200 mL round bottom Schlenk flask equipped with a stir bar was added 25.1 mg of Pd(I*i*Pr)$(OTs)_2$ (0.0300 mmol, 0.0600 equiv.), 45.2 mg of $Cu(OTf)_2$ (0.0125 mmol, 0.250 equiv.), 250 mg of freshly crushed, activated 3Å molecular sieves, and 2.50 mL dimethylacetamide under a nitrogen atmosphere. A solution of 59.1 mg 4-methylstyrene (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added to the reaction flask via syringe. A three-way joint was fitted with a balloon of O_2 and attached to the flask. The apparatus was evacuated via water aspiration and refilled with oxygen three times. The mixture was stirred at room temperature under an O_2 atmosphere for 5 min. To the stirred mixture was added 550 mg of $PhSnBu_3$ (1.50 mmol, 3.00 equiv.) slowly by syringe. After 24 h, the mixture was filtered through Whatman filter paper, rinsed with ca. 10 mL of Et_2O, and transferred to a separatory funnel and washed with 10 mL distilled water. The aqueous layer was then extracted three times with 30 mL of Et_2O, all of the organic extracts were combined, washed with 50 mL of brine, and dried over $MgSO_4$. The mixture was filtered and the solvent was removed *in vacuo*. The product was purified via silica gel flash chromatography eluting with 1 % EtOAc/hexanes. For each substrate, this procedure was performed atleast twice and the average isolated yield is reported. Yield: 76% (102 mg and 107 mg); R_f = 0.28 w/ 1% EtOAc:Hexanes(silica), PMA stain. IR (neat) 3083, 3059, 3024, 1600, 1511, 1493, 1451, 1413, 1183, 1153, 1070, 1030, 1021, 953, 819, 790, 779, 768, 748, 732, 646, 631, 620, 605, 585, 570, 554 cm^{-1}; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 2.21 (s, 3H), 3.35 (d, *J* = 7.7 Hz, 2H), 4.25 (t, *J* = 7.7 Hz, 1H), 7.05-7.30 (m, 14H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 21.3, 42.5, 52.9, 126.1, 126.4, 128.2,

128.3, 128.4, 128.6, 129.3, 129.4, 135.9, 140.7, 141.8; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 379.0616 obsd.: 379.0604

4,4'-(1-p-tolylethane-1,2-diyl)bis(fluorobenzene) (20). The same procedure used to synthesize **19** was used except 577 mg of tributyl(4-fluorophenyl)stannane (**2b**) (1.50 mmol, 3.00 equiv.) was added via syringe and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 64% (99 mg and 96 mg); R_f = 0.3 w/ Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.32 (m, 2H), 4.16 (t, *J* = 7.7 Hz, 1H), 6.9-6.9 (m, 6H), 7.1-7.2 (m, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 21.3, 41.8, 52.4, 115.1, 225.3, 115.4, 115.6, 128.0, 129.5, 129.6, 129.7, 130.6, 130.7, 136.3; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 415.0428 obsd.: 415.0442.

4,4'-(1-p-tolylethane-1,2-diyl)bis(methoxybenzene) (21). The same procedure used to synthesize **19** was used except 653 mg of tributyl(4-(methoxy)phenyl)stannane (**2c**) (1.50 mmol, 3.00 equiv.) was added via syringe and the product was purified via silica gel flash chromatography by eluting with 3% EtOAc/hexanes. Yield: 65% (110 mg and 105 mg); R_f = 0.35 w/ 5% EtOAc/hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.25 (d, *J* = 7.7 Hz, 2H), 3.76 (s, 1H), 3.77 (s, 1H), 4.13 (t, *J* = 7.7 Hz, 1H) 6.70-6.82 (m, 4H), 6.9-7.1 (m, 2H), 7.04-7.15 (m, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 21.3, 41.7, 52.3, 55.4, 55.5, 113.7, 113.9, 128.1, 129.1, 129.2, 129.3, 130.3, 132.9, 135.8, 137.3, 142.3, 158.1; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 439.0827 obsd.: 439.0828.

5,5'-(1-p-tolylethane-1,2-diyl)bis(1,3-dimethoxybenzene) (22). The same procedure used to synthesize **19** was used except 642 mg of tributyl(1,3-dimethoxyphenyl)stannane (**2d**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the product was purified via silica gel flash chromatography by eluting with 5 % Acetone:hexanes. Yield: 65 % (126 mg and 131 mg); Rf = 0.17 w/ 5% acetone:hexanes (silica), PMA stain. IR (neat) 2998, 2935, 2835, 1590, 1511, 1456, 1425, 1343, 1313, 1292, 1202, 1114, 1056, 1022, 993, 975, 937, 925, 872, 826, 776, 745, 726, 691, 646, 636, 591, 539 cm-1; 1H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.26 (d, *J* = 7.7, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 4.12 (t, *J* = 7.7 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 2H), 6.25 (t, *J* = 2.3 Hz, 1H), 6.28 (t, *J* = 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 2H), 7.10 (m, 4H); ^{13}C-NMR {1H} (75 MHz, CDCl3): δ 21.3, 42.6, 52.9, 55.5, 55.6, 98.1, 98.4, 106.7, 107.5, 128.1, 129.4, 136.1, 141.4, 143.0, 147.5, 160.7, 160.9; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 499.1039 obsd.: 499.1041.

4,4'-(1-p-tolylethane-1,2-diyl)bis((trifluoromethyl)benzene) (23). The same procedure used to synthesize **19** was used except 652 mg of tributyl(4-(trifluoromethyl)phenyl) stannane (**2e**) (1.50 mmol, 3.00 equiv.) was added via syringe and the product was purified via siliica gel flash chromatography by eluting with hexane. **5e**, Yield: 68% (135 mg and 146 mg); R_f = 0.23 w/ Hexanes (silica), PMA stain. IR (neat) 2925, 1617, 1512, 1416, 1319, 1241, 1160, 1101, 1065, 1017, 941, 886, 833, 778, 753, 634, 598, 535 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.41 (m, 2H), 4.28 (t, *J* = 8.05 Hz, 1H), 7.07(s, 4H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 21.3, 41.9, 52.6, 125.4, 125.5, 125.5, 125.6, 125.7, 125.8, 125.8, 125.9, 128.1, 128.5, 128.8,

129.0, 129.2, 129.6, 129.7, 136.8, 140.2, 144.2, 148.6, 148.6; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 515.0364 obsd.: 515.0342.

(*1-(4-methoxyphenyl)ethane-1,2-diyl)dibenzene (24).* The same procedure used to synthesize **19** was used except 67.3 mg of 4-methoxystyrene (0.500 mmol, 1.00 equiv.), dissolved in 2 mL of DMA was added via syringe and the product was purified via silica gel flash chromatography by eluting with 1% EtOAc:hexanes. **5f**, Yield: 85% (124 mg and 118 mg); R_f = 0.45 w/ 5 % EtOAc:Hexanes (silica), PMA stain.. IR (neat) 3083, 3059, 3025, 3000, 2930, 2833, 1609, 1582, 1494, 1462, 1451, 1301, 1246, 1176, 1109, 1071, 1032, 954, 869, 828, 808, 769, 749, 736, 629, 606, 557, 536, 514 cm^{-1}; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 3.32 (d, *J* = 7.72 Hz,2H), 3.72 (s, 3H), 4.21 (t, *J* = 7.72 Hz, 1H), 6.75 (d, *J* =8.7 Hz, 2H), 7.04-7.26 (m, 12H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 42.6, 52.6, 55.5, 114.0, 126.2, 126.4, 128.3, 128.4, 128.7, 129.3, 129.4, 136.9, 140.7, 145.2, 158.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 395.0565 obsd. 395.0577.

(1-o-tolylethane-1,2-diyl)dibenzene (25). The same procedure used to synthesize **19** was used except 59.1 mg of 1-methylstyrene (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added via syringe, and the product was purified via silica gel flash chromatography by eluting with 1% EtOAc:hexanes. Yield: 70% (95.0 mg and 102 mg); R_f = 0.31 w/ hexanes (silica), PMA stain. IR (neat) 3060, 3024, 2924, 1600, 1492, 1451, 1379, 1154, 1071, 1052, 1030, 953, 912, 789, 750, 735, 696, 638, 620, 597, 564, 550 cm^{-1}; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 2.17 (s, 3H), 3.35 (d, *J* = 7.72 Hz, 2H), 4.49 (t, *J* = 7.72 Hz, 1H), 7.04-7.26(m, 13H), 7.43 (d, *J* = 7.72 Hz, 1H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 19.8, 20.1, 39.6, 42.8, 48.9, 52.1, 125.9, 126.2, 126.3, 126.4, 126.5, 127.3,

128.3, 128.4, 128.5, 128.6, 128.7, 129.4, 130.1, 130.3, 130.7, 136.6, 140.6, 142.8, 144.2, 144.9; MS (E.I.) m/z (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 379.0616 obsd. 379.0634.

(1-(2-methoxyphenyl)ethane-1,2-diyl)dibenzene (26). The same procedure used to synthesize **19** was used except 67.3 mg of 2-vinylanisole (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added via syringe, and the product was purified via silica gel flash chromatography by eluting with 2% EtOAc/hexanes. Yield: 73% (105 mg and 96 mg); R_f = 0.38 w/ 5% EtOAc/hanes (silica), PMA stain; IR (neat) 3060, 3026, 2934, 2834, 2361, 1599, 1585, 1490, 1452, 1437, 1290, 1241, 1163, 1107, 1070, 1052, 1029, 954, 773, 750, 726, 697, 637, 563, 540 cm^{-1}; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 3.30 (d, *J* = 8.05Hz, 2H), 3.71 (s, 3H), 4.75(t, *J* = 8.05 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.87 (t, *J* = 8.39 Hz, 1H), 7.06-7.30 (m, 12H); ^{13}C-NMR {1H} (75 MHz, $CDCl_3$): δ 41.6, 45.5, 55.7, 76.9, 77.4, 77.8, 111.1, 120.8, 126.0, 126.2, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 129.4, 133.6, 141.1, 144.4, 157.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 395.0565 obsd.: 395.0572.

*6,6'-(1-p-tolylethane-1,2-diyl)bis(3,4-dihydro-2H-pyran)(27).*The same procedure used to synthesize **19** was used except 560 mg of tributyl(3,4-dihydro-2H-pyran-6-yl)stannane (**2f**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the product was purified via alumina gel flash chromatography by eluting with 3% Et_2O/hexanes. **5i**, Yield: 57% (81 mg and 83 mg); R_f = 0.31 w/ hexanes (alumina), PMA stain. Clear oil; IR (neat) 2925, 2845, 1669, 1512, 1463, 1447, 1434, 1386, 1347, 1299, 1231, 1192, 1155, 1112, 1084, 1058, 1021, 968, 915, 887, 817, 761, 726, 674 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.72-1.80 (m, 4H), 1.90-1.96 (m, 2H), 1.98-2.03 (m, 2H), 2.21 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.41 (s, 4H), 2.55 (dd, *J* = 14.4, 7.7 Hz, 1H), 3.50 (dd, *J* = 7.7, 7.7 Hz, 1H),

3.87-4.01 (m, 4H), 4.39 (t *J* = 3.4 Hz, 1H) 4.61(t, *J* = 3.4 Hz, 1H) 7.08 (d, *J* = 8.05 Hz, 2H), 7.23 (d, *J* = 8.05 Hz, 2H); ^{13}C-NMR {1H} (75 MHz, $CDCl_3$): δ 20.7, 20.8, 21.4, 22.8, 22.9, 38.7, 47.9, 66.4, 66.5, 96.7, 97.5, 128.0, 129.0, 135.8, 140.2, 152.7, 155.9; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 391.0827 obsd.: 391.0815.

5,5'-(1-(4,4-dimethylcyclohex-1-enyl)ethane-1,2-diyl)bis(1,3-dimethoxybenzene) (28), The same procedure used to synthesize **19** was used except a solution of 68.2 mg of 4,4-dimethyl-1-vinylcyclohex-1-ene (**1j**) (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added to the reaction flask via syringe, 642 mg of tributyl(1,3-dimethoxyphenyl)stannane (**2d**) (1.50 mmol, 1.50 equiv.) was added via syringe, and the reaction was stirred for 24 h at 45 °C. The product was purified via silica gel flash chromatography by eluting with 2% EtOAc:hexanes. Yield: 55% (111 mg and 105 mg); R_f = 0.31 w/ 5% EtOAc:Hexanes (silica), PMA stain. IR (neat) 2996, 2945, 2834, 1591, 1456, 1425, 1342, 1315, 1289, 1202, 1147, 1085, 993, 925, 885, 826, 732, 687, 639, 538 cm^{-1}; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 0.79(s, 3H), 0.82 (s, 3H), 1.23 (t, *J* = 6.37 Hz, 2H), 1.79 (m, 4H), 2.84 (dd, *J* = 13.5, 7.4 Hz, 1H), 3.10 (dd, *J* = 13.4, 7.4 Hz 1H), 3.37 (dd, *J* = 7.4, 7.4 Hz 1H), 3.67 (s, 6H), 3.69 (s. 6H), 5.55 (s, 1H), 6.20 (d, *J* = 2.01 Hz, 2H), 6.24 (t, *J* = 2.35 Hz, 2H), 6.29 (d, *J* = 2.35 Hz, 2H); ^{13}C-NMR {^{1}H} (75 MHz, CD_2Cl_2): δ 25.0, 27.6, 28.3, 28.5, 35.7, 39.4, 39.7, 55.2, 55.3, 97.7, 97.8, 106.1, 107.0, 121.1, 137.9, 143.4, 146.5, 160.5, 160.6; MS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 433.2355 obsd.: 433.2354.

4,4'-(1-(4,4-dimethylcyclohex-1-enyl)ethane-1,2-diyl)bis(fluorobenzene) (29). The same procedure used to synthesize **19** was used except a solution of 68.2 mg of 4,4-dimethyl-1-vinylcyclohex-1-ene (**1j**) (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of

DMA was added to the reaction flask via syringe, 577 mg of tributyl(4-fluorophenyl)stannane (**2b**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the reaction was stirred for 24 h at 45 °C. The product was purified via silica gel flash chromatography eluting with hexanes. Yield: 59% (95 mg and 97 mg); R_f = 0.51 w/ hexanes (silica), PMA stain. IR (neat) 3041, 2948, 2908, 1602, 1507, 1450, 1432, 1414, 1383, 1363, 1221, 1156, 1089, 1015, 866, 818, 768, 745, 559 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 3H), 0.87 (s, 3H), 1.27-1.32 (m, 2H), 1.65-1.85 (m, 4H), 2.90 (dd, *J* = 13.42, 7.72 Hz, 1H), 3.14 (dd, *J* = 13.42, 7.72 Hz, 1H), 3.37 (dd, *J* = 7.72, 7.72 Hz, 1H), 5.57 (s, 1H), 6.85-6.94 (m, 6H), 7.05-7.7.07 (m, 2H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 25.5, 28.1, 28.8, 28.9, 30.7, 35.9, 39.4, 39.7, 54.0, 114.9, 115.0, 115.2, 115.3, 121.5, 125.9, 129.6, 130.6, 130.7, 136.5, 136.6, 138.1, 139.3, 139.4, 159.9, 160.1, 163.1, 163.3; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 433.0897 obsd.: 433.0911.

(E)-4,4'-(4-phenylbut-3-ene-1,2-diyl)bis(fluorobenzene) (30). The same procedure used to synthesize **19** was used except a solution of 65.1 mg of (E)-buta-1,3-dienylbenzene (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added to the reaction flask via syringe, 518 mg of tributyl(2-methylprop-1-enyl)stannane (**2h**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the reaction was stirred for 24 h at 40 °C. the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 67% (179.6 mg and 174.4 mg); R_f = 0.61 w/ Hexanes (alumina), PMA stain. IR (neat) 3026, 2923, 1883, 1600, 1506, 1447, 1415, 1296, 1218, 1156, 1092, 1014, 964, 09, 827, 786, 774, 749, 733, 691, 618, 562, 532 cm^{-1}; ^{1}H-NMR (500 MHz, CD_2Cl_2): δ 3.05 (dd, *J* = 13.4 Hz, 8.1 Hz, 1H), 3.15 (dd, *J* = 13.4 Hz, 7.4 Hz, 1H), 3.73 (dd, *J* = 14.7 Hz, 7.4 Hz, 1H), 6.35 (d, *J* = 16.1 Hz, 1H), 6.42 (dd, *J* = 16.1 Hz, 7.4 Hz, 1H), 6.90 – 6.95

(m, 2H), 6.98 - 7.10 (m, 4H), 7.15 - 7.25 (m, 3H), 7.30 - 7.40 (m, 4H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 42.3, 50.6, 115.1, 115.4, 115.5, 115.7, 126.5, 127.7, 128.9, 129.5, 129.6, 130.5, 130.8, 130.9, 133.1, 135.5, 135.6, 137.5, 139.3, 139.4, 160.1, 160.2, 163.3, 163.4; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 33.0365 obsd.: 383.0371.

(E)-6,6'-(4-phenylbut-3-ene-1,2-diyl)bis(3,4-dihydro-2H-pyran) (31). The same procedure used to synthesize **19** was used except a solution of 65.1 mg of (E)-buta-1,3-dienylbenzene (0.500 mmol, 1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe, 560 mg of tributyl(3,4-dihydro-2H-pyran-6-yl)stannane (**2f**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the reaction was stirred for 24 h at 40 °C. The product was purified via alumina gel chromatography eluting with 4% Et_2O/pentane. Yield: 36% (52 mg and 54 mg); R_f = 0.33 w/ hexane (Alumina), PMA stain. IR (neat) 3024, 2926, 2866, 2845, 1672, 1598, 1493, 1464, 1447, 1433, 1386, 1346, 1298, 1232, 1192, 1155, 1059, 1028, 963, 917, 888, 814, 750, 733, 693 cm^{-1}. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 1.66-1.78 (m, 4H), 1.90-2.01 (m, 4H), 2.04(dd, *J* = 14.1, 7.72 Hz, 1H), 2.30(dd, *J* = 14.1, 7.72 Hz, 1H), 3.02 (dd, *J* = 7.72 Hz, *J* = 7.72 Hz, 1H), 3.63-3.99 (m, 4H), 4.47 (t, *J* = 3.69 Hz, 1H) 4.54 (t, *J* = 3.69 Hz, 1H), 6.17 (dd, *J* = 15.77, 7.72 Hz, 1H), 6.36 (d, *J* = 15.77 Hz, 1H), 7.13-7.33 (m, 5H); ^{13}C-NMR {^{1}H} (300 MHz, $CDCl_3$): δ 20.7, 20.8, 22.8, 22.9, 38.5, 46.4, 66.4, 66.6, 96.3, 97.7, 126.5, 127.2, 128.7, 130.2, 131.5, 138.2, 152.5, 155.6.

(1-(4-fluorophenyl)ethane-1,2-diyl)dibenzene (5f) + (2-(4-methylphenyl)ethane-1,1-diyl)dibenzene (5f'). The same procedure used to synthesize **19** was used except a solution of 61.1 mg of p-fluorostyrene (**1g**) (0.500 mmol, 1.00 equiv.) dissolved in 2 mL of DMA was added to the reaction flask via syringe and the product was purified via

silica gel flash chromatography by eluting with hexanes. Yield: 65% (86 mg and 92 mg); R_f = 0.33 w/ Hexanes (silica), PMA stain. IR (neat) 3061, 3026, 2923, 1601, 1506, 1493, 1451, 1220, 1157, 829, 788, 721, 694, 584 cm^{-1}; ^{1}H-NMR (500 MHz, Acetone-D_6): δ 3.38 - 3.42 (d, 2H), 4.39 (t, *J* = 8.1 Hz, 1H), 6.98 – 7.02(m, 2H), 7.12 - 7.18 (m, 5H), 7.24 - 7.28 (m, 3H), 7.32 - 7.36 (m, 4H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 41.5, 42.5, 52.6, 53.6, 115.0, 115.3, 115.5, 126.3, 128.3, 128.4, 128.7, 128.8, 129.4, 129.7, 129.8, 130.6, 130.7, 140.3, 140.3, 140.4, 144.5, 144.6, 160.0, 163.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 383.0365 obsd.: 383.0371.

Methyl4-(1,2-diphenylethyl)benzoate (5g)+methyl4-(2,2-diphenylethyl)benzoate (5g'). The same procedure used to synthesize **19** was used except a solution of 81.1 mg of *p*-acetylstyrene (**1g**) (0.500 mmol, 1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe and the product was purified via silica gel flash chromatography by eluting with 5% EtOAc/hexanes. Yield: 55% (85 mg and 90 mg); R_f = 0.27 w/ 5% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3026, 12949, 1716, 1609, 1452, 1309, 1275, 1153, 1104, 1030, 752, 696, 548 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6): δ 3.45 (d, *J* = 8.1 Hz, 2H), 3.84 (s, 1H), 4.48 (t, *J* = 8.1 Hz, 1H), 7.08-7.12 (m, 1H), 7.12-7.18 (m, 5H), 7.23-7.28 (m, 3H), 7.33-7.40 (m, 3H), 7.46-7.47 (m, 2H), 7.88-7.92 (m, 2H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 42.1, 42.4, 52.3, 53.1, 53.4, 126.4, 126.6, 126.8, 128.3, 128.5, 128.7, 128.8, 129.3, 129.4, 129.7, 130.0, 140.0, 143.9, 150.0, 167.3; HRMS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 339.1361 obsd.: 339.1368.

(1-(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)dibenzene (5h)+(1-(4-trifluoro methyl)phenyl)ethane-1,1-diyl)dibenzene (5h'). The same procedure used to synthesize **19** was used except a solution of 86.1 mg of *p*-trifluoromethylstyrene (**1h**) (0.500 mmol,

1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 51% (81 mg and 83 mg); R_f = 0.36 w/ Hexanes (silica), PMA stain. IR (neat) 3027, 2936, 1617, 1495, 1452, 1321, 1161, 1108, 1066, 1030, 1017, 742, 696 cm^{-1}; ^{1}H-NMR (500 MHz, Acetone - d_6): δ 3.46 (d, *J* = 8.1 Hz, 2H), 4.50 (t, *J* = 8.1 Hz, 1H), 7.18 - 7.20 (m, 5H), 7.22 – 7.26 (m, 3H), 7.35 – 7.40 (m, 4H), 7.55 – 7.60 (m, 4H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 43.1, 42.2, 53.1, 53.2, 125.3, 125.4, 125.5, 125.6, 126.5, 126.7, 126.9, 128.3, 128.5, 128.7, 128.8, 129.3, 129.6, 139.9, 143.8, 144.2, 148.8; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 433.0333 obsd.: 433.0328.

(2-(3-nitrophenyl)ethane-1,1-diyl)dibenzene (5j) + ((2-(3-nitrophenyl)ethane-1,1-diyl)dibenzene (5j'). The same procedure used to synthesize **19** was used except, a solution of 81.1 mg *m*-nitrostyrene(**1j**) (0.500 mmol, 1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe and the product was purified via silica gel flash chromatography eluting with 10% EtOAc/hexanes. Yield: 45% (69 mg and 65 mg); R_f = 0.31 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3062, 3026, 1694, 1600, 1523, 1494, 1346, 1072, 697, 637 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6): δ 3.50 (d, *J* = 8.1 Hz, 2H), 4.62, (t, *J* = 8.1, 1H) 7.12 - 7.20 (m, 6H), 7.21 – 7.42 (m, 8H), 7.89 - 8.02 (m, 2H); ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 41.9, 42.0, 53.0, 53.1, 121.1, 121.5, 121.7, 122.3, 123.1, 124.1, 126.3, 126. 8, 127.1, 128.2, 128.6, 128.8, 129.1, 129.3, 129.5, 129.8, 132.0, 132.5, 134.7, 139.4, 143.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 410.0310 obsd.: 410.0302.

5,5'-(nonane-1,1-diyl)bis(4-fluorobenzene) (41). The same procedure used to synthesize **19** was used except a solution of 63.2 mg of 1-nonene (0.500 mmol,

1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe, 577 mg of tributyl(4-fluorophenyl)stannane (**2b**) (1.50 mmol, 3.00 equiv.) was added via syringe and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 60% (94 mg and 97 mg); R_f = 0.61 w/ Hexanes (silica), PMA stain. IR (neat) 2924, 2854, 1602, 1505, 1465, 1227, 1156, 822, 785, 577 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 – 0.95 (m, 3H), 1.20 – 1.40 (m, 12H), 1.98 (q, *J* = 7.7 Hz, 2H), 3.83 (t, *J* = 7.7 Hz, 1H), 6.9 – 7.01 (m, 4H), 7.10 – 7.20 (m, 4H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 14.4, 23.0, 28.2, 29.6, 29.7, 29.9, 32.2, 36.3, 50.1, 115.4, 115.6, 115.9, 116.2, 128.8, 128.9, 129.4, 129.5, 141.1, 141.2, 160.0, 163.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 423.1054 obsd.: 423.1044.

5,5'-(nonane-1,1-diyl)bis(1,3-dimethoxybenzene) (42). The same procedure used to synthesize **19** was used except, a solution of 63.1 mg of 1-nonene (0.500 mmol, 1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe, 642 mg of tributyl(1,3-dimethoxyphenyl)stannane (**2d**) (1.50 mmol, 3.00 equiv.) was added via syringe, and the product was purified via silica gel flash chromatography eluting with 5 % acetone:hexanes. Yield: 56.0 % (112 mg and 114 mg); R_f = 0.49 w/ acetone:Hexanes (silica), PMA stain. IR (neat) 2997, 2925, 2853, 1590, 1456, 1425, 1344, 1287, 1202, 1149, 1059, 829, 734, 693 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.7 Hz, 3H), 1.22 - 1.40 (m, 12H), 1.98 - 2.03 (m, 2H), 3.80 (s, 12 H), 3.80 (d, 1H) 6.32 (t, *J* = 2.3 Hz, 2H), 6.45 (d, *J* = 2.3 Hz, 2H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 14.4, 23.0, 28.3, 29.6, 29.7, 29.9, 32.2, 35.8, 52.8, 52.2, 55.5, 97.9, 102.5, 147.8, 160.9; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 401.2692 obsd.: 401.2695.

(E)-4,4'-(4-phenylbut-3-ene-1,2-diyl)bis(fluorobenzene)(39-d_2). The same procedure used to synthesize **19** was used except, a solution of 65.1 mg of 1-nonene-d_2 (0.500 mmol, 1.00 equiv.) dissolved in 2.00 mL of DMA was added to the reaction flask via syringe, 577 mg of tributyl(4-fluorophenyl)stannane (**2b**) (1.50 mmol, 3.00 equiv.) was added via syringe and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 30% (48 mg and 49 mg); R_f = 0.61 w/ hexanes (silica), PMA stain. IR (neat) 2923, 2854, 2158, 1603, 1503, 1222, 1157, 822, 572 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 – 0.95 (m, 3H), 1.20 – 1.40 (m, 12H), 1.98 (t, *J* = 7.4 Hz, 2H), 6.9 – 7.01 (m, 4H), 7.10 – 7.20 (m, 4H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$): δ 14.5, 22.9, 28.1, 29.6, 29.8, 29.9, 32.2, 35.5, 35.8, 36.1, 115.4, 115.7, 129.4, 129.5, 141.2, 159.9, 163.2 ; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 425.1179 obsd.: 425.1176.

Procedure for cross-over experiment

To an oven dried 10 mL sidearm flask equipped with a stir bar was added 12.0 mg of Pd(I*i*Pr)$(OTs)_2$ (0.030 mmol, 0.060 equiv.), 18.2 mg of $Cu(OTf)_2$ (0.050 mmol, 0.250 equiv.), 100 mg of freshly crushed, activated 3Å molecular sieves and 700 μmol of DMA under a nitrogen atmosphere. A solution of 100 μmol of a 2.00 M solution of 12.6 mg of 1-nonene (0.100 mmol, 0.50 equiv) and 15.0 mg of 1-undecene (0.100 mmol, 0.50 equiv.) in DMA was added to the reaction vessel via syringe. The flask was connected to a three-way joint equipped with condensers and the three-way joint fitted with a balloon of O_2 was installed on the top of the four-neck flask. The flask was evacuated via water aspiration and refilled with oxygen three times and the mixture was

stirred for ca. 5 min at room temperature under O_2. Finally 200 µL of $PhSnBu_3$ (0.600 mmol, 3.00 equiv.) was added dropwise by syringe to the reaction vessel. The reaction mixture was stirred under a balloon of O_2 for 24 h. After 24 h, a 50 µL aliquot of the reaction mixture was removed and filtered through a small plug of silica with elution with EtOAc. The solution was analyzed by GC/MS (see data and calculations below). A second reaction was performed with 1-nonene-d_2 and 1-undecene (Figure 2.18. and 2.19).

# of Deuterium Atoms	0	1	2	3	4	5
	M	**M+1**	**M+2**	**M+3**	**M+4**	**M+5**
Molecular Ions	280	281	282	283	284	285
Adund. Unlabeled	25640	6147	722	101		
Adund. Labeled	0	199	4446	907	122	
Relative Abund. Unlabeled	100	23.97	2.82	0.40		
Relative Abund. Labeled	0	4.47	100	20.40	2.74	
Unlabeled	0	0	0	0		
difference		4.47	100	20.40	2.74	
1-Deuterium		4.47	1.07	0.13	0.02	
difference			98.93	20.27	2.73	
2-Deuterium			98.93	23.72	2.78	0.38
difference				-3.44	-0.06	
Percent Distribution:	**0**	**4.33**	**95.67**	**0**		

(M+1)/M not labeled: 0.24 4.475 * 0.24 = 1.07 98.92 * 0.24 = 23.74
(M+2)/M not labeled: 0.03 4.475 * 0.03 = 0.13 98.92 * 0.03 = 2.96
(M+3)/M not labeled: 0.01 4.475 * 0.01 = 0.02 98.92 * 0.01 = 0.84

sum relative. abund.: 103.40

Figure 2.18. Calculation shown for deuterium incorporation in 1-nonene-d_2

# of Deuterium Atoms	0	1	2
	M	**M+1**	**M+2**
Molecular Ions	308	309	310
Adund. Unlabeled	60712	15472	1874
Adund. Labeled	10508	2831	301
Relative Abund. Unlabeled	100	25.48	3.08
Relative Abund. Labeled	100	26.94	2.86
Unlabeled difference	100	25.48 1.45	3.08 -0.22
1-Deuterium difference		1.46	0.37 -0.59
Percent Distribution:	**98.56**	**1.44**	**0**

(M+1)/M not labeled: 0.25
(M+2)/M not labeled: 0.03

sum relative. abund:
101.47

1.46 * 0.25 = 0.37

Figure 2.19. Calculation shown for deuterium incorporation in 1-undecene.

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CHAPTER 3

PALLADIUM-CATALYZED THREE-COMPONENT COUPLINGS OF VINYL TRIFLATES, TERMINAL ALKENES, AND ORGANOSTANNANES

Introduction

The development of new chemical transformations to produce complex chemical structures in a rapid way is an important area of research in organic synthesis.[1-3] Such strategies avoid time consuming and costly protection-deprotection steps as well as purification processes, and therefore, they can be considered as environmentally benign and also atom economical.[4,5] In addition, such transformations are highly desirable for the rapid generation of libraries of small molecules for high throughput screening in search for new drug candidates. It is therefore not surprising that significant efforts are being devoted to the development of new methods in this area of research. The outstanding potential of Pd to catalyze a large variety of reactions with high levels of chemo-, regio-, and stereo-selectivity, and excellent functional group tolerance has been recognized for the development of multicomponent reactions. As a consequence, a number of multicomponent reactions have been discovered and developed based on the

use of palladium catalysis.

In the previous chapter, the development of diarylation reactions of styrenes and terminal alkenes to produce 1,2- and 1,1-diarylation products (Figure 3.1) has been described.[6,7] Although this reaction generates two carbon-carbon bonds in a single step, it is limited to the installation of two identical groups.

In order to expand the versatility of this reaction, we were interested in developing a method that controls the coupling of three different groups in a single step. This chapter describes our approach for the development of a three component reaction utilizing Pd as the catalyst, and the mechanistic insight gained from the oxidative diarylation method for the design of these reactions (Figure 3.2).[6,7]

Background

Palladium-catalyzed three-component reactions

As described, reactions that can install multiple carbon-carbon bonds in a single step are valuable synthetic methods in organic synthesis. In practice, the development of these reactions is difficult.[8,9] Ideally, simultaneous addition of all reactants, reagents, and the catalyst is desirable, but as a result the number of reactive starting materials increases along with the possibility to generate side products. This makes the reactions difficult to optimize for the formation of the desired product. In recent years, the design of effective reaction conditions in palladium catalysis has allowed for the development of many interesting three-component coupling reactions. This section focuses on some of the recent advancements in the field of three-component coupling reactions involving Pd-

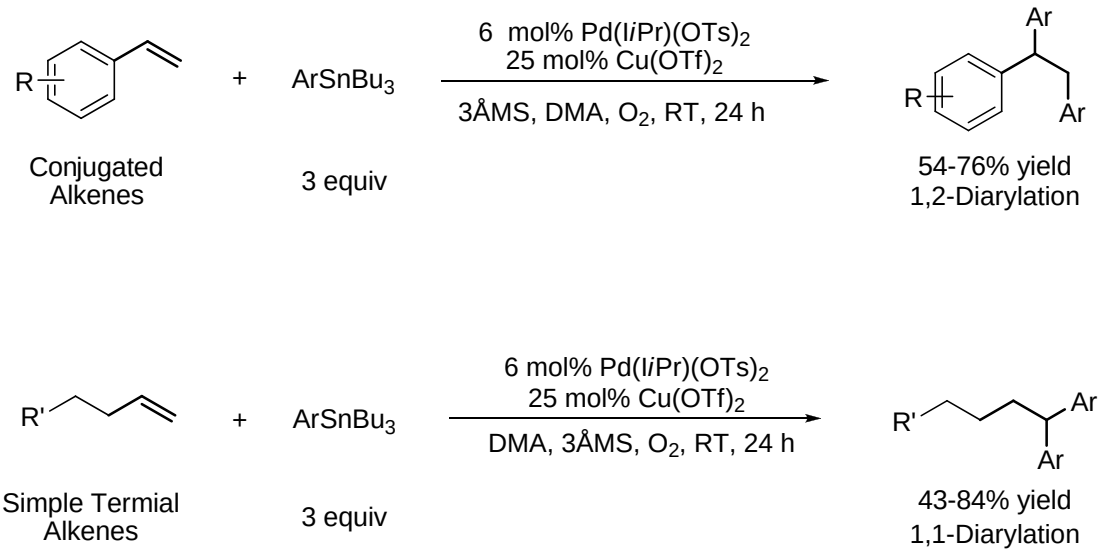


Figure 3.1. Pd(II)-catalyzed oxidative coupling of alkenes and organostannanes to generate 1,2-diarylation product when using conjugated alkenes and 1,1-diarylation product when using simple terminal alkenes.

Figure 3.2. Pd(0)-catalyzed three-component coupling of a vinyl triflate, a terminal alkene and a organostannane to generate 1,1-difunctionalized product.

catalysis.

A primary strategy towards the design of a three-component reaction is generating an alkyne tethered nucleophile precursor in situ through reaction between two readily available reagents and uses that for the coupling with another reagent.[10-12] For example, Balme and coworkers developed a palladium-catalyzed three-component coupling utilizing this strategy in which an alkyne-tethered nucleophile **A** is generated in situ through reaction between propargyl alkoxides and conjugate acceptors (Figure 3.3).[13] This is used in conjugation with various organic halides to produce tetrahydrofuran products. Another interesting three-component method was reported by Muller and coworkers.[14] In this reaction, electron-deficient aryl or heteroaryl and terminal propargyl alcohols were heated in THF in the presence of Et_3N, catalytic $PdCl_2(PPh_3)_2$ and CuI. The resulting enones **B** were then treated in situ with N-methylhydrazine to produce pyrazolines (Figure 3.4).

In addition to alkynes, there have been numerous examples of three-component palladium-catalyzed reactions with allene substrates.[15-17] The carbopalladation of allenes with aryl halides represents a well-known method for the generation of π-allyl Pd species. In this process, addition of a Pd-aryl species, originating from oxidative addition of the aryl halide to Pd^0, to the allene occurs at the central carbon atom. The π-allyl-Pd intermediate **A** may then be trapped by a nucleophilic partner or a transmetalating agent to yield the product. Utilizing this strategy, Cheng and coworkers developed a three-component coupling of allenes, organic halides, and aryl boronic acids to generate tri- and tetra-substituted olefins (Figure 3.5).[18]

Cyclization of Alkyne Containing Nucleophiles

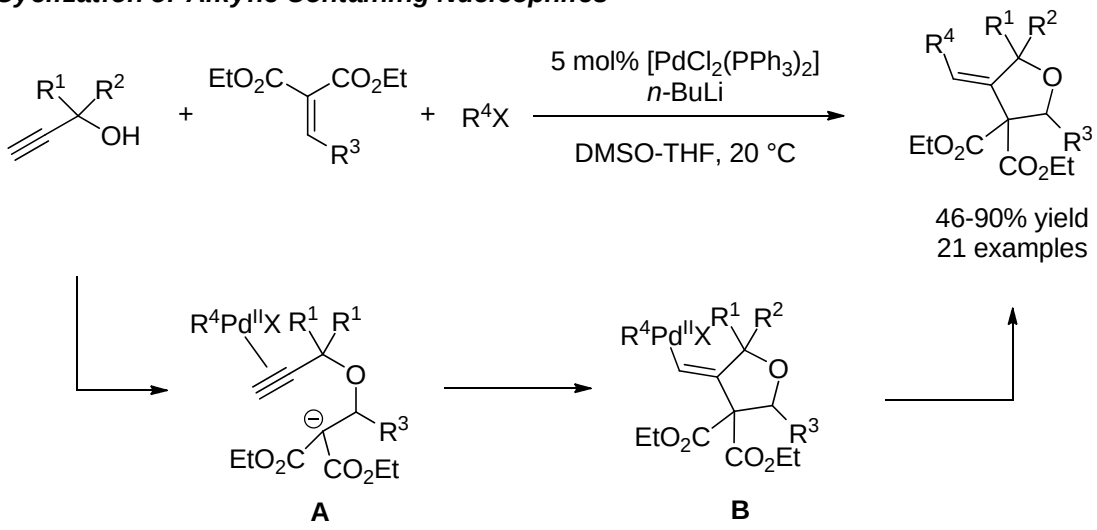


Figure 3.3. Pd-catalyzed three-component coupling reaction that utilizes an alkyne-tethered nucleophile in situ through reaction between propargyl alkoxides and conjugate acceptors to generate the coupling product.

Cross-Coupling between Terminal Alkynes and Organic Halides

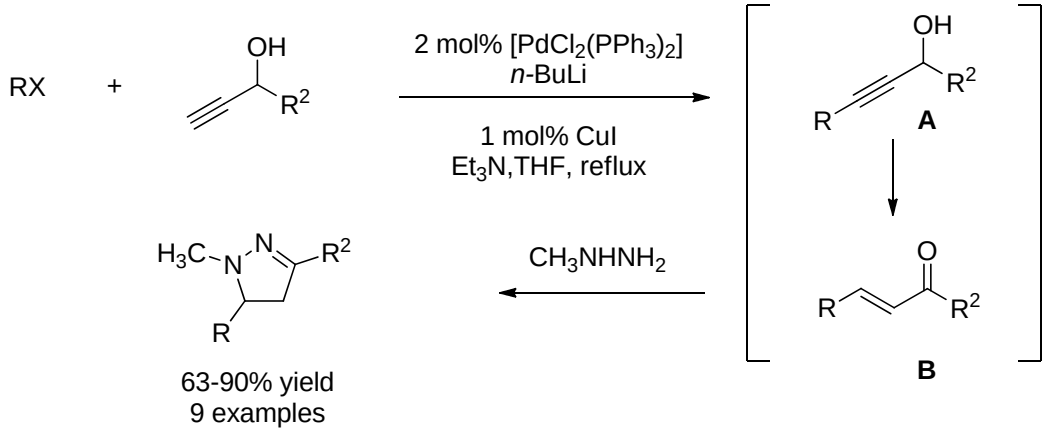


Figure 3.4. Pd-catalyzed three-component coupling reaction of electron-deficient aryl or heteroaryl, terminal propargyl alcohols and N-methylhydrazine to generate pyrazolines derivatives.

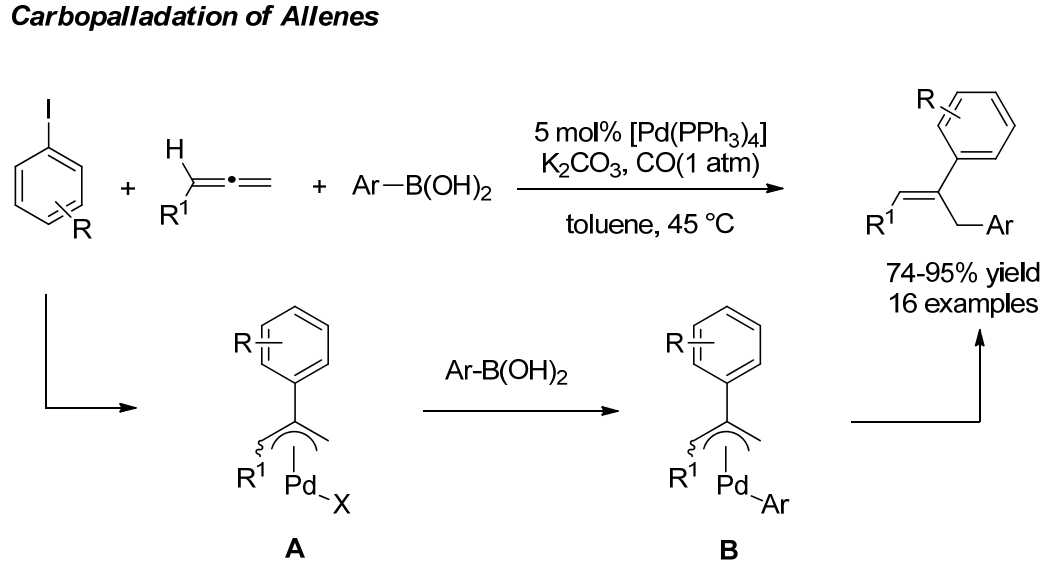
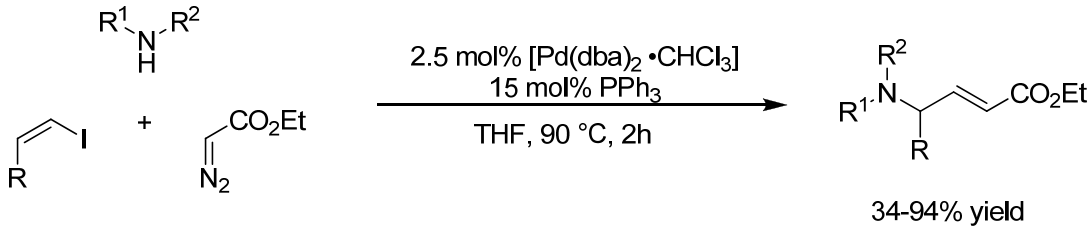


Figure 3.5. Cheng's Pd-catalyzed three-component coupling to allene using organic halides and arylboronic acid to generate trisubstituted olefin compounds and their proposed mechanism.

In 2009, Vranken and coworkers reported a unique Pd-catalyzed coupling of α-diazoethers, vinyl halides, and primary or secondary amines (Figure 3.6).[19] In this methodology, a number of α,β-unsaturated γ-amino esters were synthesized through a Pd-catalyzed three-component coupling reaction. During the optimization of this reaction, two potential competing pathways made this reaction more challenging. First, cross-coupling of the vinyl halide and the diazo compound could occur.[20] Secondly, Pd^{II} species also can promote the polymerization of ethyl diazoacetate.[21] This problem was addressed by the slow addition of the diazoacetate. The authors mention that this was crucial for obtaining high yields of the products. The yield is decreased to 24%, if added simultaneously with the other reagents. Finally, the reaction was optimized to generate good yields of the desired products (Figure 3.6).

The proposed mechanism of the reaction is thought to start with oxidative addition of the vinyl halide to palladium to generate vinyl palladium complex **B**, and subsequent formation of a palladium carbene **C** with the α-diazoester. Migration of the vinyl ligand to the empty p-orbital of the carbene ligand generates the η^1-allyl palladium complex **D**.[22] Presumably, the η^1-allyl palladium complex rearranges to form an η^3-allyl palladium intermediate **E** that is then attacked by the amine nucleophile at the position distal from the ester group to generate the product.[23] When the scope of the reaction was explored, it was found that secondary and primary amines work in good to moderate yield, and the scope of the vinyl iodide substrates was limited to monosubstituted alkenes. It should be noted that in this transformation the Pd-alkyl intermediate generated is stabilized as a π-allyl intermediate, which allows for the nucleophilic addition to occur before β-hydride elimination.

Three Component Coupling Reaction



Mechanistic Proposal

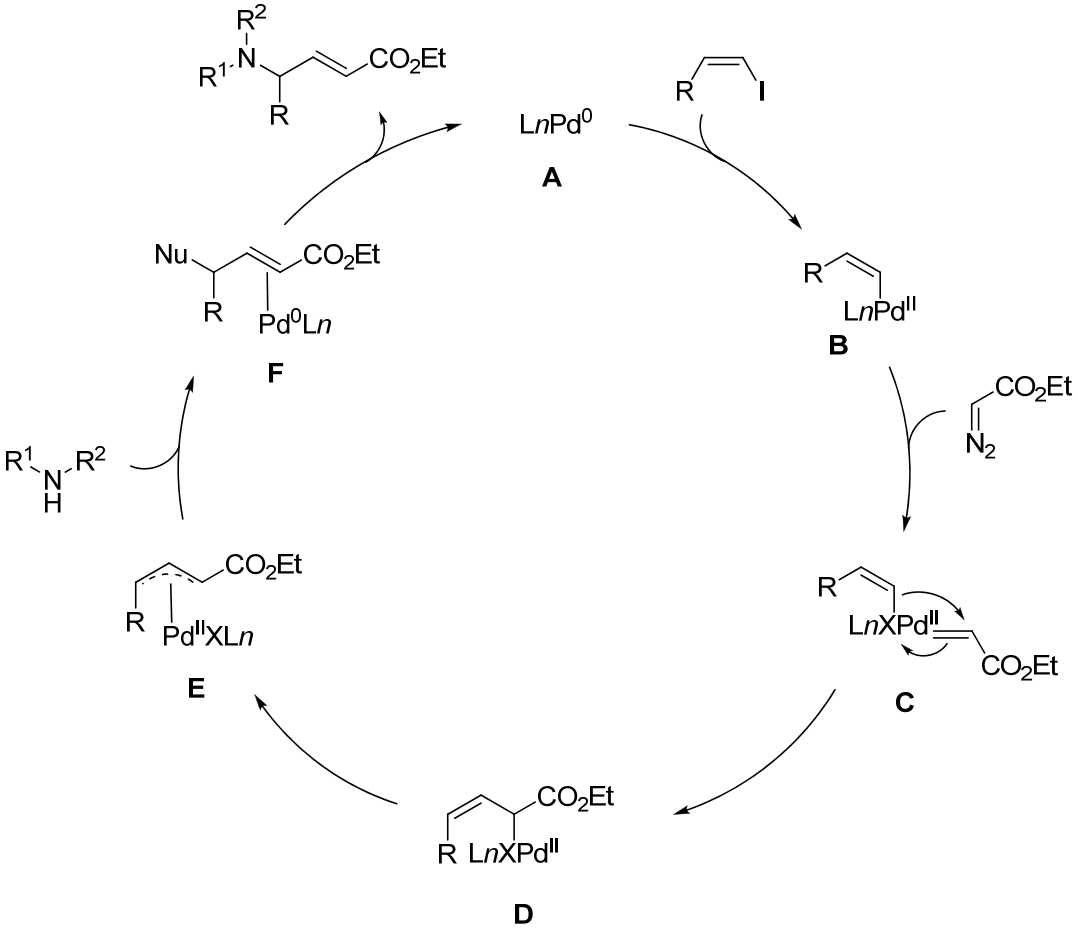


Figure 3.6. Pd-catalyzed coupling of vinyl halides, α-diazoesters and secondary amines to generate α,β-unsaturated γ-amino esters and the proposed mechanism reported by Vranken and coworkers.

Recently, Wang and coworkers developed an elegant three-component coupling of *N*-tosylhydrazones with terminal alkynes and aryl halides (Figure 3.7).[24] Similar to the previous reports, this catalytic cycle is also initiated by oxidative addition of aryl bromide to Pd^0 to afford intermediate **B**, and simultaneously a diazo substrate is generated in situ from *N*-tosylhydrazone in the presence of base.

Decomposition of the diazo compound by Pd^{II} species **B** leads to palladium carbene **C**. Migratory insertion of an aryl group to the carbenic carbon gives intermediate **D** from which intermediate **E** is generated by transmetallation with a copper acetylide followed by reductive elimination to afford the product. In this communication, the substrate scope of both aryl groups is limited to phenyl or arenes with similar electronic nature. *N*-tosylhydrazone **1** derived from acetophenone was not compatible under these conditions, because the Pd-alkyl generated from this intermediate can undergo β-hydride elimination, thereby disrupting the three-component coupling and consequently, the Heck product **4** was mainly observed (Figure 3.7).

In 2009, Ma and coworkers described the Pd^0-catalyzed three-component coupling cyclization reaction of 1,5-bisallenes **5** with propargylic carbonates in the presence of arylboronic acids to generate an interesting cis-bicyclo[4.3.0]nonene skeleton in the final product (Figure 3.8).[25] This reaction mechanism involves three sequential carbo-palladation reactions, starting with oxidative addition of propargylic carbonate to the Pd^0 to yield 1,2-allenyl palladium intermediate **B**. Subsequent carbopalladiation of the 1,5-bisallene with intermediate **B** would form the delocalized π-allyl species **C**,[15] which undergoes intramolecular carbometallation to afford the vinyl palladium species **D**. Finally, intermediate **E** isomerizes to **F**. The final product is subsequently formed by a

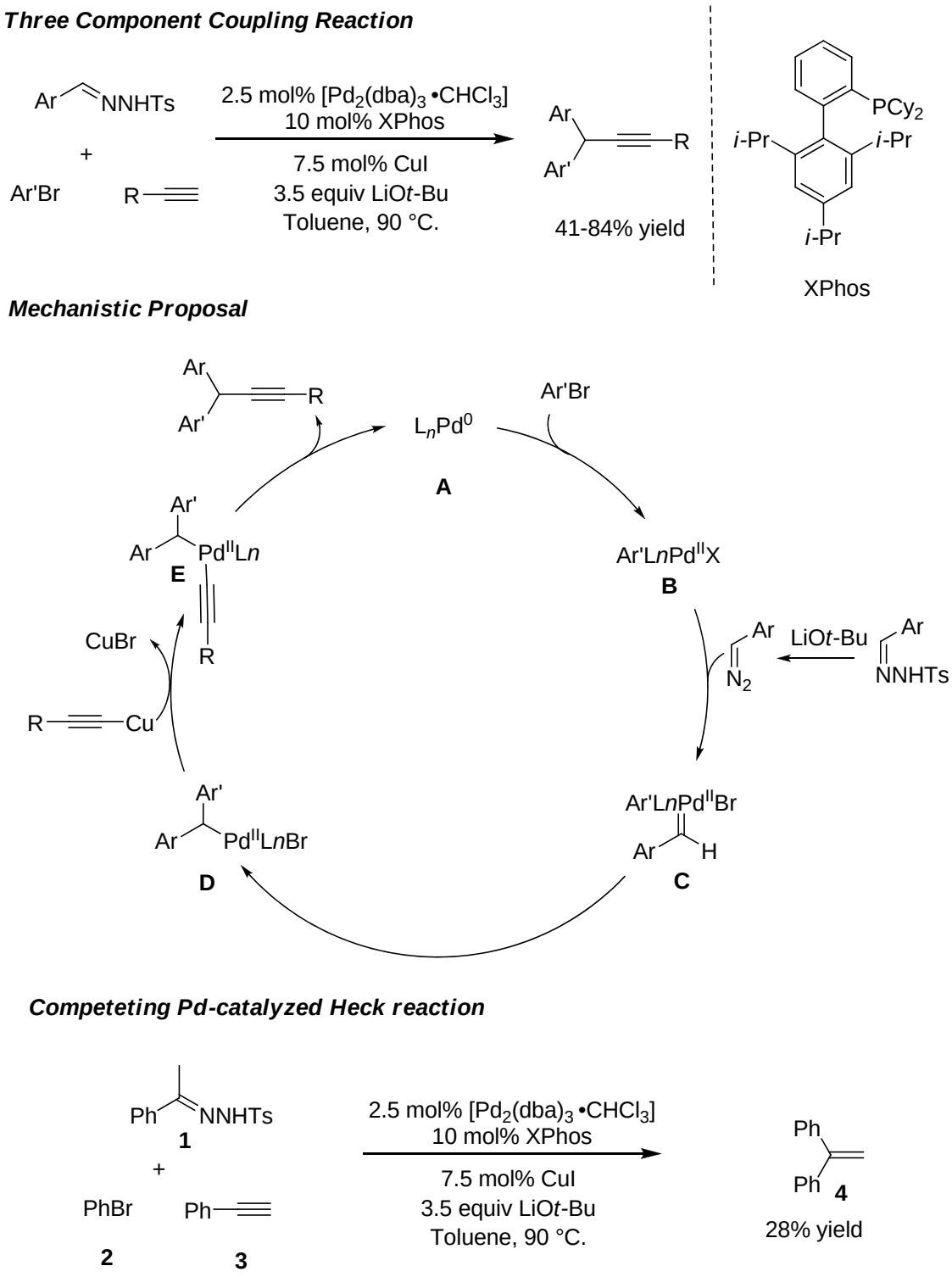
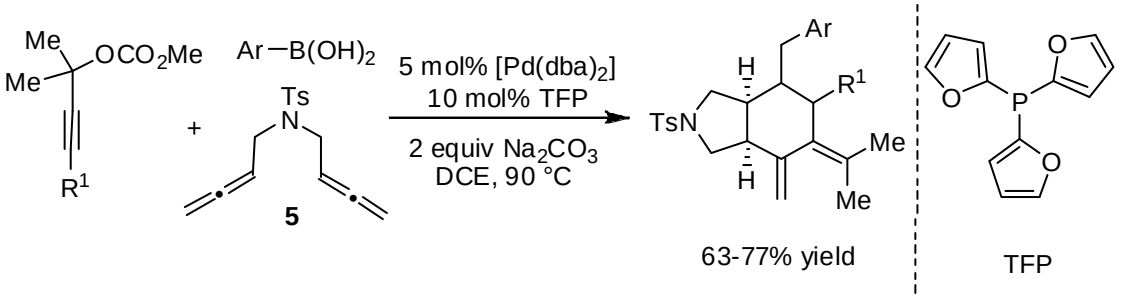


Figure 3.7. Wang's Pd-catalyzed coupling of *N*-tosylhydrazones, terminal alkynes and aryl halides to generate diaryl acetylene derived product, proposed mechanism and the competing Pd-catalyzed Heck reaction.

Three Component Coupling Reaction



Mechanistic Proposal

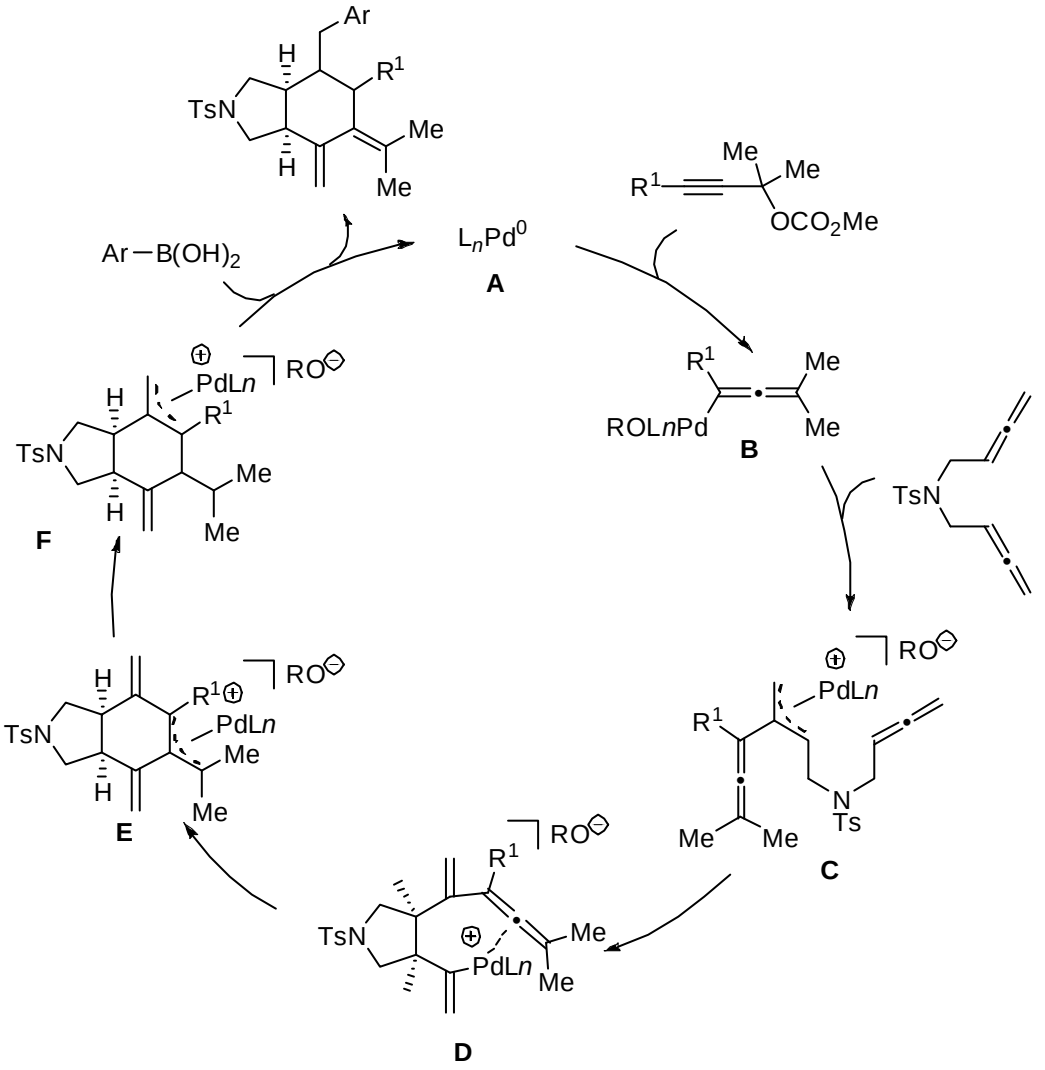


Figure 3.8. Pd-catalyzed coupling reaction that involves cascade cyclization of bisallenes with propargylic carbonates and organoboronic acids developed by Ma and coworkers and their proposed mechanism for three-component cyclization reaction.

Suzuki-type coupling of **F** with an organoboronic acid. Good yields were obtained with different R^1 groups on the propargyl carbonates; however, 1,5-bisallenes and aryl boronic acid have a limited substrate scope.

Another interesting extension for the utilization of propargyl carbonates was reported by Yamamoto and coworkers (Figure 3.9).[26] They developed a novel Pd^0-catalyzed three-component [3 + 2] cycloaddition reaction which employs ethylidene malononitriles and allyltributyltin **6** in the presence of propargyl trifluoroacetates affording substituted cyclopentenes in good to high yield under mild reaction conditions. This reaction is again initiated by oxidative addition of propargyl trifluoroacetates to the palladium catalyst to form 1,2-allenyl Pd intermediate **B**. The nucleophile, allyltributylstannane, attacks the center sp^2 carbon of the 1,2-allene moiety to form the palladium carbene complex **C**, which reacts with alkyl or arylidene malononitrile to give a π-allyl Pd-complex **D**, which undergoes intramolecular C-alkylation with the stable carboanion to give cyclopentene compounds.

Another interesting transformation is the Pd^0-catalyzed olefin difunctionalization reaction to generate two carbon-carbon bonds in the three-component coupling reaction.[27-32] In these reactions, the Pd^{II}-alkyl intermediate is routinely generated from an olefin substrate by insertion of the alkene into the Pd^{II}-aryl intermediate, which is prone to β-hydride elimination. For this reason, reported examples are mainly restricted to norbornane type substrates, or substrates that do not have a hydrogen β to the Pd^{II}-alkyl species.[33,34]

For example, Goodson and coworkers have described a methodology to generate a 5,6-diarylation product of norbornene compounds (Figure 3.10).[32]In these reactions, the

[3 + 2] Cycloaddition Reaction and Mechanistic Propsal

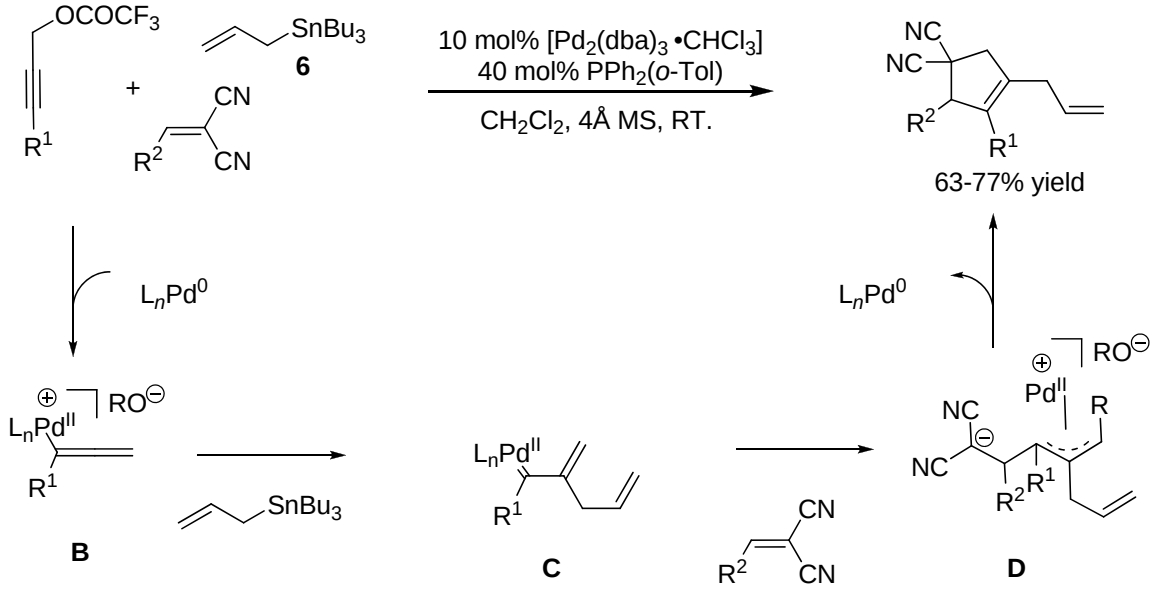
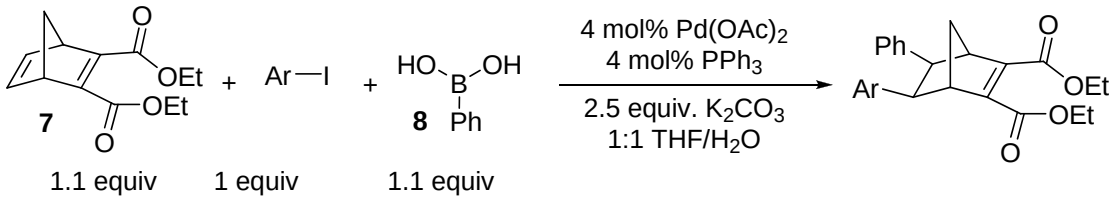
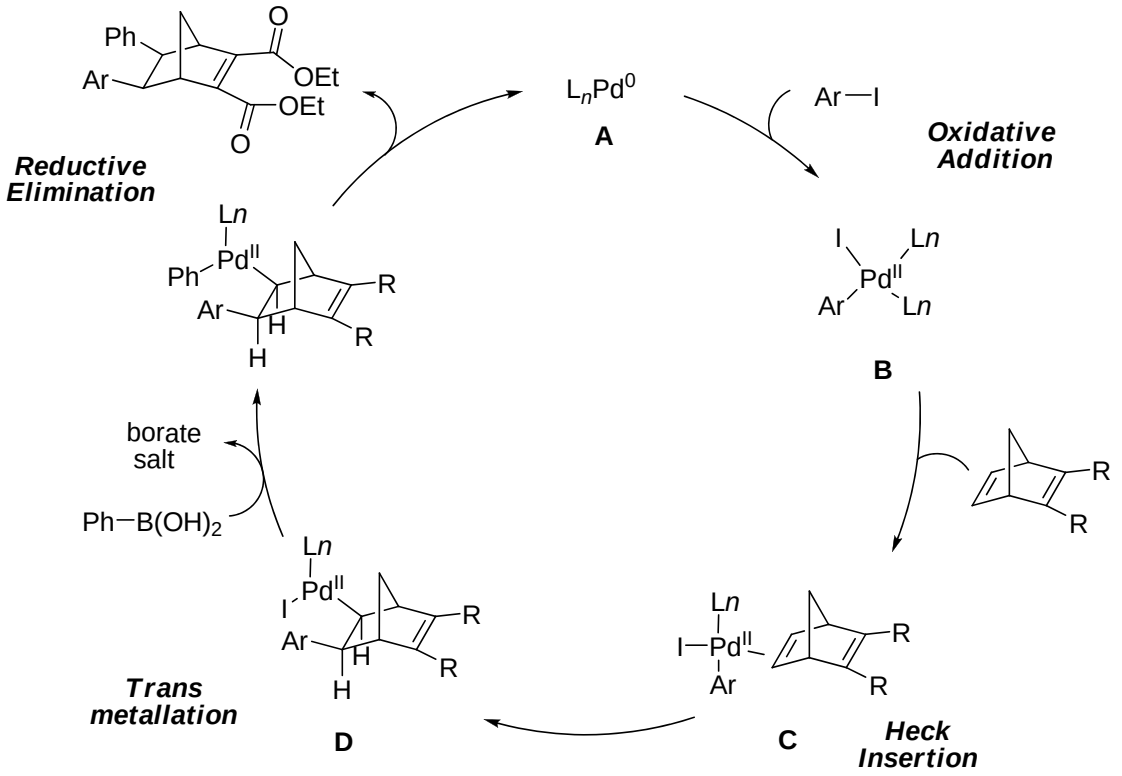


Figure 3.9. Yamamoto and coworkers [3+2] cycloaddition of propargyl trifluoroacetates, ethylidene malononitriles and allyltributylstannane using Pd catalyst and the proposed mechanism.

Three Component Coupling Reaction



Mechanistic Proposal



Competeting Pd-catalyzed Cross-coupling

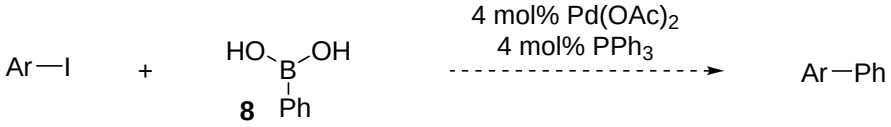


Figure 3.10. Goodson and coworkers Pd-catalyzed diarylation of norbornene utilizing aryl iodines and phenyl boronic acids and their proposed mechanism. Competitive cross-coupling pathway that form without the presence of norbornene.

proposed mechanism starts with initial oxidative addition of an aryl iodide onto a Pd^0 species which forms a Pd^{II}-aryl species **A**. Next, the Pd^{II}-aryl intermediate will coordinate and insert into a norbornene to generate the Pd^{II}-alkyl intermediate **B** which can undergo the subsequent transmetallation followed by reductive elimination to yield the difunctionalized product. The success of this difunctionalization reaction is due to the utilization of the privileged norbornene type substrates because the Pd^{II}-alkyl intermediate formed from the norbornene substrate cannot undergo β-hydride elimination due to non-availability of of *cis*-β-hydrogen. Moreover, norbornenes are an activated class of olefins, which enhances their reactivity toward alkene insertion than competitive cross-coupling pathways. Consequently, this reaction would be able to generate two carbon-carbon bonds in a single step.

In addition to 5,6-diarylation of norbornene, several alkene difunctionalization reactions of norbornene have been reported. In 1992, Torii and coworkers reported a palladium-catalyzed coupling of cis-alkenyl iodide **10**, norbornene **9**, and terminal alkyne (Figure 3.11).[35] Following this, the same group reported the palladium-catalyzed coupling of cis-alkenyl iodide **10**, norbornene **9** and cyano nucleophiles that lead to *cis*-exo-2,3-disubstituted norbornanes (Figure 3.12).[30]

Results and discussion

As described, a wide range of reactivity of organopalladium reagents along with their excellent functional group tolerance has greatly supported the development of a variety of Pd-catalyzed three-component coupling reactions. As a part of research in Prof.

Three Component Coupling Reaction

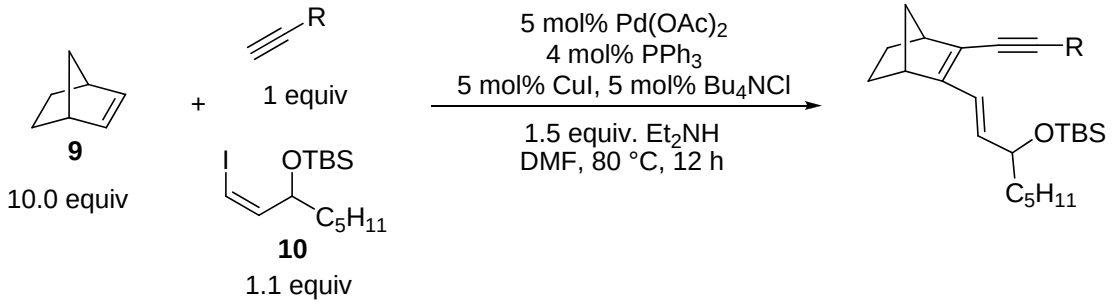


Figure 3.11. Pd-catalyzed three-component coupling reaction that utilizes norbornene, vinyl iodide and alkyne developed by Torii and coworkers.

Three Component Coupling Reaction

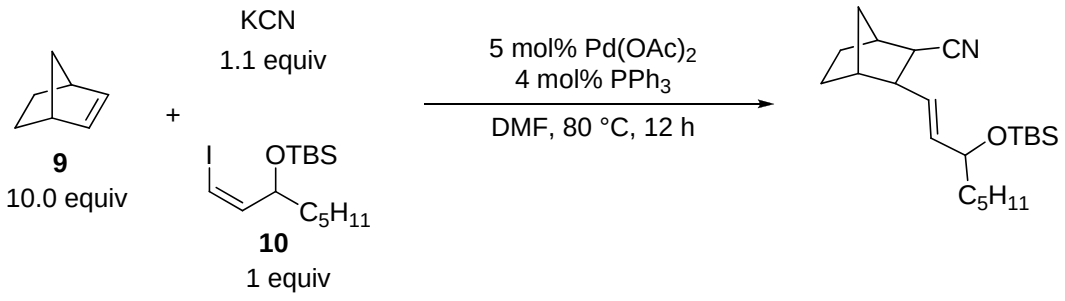


Figure 3.12. Pd-catalyzed three-component coupling reaction that utilizes norbornene, vinyl iodide and potassium cyanide developed by Torii and coworkers.

Sigman lab, we wanted to develop a three-component coupling reaction utilizing simple olefins such as styrenes and straight chain alkenes as a reaction partner.[6,7] However, the challenge associated with these olefin substrates is competitive β-hydride elimination from a Pd^{II}-alkyl intermediate **A** (Figure 3.13).[36] Therefore, we were interested in developing difunctionalization reaction of olefins to generate two different carbon-carbon bonds in a single step using a similar approach to oxidative difunctionalization described in the last chapter.

As demonstrated in the second chapter, our lab has reported a three-component coupling reaction, in which we were able to generate two carbon-carbon bonds with a variety of olefin substrates such as styrene derivatives and simple terminal alkenes. However, this oxidative diarylation reaction was limited to the installation of two identical groups onto the double bond (Figure 3.14).

In order to install two different groups on the olefin substrates, a Pd^{0}-catalysis approach was proposed, similar to the method adopted for difunctionalization of norbornene (Figure 3.12).[8,32] As described, the challenge associated with these difunctionation reactions is the Pd^{II}-alkyl intermediate **C** generated from these reactions can undergo β-hydride elimination leading to undesired side products. We hypothesize that the β-hydride elimination would be controlled by the utilization of electrophilic palladium in the transformation.

As described in the second chapter, in the oxidative alkene difunctionalization reactions, we believe that a strong electrophilic nature of the palladium is crucial for the success of the diarylation of olefins (Figure 3.14). In the oxidative difunctionalization reaction, it was proposed that the cationic intermediate **B** can help to promote the coordi-

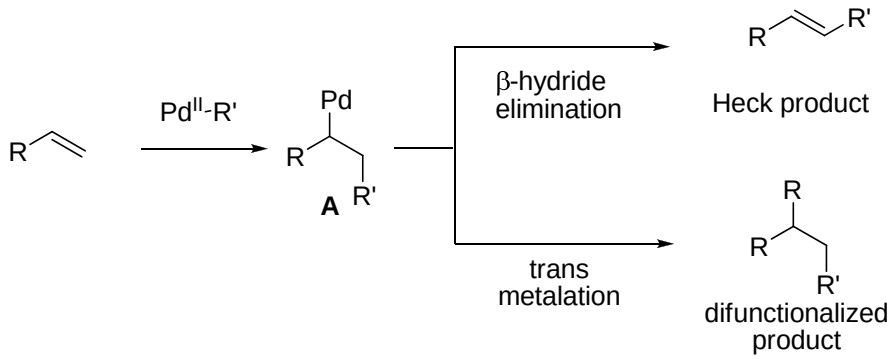


Figure 3.13. Pd-catalyzed alkene functionalization reaction and the competing β-hydride elimination that leads to Heck reaction.

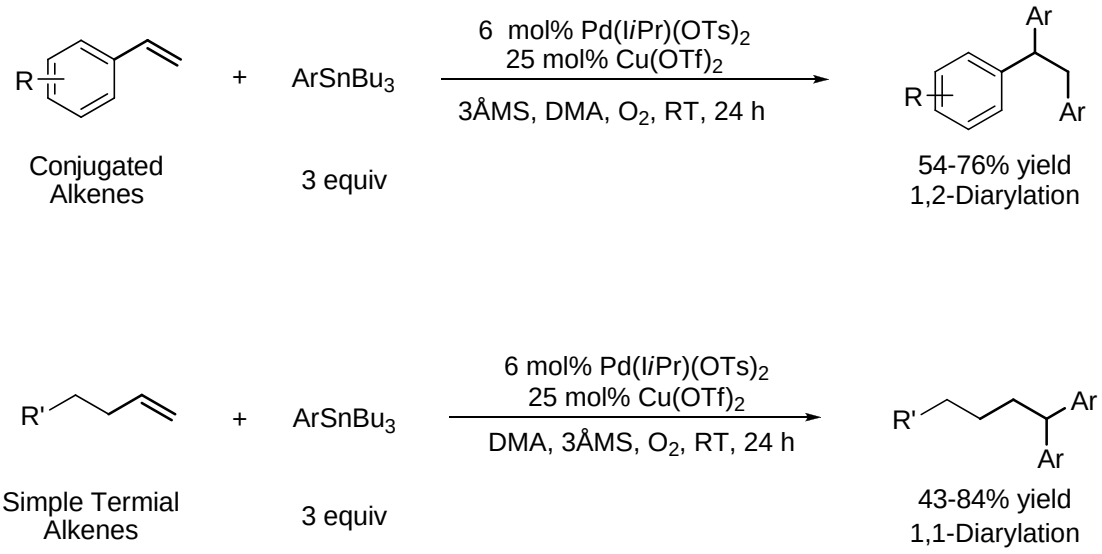


Figure 3.14. Pd(II)-catalyzed oxidative coupling of alkenes and organostannanes to generate 1,2-diarylation products when using conjugated alkenes and 1,1-diarylation products when using simple terminal alkenes.

nation of the olefin, thereby slowing the rate of organometallic homocoupling. Moreover, the Pd-alkyl intermediate formed can convert into the η^3-π-benzyl species **D** in order to stabilize the electrophilic palladium. This η^3-π-benzyl prevents the agostic interaction between a C-H bond on the alkyl group that is β to the alkyl-metal bond and the Pd, slowing down β–hydride elimination. This process allows sufficient time for the second transmetallation to occur before β-hydride elimination, and thus leads to diarylation products. Based on this hypothesis, we proposed to utilize cationic Pd complexes for the coupling of three different reaction partners. Specifically, we proposed to use an aryl triflate, to be generated the electrophilic Pd^{II}-aryl intermediate **B'** similar to intermediate **B** that was proposed to generate from the transmetallation of an organostannane reagent to the electrophilic Pd^{II} complex in the oxidative chemistry (Figure 3.15).

Based on this hypothesis, we began our studies by examining the cross-coupling reaction that was reported by Fu and coworkers (Figure 3.16),[37,38] in which an aryltriflate is treated with phenyl stannane using Pd^0/phosphines to generate the Stille cross-coupling products. In this reaction, Pd^0 undergoes an oxidative addition with the aryl triflate to generate a Pd^{II}-aryl intermediate, which subsequently reacts with the organometallic reagent to generate the cross-coupled product. We hypothesized that if the alkene is introduced into the reaction system, then the electrophilic Pd^{II}-aryl generated *in situ* might undergo alkene insertion rather than transmetallation to yield the three-component coupling product. However, using 4-methyl styrene as the alkene under similar conditions with I*i*Pr carbene as the ligand and dioxane as the solvent, only a 28% yield of the cross-coupling product was observed and unfortunately, no three-component coupling product was observed under these conditions.

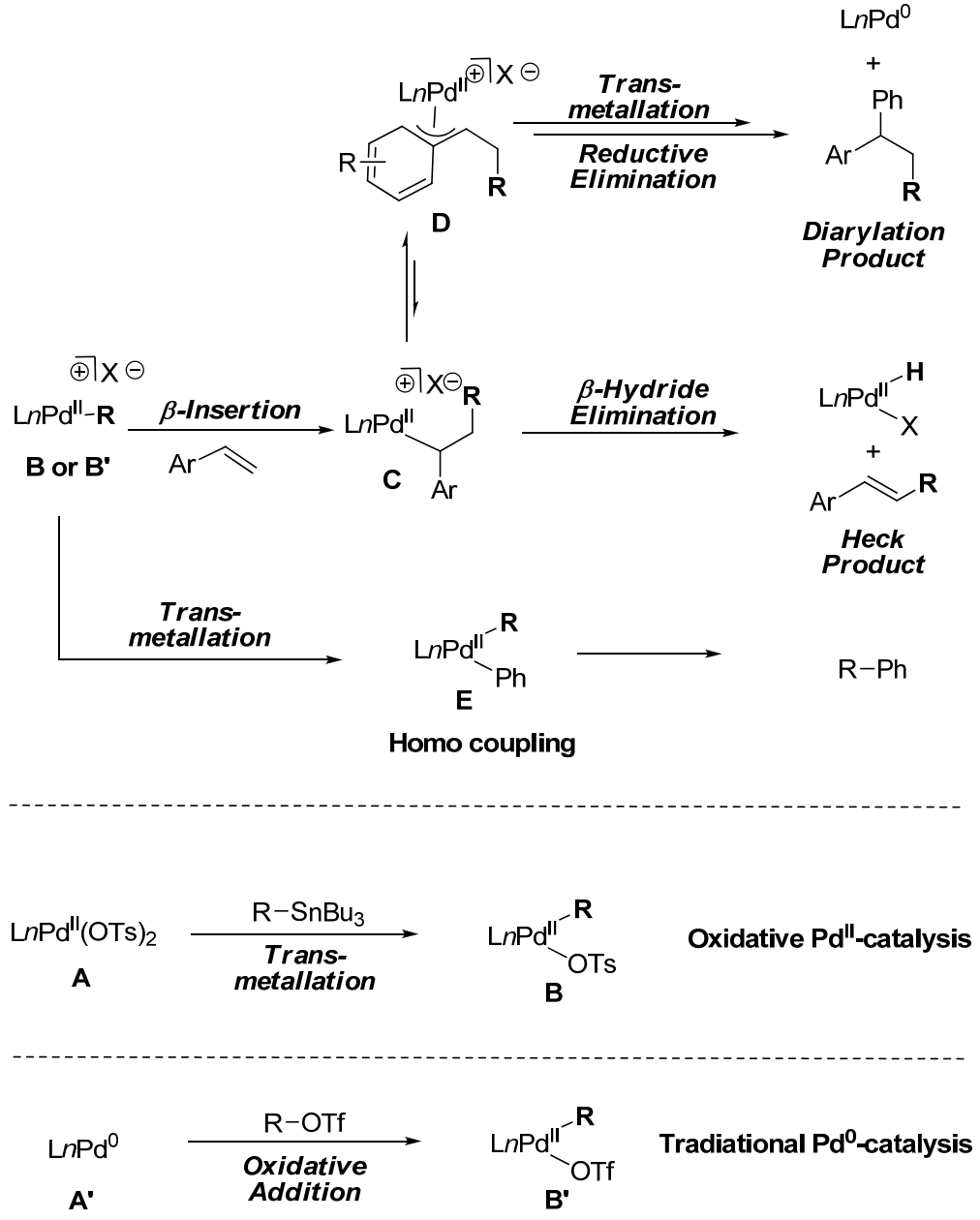


Figure 3.15. Envisioned mechanism for the Pd-catalyzed three-component reaction that invokes the electrophilic palladium to alter the pathway and to achieve the diarylation product. The proposed electrophilic intermediate **B** in oxidative diarylation and the envisioned electrophilic intermediate **B'** from the Pd^0 catalysis.

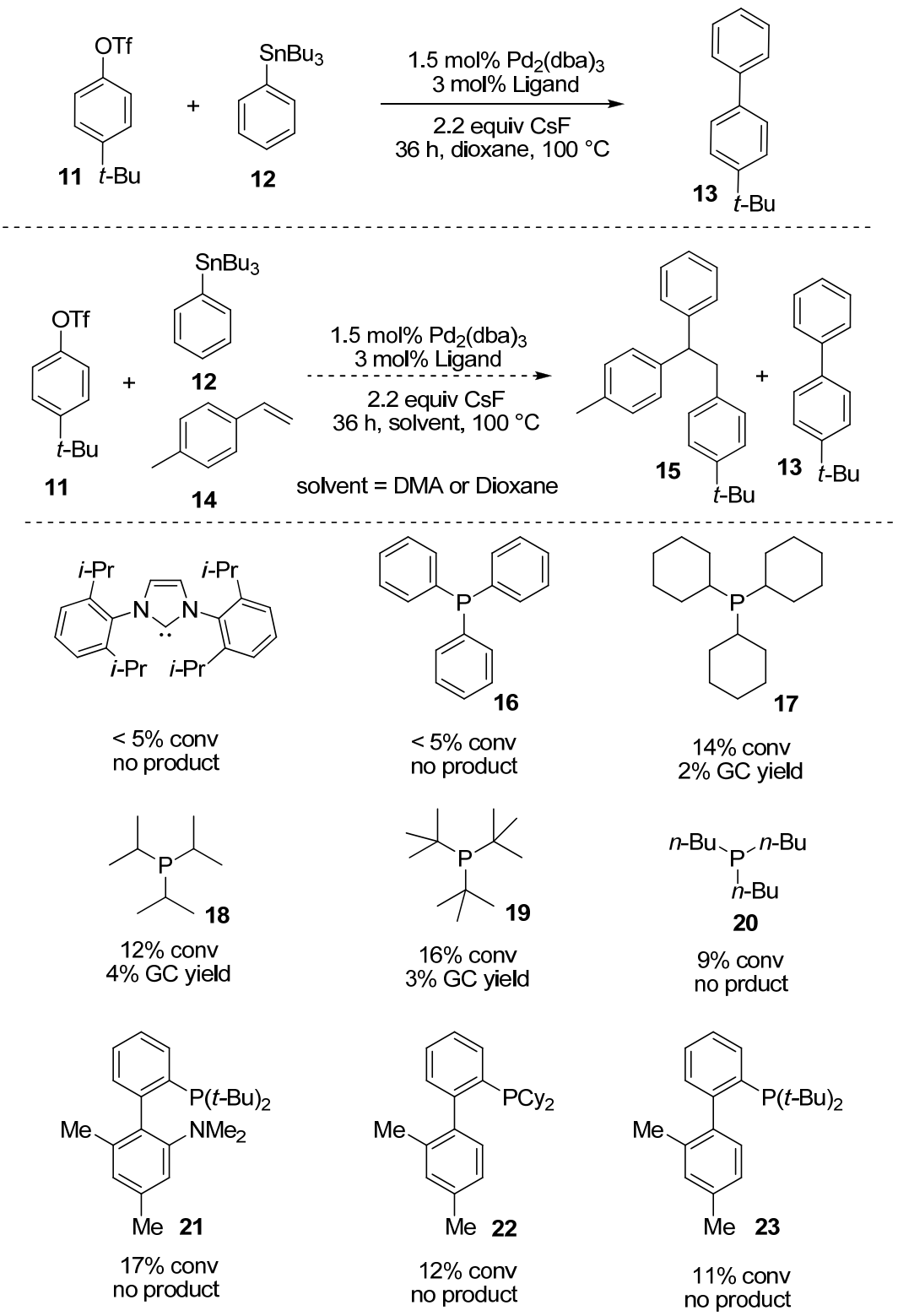


Figure 3.16. Evaluation of different phosphine ligands for the Pd-catalyzed three-component reaction.

One possible reason might be the use of CsF, since F^- could bind to Pd and render it less electrophilic, thus inhibiting product formation. Removal of CsF also did not yield the desired product, and increasing the temperature and/or changing solvent were also ineffective for product formation. Moreover, we did not observe any conversion of starting material or formation of cross coupling products, indicating that the oxidative addition step is potentially prohibitively slow under these conditions.

Fu and coworkers have described that electron rich phosphines such as alkyl phospine facilitate oxidative addition of difficult aryl electrophiles such as aryl chlorides, and alkyl chlorides. Based upon this proposal, we performed the reaction with different electron-rich phosphine ligands, but we did not observe any desired product or conversion of starting materials (Figure 3.16). Other efforts involving changes in the solvent or temperature also did not yield the desired product.

Next, we explored other electrophiles which might undergo oxidative addition under milder conditions. Interestingly, by replacing the aryl triflate with 1-cyclohexenyl triflate using $Pd_2(dba)_3$ and I*i*pr carbene as ligand and DMA solvent, complete conversion of the starting material was observed, and the desired product was isolated in 75% yield (Figure 3.17). However, the isolated product proved to be a 2:1 mixture of regioisomeric products. The 1,1-difunctionalized product is most likely generated *via* β-hydride elimination and reinsertion, which would form a stable π-allyl Pd-complex. This complex could then undergo a second transmetallation and subsequent reductive elimination to yield the 1,1-difunctionalized product.

Although this reaction resulted in poor regioselectivity, it suggested that our concept of generating a cationic Pd^{II}-vinyl intermediate in situ to perform a three-

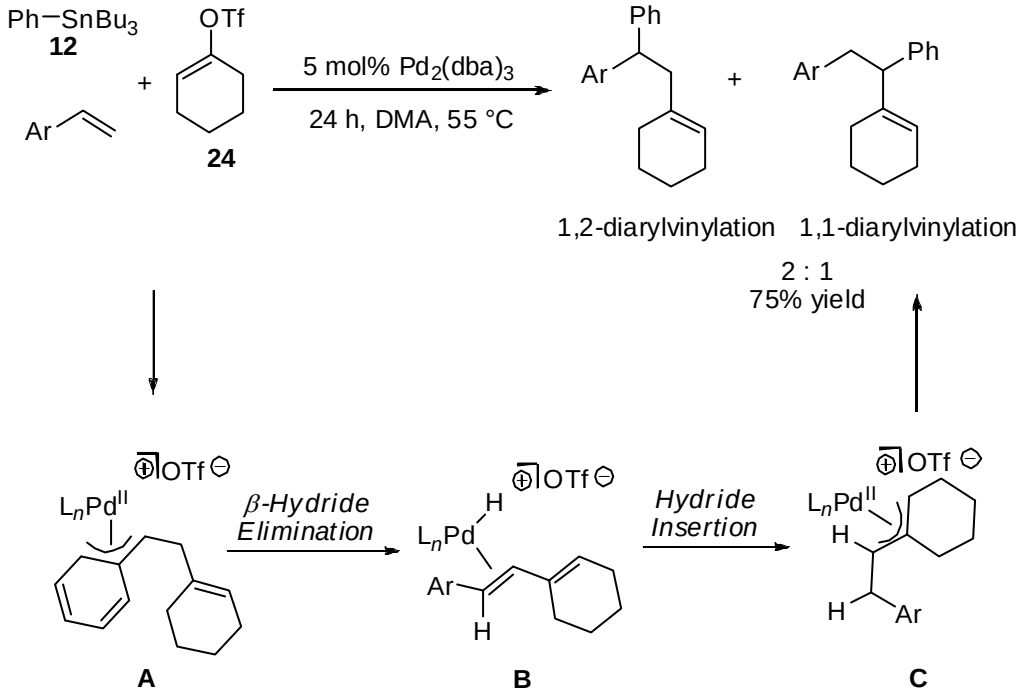


Figure 3.17. Evaluation of cyclichexyl triflate under the Pd-catalyzed condition for the three-component coupling system.

component coupling is possible. In order to avoid the regioselectivity issues, a simple terminal alkene was tested, where intermediate **A** could not be stabilized as a π-benzyl species. We previously reported an oxidative 1,1-diarylation of terminal alkenes using organostannane reagent which only yield the 1,1-diarylation product.[6,7] Excitingly, when 1-nonene was tested as a substrate in the three-component coupling, the reaction gave the expected product in good yield. Furthermore, when optimizing the reaction conditions, it was found that the reaction proceeds in the absence of ligand. Next, the scope of the transformation was explored to synthesize a variety of aryl vinyl methine products under the optimized conditions. A number of olefins bearing functional groups including a chloride, an alcohol, an ester, and a ketone (Table 3.1, Entries 1 - 5) were found to be effective coupling partners under these conditions. Cyclic vinyl triflate derivatives such as N-Boc-5,6-dihydropyridine triflate and 3,6-dihydro-2H-pyran-4-yl triflate are well tolerated. Aryl stannanes containing electron withdrawing as well as electron donating groups are also successfully used (Table 3.2, Entries 6 - 10).

The proposed mechanism (Figure 3.18) for the transformation starts with the oxidative addition of vinyl triflate to Pd^0 generating cationic Pd^{II} intermediate **B**, which can coordinate to an olefin followed by insertion to yield Pd-alkyl intermediate **D.** The σ-lkyl-Pd isomerizes to the more stable π-allyl species through β–hydride elimination and reinsertion via a coordinated alkene **E.** This is proposed to undergo transmetallation to form **G** and subsequent reductive elimination to generate the 1,1-difunctionalized product with an endocyclic double bond.

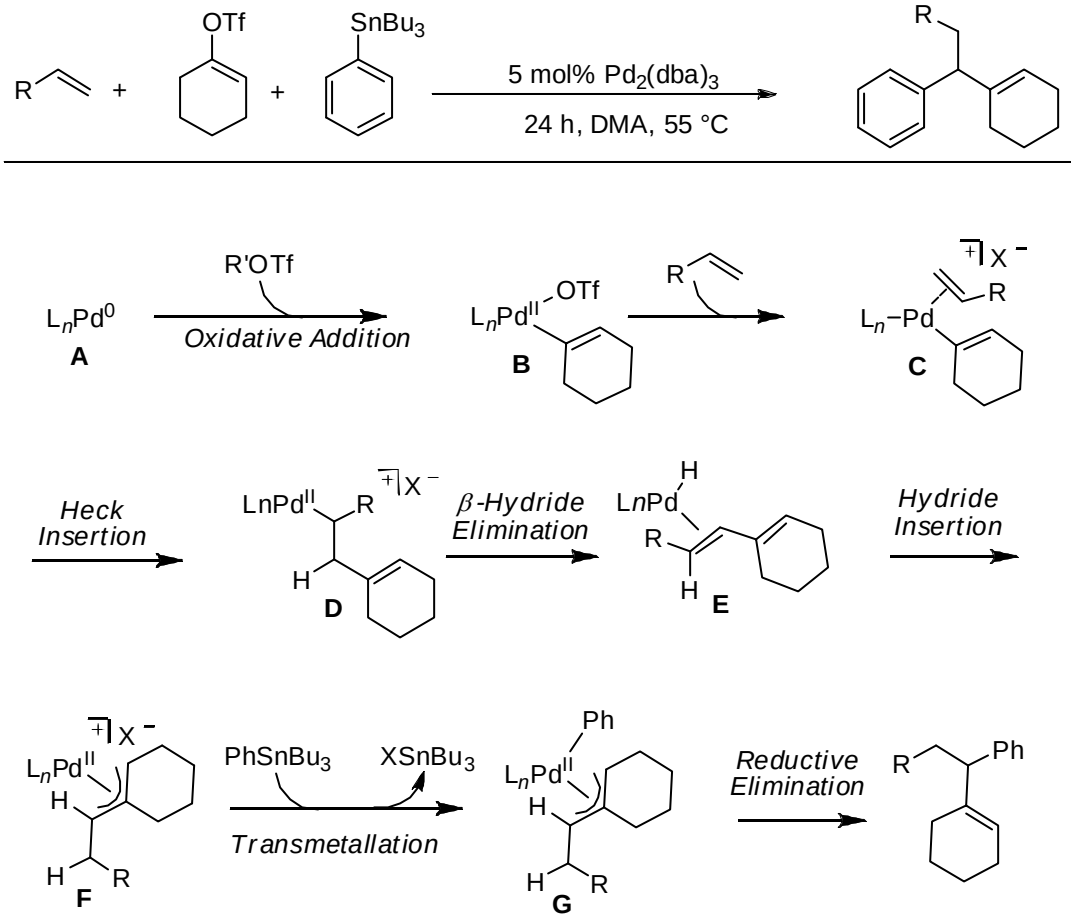
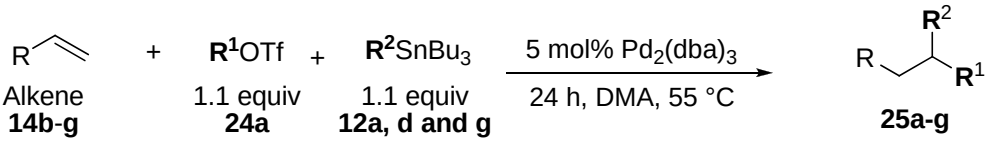
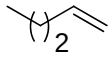
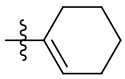
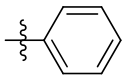
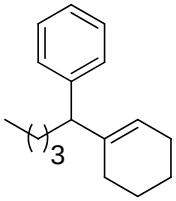
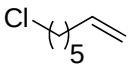
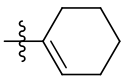
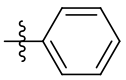
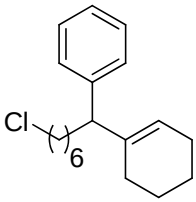
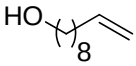
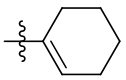
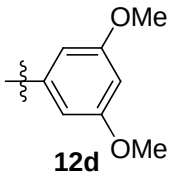
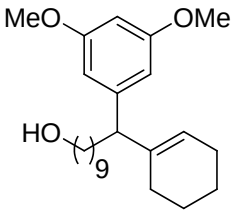
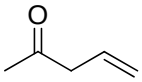
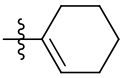
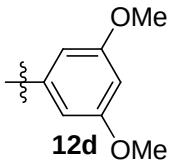
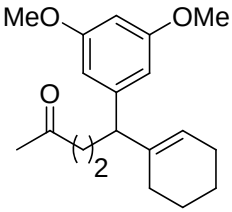
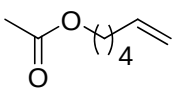
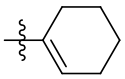
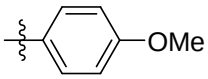
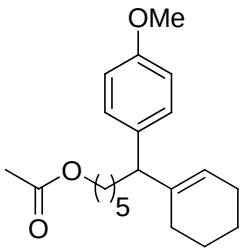


Figure 3.18. Proposed mechanism for Pd-catalyzed three-component coupling reaction.

Table 3.1. Scope of the Pd-catalyzed three-component coupling reaction.

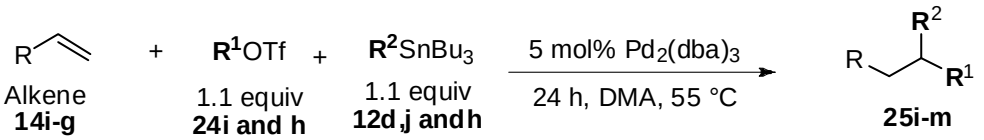


Alkene **14b-g** | 1.1 equiv **24a** | 1.1 equiv **12a, d and g** | **25a-g**

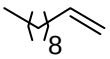
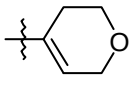
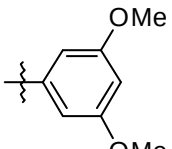
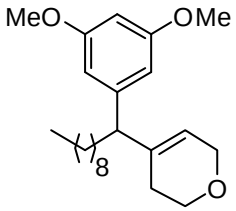
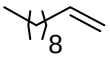
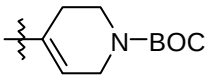
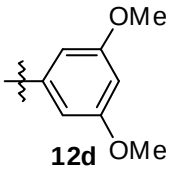
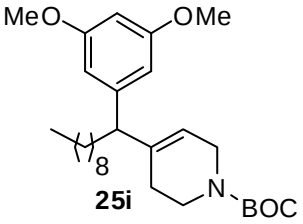
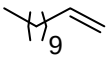
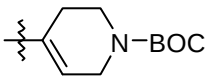
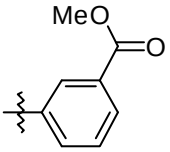
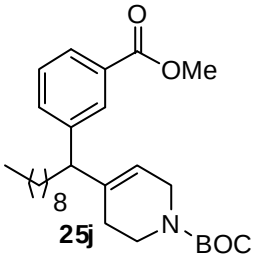
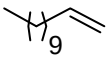
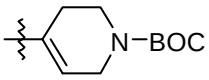
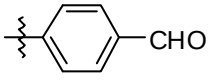
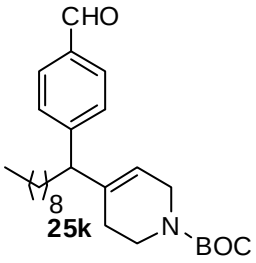
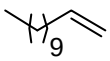
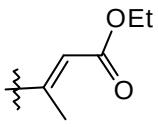
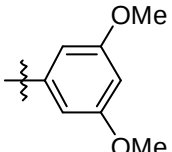
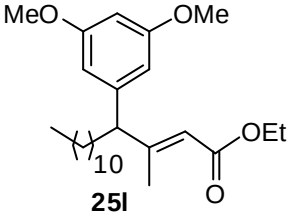
Entry	Alkene	R^1	R^2	Product	Yield (%)[a]
1	 **14b**	 **24a**	 **12a**	 **25b**	75
2	 **14c**	 **24a**	 **12a**	 **25c**	75
3	 **14d**	 **24a**	 **12d**	 **25d**	72
4[b]	 **14f**	 **24a**	 **12d**	 **25f**	74
5	 **14g**	 **24a**	 **12g**	 **25g**	69

[a]Average isolated yield of two experiments performed on 0.5 mmol scale.

Table 3.2. Scope of the Pd-catalyzed three-component coupling reaction.



Alkene **14i-g** | 1.1 equiv **24i and h** | 1.1 equiv **12d,j and h** | **25i-m**

Entry	Alkene	R^1	R^2	Product	Yield (%)[a]
6[c]	 **14h**	 **24h**	 **12d**	 **25h**	63
7	 **14i**	 **24i**	 **12d**	 **25i**	66
8	 **14j**	 **24i**	 **12j**	 **25j**	66
9	 **14j**	 **24i**	 **12h**	 **25k**	63
10	 **14j**	 **24j**	 **12d**	 **25l**	43

[a]Average isolated yield of two experiments performed on 0.5 mmol scale.

Limitations and applications

One of the main limitations of this reaction was the requirement for the use of symmetrical cyclovinyl derived triflate, when evaluating α-styrenyl triflate **26** in this reaction, regio-isomeric olefin difunctionationation products are observed. As described in the substrate scope, when utilizing six membered cyclic vinyl triflates, the ratio of endocyclic and exocyclic derived products was > 20:1. However, when testing a five- and seven- membered cyclic vinyl triflate a mixture of these two isomers is observed (Figure 3.19).

Interestingly, when the reaction was performed with phenylstannane **12a**, cyclohexenyl triflate **24a** and a balloon of propene gas **27**, we were able to isolate 56% of the desired product, which highlights the potential utility of this methodology to use simple commodity chemicals. Attempts to use tethered alkene triflates to perform a three-component coupling in intramolecular fashion were performed by a postdoctoral researcher, Dr. Ranjan Jana. When synthesized the tethered alkene triflates (**29** and **30**), generate the five- and seven-membered cyclic compound and tested under this condition, we did not observe any expected product; however, organostannane tethered olefin **31** gave the desired cyclic product **32** in 55 % yield (Figure 3.20).

The development of this system, which efficiently couples three-components together, sets a stage for the discovery of other new transformations. For example, fourth year graduate student Longyan Liao found that using a terminal 1,3-diene **33** instead of a terminal olefin, the 1,2-difunctionalized products **34** are isolated. Moreover, Longyan Liao expanded this methodology to the use of arylboronic acids as the transmetallating agent (Figure 3.21).

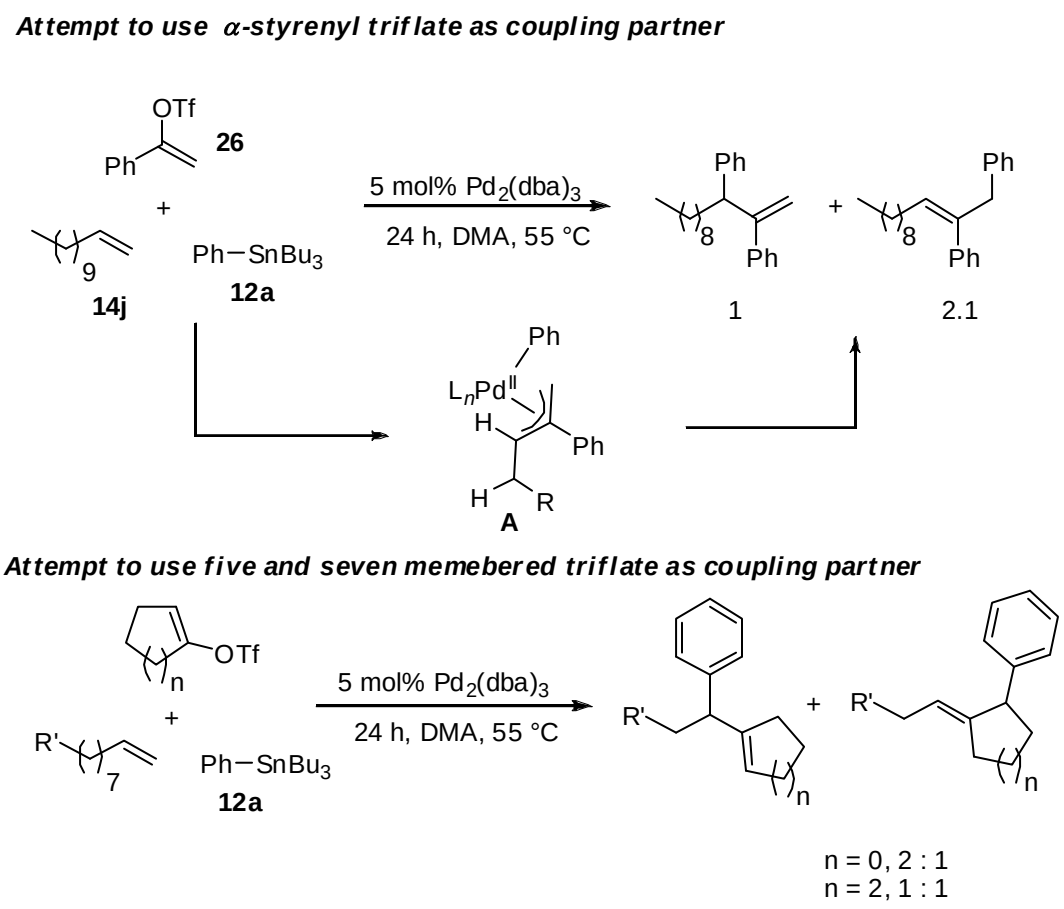
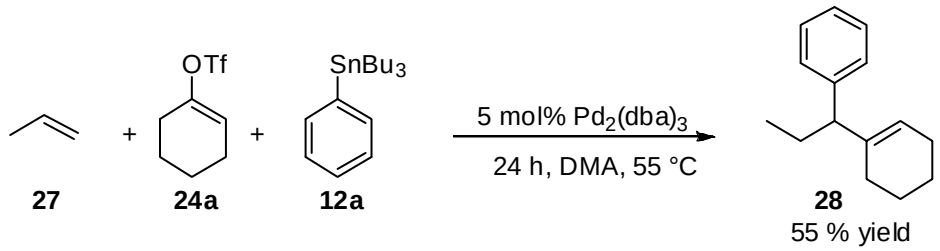


Figure 3.19. Pd-catalyzed three- component coupling reaction that utilizes α-styrenyl triflate, five and seven- membered cyclic vinyl triflates.

Attempt on the propene gas



Expand the Scope to Include therthed alkene trifate

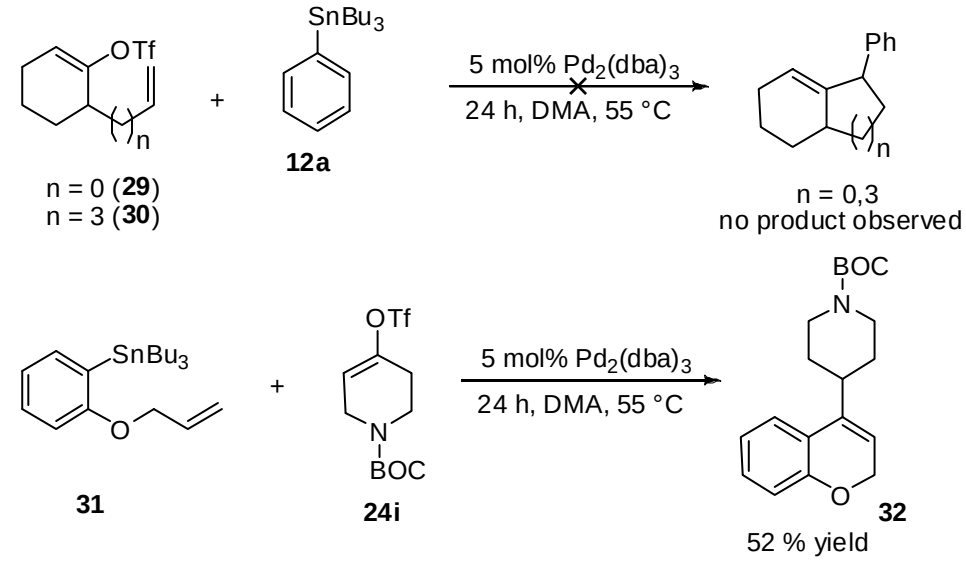


Figure 3.20. Chemical propene gas can be used in the three-component coupling reaction and the expansion of substrate scope to use tethered organostannane reagent with alkenes.

Attempt on the phenyldiene

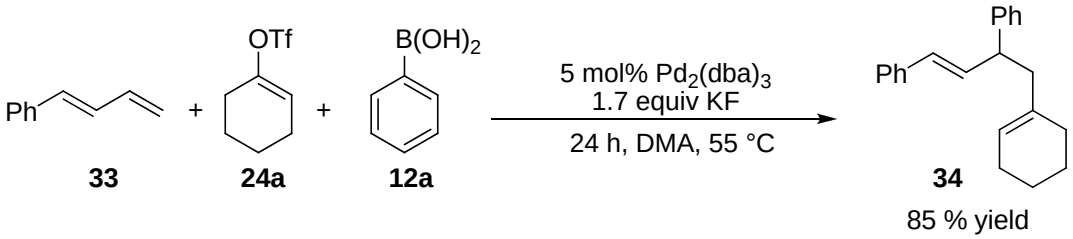


Figure 3.21. Pd-catalyzed three-component coupling reaction that generates 1,2-difunctionalized products.

Conclusion

In conclusion, we have disclosed a new method for the coupling of vinyl triflates, aryl stannanes, and terminal alkenes in a single step by utilizing palladium catalysis. The mechanistic hypothesis for the development of this reaction originated from the oxidative Pd-catalyzed diarylation reaction. The electrophilc Pd-alkenyl species, which is generated from the oxidative addition of vinyl triflate is proposed to be an important intermediate for the success of this three-component coupling reaction. This mechanistic hypothesis will allow for the development new types of reactions.

Experimentals

General considerations

Dry DMA was purchased from Aldrich, THF was dried by distilling from sodium benzophenone ketyl. CH_2Cl_2 and triethylamine (TEA) were dried by distilling from calcium hydride. All styrenes and simple alkenes are purchased from Aldrich or Acros and were purified by passing through a small plug of activated alumina. Bu_3SnCl and $PhSnBu_3$ were purchased from Gelest Inc. Palladium(II) chloride was purchased from Pressure Chemicals. $[Pd(allyl)Cl]_2$, $Pd(I\textit{i}Pr)(OAc)_2(H_2O)$[3], and $[Pd(I\textit{i}Pr)Cl_2]_2$[4] were synthesized according to literature procedures. ^{1}H-NMR spectra were obtained at 500 MHz or 300 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.27 ppm and CH_2Cl_2 at 5.30 ppm. ^{13}C-NMR spectra were obtained at 100 MHz or 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.3 ppm. Flash chromatography was performed either using EM reagent silica 60 (230-400 mesh)

or GFS Chemicals activated alumina Brockmann 1. All melting points are uncorrected and were recorded on an electrothermal melting point apparatus. IR spectra were recorded using a FTIR brand instrument and GC/MS were obtained with a HP 5890 (EI) 50:1 split using a DB-5 column. HRMS were obtained with either an ESI or APCI source with an Waters LCT Premier XE. GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 25:1 split.

General procedure for optimization of the Pd^0-catalyzed difunctionalization reaction

In a glove box, 22.8 mg of $[Pd_2(dba)_3]$, (0.025 mmol, 0.005 equiv.) were added to a flame dried Kimble Chase vial equipped with a stir bar. To the vial were then added 2 mL of DMA, and the mixture was stirred for 5 min. To a separate 10 mL vial, 18.5 mg alkene (0.10 mmol, 1.00 equiv.), 21.2 mg of triflate (0.55 mmol, 1.10 equiv.) and 21.2 mg of stannane (0.55 mmol, 1.10 equiv.) were weighed and transferred to the reaction flask and it was rinsed with 1.00 mL of DMA and was added to the reaction vessel and was stirred for 2-3 min at room temperature. The reaction mixture was stirred at room temperature for 24 h. A small aliquot of the 1.00 M solution of **1a** with undecane as the internal standard was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 µL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using response factors (^{1}H-NMR was used to measure the response factors to account for

varying detector response).

General procedure for three-component coupling reaction

(1-cyclohexenylpentyl)benzene (25b). In a glove box, 22.8 mg of $[Pd_2(dba)_3]$, (0.025 mmol, 0.005 equiv.) were added to a 50 mL round bottom flask equipped with a stir bar. To the flask were then added 2.00 mL of DMA and the mixture was stirred for 5 min. To a separate 10 mL vial, 181.5 mg alkene (0.50 mmol, 1.00 equiv.), 216.2 mg of triflate (0.55 mmol, 1.10 equiv.) and 216.2 mg of stanane (0.55 mmol, 1.10 equiv.) were weighed and transferred to the reaction flask and it was rinsed with 1 mL of DMA and was added to the reaction vessel and was stirred for 2-3 min at room temperature. The reaction vessel was then removed from the glove box and was stirred at 55 °C. After 24.0 h, 50 mL of DI water were added to the reaction mixture and the mixture was transferred to the separatory funnel. The aqueous layer was extracted three times with 50 mL of ethyl acetate and all of the organic extracts were combined, washed with 50 mL of brine, and dried over $MgSO_4$. The mixture was filtered and the solvent was removed in vacuo. The product was purified via silica gel flash chromatography by eluting with hexane. For each substrate, this procedure was performed at least twice and the average isolated yield is reported. Yield: 95% (118 mg and 116 mg); R_f = 0.58 w/ Hexanes (silica), PMA stain. IR (neat) cm^{-1}; ^{1}H-NMR (500 MHz, CD_2Cl_2): δ 0.80-1.00 (t, J = 7.7 Hz, 3H), 1.20-1.40 (m, 4H), 1.50-1.60 (m, 4H), 1.65-1.82 (m, 4H), 2.01-2.10 (m, 2H), 3.10-3.12 (t, J = 7.7 Hz, 3H), 5.60-5.65 (s, 1H), 7.15-7.24 (m, 3H), 7.25-7.34 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.1, 21.2, 23.5, 25.8, 27.0, 30.1, 30.1, 32.8,

53.4, 121.5, 126.1, 128.2, 128.3, 141.0, 145.1[5]; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 453.1478 obsd.: 453.1476.

(11-chloro-1-cyclohexenylundecyl)benzene (25c). The same procedure used to synthesize **3a** were used except 94.4 mg 11-chloro-1-undecene (0.50 mmol, 1.00 equiv.), was added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 95% (118 mg and 116 mg); R_f = 0.58 w/ Hexanes (silica), PMA stain. IR (neat) 2923, 2853, 1492, 1449, 1307, 1136, 1031, 919, 724, 699 cm^{-1}; ^{1}H-NMR (500 MHz, CD_2Cl_2): δ 1.22-1.42 (m, 12H), 1.42-1.59 (m, 2H), 1.60-1.75 (m, 3H), 1.76-1.98 (m, 6H), 2.17-2.22 (m, 2H), 3.19-3.22 (t, *J* = 7.7 Hz, 1H), 3.60-3.70 (t, *J* = 7.7 Hz, 2H), 5.70-5.78 (s, 1H), 7.28-7.39 (m, 3H), 7.40-7.51 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 23.0, 23.4, 25.8, 27.0, 27.2, 28.2, 29.2, 29.7, 29.8, 29.8, 30.1, 33.0, 45.5, 53.3, 121.5, 126.1, 128.2, 128.3, 141.0, 145.2; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 411.2875 obsd.: 411.2873.

11-cyclohexenyl-11-(3,5-dimethoxyphenyl)undecan-1-ol (25d). Procedure used to synthesize **3a** was used except 85.15 mg of 10-undecen-1-ol (0.50 mmol, 1.00 equiv.) and 235 mg of tributyl(1,3-dimethoxyphenyl)stannane were added and the product was purified via silica gel flash chromatography eluting with 15 % EtOAc/hexanes. Yield: 96% (123 mg and 129 mg); R_f = 0.76 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2923, 2852, 2360, 2340, 1717, 1635, 1593, 1457, 1436, 1203, 1152, 1059, 830, 702, 684 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.20-1.40 (m, 0.0 Hz, 18H), 1.50-1.60 (m, 7H), 1.70-1.81 (m, 4H), 2.01-2.12 (m, 2H), 3.00-3.12 (t, *J* = 7.7 Hz, 1H), 3.60-3.68 (t, *J* = 7.7 Hz, 2H), 3.75-3.81 (s, 6H), 5.60-5.62 (s, 1H), 6.25-6.40 (x, *J* = 0 Hz, xxH); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 22.9, 23.4, 25.7, 26.1, 27.0, 28.2, 29.8, 29.9m, 30.1,

32.9, 33.2, 53.5, 55.6, 63.5, 97.7, 106.6, 121.6, 140.3, 147.9, 160.8; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 339.1936 obsd.: 339.1928.

5-cyclohexenyl-5-(3,5-dimethoxyphenyl)pentan-2-one (25f). The same procedure used to synthesize **3a** was used except 49 mg of 5-hexen-2-one (0.50 mmol, 1.00 equiv.) and 235 mg of tributyl(1,3-dimethoxyphenyl)stannane were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 80% (96 mg and 106 mg); R_f = 0.55 w/ Hexanes (silica), PMA stain. IR (neat) 2956, 2922, 2852, 1509, 1222, 830, 550 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 1.51-1.60 (m, 4H), 1.72-1.80 (m, 3H), 1.99-2.10 (m, 2H), 2.11-2.16 (s, 3H), 2.39-2.48 (t, *J* = 7.7 Hz, 2H), 2.98-3.12 (t, *J* = 7.7 Hz, 1H), 3.78-3.80 (s, 6H), 5.58-5.62 (s, 1H), 6.20-6.40 (m, *J* = 6.7 Hz, 3H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.0, 28.1, 28.8, 29.7, 29.8, 29.9, 30.0, 32.3, 52.8, 55.6, 98.0, 106.6, 146.5, 161.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 397.2719, obsd.: 397.2719.

6-cyclohexenyl-6-(4-methoxyphenyl)hexyl acetate (25g). The same procedure used to synthesize **3a** were used except 71 mg of hex-5-en-1-yl acetate (0.50 mmol, 1.00 equiv.), 235 mg of tributyl(4-methoxyphenyl)stannane (0.50 mmol, 1.1 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5% EtOAc/hexanes. Yield: 92% (123 mg and 118 mg); R_f = 0.76 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.20-1.40 (m, 5H), 1.49-1.50 (m, 4H), 1.58-1.70 (m, 4H), 1.70-1.80 (m, 4H), 2.00-2.10 (m, 6H), 3.00-3.08 (t, *J* = 7.7, 1H), 3.78-3.82 (s, 4H), 4.05-4.10 (t, *J* = 7.7 Hz, 2H), 5.58-5.61 (s, H), 6.80-6.89 (d, *J* = 6.7 Hz, 2H), 7.10-7.15

(d, J = 6.7 Hz, 2H) ; ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 21.3, 23.0, 23.4, 26.0, 26.4, 27.0, 28.0, 29.0, 33.0, 52.4, 56.0, 65.0, 114.0, 121.2, 129.0, 130.0, 137.0, 141.0, 158.0, 172.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 353.2093 obsd.: 353.2091.

4-(1-(3,5-dimethoxyphenyl)undecyl)-3,6-dihydro-2H-pyran (25h). The same procedure to synthesize **3a** was used except 85.15 mg of 1-undecene (0.50 mmol, 1.00 equiv.), 235.5 mg of tributyl(1,3-dimethoxyphenyl)stannane (0.50 mmol, 1.1 equiv.), and 127.6 mg of N-Boc-cyclohexyltriflate (0.55 mmol, 1.1 equiv.), were added and the product was purified via silica gel flash chromatography eluting with 50% EtOAc/hexanes. Yield: 87% (131 mg and 120 mg); R_f = 0.27 w/ 50% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2932, 2852, 2360, 1700, 1683, 1635, 1593, 1558, 1540, 1457, 1426, 1340, 1203, 1153, 1129, 1062, 908, 730, 695, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89-0.92 (t, J = 7.7 Hz, 3H), 1.21-1.30 (m, 17H), 1.60-1.75 (m, 1H), 1.73-1.89 (m, 1H), 1.90-1.98 (m, 2H), 3.05-3.19 (t, J = 7.7 Hz, 1H), 3.78-3.82 (s, 6H), 4.18-4.20 (s, 2H), 5.58-5.61 (s, 1H), 6.30-6.38 (d, J = 6.7 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.0, 27.3, 28.1, 29.7, 29.9, 30.0, 30.1, 30.7, 32.3, 32.7, 52.7, 55.6, 65.0, 66.0, 98.0, 106.7, 120.2, 138.5, 146.6, 161.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 508.3403 obsd.: 508.3402.

Tert-butyl4-(1-(3,5-dimethoxyphenyl)undecyl)-5,6-dihydropyridine-1(2H)-carboxylatee (25i). The same procedure to synthesize **3a** was used except 85.15 mg of 1-undecene (0.50 mmol, 1.00 equiv.), 235 mg of tributyl(1,3-dimethoxyphenyl)stannane (0.50 mmol, 1.1 equiv.), and 183 mg of N-Boc-cyclohexyltriflate (0.55 mmol, 1.1 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 10.0 % EtOAc/hexanes. Yield: 55% (74 mg and 77 mg); R_f = 0.54 w/ 10%

EtOAc/Hexanes (silica), PMA stain. IR (neat), 2924, 2853, 1740, 1695, 1593, 1457, 1457, 1364, 1339, 1237, 1204, 1153, 1111, 1058, 984, 829, 768, 697 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 0.82-0.90 (t, *J* = 7.7 Hz, 3H), 1.21-1.38 (m, 15H), 1.42-1.51 (m, 9H), 1.60-1.81 (m, 2H), 1.90-1.98 (m, 1H), 3.05-3.19 (t, *J* = 7.7 Hz, 1H), 3.30-3.55 (m, 2H), 3.78-3.82 (s, 1H), 3.90-3.98 (m, 1H), 5.50-5.61 (s, 1H), 6.30-6.42 (d, *J* = 6.7 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.0, 27.3, 28.1, 28.1, 29.7, 29.8, 29.9, 30.0, 31.0, 32.3, 52.7, 55.6, 65.0, 66.0, 97.9, 106.6, 120.2, 138.5, 147.0, 161.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 478.3297 obsd.: 478.3301.

Tert-butyl4-(1-(3-(methoxycarbonyl)phenyl)dodecyl)-5,6-dihydropyridine-1(2H)-carboxylate (25j). The same procedure to synthesize **3a** was used except 85.15 mg of 1-undecene (0.50 mmol, 1.00 equiv.), 233 mg of tributyl(3-acetylphenyl)stannane (0.50 mmol, 1.1 equiv.), and 183.3 mg of N-Boc-cyclohexyltriflate (0.55 mmol, 1.1 equiv.) were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 80% (92 mg and 80 mg); R_f = 0.56 w/ Hexanes (silica), PMA stain. IR (neat) 2923, 2853, 2360, 1724, 1696, 1586, 1558, 1521, 1456, 1417, 1338, 1279, 1237, 1170, 1108, 1054, 754, 697, 675, 668 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85-0.90 (t, *J* = 7.7 Hz, 3H), 1.03-1.38 (m, 17H), 1.41-1.58 (m, 9H), 1.61-1.79 (m, 1H), 1.80-1.95 (m, 3H), 3.20-3.29 (t, *J* = 7.7 Hz, 1H), 3.30-3.50 (m, 2H), 3.90-3.99 (s, 5H), 5.50-5.61 (s, 1H), 7.35-7.40 (m, 2H), 7.83-7.89 (m, 1H), 7.90-7.93 (m, 1H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.0, 28.0, 29.0, 30.0, 32.3, 32.7, 52.5, 80.0, 128.0, 128.7, 129.4, 130.5, 132.9, 144.3, 167.7; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 415.1885 obsd.: 415.1890.

Tert-butyl4-(1-(4-formylphenyl)dodecyl)-5,6-dihydropyridine-1(2H)-carboxylate (25k). The same procedure to synthesize **3a** was used except 85.15 mg of 1-undecene (0.50 mmol, 1.00 equiv.), 233 mg of tributyl(4-benzaldehyde)stannane (0.50 mmol, 1.1 equiv.), and 183.3 mg of N-Boc-cyclohexyltriflate (0.55 mmol, 1.1 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5% EtOAc/hexanes. Yield: 85% (194 mg and 210 mg); R_f = 0.73 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2923, 2853, 2360, 2339, 1739, 1696, 1604, 1558, 1540, 1418, 1364, 1338, 1237, 1167, 1111, 1046, 843, 732, 667 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85-0.90 (t, *J* = 7.7 Hz, 3H), 1.30-1.40 (m, 18H), 1.41-1.58 (m, 10H), 1.62-1.79 (m, 1H), 1.80-1.95 (m, 3H), 3.20-3.29 (t, *J* = 7.7 Hz, 1H), 3.30-3.50 (m, 2H), 3.89-4.00 (s, 2H), 5.50-5.70 (s, 1H), 7.30-7.40 (d, *J* = 6.7 Hz, 2H), 7.80-7.90 (d, *J* = 6.2 Hz, 1H), 9.89-10.00 (d, *J* = 6.7 Hz, 1H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 23.0, 23.1, 28.0, 28.8, 29.7, 29.8, 29.9, 30.0, 32.3, 32.7, 52.9, 79.9, 129.0, 130.2, 135.2, 151.3, 192.2, 192.3; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 334.1783 obsd.: 334.1785.

(E)-ethyl4-(3,5-dimethoxyphenyl)-3-methylpentadec-2-enoate (25l). The same procedure to synthesize **3a** was used except 57.0 mg of 5-hexenenitrile (0.50 mmol, 1.00 equiv.) and 235 mg of tributyl(1,3-dimethoxyphenyl)stannane were added and the product was purified via silica gel flash chromatography eluting with 2% EtOAc/hexanes. Yield: 55% (68 mg and 75 mg); R_f = 0.53 w/ EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR 500 MHz, $CDCl_3$): δ0.85-0.90 (t, *J* = 7.7 Hz, 3H), 1.20-1.40 (m, 23H), 1.69-1.81 (m, 2H), 2.02-2.09 (s, 3H), 3.20-3.29 (t, *J* = 7.7 Hz, 1H), 3.75-3.80 (s, 6H), 4.10-4.20 (q, 2H), 5.81-5.89 (s,

1H), 6.30-6.32 (d, *J* = 6.7 Hz, 2H), 6.33-6.40 (d, *J* = 6.7 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 14.7, 17.5, 23.1, 28.0, 29.7, 29.8, 30.0, 30.7, 32.3, 32.6, 55.7, 60.0, 98.4, 106.7, 116.2, 144.9, 161.8; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 441.2981 obsd.: 441.2973.

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CHAPTER 4

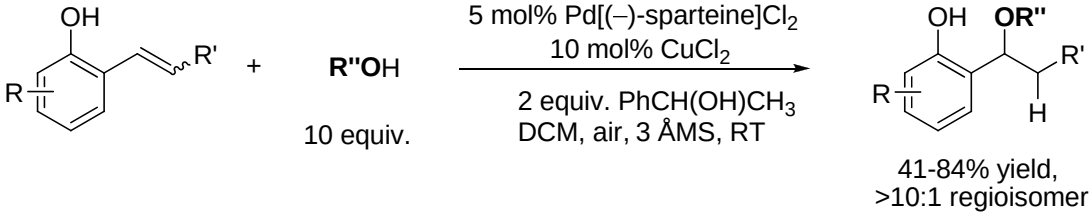
PALLADIUM-CATALYZED HYDROALKYLATION OF STYRENES USING ORGANOZINC REAGENTS UNDER OXIDATIVE CONDITIONS

Introduction

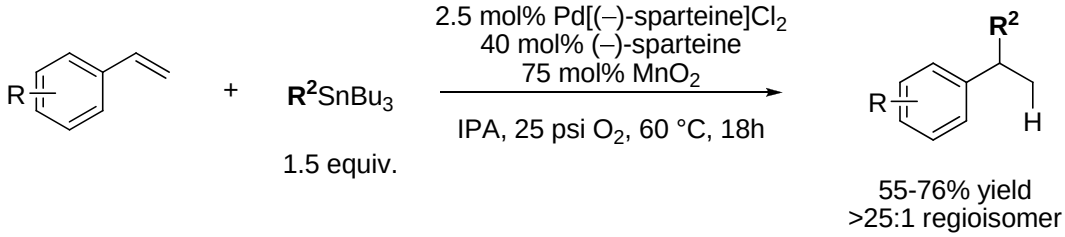
The installation of hydrogen and a functional group across a double bond as in hydroamination, and hydroalkoxylation can lead to highly useful transformations of olefins.[1,2] A recent focus in the Sigman laboratory has been on palladium-catalyzed alkene functionalization reactions, including Pd-catalyzed alkene hydrofunctionalization reactions, such as the hydroalkoxylation and hydroarylation of *ortho*-vinyl phenols and styrenes respectively (Figure 4.1).[3,4] These reactions utilize Pd^{II}-catalyzed alcohol oxidation to generate a Pd^{II}-hydride species, followed by alkene insertion into the Pd-hydride to generate a Pd-alkyl intermediate, which is subsequently functionalized.

Following the development of these alkene functionalization methods, a long standing goal in Sigman lab was to use alkyl nucleophiles as coupling partners with the alkene. However, the challenge associated with these palladium-catalyzed alkene hydrofunctionalization reactions is that Pd-alkyl intermediates, generated from alkene

Hydroalkoxylation of Styrenes Containing a Phenol



Hydroarylation of Styrenes



Hydroalkylation of Styrenes

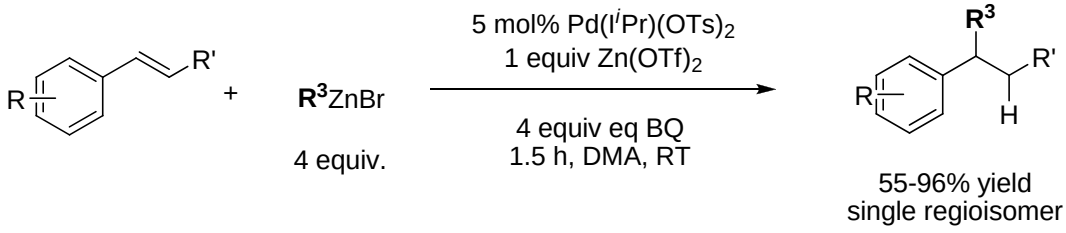


Figure 4.1. Pd-catalyzed alkene hydrofunctionalization reactions that generate hydroalkoxylation, hydroarylation and the hydroalkylation products.

insertion are prone to β-hydride elimination. This issue is more pronounced when an alkyl nucleophile is used in the reaction, which will be discussed later in this section. For this reason, alkene hydroalkylation reactions utilizing simple alkyls as nucleophiles have been explored to a lesser extent. In an effort to address this issue, we developed a mechanistically distinct reaction to explore this alkene hydroalkylation reaction (Figure 4.2). This chapter will briefly outline some important alkene hydrofunctionalization reactions and our approach to address this problem.

Metal-catalyzed alkene hydrofunctionalization

Reaction background and mechanism

A common type of metal-catalyzed hydrofunctionalization reaction involves the activation of the alkene towards nucleometalation followed by protonation to generate the coupling products. Based on this approach, there have been numerous examples of intramolecular[5-7] and intermolecular[8-12] hydrofunctionalization reactions of styrenes, norbornene, alkynes, and Michael acceptors containing various nitrogen-, oxygen-, and carbon-based nucleophiles.

One of first notable contributions towards intramolecular hydroalkoxylation of an unactivated alkene was report by Widenhoefer and coworkers.[13] They reported that a variety of primary and secondary alcohols suitably tethered with an alkene, could be used as a substrate for the formation of heterocycles catalyzed by a Pt^{II} catalyst with a phosphine ligand at 70 °C (Figure 4.2). The proposed mechanism involves the activation of an alkene by Pt^{II} catalyst to form intermediate **A**. Intramolecular nucleophilic addition

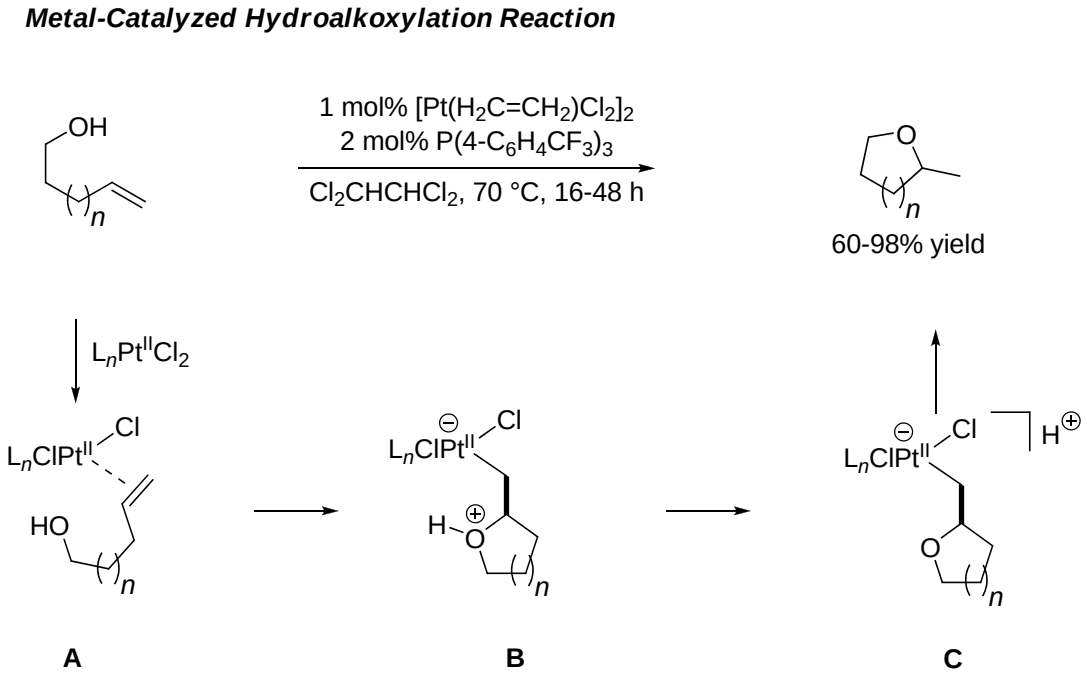


Figure 4.2. Intramolecular metal-catalyzed hydroalkoxylation reaction of unactivated alkenes disclosed by Widenhoefer and coworkers and proposed mechanism of the Pt(II)-catalyzed hydroalkoxylation of unactivated alkenes.[13]

of an alcohol to the Pt-coordinated alkene generates the intermediate **B**, and subsequent ionization forms a contact or solvent-separated ion pair **C**. Finally, protonation of the metal-carbon bond liberates the cyclic ether product and regenerates the active catalyst. Following this report, there have been additional reports of Lewis acid-catalyzed activated alkene hydrofunctionalization reactions involving oxygen and nitrogen nucleophiles.[14-16]

In addition to oxygen nucleophiles, carbon based nucleophiles also have been extensively studied. For example, Darses and coworkers reported a hydroarylation reaction which employs a Ru^{II}-catalyst for the *anti*-Markovnikov addition of a variety of acetophenone derivatives to styrenes.[17] Electron-rich and deficient styrene derivatives can be used under these reaction conditions with acetophenone analogs to generate the desired product with good yield and selectivity. The proposed mechanism for the regio-selective alkene functionalization to generate the *anti*-Markovnikov addition is illustrated in Figure 4.3. The metal catalyst initially is coordinated by the carbonyl and reacts at the *ortho* positon of the arene to generate metal-aryl species **A**. Coordination of the olefin produces the alkene-bound metal complex **B**. Subsequent migratory insertion yields the metal alkyl intermediate **C** and coordination of another arene followed by transfer of a hydrogen atom yields the product. It is proposed that the hydrogen atom is transferred through the C-H activation of another arene through a closed transition state. In addition to the above transformations, there have been number of examples of alkene hydroarylation reactions that generate the *anti*-Markovnikov and Markovnikov product. In 2004, Widenhoefer and coworkers developed hydroarylation that is specific to 2-(4-pentenyl)-substituted indoles.[19,20] In this report, hexenyl-substituted indoles generate the

cis-fused tetracycle in 82% yield as a single diastereoisomer (Figure 4.4).

Although it was initially envisioned as a nucleophilic attack of the indole on a platinum-complexed olefin followed by protonation, this mechanism can either proceed via inner-sphere or outer-sphere pathways. Based on deuterium labeling studies, they determined that it most likely proceeded via an outer-sphere mechanism. This reaction is proposed to proceed via coordination of $PtCl_2$ to an unactivated olefin intermediate **A** followed by the carbopalladation of the olefin tethered indole to generate intermediate **B.** The product and the active catalyst are generated from hydrolysis.[5]

In addition to the Csp^2 nucleophile in the alkene functionalization reaction, Csp^3 nucleophiles were also explored.[21] In 2001, Widenhoefer and coworkers reported the Pd(II)-catalyzed intramolecular hydroalkylation of 3-butenyl β-diketones to form cyclohexanones, which represents the first example of the transition metal-catalyzed hydroalkylation of an unactivated alkene (Figure 4.5).[22] In this reaction they were able to generate a sp^3-sp^3 carbon-carbon bond via hydroalkylation which is considered a challenging bond connection due to the potential β-hydride elimination from the Pd-alkyl intermediate. However, in this transformation they utilized a series of rapid and reversible β-hydride elimination/addition steps to migrate the Pd-alkyl species to a Pd-enolate for the generation of alkyl-alkyl bond. The proposed mechanism proceeds *via* an initial carbopalladation by the anionic β-diketones and the Pd–C bond protonolysis is preceded by a series of rapid and reversible β-hydride elimination/addition steps during which the Pd-alkyl intermediate **C** migrates from the C(4) to the C(6) position of cyclohexyl ring to form Pd-enolate complex **G**. Finally, Pd–C bond protonolysis with the HCl releases the cyclohexanone. Though successful alkene hydroalkylation is achieved it is restricted to 3-

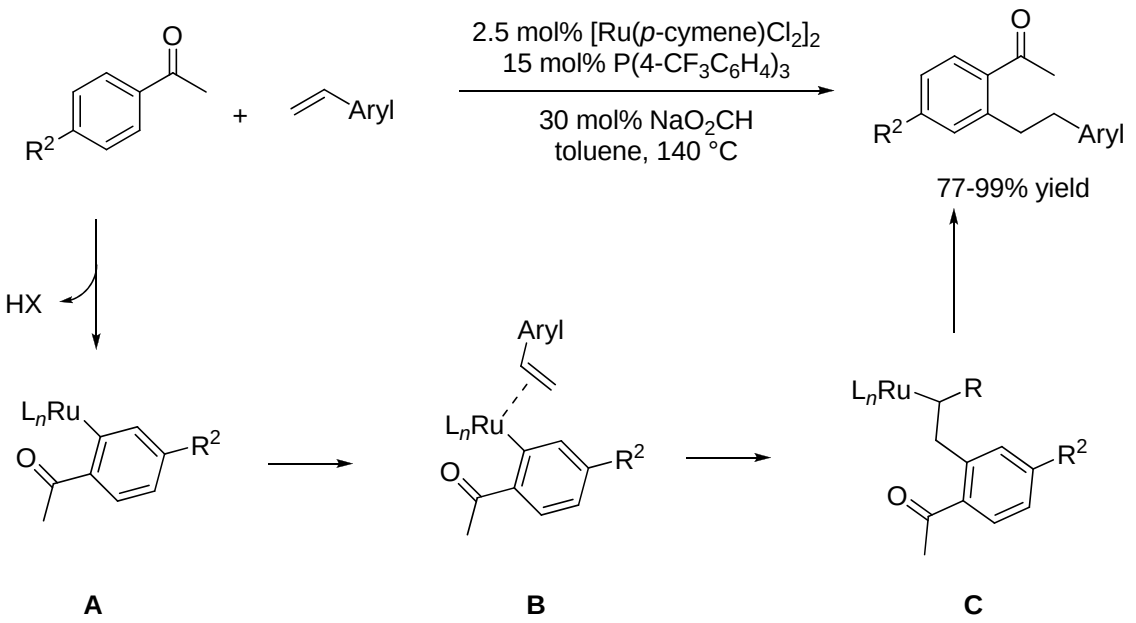


Figure 4.3. Darses and coworkers Ru-catalyzed *anti*-Markovnikov hydroarylation of styrenes and the proposed mechanism for the *anti*-Markovnikov hydroarylation product.[18]

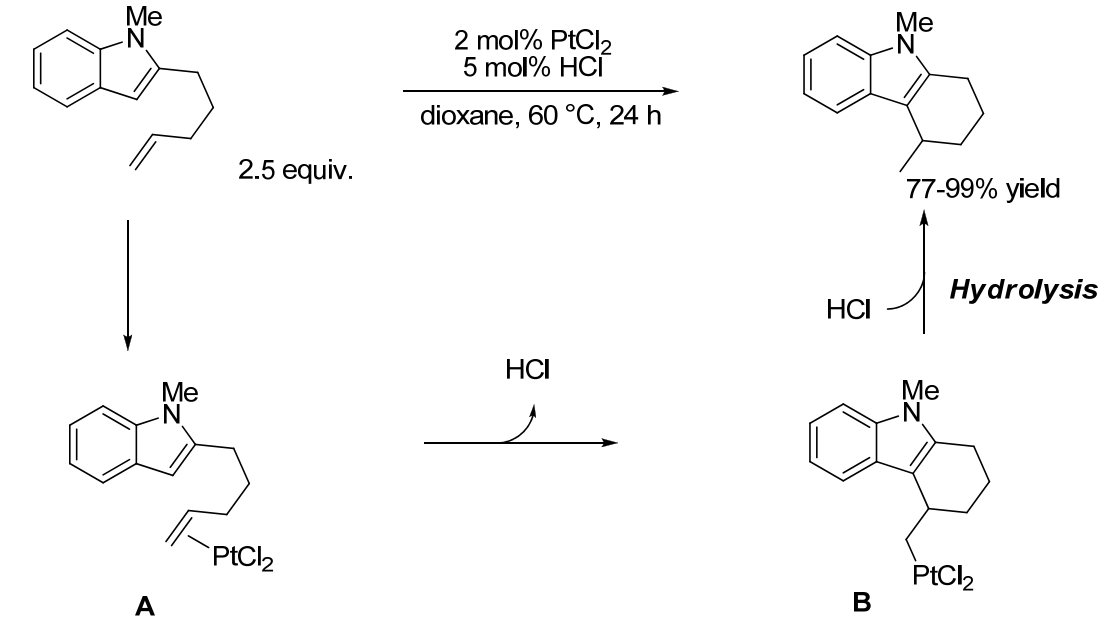
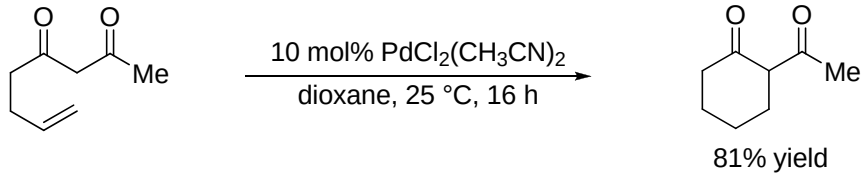


Figure 4.4. Widenhoefer and coworkers hydroarylation of 2-(4-pentenyl)indoles derivatives, which is proposed to proceed *via* carbopalladation of tethered indole followed by hydrolysis.

Reductive Cross-Coupling Reaction



Mechanistic Proposal

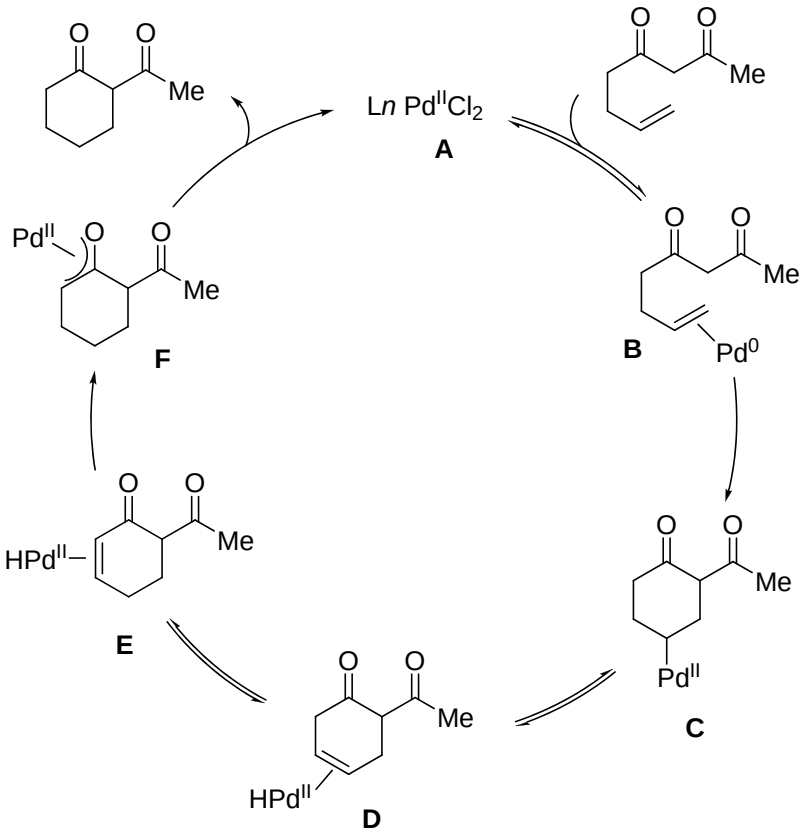


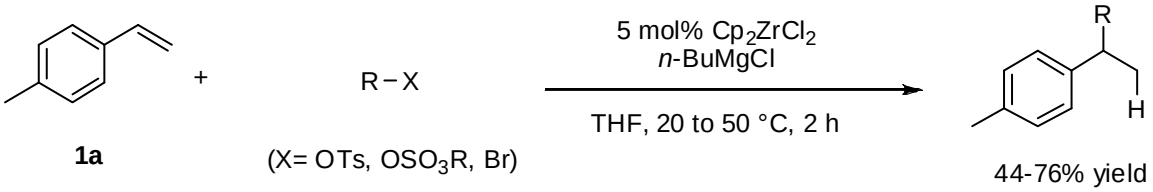
Figure 4.5. The proposed mechanism for Widenhoefer and coworkers hydroalkylation of 3-butenyl β-diketones to form cyclohexanones derivatives.

In addition to nucleometalation followed by protonation mechanism, hydrogen shift from the dialkyl metal is also reported to generate the hydrofunctionalized product[23,24] from butenyl β-diketones substrates. For example, Sonoda and coworkers reported zirconocene-catalyzed alkylation of aryl alkenes with alkyl tosylates, sulfates and bromides. This reaction proceeds under mild conditions using a catalytic amount of a zirconocene complex in the presence of a Grignard reagent to give saturated alkylation products in which an alkyl moiety is introduced in an electrophilic manner at the benzylic carbon atom (Figure 4.6).

The plausible reaction pathway is shown in Figure 4.7. The mechanism begins with the reaction of two equivalents of magnesium bromide and Cp_2ZrCl_2 to afford zirconocene complex **B**, liberation of *n*-butane generates the cyclopropyl zirconate intermediate **C** and subsequent transfer of the conjugated alkene to the cyclopropyl zirconate **C** yields the more stable cyclopropyl zirconate intermediate **D**, which reacts with butyl magnesium chloride to form alkyl zirconate complexes **E**. This intermediate reacts with another equivalent of alkylating reagent at the benzylic carbon leading to the dialkyl zirconocene complex **F**. The successive hydrogen abstraction proceeds exclusively at the less hindered butyl group to afford the corresponding alkylated product along with the Cp_2Zr-butane complex **C** which is used again in the catalytic cycle.

Sigman group reported an alternative methodology for alkene hydroalkoxylation reactions.[3,4,25] One of the notable reactions that was developed by a former graduate student, Dr. Keith M. Gligorich is the Pd-catalyzed aerobic hydroalkoxylation reaction of styrenes containing phenol at the 2 or 4 position on the arene ring under oxidative condition to generate the hydroalkoxylation product (Figure 4.7).[3]

Zirconocene-Catalyzed Alkylation of Aryl Alkenes



Mechanistic Proposal

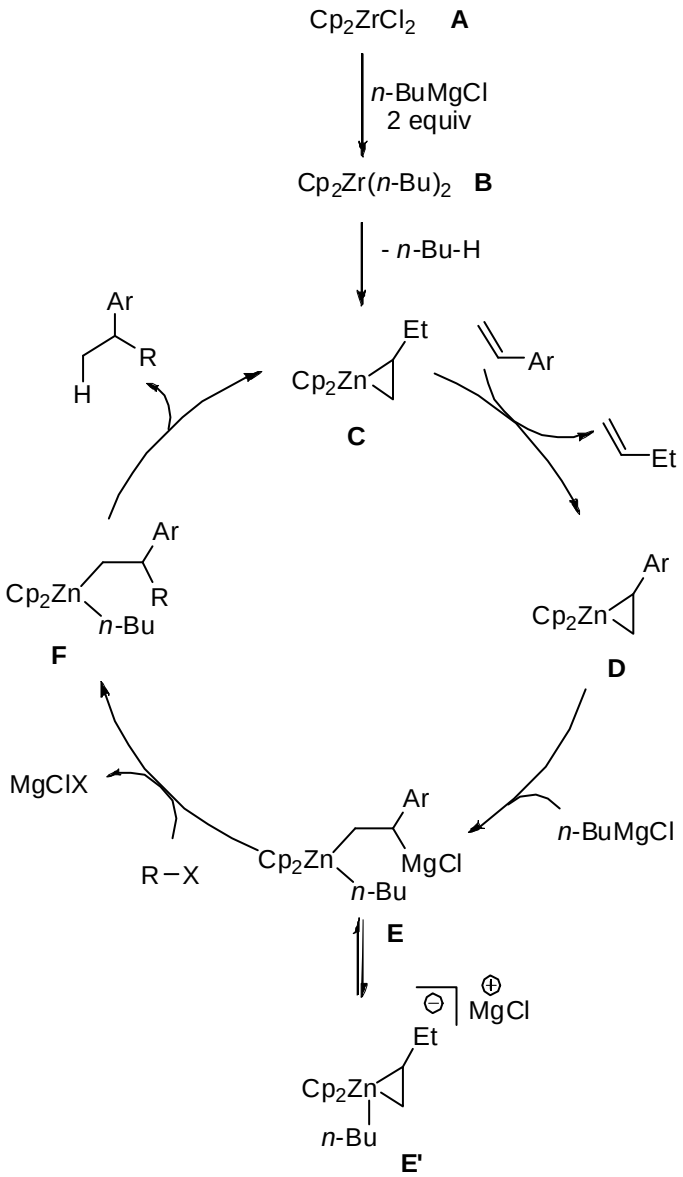
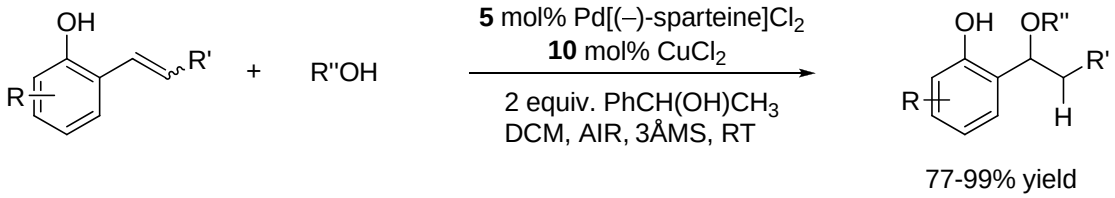


Figure 4.6. The proposed mechanism by Sonoda and coworkers for Zr-catalyzed coupling hydroalkylation of aryl alkenes using alkyl tosylates, sulfates and bromides.

Hydroalkoxylation of Styrenes Containing Phenol.



Proposed Mechanism

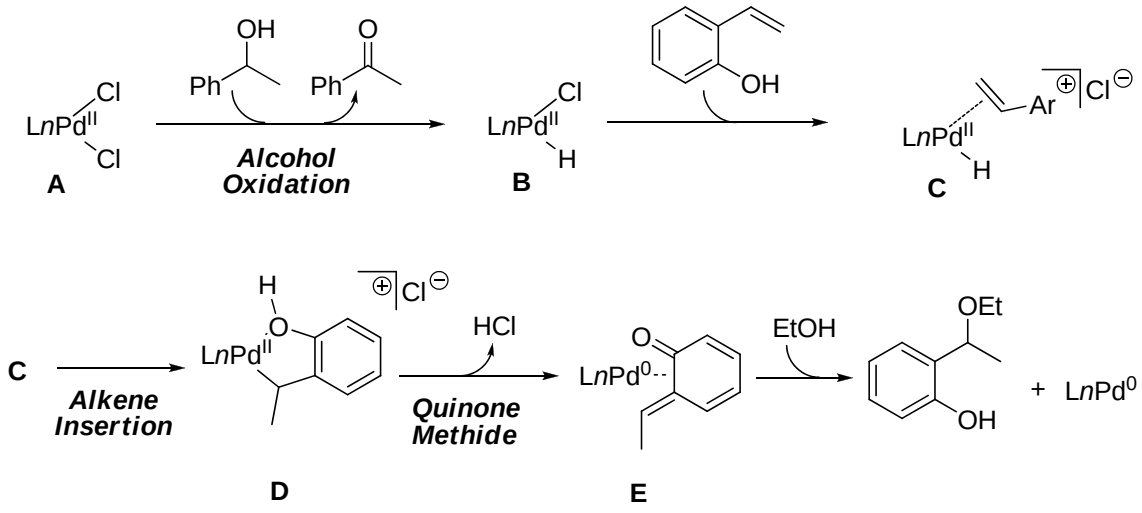


Figure 4.7. Proposed mechanism for Pd-catalyzed alkene hydroalkoxylation reaction.

Mechanistically this reaction differs from the previous method by utilizing a hydride instead of proton source to install a hydrogen atom at one end of the olefin. This mechanism is proposed to begin with oxidation of the alcoholic solvent by the Pd^{II} catalyst **A** to generate a Pd^{II}-hydride intermediate **B.** Coordination of the substrate to **B** generates the alkene bound cationic Pd^{II}-hydride species **C.** Subsequent insertion of the alkene into the Pd^{II}-hydride complex yields the Pd^{II}-alkyl intermediate **D**, which is believed to form an *ortho*-quinone methide intermediate **E** with concomitant reduction of the catalyst.[26] Conjugate addition of alcohol to the *ortho*-quinone methide intermediate generates the carbon-oxygen bond and $CuCl_2$ or O_2 oxidizes the Pd^0 intermediate to regenerate the active catalyst.

In addition to the above reaction, Sigman lab has also developed Pd-catalyzed reductive coupling reactions, which utilize alkenes that do not contain a phenol in combination with an organometallic reagent as a carbon nucleophile (Figure 4.8).[4,27] Similar to the above method, a hydride is employed as the hydrogen source for the installation at the one end of the alkene, which is analogous to protonolysis for hydrogen installation. The proposed mechanism begins with the oxidation of the alcoholic solvent with Pd^{II} catalyst to form the Pd^{II}-hydride intermediate **A**. Coordination and insertion of the alkene into the Pd^{II}-hydride yields the Pd^{II}-alkyl intermediate **B**, transmetallation then forms C and subsequent reductive elimination generates the reductive coupling product**.** In the overall reaction, the sp^2-hybridized carbon centers of the alkene are transformed to the sp^3 center.

All of the alkene hydrofunctionalization reactions discussed have a wide scope in utilizing both nitrogen and oxygen nucleophiles. However, carbon nucleophiles are most

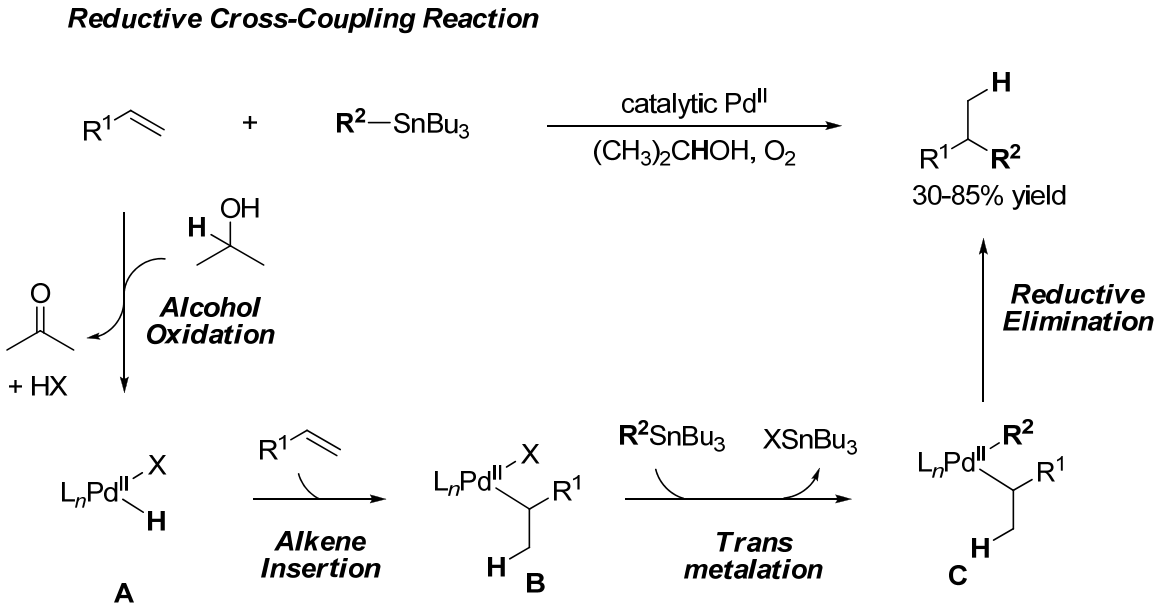


Figure 4.8. Proposed aerobic alcohol oxidation initiated Pd(II)-catalyzed reductive cross-coupling of alkenes and organostannanes and the proposed mechanism.

limited to Csp^2 substrates. As described Csp^3 nucleophiles have limited examples and the reaction condition are usually forcing with a narrow substrate scope. Thus, there is a need to develop new types of alkene hydroalkylation reactions that are more selective and employ milder reaction conditions. This chapter will detail the development of a highly selective Pd^{II}-catalyzed hydroalkylation reaction of styrenes with organozinc reagents used as the transmetallating reagents.

Results and discussion

As discussed above, the Sigman laboratory is interested in developing reductive coupling reactions between alkenes and simple alkyl metal reagents.[28] This reaction requires the regioselective addition of hydrogen and an alkyl group across a double bond. An initial lead for this type of transformation was discovered when $SnBu_4$ was exposed instead of phenylstannnane under the oxidative diarylation system, which was described in Chapter 2 (Figure 4.9).[4,29] When styrene was reacted with tetrabutystannane in presence of 5 mol% Pd(I*i*Pr)$(OTs)_2$ and 25 mol% $Cu(OTf)_2$ in N,N-dimethylacetamide under an O_2 atmosphere at 55 °C, the hydroalkylation product was observed in 25% GC yield as single regioisomer.

The proposed mechanism begins with the transmetallation of one butyl group from tetrabutylstannane to the Pd(I*i*Pr)$(OTs)_2$ to generate the Pd^{II}-alkyl intermediate **B**. The unfunctionalized Pd^{II}-alkyl intermediate undergoes β-hydride elimination to generate a Pd^{II}-hydride species **C** and the olefin side product.[3,25,27] Coordination of styrene roduces the alkene-bound Pd^{II} complex **D**. Subsequent insertion could occur at the α or β-position

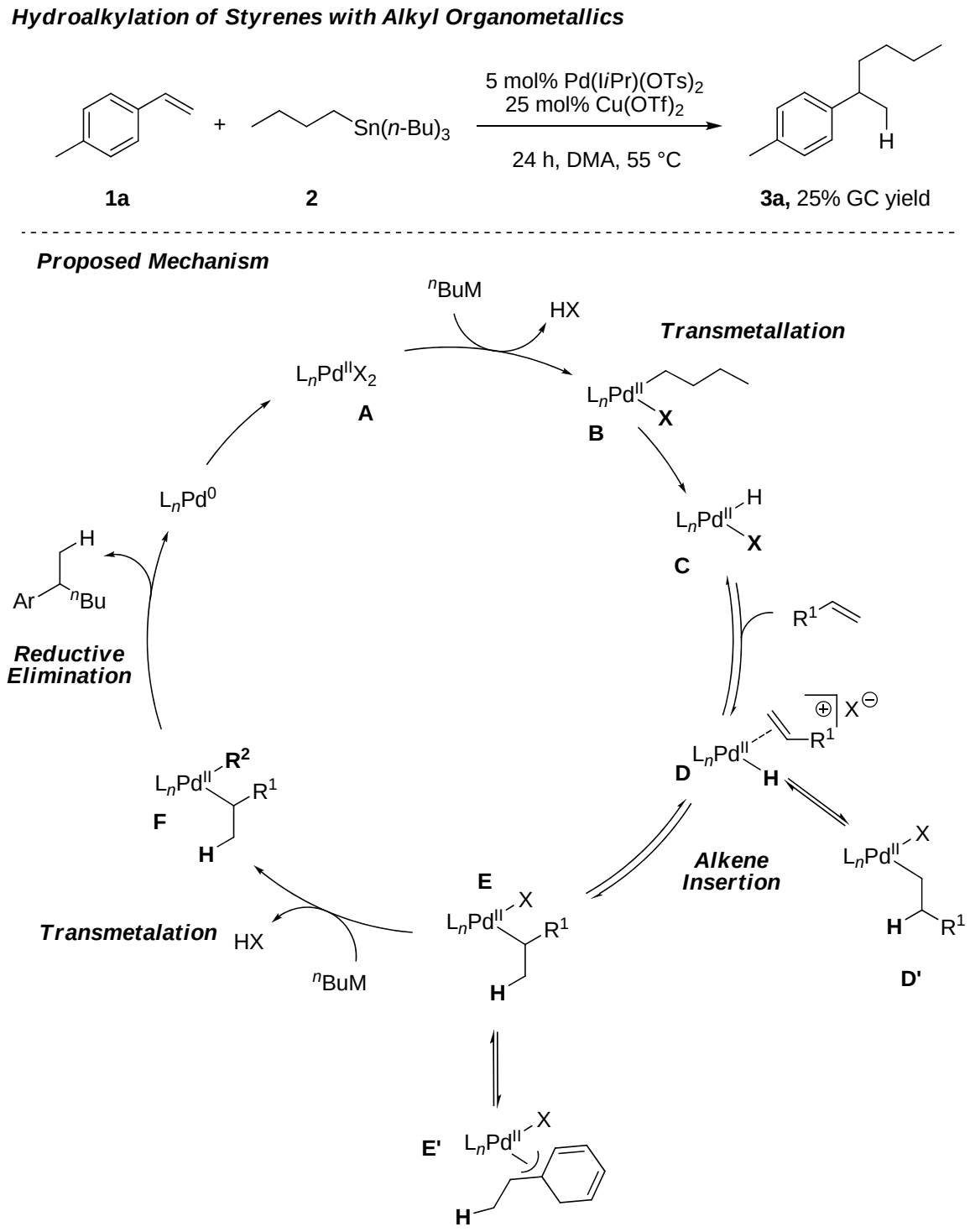


Figure 4.9. Exposure of tetrabutylstannane instead of phenylstannane to the oxidative diarylation catalytic conditions leads to the hydrobutylation product and the proposed mechanism for the hydroalkylation product.

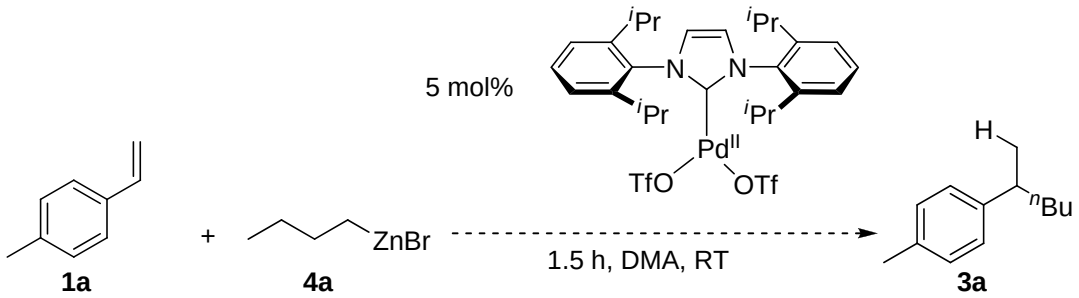
of the styrene, the insertion at the β position leads to an unstabilized Pd^{II}-alkyl intermediate **D'**, which can undergo β-hydirde elimination to regenerate the same intermediate **D**. In contrast, the insertion at the α-position leads to a Pd^{II}-alkyl intermediate **E,** leads to a π-benzyl species **E'**. It is proposed that this process allows sufficient time for the second transmetallation to occur before β-hydride elimination, and thus can lead to the dialkyl Pd^{II} intermediate **F**. Subsequent reductive elimination would then generate the hydroalkylation product.

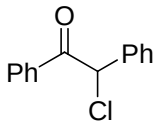
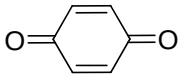
Though the result of hydroalkylation was interesting, the use of the organostannane reagent was not attractive because a minimum of eight equivalents of the alkyl electrophile was needed for the synthesis of the corresponding alkylstannane reagent.[30] In order to improve the efficiency of this methodology, we turned our attention towards a different transmetallating agent source.

When testing alternative transmetallating agents such as butyl boronic acid[31], butylzinc bromide, and nonyl-B-9BBN[32] with molecular oxygen as the terminal oxidant, only butylzinc bromide gave a trace amount of the desired hydroalkylation product (Table 4.1, Entry 1).[33,34] Moreover, alkylzinc bromides have previously been shown to be efficient transmetallating agents for the alkyl-alkyl cross-coupling under the Pd^0 catalyzed conditions with good functional group tolerance.[35] Therefore, we decided to use butylzinc bromide as a transmetallating agent for further optimization.

Initial screening of the alkylzinc reagent was performed with catalytic $Pd(I\textit{i}Pr)(OTs)_2$ and 25 mol% $Cu(OTf)_2$ in *N*,*N*-dimethylacetamide under an O_2 atmosphere. Though trace amount of product was observed under the aerobic oxidative conditions, standard changes such as a decrease in temperature and a change in solvent

Table 4.1. Substrate scope of the Pd-catalyzed hydroalkylation of styrene derivatives.



Entry[a]	conditions	Conv. (%)[a]	**3a** (%)[b]
1[e]	25 mol% $Cu(OTf)_2$ under an O_2 0 °C to RT	<10	<5
2	2 equiv $Cu(OTf)_2$	<5	<5
3		<5	<5
4		55	42
5	LiCl	14	6
6	LiOTf	23	16
7	$ZnCl_2$	34	22
8	$Zn(OTf)_2$	80	70
9	4 eq *n*-BuZnBr, 1 eq $Zn(OTf)_2$, 4 eq BQ	99	97
10	4 eq *n*-BuZnBr, 1 eq $Zn(OTf)_2$, 4 eq BQ	99	98

[a]Percent conversion measured by GC using an internal standard. [b]GC yield. [c]Reaction proformed at 55 °C

led to no improvement in product yield. So we believed that the alkylzinc reagent might not be compatible with molecular oxygen as the terminal oxidant. Therefore, we evaluated alternative oxidants such as $Cu(OTf)_2$, desyl chloride, and benzoquinone (Table 4.1, Entries 2-4).[36,37] Excitingly, we observed an increase to 42% yield of the hydroalkylation product, when using four equivalents of benzoquinone as the terminal oxidant.

Attempts to further enhance the reaction conversion by modifying the standard reaction conditions such as temperature, solvent, and varying the number of equivalents of benzoquinone did not lead to any improvement in the product yield. However, we found when optimizing this reaction, that the conversion of the starting material was always similar to product yield, suggesting that the starting material is efficiently converting into the product without any major side processes. However, retardation of rate was observed as the reaction progressed, suggesting that either catalyst decomposition or product inhibition was preventing the reaction from going to completion.

We hypothesize that the absence of two protons under these reaction conditions facilitates the oxidation of Pd^0 to Pd^{II} in the presence of benzoquinone, thus inhibiting the catalysis. However, in presence of alkylzinc reagents, the use of a Brønsted acid could lead to the decomposition of the transmetallating agent. Therefore, Lewis acids were evaluated in order to mimic the reactivity of Brønsted acids. A number of Lewis acids such as $ZnCl_2$, LiCl, LiOTf and $Zn(OTf)_2$ (Table 4.1, Entries 5-8) were screened. Excitingly, $Zn(OTf)_2$ (Table 4.1, Entry 8) was found to enhance the performance of the system with a product GC yield of 70% (Table 4.1, Entry 5). It should be noted that this

is the first example of using a Lewis acid instead of Bronsted acid for the oxidation of Pd^0 in presence of benzoquinone.

Additionally, when testing different Lewis acids for the effective Pd^0-oxidation, it was observed that the uses of Cl^- as the counterion from the Lewis acids, such as LiCl, or $ZnCl_2$, slowed the rate of the reaction (Table 4.1, Entries 5-7).[38] It was initially thought that the chloride counterion might exchange with the triflate ion, which could have a harmful effect on catalysis. Previously, we observed that the electrophilic nature of the Pd-complex is crucial for the stabilization of the π-benzyl species, which is essential for the hydroalkylation reaction. It was found that in the commercially available butylzinc reagent it is reported to have some concentration of LiCl, which was thought to be the reason for the reaction inhibition. To test our hypothesis, other sources of BuZnBr which lack chloride ions were evaluated. A halide-free butylzinc reagent was prepared via Rieke zinc using the following procedure: Rieke reactive zinc metal was first prepared by the reduction of zinc chloride with lithium naphthalene in THF. The Rieke zinc was washed three times by using dry THF in order to, remove the excess LiCl from the solution. It was allowed to react with the alkyl bromide in THF at 25 ^oC for 3 h which provided the alkylzinc reagents in excellent yields and purity. The formation of the alkylzinc reagent was monitored by Gas Chromatography. A small aliquot of the alkylzinc solution was removed and added to the 10 mL vial containing 2 mL of 1M HCl solution and 2 mL hexane. The hexane layer was analyzed in the GC and the disappearance of the alkyl bromide was calculated.

When we evaluated the hydroalkylation reaction with the alkylzinc reagents synthesized using Rieke zinc, we observed a significant enhancement in the yield of the

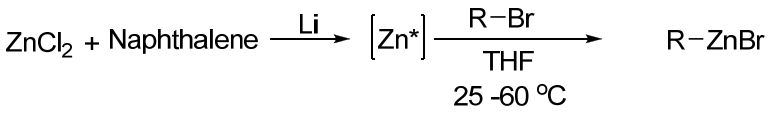
reaction to 97% (Table 4.1, Entry 9). It should be noted that when the Rieke metal was not washed with THF, we observed a decrease in the yield of the product, which might be due to the presence of chloride ion (Scheme 4.1).

Alternatively, BuZnBr can be prepared by using the method reported by Huo.[39,40] In this method, zinc dust was first activated by heating at 80 °C under high vacuum, followed by cooling it to room temperature and treated with a catalytic amount of iodine. DMA and the alkyl halide was then added and refluxed at 80 °C overnight to produce the alkylzinc reagent. This method of synthesizing alkylzinc reagents is simple; moreover, no chloride ion is involved; considering the simple and cost effective procedure, butylzinc bromide based on Huo's method was synthesized and tested under our conditions, we found an excellent yield of 98 % (Table 4.1, Entry 10) and, considering the ease of this route, it was used throughout the remainder of the study.

The substrate scope of the reaction under the optimized conditions was further examined by exploring the nature of the styrene derivative. The major concern in the alkene functionalization is the formation of regioisomers. Interestingly, in all the reactions, we only observed addition of the alkyl group at the α-carbon of the styrene, which highlights the selectivity of this methodology.

Butylzinc bromide gave an isolated product yield of 95% (Table 4.2, Entry 1). A longer alkyl zinc reagent was also tested under this condition and gave 95% yield (Table 4.2, Entry 2). Both electron rich and poor substituents on the styrene (Table 4.2, Entries 2-6) are tolerated and generally lead to high yields as highlighted by a styrene bearing a nitro group (Table 4.2, Entry 5). Also, ortho substituton is allowed with a 93% yield (Table 4.2, Entry 7). Various alkyl zinc reagents were then explored, including the

Scheme 4.1. Preparation of alkylzincs with Rieke zinc (Rieke and coworkers, 1996).



Scheme 4.2. Iodine-catalyzed in situ preparation of alkylzinc reagents (Huo, 2003).

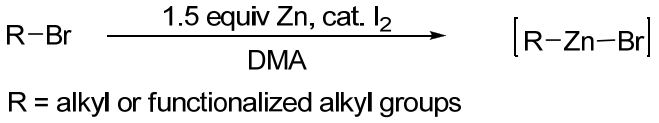
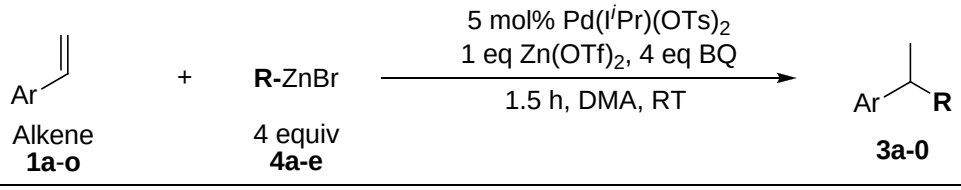
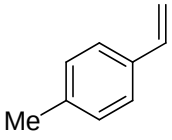
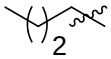
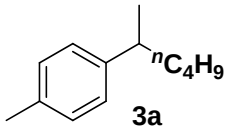
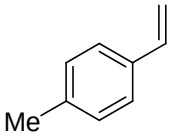
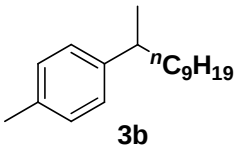
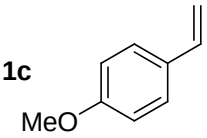
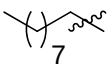
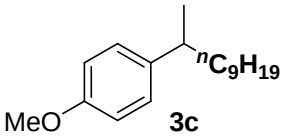
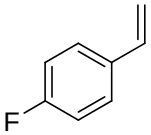
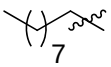
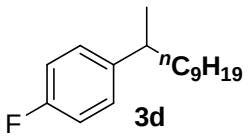
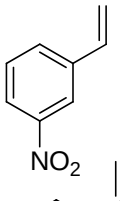
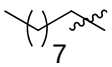
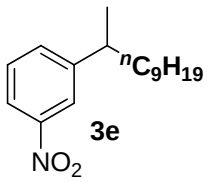
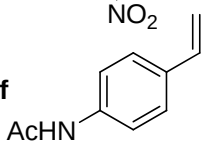
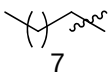
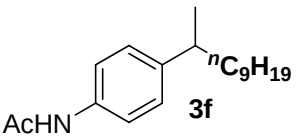
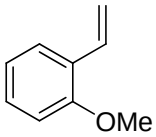
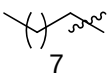
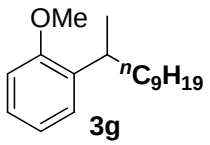


Table 4.2. Substrate scope of the Pd-catalyzed hydroalkylation of styrene derivatives.



Alkene **1a-o** | 4 equiv **4a-e** | **3a-0**

Entry	Alkene	R^2	Product	Yield (%)[a]
1	**1a** 	**4a** 	**3a** 	95
2	**1a** 	**4b** 	**3b** 	95
3	**1c** 	**4b** 	**3c** 	96
4	**1d** 	**4b** 	**3d** 	78
5	**1e** 	**4b** 	**3e** 	55
6[c]	**1f** 	**4b** 	**3f** 	86
7	**1g** 	**4b** 	**3g** 	93

[a]Average isolated yield of two experiments performed on 0.5 mmol scale.

successful use of cyclohexylmethyl zinc bromide, which contains substitution at the β-position (Table 4.2, Entry 1). Functionalized organozinc reagents were examined, TBS protected alcohol was not tolerated, however TBDPS protected alcohol gave 85% yield (Table 4.2, Entry 2), wherein an alkyl chloride gave 76% yield of the hydroalkylation product (Table 4.2, Entry 3) and a less sterically hindered ester such as an ethyl ester did not give useful yields of the product, but pivalate esters were found to be competent coupling partners (Table 4.2, Entry 4). The reaction is not limited to terminal alkenes wherein substituted styrenes, including indene and a β-methyl styrene derivative, undergo the hydroalkylation reaction in good yields (Table 4.2, Entries 6-7). Finally, the reaction of a 1,1-disubstituted styrene proceeds to furnish an all-carbon quaternary center albeit in reduced yield.

To determine the origin of the hydrogen incorporated into the product and to probe our mechanistic hypothesis, a perdeuterated alkylzinc reagent was prepared and submitted to the hydroalkylation reaction conditions. Approximately one deuterium atom is incorporated into the product as determined by ^{1}H NMR spectroscopy, which is consistent with the hydrogen added to the alkene originating from the organozinc reagent. Interestingly, incorporation of deuterium is observed at both the methyl and methine position, which indicates insertion of the alkene occurs from either side, but the resultant Pd-alkyl intermediate **A'** most likely rearranges via β-hydride elimination to the form the more stable π-benzyl intermediate **B'**, which leads to the desired product (Figure 4.10) (Table 4.3). The development of this system, which requires only one equivalent of a sacrificial alkyl zinc reagent, sets the stage for the discovery of future transformations. For example, second year graduate Ryan DeLuca observed *anti*-Markovnikov hydro-

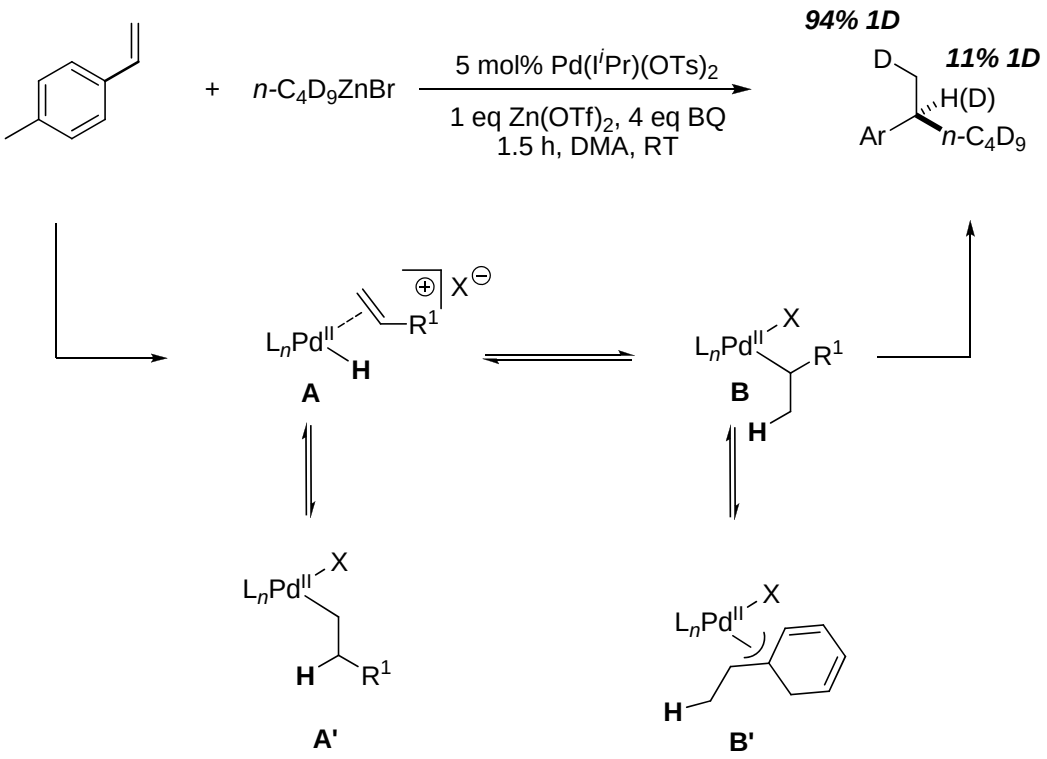
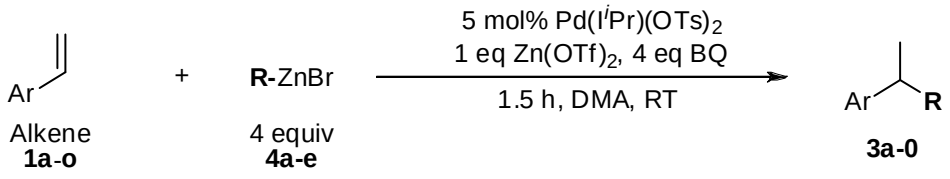
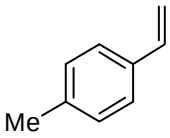
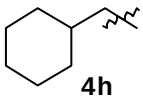
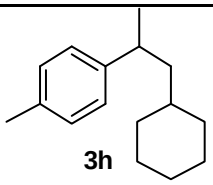
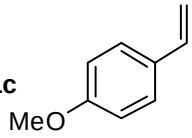
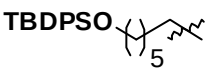
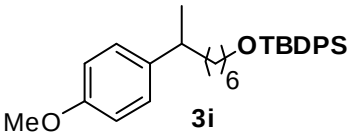
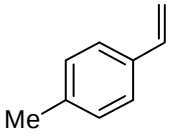
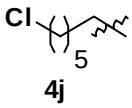
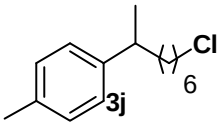
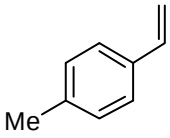
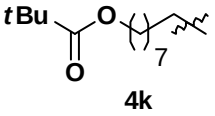
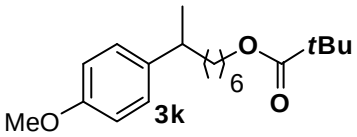
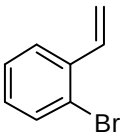
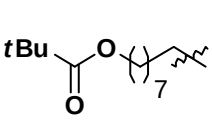
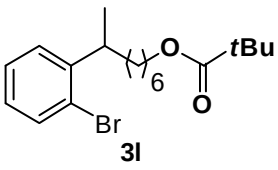
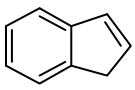
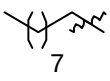
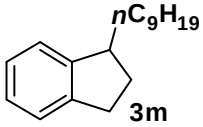
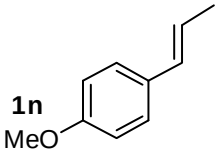
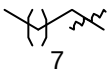
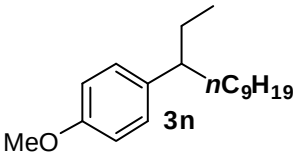
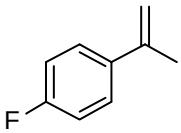
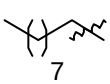
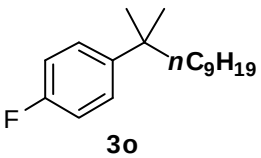


Figure 4.10. Deuterium labeling experiment for the determination of the source of hydride that incorporates into a styrene.

Table 4.3. Substrate scope of the Pd-catalyzed hydroalkylation of styrene derivatives.



Alkene **1a-o** | 4 equiv **4a-e** | **3a-0**

Entry	Alkene	R^2	Product	Yield (%)[a]
1	**1a** 	**4h** 	**3h** 	75
2	**1c** 	**4i** 	**3i** 	85
3	**1a** 	**4j** 	**3j** 	76
4	**1a** 	**4k** 	**3k** 	91
5	**1l** 	**4k** 	**3l** 	55
6	**1m** 	**4b** 	 **3m**	70
7	**1n** 	**4b** 	 **3n**	66
8	**1o** 	**4b** 	 **3o**	43

[a]Average isolated yield of two experiments performed on 0.5 mmol scale.

alkylation product when using allylic phthalimides under the optimized hydroalkylation condition; the proposed regioselectivity is thought to arise from the coordination of pthalimide to the Pd (Figure 4.11).

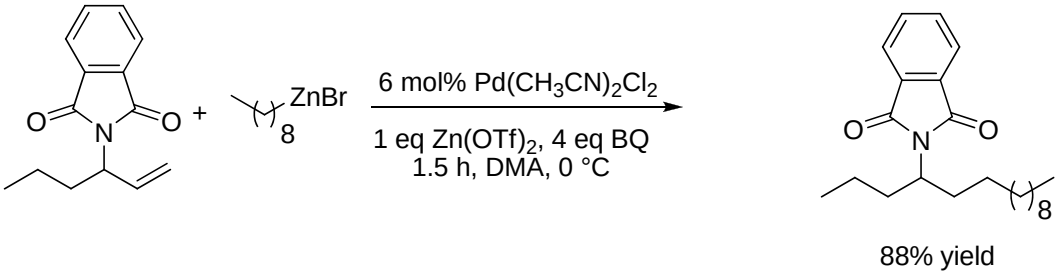
One of the future challenges in the alkene hydroalkylation reaction is identifying a ligand for the asymmetric reaction. Chiral ligands such as (R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binap,(1R,1'R,2S,2'S)-DuanPhos, (R,R)-i-Pr-DUPHOS have been evaluated under the optimized conditions, but no enantioselectivity has been observed. This may be attributed to the presence of DMA as the solvent or to the use of benzoquinone, which has been shown to adversely affect the enantioselectivity by not allowing the chiral ligand to coordinate to the Pd (Figure 4.11).

One of the limitations in the alkene hydroalkylation is the use of primary alkyl zinc reagents. When using secondary alkyl zinc reagents such as cyclohexyl zinc bromide, less than 13 % of the desired product was observed (Figure 4.11).

Conclusion

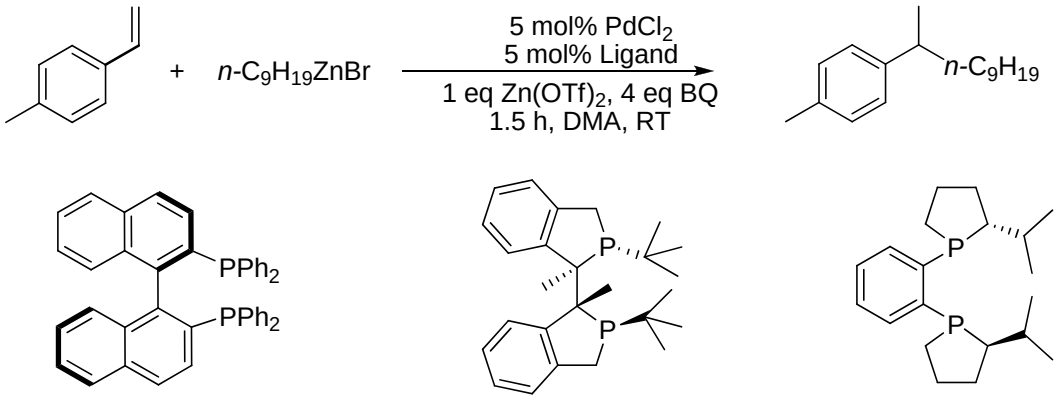
In conclusion, an efficient method to couple secondary and primary sp^3-sp^3 carbon under oxidative Pd-catalyzed condition has been discovered. The ability to form a quaternary carbon center from the 1,1-disubstituted styrenes highlights the scope of the reaction. Isotopic labeling experiments indicate that the hydroalkylation process most likely proceeds by initial transmetallation of the alkylzinc reagent, followed by formation of a Pd-H, which is trapped with a styrene. Future work is focusing on expanding the scope of coupling partners that can be utilized in this process and the development of

Anti-Markovnikov hydroalkylation of allylic phthalimides



88% yield

Attempted enantioselective hydroalkylation

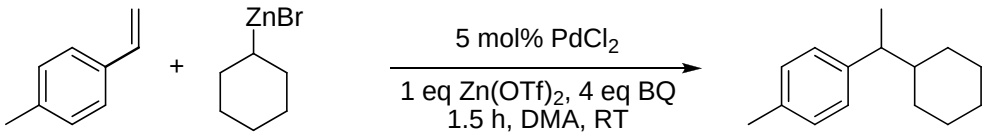


(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binap
67% yield, 0% ee

(1R,1'R,2S,2'S)-DuanPhos
54% yield, 0% ee

(R,R)-i-Pr-DUPHOS
57% yield, 0% ee

Future Scope of the hydroalkylation



13% GC yield

Figure 4.11. Pd-catalyzed alkene hydroalkylation that lead to *anti*-Markovnikov selectivity. Attempts for enantioselective hydroalkylation and the evaluation of secondary alkyl zinc reagent in the hydroalkylation reaction condition.

enantioselective variants.

Experimentals

General considerations

Dry DMA was purchased from Aldrich, THF and CH_2Cl_2 were passed through aluminum column (innovative technology) solvent system. Triethylamine (TEA) was dried by distilling from calcium hydride. Molecular sieves (3ÅMS) were powdered and activated by heating with a Bunsen burner while under vacuum. All styrenes are purchased from Aldrich or Acros. 4-methylstyrenes were purified by passing through a small plug of activated alumina. Bu_4Sn was purchased from Gelest Inc. Palladium(II) chloride was purchased from Pressure Chemicals. $[Pd(allyl)Cl]_2$, $[Pd(I\mathit{i}Pr)Cl_2]_2$[1], $Pd(IiPr)(OTs)_2$[2] and 6-bromohexyl[3] pivalate were synthesized according to literature procedures. ^{1}H-NMR spectra were obtained at 500 MHz, chemical shifts were reported in ppm, and referenced to the $CHCl_3$ singlet at 7.27 ppm. ^{13}C-NMR spectra were obtained at 125 MHz referenced to the center line of the $CDCl_3$ triplet at 77.36 ppm. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). All melting points are uncorrected and were recorded on an electrothermal melting point brand apparatus. IR spectra were recorded using a FTIR brand instrument. HRMS were obtained with either an ESI or APCI source with a Waters LCT Premier XE. GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 25:1 split.

Optimization of the Pd-catalyzed oxidative intermolecular difunctionalized reaction (Table 4.1)

To an oven dried 10 mL sidearm flask equipped with a stir bar, were added 4.2 mg $Pd(IiPr)(OTs)_2$ (0.005 mmol, 0.050 equiv.), 9.1 mg of $Cu(OTf)_2$ (0.025 mmol, 0.250 equiv.), 700 μL of DMA and 200 μL of a 1.00 M solution of 4-methylstyrene (1a) (0.100 mmol, 1.00 equiv.) in DMA, which contained ca. 1% undecane as an internal standard. The flask was installed on a four-neck cow equipped with condensers (repeated three more times to perform four reactions at once) and a three-way joint fitted with a balloon of O_2 was installed on the top of the four-neck cow. The flasks were evacuated via water aspiration and refilled with oxygen three times, and the mixture was stirred vigorously for ca. 5 min at room temperature under O_2. Finally, 100 μL of $SnBu_4$ (0.300 mmol, 3.00 equiv.) was added dropwise to the reaction vessel. The reaction mixture was stirred vigorously under a balloon of O_2 at temperature of 55 °C for 24 h. A small aliquot of the 1.00 M solution of 1a with undecane as the internal standard was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 μL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using response factors (^{1}H-NMR was used to measure the response factors to account for varying detector response).

Optimization of the Pd-catalyzed oxidative intermolecular difunctionalized reaction (Table 4.1)

Entry 1. To an oven dried 10 mL sidearm flask equipped with a stir bar were added 4.2 mg of Pd(IiPr)$(OTs)_2$ (0.005 mmol, 0.050 equiv.), 300 μL of DMA and 100 μL of a 1.00 M solution of 4-methylstyrene (**1a**) (0.100 mmol, 1.00 equiv.) in DMA, which contained ca. 1% undecane as an internal standard. The flask was installed on a four-neck cow equipped with condensers (repeated three more times to perform four reactions at once) and a three-way joint fitted with a balloon of O_2 was installed on the top of the four-neck cow. The flasks were evacuated via water aspiration and refilled with oxygen three times, and the mixture was stirred for 5 min at room temperature under O_2. Finally, 800 μL of nBuZnBr (0.400 mmol, 4.00 equiv.) was added dropwise to the reaction vessel. The reaction mixture was stirred under a balloon of O_2 at ambient temperature for 24 h. A small aliquot of the 1.00 M solution of **1a** with undecane as the internal standard was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 μL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using response factors.

Entry 2. To a 10 mL Kimble Chase vial equipped with a stir bar were added 4.2 mg of Pd(IiPr)$(OTs)_2$ (0.005 mmol, 0.050 equiv.), $Cu(OTf)_2$ (0.200 mmol, 2.000 equiv), 300 μL of DMA and 100 μL of a 1.00 M solution of 4-methylstyrene (**1a**) (0.100 mmol, 1.00 equiv.) in DMA, which contained ca. 1% undecane as an internal standard, the vial was capped and the mixture was stirred for 5 min. Finally, 600 μL of BuZnBr (0.600 mmol, 3.00 equiv.) was added dropwise to the reaction vessel. The reaction

mixture was stirred at room temperature for 24 h. A small aliquot of the 1.00 M solution of **1a** with undecane as the internal standard was analyzed by GC and used to calculate the conversion of the substrate. After 24 h, a 50 μL aliquot of the reaction mixture was removed and filtered through a small plug of silica eluting with EtOAc. The mixture was analyzed by GC and both the conversion of the substrate and the GC yields for the products were calculated using response factors

Entry 3. The same procedure as described for entry 3 was used except desyl chloride was added instead of $Cu(OTf)_2$.

Entry 4. The same procedure as described for entry 2 was used except benzoquinone was added instead of $Cu(OTf)_2$.

Entry 5. The same procedure as described for entry 2 was used except benzoquinone and LiCl was added instead of $Cu(OTf)_2$.

Entry 6. The same procedure as described for entry 2 was used except benzoquinone and LiOTf was added instead of $Cu(OTf)_2$.

Entry 7. The same procedure as described for entry 2 was used except benzoquinone and $ZnCl_2$ was added instead of $Cu(OTf)_2$.

Entry 8. The same procedure as described for entry 3 was used except benzoquinone and $Zn(OTf)_2$ was added instead $Cu(OTf)_2$.

Entry 9. The same procedure was used as described for entry 8, except BuZnBr was synthesized from Reike zinc (washed four times with THF to get rid of LiCl).

*Entry 7.*The same procedure was used as described for entry 8, except BuZnBr was synthesized from activated Zn^0.

General procedure for the synthesis of organozinc reagents

A 25-mL Schlenk flask was charged with 0.98 g of zinc powder (15 mmol, 1.50 equiv.) and heated to 80 °C under high vacuum for 30 min. After back-filling with argon, DMA (to give a total volume of 10 mL) and then 0.76 g of iodine (0.30 mmol, 0.03 equiv.) were added. After the red color of iodine had faded, the freshly distilled alkyl halide (10.0 mmol) were added. The colorless reaction mixture was stirred for 16 h at 80 °C, the disappearance of the alkyl halide and the formation of the organozinc reagent being monitored by ^{1}H NMR. The gray solution (~1.0 M) was transferred into a dry vessel via cannula. These organozinc solutions can be stored at room temperature under a dry atmosphere for several weeks without deterioration.

General procedure for hydroalkylation of styrenes

*1-(hexan-2-yl)-4-methylbenzene (3a).*To a flame dried 50 mL round bottom flask equipped with a stir bar were added 20.9 mg of Pd(IiPr)$(OTs)_2$ (0.025 mmol, 0.005 equiv.), 181.5 mg $Zn(OTf)_2$ (0.50 mmol, 1.00 equiv.), 216.2 mg of benzoquinone (2.00 mmol, 4.00 equiv.). The flask was purged with nitrogen atmosphere for 5 min and then 2 mL of DMA was added. The mixture was stirred for 2-3 min at room temperature. In a dry 10 mL vial 59.1 mg of 4-methylstyrene (0.50 mmol, 1.00 equiv.) was weighed and was transferred to the reaction vessel, which was rinsed with 1 mL of DMA and was added to the reaction vessel and then 2 mL of ~1.0 M *n*-butylZnBr was added slowly to the reaction vessel. The resulting dark drown reaction mixture was stirred at room temperature for 1.5 h. After 1.5 h, 50 mL of DI water and 50 mL of saturated NH_4Cl was

added to the reaction mixture and the mixture was transferred to the separating flask. The aqueous layer was extracted three times with 30 mL of hexane and all of the organic extracts were combined, washed with 50 mL of brine, and dried over $MgSO_4$. The mixture was filtered and the solvent was removed in vacuo. The product was purified via silica gel flash chromatography by eluting with hexane. For each substrate, this procedure was performed at least twice and the average isolated yield is reported. Yield: 95% (85 mg and 83 mg); R_f = 0.58 w/ Hexanes (silica), PMA stain. The ^{1}H-NMR spectrum was compared to a previously reported spectrum.

*1-methyl-4-(undecan-2-yl)benzene (3b).*The same procedure used to synthesize **3a** was used except 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) was added via syringe and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 95% (118 mg and 116 mg); R_f = 0.58 w/ Hexanes (silica), PMA stain. IR (neat) 2955, 2921, 2852, 1514, 1456, 1375, 813, 720, 551 cm^{-1}; ^{1}H-NMR (500 MHz, CD_2Cl_2): δ 0.88 (t, *J* = 3H), 1.71-1.27 (m, 20H), 2.33 (s, 3H), 2.64 (m, 1H), 7.07-7.12 (m, 4H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 14.5, 21.3, 22.7, 23.0, 29.6, 30.0, 30.1, 32.3, 38.8, 39.8, 127.2, 129.3, 135.4, 145.3; MS (ESI/APCI) m/z $(M+109Ag)^+$ calcd.: 355.1395 obsd.: 355.1391.

*1-methoxy-4-(undecan-2-yl)benzene (3c).*The same procedure used to synthesize **3a** was used except 67.1 mg of 4-methoxystyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5 % EtOAc/hexanes. Yield: 96% (123 mg and 129 mg); R_f = 0.76 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2954, 2921, 2852, 1511, 1463, 1244, 1176, 1038, 826 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$):

δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20-1.31 (m, 18H), 1.50-1.59 (m, 2H), 2.60-2.66 (m, 1H), 3.80 (s, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.5, 22.8, 23.0, 28.0, 29.6, 29.9, 30.0, 30.1, 32.2, 38.9, 39.4, 55.5, 113.9, 128.1, 140.4, 157.9m; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 369.1348 obsd.: 369.1351.

*1-fluoro-4-(undecan-2-yl)benzene (3d).*The same procedure used to synthesize **3a** except that 61 mg of 4-fluorostyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 80% (96 mg and 106 mg); R_f = 0.55 w/ Hexanes (silica), PMA stain. IR (neat) 2956, 2922, 2852, 1509, 1222, 830, 550 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.20-1.31 (m, 18H), 1.50-1.59 (m, 2H), 2.61-2.71 (m, 1H), 6.95-7.01 (m, 2H), 7.12-7.16 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 22.8, 23.0, 28.0, 29.6, 29.9, 30.4, 32.2, 38.9, 39.6, 15.1, 128.5, 143.8, 160.4,162.4; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 357.1148 obsd.: 357.1142.

*1-nitro-3-(undecan-2-yl)benzene (3e).*The same procedure used to synthesize **3a** was used except 81.1 mg of 3-nitrostyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5 % EtOAc/hexanes. Yield: 55% (74 mg and 77 mg); R_f = 0.54 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2956, 2922, 2852, 1527, 1377, 1347, 737, 688 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.20-1.31 (m, 17H), 1.56-1.64 (m, 2H), 2.77-2.86 (m, 1H), 7.43-7.47 (m, 1H), 7.50-7.53 (m, 1H), 8.04-8.07 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 22.3,

28.0, 27.8, 29.6, 29.8, 29.9, 32.2, 38.5, 40.1, 121.3, 122.2, 129.4, 133.8, 150.3; MS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 278.2120 obsd.: 278.2126**.**

*N-(4-(undecan-2-yl)phenyl)acetamide(3f).*The same procedure used to synthesize **3a** was used except 80.6 mg of 4-acetamidestyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 50% EtOAc/hexanes. Yield: 87% (131 mg and 120 mg); R_f = 0.27 w/ 50% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.32 (m, 2H), 4.16 (t, *J* = 7.7 Hz, 1H), 6.9-6.9 (m, 6H), 7.1-7.2 (m, 6H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 22.6, 23.0, 24.8, 28.0, 29.6, 29.9, 30.0, 32.2, 39.7, 39.7, 120.3, 127.7, 135.8, 144.4, 168.3; MS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 312.2303 obsd.: 312.2304**.**

*1-methoxy-2-(undecan-2-yl)benzene (3g).*The same procedure used to synthesize **3a** was used except 67.1 mg of 2-methoxystyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5% EtOAc/hexanes. Yield: 92% (123 mg and 118 mg); R_f = 0.76 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.20-1.36 (m, 17H), 1.48-1.57 (m, 1H), 1.60-1.70 (m, 1H), 3.18-3.28(m, 1H), 6.87 (d, *J* = 8.0) 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 7.18 (dd, J = 12.7, 7.4 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 21.3, 23.0, 28.0, 29.7, 29.9, 30.0,

30.1, 32.0, 32.2, 37.4, 55.7, 110.7, 120.8, 126.7, 127.0, 136.5, 157.3; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 369.1348 obsd.: 369.1349.

*1-(1-cyclohexylpropan-2-yl)-4-methylbenzene (3h).*The same procedure used to synthesize **3a** was used except 2 mL of ~1.00 M (cyclohexylmethyl) ZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 80% (92 mg and 80 mg); R_f = 0.56 w/ Hexanes (silica), PMA stain. IR (neat) 2955, 2918, 1513, 1447, 813, 546 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85-0.96 (m, 1H), 1.13-1.25 (m, 7H), 1.37-1.44 (m, 1H), 1.47-1.56 (m, 5H), 1.60-1.74 (m, 1H) 2.35 (s, 3H), 2.78-2.87 (m, 1H), 7.09-7.15 (m, 4H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 21.3, 23.2, 27.0, 33.6, 34.0, 35.3, 36.5, 46.7, 127.1, 129.3, 135.4, 145.5; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 323.0929 obsd.: 323.0933.

tert-butyl(7-(4-methoxyphenyl)octyloxy)diphenylsilane (3i). The same procedure used to synthesize **3a** was used except 67.1 mg of 4-methoxystyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M OTBDPShexylZnBr (2.00 mmol, 4.00 equiv.) was added and the product was purified via silica gel flash chromatography eluting with 2.5% EtOAc/hexanes. Yield: 85% (194 mg and 210 mg); R_f = 0.73 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 2928, 2855, 1511, 1471, 1427, 1245, 1105, 1038, 823, 699, 686, 612 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.15-1.39 (m, 9H), 1.45-1.60 (m, 4H), 2.58-2.68 (m, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.80 (s, 3H), 6.85 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.30-7.50 (m, 1H), 7.63-7.75 (m, 1H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 19.5, 22.8, 26.0, 27.2, 27.9, 29.7, 32.8, 38.8, 39.3, 55.5, 64.3, 113.9, 127.9, 128.1, 129.8, 134.5, 135.9, 140.4, 157.9; MS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 497.2852 obsd.: 497.2853.

1-(8-chlorooctan-2-yl)-4-methylbenzene (3j). The same procedure used to synthesize **3a** was used except 2 mL of ~1.00 M 1-chlorohexyl ZnBr (2.00 mmol, 4.00 equiv.) was added and the product was purified via silica gel flash chromatography eluting with 2% EtOAc/hexanes. Yield: 76% (95 mg and 86 mg); R_f = 0.33 w/ Hexanes (silica), PMA stain. IR (neat) 2954, 2925, 2854, 1513, 1454, 814, 721, 651, 551 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.15-1.50 (m, 9H), 1.50-1.70 (m, 2H), 1.70-1.90 (m, 2H), 2.36 (s, 3H), 3.54 (t, *J* = 6.7 Hz, 2H), 7.05-7.20 (m, 4H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 21.3, 22.8, 27.1, 27.8, 29.2, 32.9, 38.6, 39.8, 45.4, 127.1, 129.3, 135.5, 145.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 345.0539 obsd.: 345.0533

7-(4-methoxyphenyl)octyl pivalate (3k)**.** The same procedure used to synthesize **3a** was used except 67.1 mg of 4-methoxystyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M pivalate-hexyl ZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 5% EtOAc/hexanes. Yield: 90% (140 mg and 149 mg); R_f = 0.61 w/ 10% EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.15-1.35 (m, 19H), 1.45-1.63 (m, 4H), 2.55-2.69 (m, 1H), 2.80 (s, 3H), 4.02 (t, *J* = 6.7 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.9 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 22.9, 26.1, 27.5, 27.9, 28.9, 29.6, 38.8, 39.0, 39.3, 55.5, 64.7, 113.9, 128.1, 140.2, 157.9, 178.9; MS (ESI/APCI) m/z $(M+Na)^+$ calcd.: 343.2249 obsd.: 343.2258.

7-(2-bromophenyl)octyl pivalate (3l). The same procedure used to synthesize **3a** was used except 91.5 mg of 2-bromoostyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M pivalate-hexylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was

purified via silica gel flash chromatography eluting with 2% EtOAc/hexanes. Yield: 55% (68 mg and 75 mg); R_f = 0.53 w/ EtOAc/Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR 500 MHz, $CDCl_3$): δ 1.15-1.52 (m, 9H), 1.52-1.63 (m, 2H), 1.68-1.85 (m, 2H), 2.60-2.80 (m, 1H), 3.50 (t, *J* = 6.7 Hz, 2H), 7.10 (d, *J* = 8.3, 2H), 7.25 (d, *J* = 8.3, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 21.5, 26.1, 27.5, 27.6, 28.9, 29.6, 37.6, 38.2, 64.7, 125.1, 127.5, 127.6, 127.9, 133.1, 146.8, 179.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 351.1242 obsd.: 351.1247**.**

1-nonyl-2,3-dihydro-1H-indene (3m). The same procedure used to synthesize **3a** was used except 58.1 mg of indene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonylZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 70% (90 mg and 83 mg); R_f = 0.55 w/ Hexanes (silica), PMA stain. IR (neat) 2920, 2851, 1476, 1457, 763, 741 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.25-1.50 (m, 16H), 1.66-1.74 (m, 1H), 1.82-1-92 (m, 1H), 2.27-2.35 (m, 1H), 2.82-2.90 (m, 1H), 2.91-2.98 (m, 1H), 3.08-3.16 (m, 1H), 7.14-7.22 (m, 2H), 7.21-7.26 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 23.0, 28.1, 29.7, 30.0, 30.2, 31.7, 32.3, 32.5, 35.4, 45.2, 123.9, 124.7, 126.2, 126.4, 144.3, 148.2 (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 364.9993 obsd.: 364.9977.

1-(dodecan-3-yl)-4-methoxybenzene (3n). The same procedure used to synthesize **3a** was used except 74.1 mg of 1-methoxy-4-[(1E)-1-propenyl]benzene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonyllZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with 2.5% EtOAc/hexanes. Yield: 67% (89 mg and 96 mg); R_f = 0.67 w/ Hexanes (silica), PMA

stain. IR (neat) 2955, 2921, 2852, 1510, 1245, 1176, 1038, 826 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H), 1.03-1.40 (m, 15H), 1.45-1.58 (m, 2H), 1.58-1-72 (m, 2H), 2.28-2.40(m, 1H), 3.81 (s, 3H), 6.50 (t, *J* = 8.4 Hz, 2H), 7.06 (t, *J* = 8.4 Hz, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 12.5, 14.4, 23.0, 27.9, 29.6, 29.9, 30.1, 30.2, 32.2, 37.0, 47.3, 55.4, 113.8, 128.8, 138.4, 157.9; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 383.1504 obsd.: 383.1515

1-fluoro-4-(2-methylundecan-2-yl)benzene (3o). The same procedure used to synthesize **3a** was used except 68.1 mg of 4-fluoroalphamethylstyrene (0.50 mmol, 1.00 equiv.) and 2 mL of ~1.00 M *n*-nonyll ZnBr (2.00 mmol, 4.00 equiv.) were added and the product was purified via silica gel flash chromatography eluting with hexanes. Yield: 43% (58 mg and 54 mg); R_f = 0.76 w/ Hexanes (silica), PMA stain. IR (neat) 3040, 1883, 1601, 1505, 1447, 1414, 1379, 1219, 1156, 1111, 1090, 1038, 1015, 957, 929, 908, 883, 813, 784, 750, 738, 713, 576, 557, 540 cm^{-1}; ^{1}H-NMR(500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.00-1.10 (m, 2H), 1.15-1.35 (m, 18H), 1.55-1-61 (m, 2H), 6.98 (t, *J* = 8.8 Hz, 2H), 7.27-7.31 (m, 2H); ^{13}C-NMR {^{1}H} (125 MHz, $CDCl_3$): δ 14.4, 23.0, 25.0, 29.4, 29.6, 29.9, 30.6, 32.2, 37.6, 45.0, 114.7, 114.9, 127.5, 145.7, 160.1, 162.0; MS (ESI/APCI) m/z $(M+Ag)^+$ calcd.: 371.1304 obsd.: 371.1285**.**

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