MECHANISM OF THE HECK REACTION: NATURE OF OXIDATIVE ADDITION AND ALKENE INSERTION

A Thesis

by

ANTHONY S. EVANS

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

August 2004

Major Subject: Chemistry

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Approved as to style and content by:

Daniel A. Singleton (Chair of Committee)	Stephen A. Miller (Member)
David M. Ford (Member)	Emile A. Schweikert (Head of Department)

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ABSTRACT

Mechanism of the Heck Reaction: Nature of Oxidative Addition and Alkene Insertion. (August 2004)

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Chair of Advisory Committee: Dr. Daniel Singleton

The mechanism of carbon coupling reactions is traditionally represented in a very broad schematic. This thesis seeks to explore the mechanism of these reactions by focusing on Heck olefination. The Heck reaction has become a powerful tool in synthetic labs but the mechanism of this reaction has remained a topic of debate since the reaction's discovery. The catalytic cycle that has come to be accepted, while accurate in its own right, is not nearly as detailed as the complexity of the various stages of the Heck reaction suggest it should be. This study seeks to elucidate the nature of the oxidative addition of aryl halide to a palladium catalyst using a ligand that has been shown to have high activity in facilitating oxidative addition of aryl chlorides and bromides in other coupling reactions. This information is then compared to other studies in the field so that conclusions can be drawn about the oxidative addition. Also, selectivity studies seek to determine the nature of the migratory insertion of an olefin into the Pd-Ar bond. Again, comparison of results obtained in this study are compared to previous results so that a more definitive conclusion can be drawn about the oxidative addition.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation and gratitude to all of my mentors, past and present, as well as to my family and friends.

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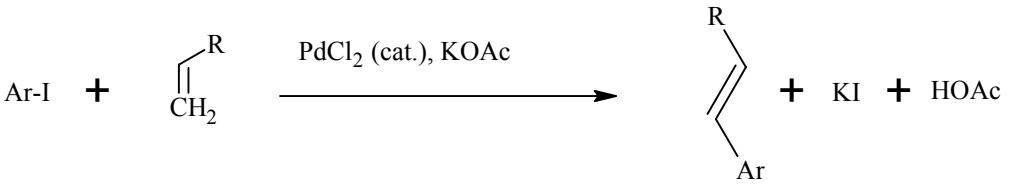
CHAPTER I

INTRODUCTION

Background information on the Heck reaction

Over the last fifty years many new carbon-carbon bond forming reactions have been discovered. Within that broad genus lies the art of coupling reactions (reactions that catalytially bring together two neutral organic precursors). [1,2,3,4,5,6] One important participant in this particular field is the Heck olefination reaction. In its most basic form, the Heck olefination is the palladium catalyzed coupling of an aryl halide and an olefin to afford an aryl alkene. The first example of such a reaction was discovered in 1971 by Mizoroki (sheme 1).[4]

Scheme 1.

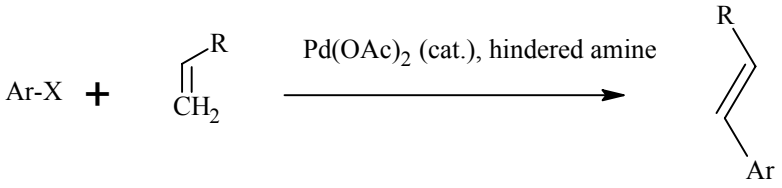


Mizoroki was able to perform the the coupling at 105 ^{o} C in methanol, using potassium acetate as a base in the reaction, and $PdCl_2$ as the catalyst. Without neglecting the importance of this discovery it is important to note the flaws in Mizoroki's system.

This thesis follows the style of the *Journal of the American Chemical Society*.

The reaction conditions for Mizoroki's system were fairly demanding. In particular, the reaction must be conducted in a sealed reaction vessel in order for methanol to reach the desired reaction temperature.

Scheme 2.



In January of 1972, Richard Heck reported an optimized and improved coupling based on the work reported by Mizoroki (Scheme 2).[4] Heck's experimental procedure calls for at 1% catalyst loading of palladium acetate, the olefin, aryl halide, and some hindered amine to act as a base to neutralize HX produced as a byproduct of the catalytic cycle.[1] In this way, Heck demonstrated that the reaction was practical, useful, and reasoably general. This has lead to continuing interest over the past thirty plus years. Since the discovery of this reaction, chemists have discovered ways to alter the original procedure to bend the outcome towards more favorable results for their individual needs.[7,8] The general reaction procedure has largely remained unchanged from the original with the exception of use of ligands to promote catalytic turnover rates as well as to induce stereoselectivity in appropriate substrates.[9,10] Heck

noted in his original paper that $Pd(PPh_3)_4$ had been observed (by Fitton) to form oxidative addition products with a variety of organic halides.[1,11] Heck did not initially use phosphine ligands, but the use of triphenylphosphine would become the standard in his reaction![12] The important oxidative addition observations sparked a whole sub-field of chemistry in reference to C-C coupling reactions. Extrapolation of Fittons work combined with the observations of Heck allowed a tentative mechanism to be proposed. Heck stated, "In the reaction reported herein, a similar oxidative addition apparently occurs between palladium metal and organic halides".[1] He was able to draw this conclusion based upon previous observations of alkyl halide reacting with organomercury compounds and concluded that an oxidative addition is common to both systems.[13] This has become the accepted first step of the reaction. He then stated, "When prepared in the presence of olefinic compounds these organopalladium halides undergo an addition reaction with the olefin, and the adduct decomposes by elimination a hydridopalladium halide, forming the substituted olefinic compound." Professor Heck was astute in his chemical clairvoyance, accurately predicting the mechanism that would become accepted as the years progressed.

The area of palladium catalyzed olefinations still faced many challenges. For instance, while aryl halides containing iodine and bromine were known to work, those that used chlorides did not.[1] This trend encompassed not only olefinations but other palladium catalyzed cross couplings as well. Reactions such as those discovered by Suzuki, Stille, Hartwig-Buchwald[2,3,5,14,15] and others have suffered from the same limitation. Recent developments in palladacycles (Figure 1-1) and other ligand

systems have allowed chemists access to the much less expensive, and more available, organic chlorides in many systems.[16,17] It is clear that this is still a developing field, even after thirty years. Some significant advances have been made with regard to stereocontrol and the ability to form quaternary carbon centers utilizing this reaction.[18,19]

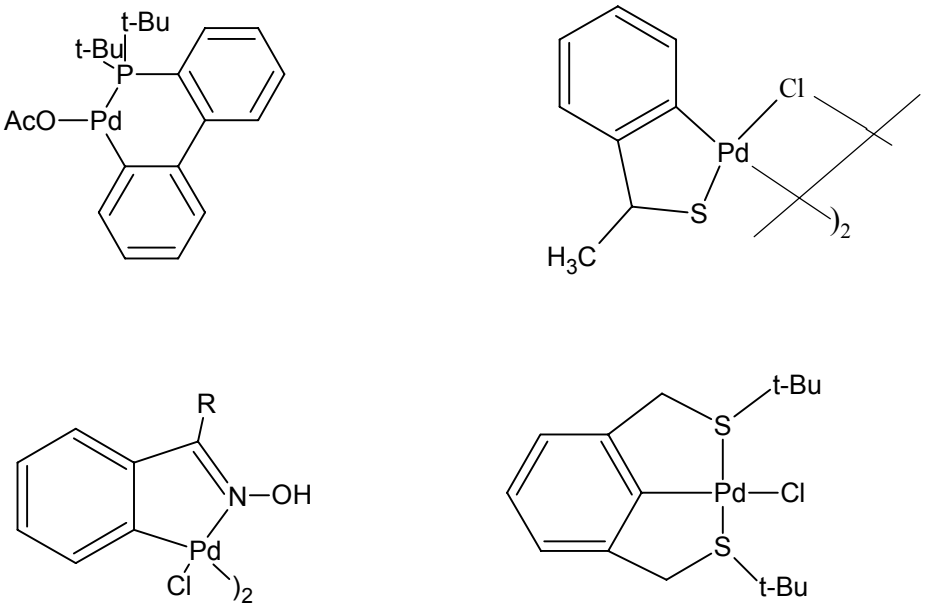


Figure 1-1 Recent example of palladacycles used in cross coupling reactions. Palladacycles have recently been utilized to facilitate the reactions with aryl chlorides.[19,20,21,22]

New advances in catalyst, namely the ligands used in these transformations, have brought about a host of new questions for science to answer. Many problems remain for us to answer such as the nature of the oxidative addition, nature of the

alkene selectivity step, and the mechanistic effect of these new ligands on any and all steps of the catalytic cycle. The research in this thesis seeks to address some of these issues.

Reaction conditions of the Heck reaction

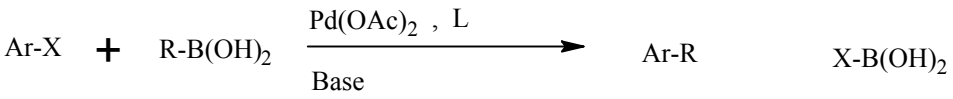
The original reaction conditions that Professor Heck reported are, in some ways, more desirable than those that are commonly used today. In his system, all reactions were carried out on the benchtop, essentially neat, and when heat was required a steam bath was the heat source.[1] Over time, with the development of new ligand systems for the reaction, the conditions have had to evolve as well. It is now very common to see these reactions carried out in some polar solvent (including but not limited to THF, DMF, DMA, dioxane, and even in water mixtures) at elevated temperatures. Generally these solvents must be degassed to protect the integrity of the catalyst or the phosphine ligands, as they will oxidize in the presence of oxygen. $Pd(OAc)_2$ is still commonly used, as well as other Pd sources such as $Pd_2(dba)_3CHCl_3$.[19] The diversity of conditions makes the reaction a challenge for mechanistic study. Small changes in the reaction conditions could have mechanistic implications. The work in this thesis is to gauge the similarity of mechanism under various conditions.

Other reactions involving similar steps

To further understand the Heck reaction, one must also consider those reactions that are similar to it. Some examples of these are the Suzuki, Stille, and Sonogashira,

and the Hartwig-Buchwald couplings.[5,14,15,24] The Suzuki reaction is the reaction between an aryl halide and a boronic acid (Scheme 3).

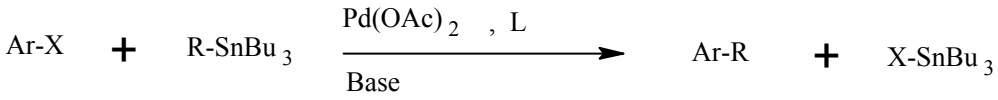
Scheme 3.



L= ligand, usually a phosphine

The reaction conditions are very similar to those used in the Heck reaction. That is, similar solvent systems are utilized, the same catalysts generally work for both reactions, and both reactions require some base be present in order to facilitate reductive elimination.[2,15] The Stille reaction is also quite similar to both the Heck and Suzuki reactions (Scheme 4).

Scheme 4.

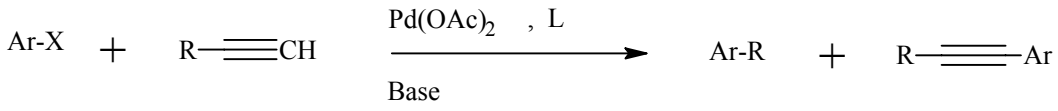


L= ligand, usually a phosphine

The conditions for the Stille again use an aryl halide, palladium/phosphine catalyst, some polar solvent, and base to facilitate reductive elimination. The difference here is that organostannanes are coupled to the aryl halides as opposed to boronic acids or

olefins.[3,14] Also of interest is the Sonogashira coupling. This reaction actually appears to bear the most resemblance to the Heck reaction. In the Sonogashira an alkyne is reacted with the aryl halide with all other reaction conditions remaining fairly similar to the other coupling reactions discussed here, though in some cases a metal cocatalyst is necessary (Scheme 5).

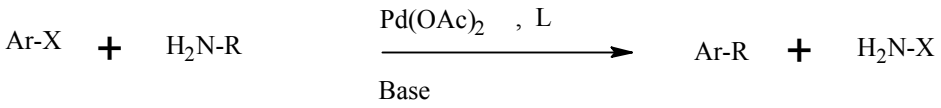
Scheme 5.



L= ligand, usually a phosphine

The similarities drawn between the Sonogashira and Heck reactions are based upon the relationship between alkenes and alkynes compared to the boronic acids, organostannanes, and amines.[24,25] One would suspect that these two species would behave in a similar fashion. However, as we shall see this may not be the case. Finally we should consider the Hartwig-Buchwald coupling (Scheme 6).

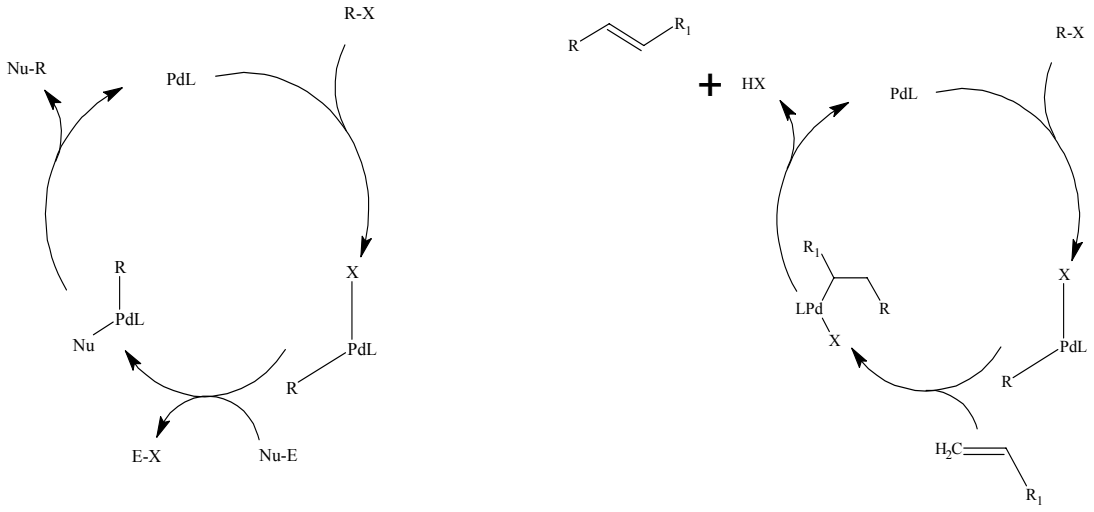
Scheme 6.



L= ligand, usually a phosphine

In this reaction aryl or vinyl halides are coupled with amines. Again, this reaction is presumed to follow a similar mechanistic pathway as those mentioned above.[5]

To get a better understanding of the relationship among these reactions lets examine the accepted mechanisms for each, as seen in Figure 1-2**.** It is accepted that all of these reactions proceed first by oxidative addition of the aryl halide, then either a migratory insertion (in the case of Heck and Sonogashira) or transmetallation (Suzuki, Stille), followed by a β-hydride elimination, and finally a reductive elimination to reform the active Pd(0) species and HX.[2,3,23,25,26,27,28] The primary difference in these reactions is obviously the interaction of the Pd/aryl halide oxidative addition product with the transmetallation/migratory insertion species. There must be some universal similarity in the nature of this step since all of these reactions are perceived to proceed through the same general pathway. While the oxidative addition is accepted to occur basically as Heck originally described it, the fine details may be quite complex.[1,29,30,31,32] The exact nature of this step as well as the subsequent steps still remains to be thoroughly investigated.



Suzuki, Hartwig-Buchwald, Stille and Sonogashira Couplings Heck Coupling

Figure 1-2 The general catalytic cycles for palladium catalyzed cross coupling reactions. In the case of Suzuki, Nu-E is equivalent to a boronic acid [R-B(OH)$_2$]. For Harwig-Buchwald couplings, Nu-E is R-NH$_2$ where R is generally an aryl group. For Sonogashira, Nu-E is equal to an alkyne and for Stille it is R-Sn(R')$_3$.

As one can see, while these other mechanisms appear to have similar steps, the transmetallation/migratory insertion step clearly differs. For sake of simplicity lets assume that the Heck reaction will fall under the migratory insertion category and the other couplings mentioned fall under the transmetallation category. It is classically represented that in the case of transmetallation, a nucleophile-electrophile pair will undergo the transmetallation step with the nucleophile replacing the halogen on the active palladium species, and the electrophile/halogen ion pair leaving.[12] Interestingly, this is the case for the Sonogashira coupling as well. As shown in Figure 1-1, the

alkyne reacts with the palladium in a pseudo transmetallation step.[24,25] That is, the alkynyl carbon distal to the R group will act as the nucleophilic center and the proton attached to it will behave as the electrophilic site much the way tin, boron, and nitrogen do in their respective reactions. This is most interesting because this is quite unlike the classic representation of the Heck reaction. As you can see in Figure 1-2, the olefin in the Heck reaction coordinates to the palladium, then undergoes an insertion into the C-C π bond with concurrent migration of the aryl group to the adjacent carbon.[12,26,27] The newly coupled aryl-olefin compound is then eliminated via a β-hydride elimination followed by a base deprotonation of the Pd(II) species and loss of halogen to form a salt with the formula $R_3NH^+X^-$. It is therefore clear that while these reactions have many things in common, the complexity of each individual step combined with the montage of possible rate limiting steps and reactive alternatives, provides no definite correlation. Any similarities drawn between the Heck reaction and the other couplings can only be tentative until experimentally proven; and even then may not always hold true.

Ligand modifications and advances

Traditionally, triphenyl phosphine has been used as the ligand in Heck, and other coupling reactions. While this ligand works quite well to facilitate the coupling reaction, it suffers from several shortcomings. First, PPh_3 imparts no regio or stereo control to the catalytic system. Secondly, this ligand is poor at promoting oxidative addition of aryl bromides, and chlorides. These are issues that have been addressed,

although not completely solved.[22,33,34] Figure 1-3 shows some examples of ligands that can be used to facilitate the Heck reaction.

One fairly simple method of controlling stereochemistry has been the application of chiral ligands into the catalytic system.[35,28] One of the first such successes was the use of BINAP.[36,37] In 1990 Noyori found that by using BINAP as the phosphine ligand many reactions could be catalyzed to form asymmetric products with good *ee*'s. This led to the development of catalytic systems using BINAP in Heck couplings. The results from these reactions were promising. Reported values for *ee* are good (96% *R* when *R*-BINAP is used), however yields are lower than those obtained with triphenylphosphine.[36] Soon thereafter, (1993) significant strides were made by Pfaltz. His catalyst system employed phosphinooxazolines as the chiral ligand. This was an important step because instead of using a bidentate ligand with two phosphorus binding sites, a ligand was used that contained a phosphorus and a nitrogen binding site. The results of this experiment were very high *ee'*s (99%) and nearly quantitative yields.[36] The drawback of Pfaltz's system is that the catalyst is extremely sensitive to halide ions. Therefore, it will only work with analogous aryl triflates and when all possible halogen sources are eliminated. Newly developed ligands from Iyer address the issue of poor reactivity towards aryl halides other than Ar-I. This ligand system contains nitrogen-oxygen based bidentate ligands. Some examples include dimethylglyoxime, 8-hydroxyquinoline, and diimines.[12,44,45,46,47] These ligands were shown to catalyze the less reactive aryl bromides to good yields

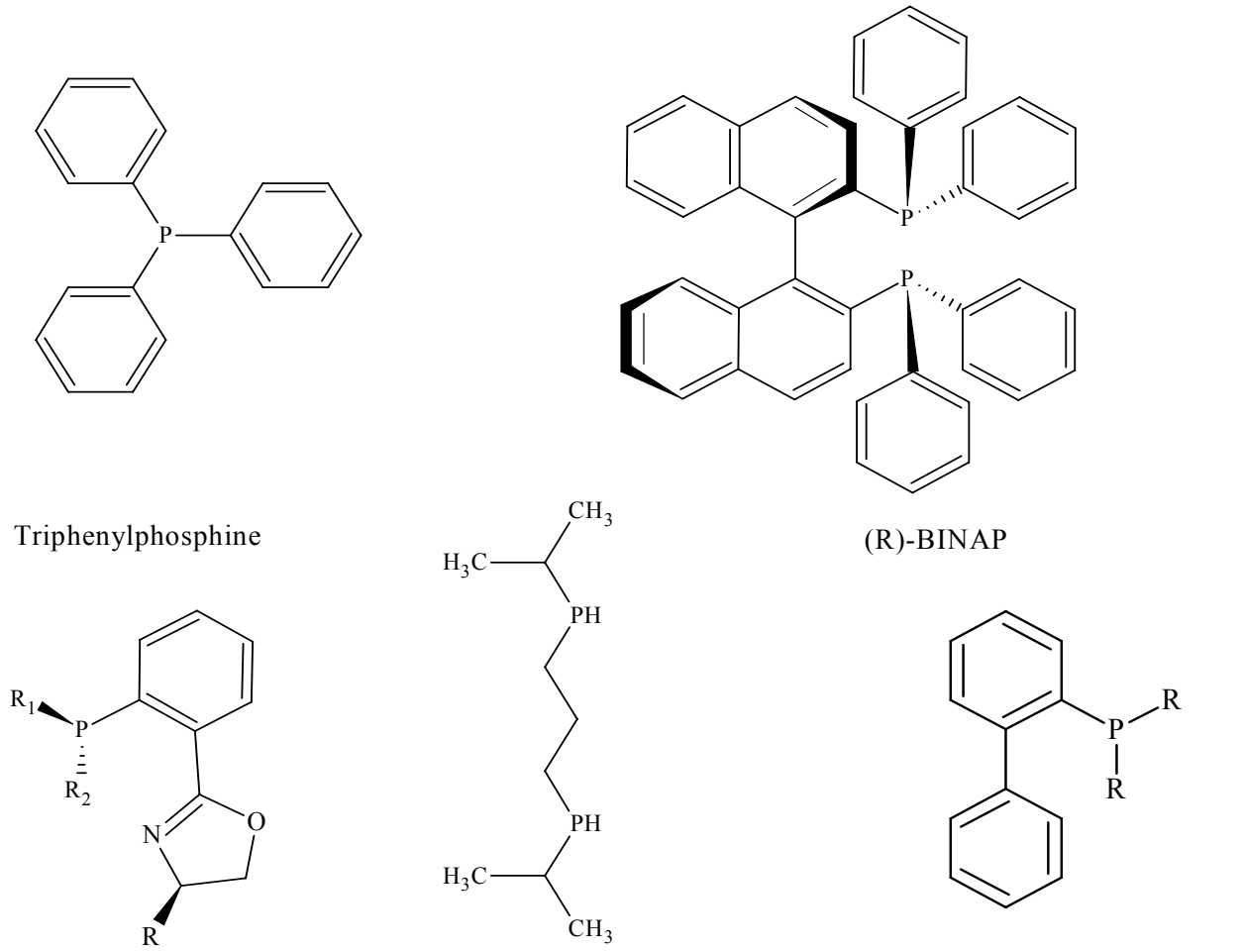


Figure 1-3 Examples of phosphine ligands discussed in this thesis. Triphenylphosphine is the most common and widely used ligand for this reaction. BINAP and phosphinooxazolines are used to induce stereoselectiviy with the appropriate substrates. Dialkylphosphino biphenyl is used to facilitate oxidative addition of aryl chlorides in Suzuki and Hartwig-Buckwald couplings and will be the focus of my mechanistic studies. The bidentate 1,3 bis [diisopropylphosphino] propane is used to activate aryl chlorides, as well as a mechanistic probe. [22,23,34,36]

and turn-over rates. Another contributor to this field is Buchwald.[16,44,45] His research group has designed a series of ligands, used primarily in Suzuki and Hartwig-Buchwald couplings, that readily react with aryl chlorides. It is a ligand from this group that will be the focus of my experimental studies. This catalyst system utilizes a dialkyl phosphino biphenyl ligand to facilitate the reaction between boronic acids or amines and aryl chlorides. No reactions have been reported using these ligands as catalysts in Heck couplings, but as you will see later they are indeed active in some systems.

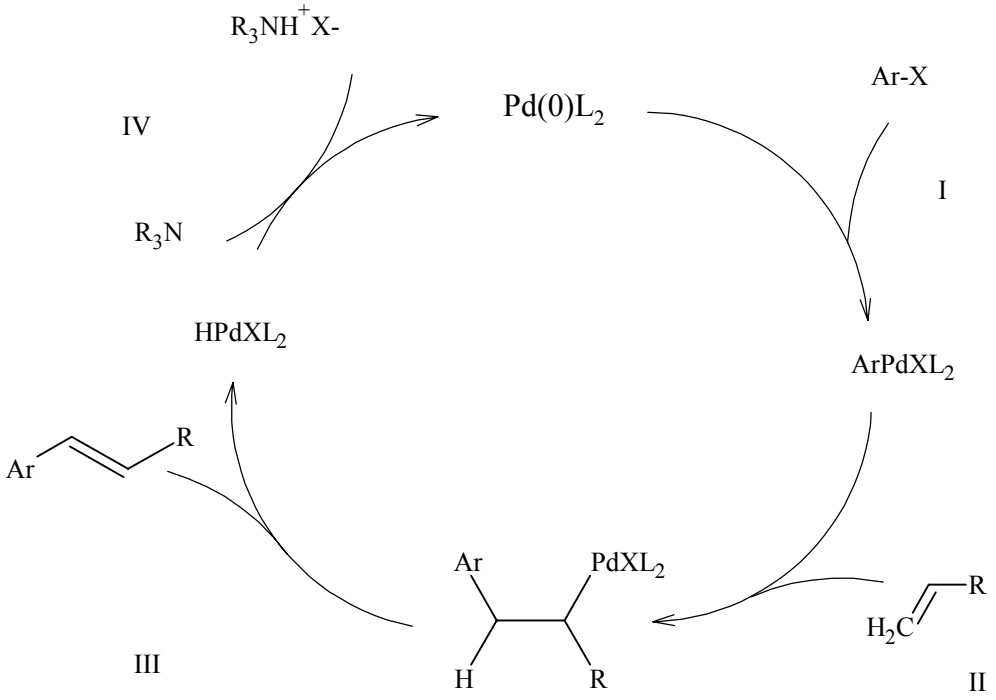
Mechanistic studies of the Heck reaction

Mechanistic studies on organometallic systems are generally done by studying the metal center through electronic means (i.e. voltammetry, amperometry, chronamperometry, etc…)[29] These methods detect changes in the oxidation states of the metal centers during various stages of the catalytic cycle. The reactivity of individual species can also be monitored as a result of changes in the reduction/oxidation currents caused by changes in the concentration of particular species in solution. Longer lived species in solution will be those that are less reactive, shorter lived are more reactive. Most commonly, voltammetry is used to measure these characteristics. There are two kinds of voltammetry that can be utilized, steady state voltammetry and cyclic voltammetry.[29] Steady state voltammetry is used to identify metal complexes that have already formed in the solution. The concentration of this species is measured by the value of its reduction/oxidation potential. If, during the

course of a reaction, new metal species are formed, steady state voltammetry can detect these species and identify the concentration of them in the reaction mixture. Therefore, voltammetry can be used both a means to measure oxidation states of the complexes formed, and as a kinetic probe. A sub-field of steady state voltammetry is transient voltammetry. This technique is performed to measure the thermodynamics and kinetics of equilibrium. This is accomplished by varying the scan rate. With a very fast scan rate, the equilibrium of species will be much smaller as there is less time between scans for the species to change. Longer scan times will therefore show what the true equilibrium is, because species will have long amounts of time to equilibrate. By measuring this variation in equilibrium, the equilibrium constant (k_{eq}) can be determined.[29] Cyclic voltammetry allows for the formation of intermediate species by oxidation/reduction of metal species formed at the beginning of the reaction. By following these species, one can get information about the oxidation states of possible intermediates. Again this technique allows you to measure reaction kinetics by giving you the freedom to adjust the time scale for the chemical reaction. While voltammetry is undoubtedly a crucial mechanistic probe, there are some disadvantages. Most important is that while this technique provides information on the kinetics and thermodynamics, it gives no definitive information on structure. Luckily, NMR spectroscopy does provide structural information.[34] It is through the combination of information from voltammetry and NMR spectroscopy along with data from other spectroscopic methods that many organometallic mechanisms are proposed.

To understand the mechanism of the Heck reaction we must take a closer look at each stage of the mechanistic cycle (Scheme 7).

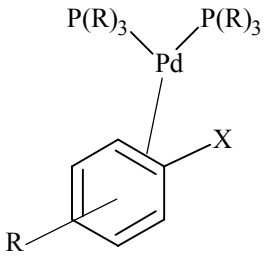
Scheme 7.



For simplification we shall consider the cycle as having four distinct steps. In doing this we are essentially excluding such issues as effects of halide and acetate anions, ligand effects, effects of olefin selection, bases, and solvent. Each stage of the cycle contains a series of mechanistic steps and possibilities. The first stage of the mechanistic cycle is the oxidative addition of the aryl halide to the active Pd (0) complex (stage I). It is generally accepted that oxidative addition proceeds through a

14 electron Pd (0) intermediate. However, there are many imaginable ways this reaction could occur.[23,29,34,46] Some possibilities are formation of a η^2 π- complex prior to the oxidative addition, either a one or two electron transfer from the metal center to the organic molecule (i.e. a nucleophilic like attack by Pd on carbon or a radical mechanism), and other possible ligations of the aryl halide to the palladium. It has been postulated that the oxidative addition mechanism can be broken down into two fundamental possibilities: a concerted, neutral three-center transition state or a charged ionic transition state.[46,47,48,49,50] Calculation predicts formation of the η^2 π-complex as the initial interaction between the palladium species and the aryl halide (Scheme 8).[51]

Scheme 8.

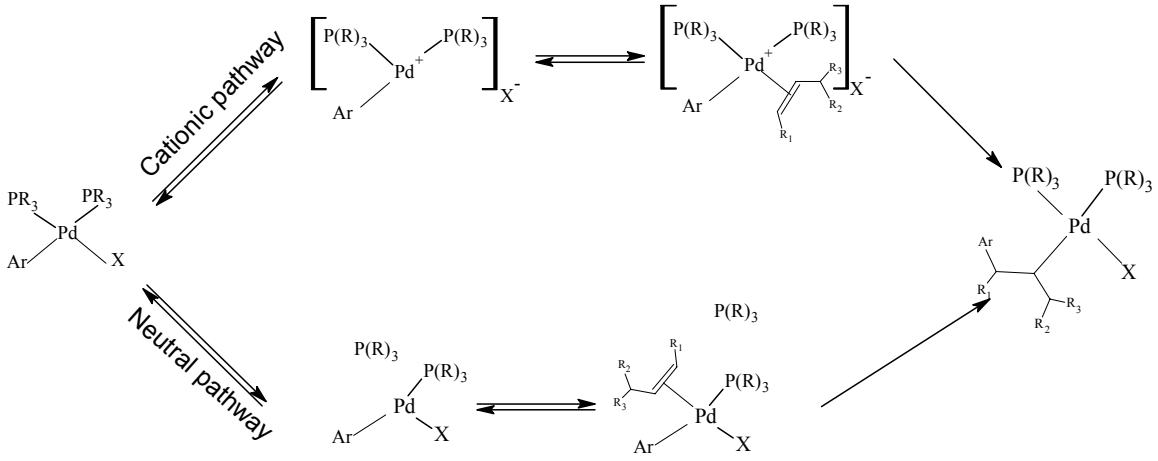


However, a lack of experimental evidence makes elucidation of this step difficult. The experimental evidence that has been gathered on this step of the reaction does little to validate or disprove a π-complex formation. Additionally, the importance of this complex should not be ignored as its formation may play some role in the activation of the C-X bond, which would prove especially crucial information in the cases of the less reactive aryl chlorides and bromides. Experimental evidence does exist for the electron

transfer hypothesis, which would fall under the category of a charged ionic transition state. A Hammet ρ value of 5.2 was measured for the reaction of Ph-Cl with a Pd/dippp (dippp = 1,3 bis [diisopropylphosphino] propane) complex.[34,52] This suggests that there is a large amount of charge being built up at the transition state of the oxidative addition. Other research has found ρ values in excess of 2, which also supports this hypothesis[53] The build up of charge at the transition state is indicative of an electron transfer reaction. Conflicting experimental evidence exists however. Reaction barriers were measured for the reaction of Ar-I with $Pd(Ph)_4$ in both toluene and THF, and were shown to be similar. This suggests that there is no, or very little charge built up at the transition state of this reaction.[46,54] Careful scrutiny of the data presented in these papers leads one to conclude that there are a large number of factors that contribute to the overall mechanism of the oxidative addition in each case. Important considerations are the coordination sphere of the transition state metal complex, nature of the interactions between each participant in light of steric effects of any and all members of the transition state, and inherent differences in systems using structurally different but electronically similar systems. Some of these issues have been addressed but many remain to be fully investigated.

The second distinct step (stage II in Scheme 5) in the catalytic cycle is coordination of alkene and insertion into the aryl-Pd bond. This step has been recognized as the step that governs stereo and regiochemistry of the olefinated aryl product.[9,55] There have been two major possibilities put forth in the literature pertaining to this step in the catalytic cycle (Scheme 9). [10,23,27,28,55]

Scheme 9.



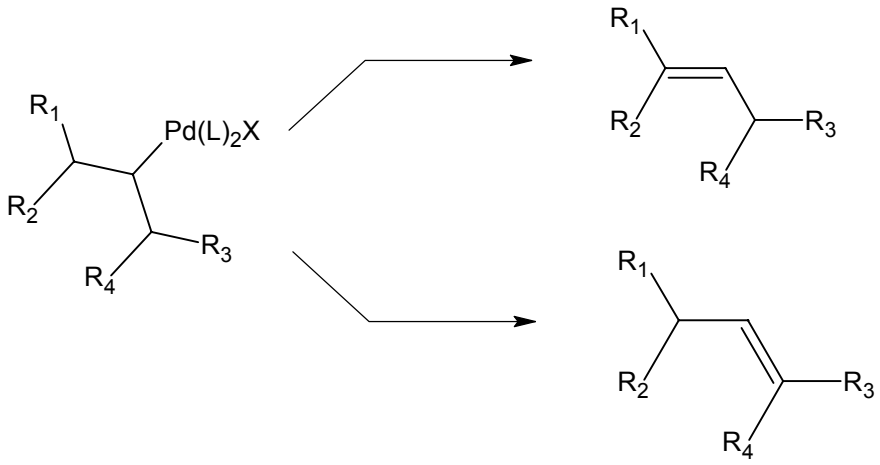
The first involves a cationic species. In this species the halide (or triflate) dissociates from the $ArPdL_2$ species giving X^- and a cationic Pd^{II} intermediate. The olefin then coordinates to the Pd followed by insertion into the Ar-Pd bond. The other possibility is dissociation of a phosphine giving the neutral intermediate ArPdXL. Subsequent coordination and insertion of the alkene into the Ar-Pd bond yields the same product as the cationic model.[23] A good probe for this step has been discovered. The use of chiral bidentate phosphine ligands will facilitate asymmetric induction. Work by Vogl states that if the mechanism proceeds via the cationic pathway the phosphines remain ligated to the Pd center throughout the mechanism thus enabling high *ee*'s to be achieved. If the neutral transition state is employed the phosphine will be monodentate as the olefin coordinates thus decreasing the asymmetric induction and lowering *ee*.[23] Furthermore,

evidence exists that the nature of the halogen (or triflate) on the palladium can also play a role in determining which mechanism is followed. For instance, due to the weakness of the Pd-OTf bond, reactions containing aryl triflates will undergo the cationic pathway.[23,56] This holds true because the triflate will dissociate more easily than the phosphines. Studies into control of this phenomenon have been conducted, and show that addition of silver salts (known to be halophilic) to the system will sequester the halides from forming the $ArPdXL_2$ species.[23,46] This will cause the cationic mechanism to dominate, since X^- is being removed from the Pd. Conversely, when an excess of halide ions is added to a Pd-OTf species the neutral pathway is more prevalent since the halide ions will displace the triflate from the palladium center, forming a stronger, Pd-X bond.[57,58] Overman has found a neutral system that induces stereochemistry as well. Initial studies were directed towards conducting asymmetric Heck reactions using various ligands to induce stereoselectivity.[59] It was discovered that BINAP was a ligand that induced stereoselectivity. Success at this prompted a mechanistic study to explain the results as bidentate phosphorus ligands are generally known to depress stereoselectivity.[35,55,59] In Overman's system, he suggests the neutral pathway predominates.[55] His studies show that the BINAP is monodentate at the insertion, which would indicate the neutral pathway. To support this theory Overman substituted analogues for BINAP that contained only one phosphorus thus allowing only monodentation.[55] This observation again shows the complexity involved with the mechanism of the Heck reaction.

Another issue that needs exploration is the nature of the alkene. The cationic pathway is favored when electron rich alkenes are used. However, electron poor alkenes favor the neutral pathway.[23,27] This observation dictates that electron rich olefins should work better for asymmetric induction and this is what has been observed in most cases.[23]

The next stage (III) in the catalytic cycle is elimination of the alkene. It is generally accepted that this occurs via a β-hydride elimination. The difficulty arises when the olefin has two β-hydride bearing carbons. This effect is most obvious when working with a non-terminal olefin. In cases such as this, the alkene can eliminate from the Pd forming two separate products.[23] Scheme 10 depicts such a situation.

Scheme 10.



Both alkenes are possible β-hydride elimination products from the palladium complex.[23]

Stage IV is the regeneration of the Pd (0) species by deprotonation of the palladium. It is important to consider the factors that may contribute to this step. Most notably is the nature of the base that is used in the reaction. Generally, tertiary amines are chosen for this role.[1] This is because they are good Lewis bases and will eagerly attack any acidic protons available (i.e. those bound to palladium). Upon formation of the cationic amine complex, ionic pairing with the previously jettisoned halogen anion occurs, thus removing both the left over hydrogen and the halide ions from solution. It is important to note the interesting information that studies on the effect of base on the rate of reaction have provided. It was found that by neutralizing protons, triethyl amine actually accelerated the reaction of alkene with the Pd complex, while decelerating the rate of oxidative addition by stabilizing anionic character in the Pd species.[29] This, in essence, slows down fast reactions and speeds up slow ones thereby providing an overall more efficient catalytic cycle.

CHAPTER II

PROBLEMS TO BE STUDIED

The nature of oxidative addition

It is accepted that oxidative addition is the initial step in many C-C coupling reactions, the Heck reaction included. However, the nature of this step is not completely understood. Studies have been conducted to elucidate this information, but conclusive evidence remains elusive. Electrochemical studies on various species by Amatore and Jutland,[29,46,60] stereoselectivity studies by Shibasaki and Jutland,[23] and kinetic studies by Milstein and Portnoy are excellent examples of typical studies done on oxidative addition.[34] Amatore and Jutland have also studied rates of oxidative addition in the presence of olefin and concluded that rate is decelarated when alkenes are present.[61] This suggests that the nucleophile plays some role in earlier stages of the catalytic cycle than generally accepted. Since olefins are not expected to react with the catalyst before oxidative addition occurs this is an interesting find. Another study of particular interest is was conducted by Hartwig.[62] This study was conducted using a 1:1 ratio of Pd to phosphine ligand [P(t-Bu)$_3$] to insure only one phospine was ligated to the Pd. A rate study was conducted by varying factors such as base and addition of extraneous halide ions and measuring change in rate against a control. The rate observations made were ambiguous however. Inconsistent k_{obs} for various concentrations of base was unlike previous studies with bidentate phosphines.[63] Previous studies have shown the reaction to be zero order in base.[64] Hartwig found that the rate order was inconsistant and was zero order in base sporadically. The

conclusion ultimately drawn by Hartwig is that oxidative addition with monoligated palladium catalysts proceeds via a different mechanism than with doubly ligated palladium catalysts, possibly thorough a combination of both anionic and neutral pathways.[62] While the scientific community has made strides in understanding the fundamentals behind this process, it is evident decisive answers have not been found. Calculation has shown that the reaction may proceed through a η^2 π- complex, although there are a host of other possibilities.[52,53] Alternatively, it has been suggested that oxidative addition is initiated by electron transfer from zerovalent metals to the organic substrate.[65] However, these theories are difficult to support experimentally, and there is no evidence supporting the existence of an η^2 π intermediate. The primary problem in discerning the nature of this step is the difficulty in finding a suitable method for measuring such interactions. Studies have been done to validate the hypothesis that this step proceeds through a charged ionic transition state.[34,52,53] Unfortunately there is also evidence that supports a neutral transition state.[46,54] With that in mind, several conclusions can be drawn about this stage of the reaction. First, we do not yet fully understand what is occurring in this stage. Experimental data supports two conflicting theories. Our inability to firmly form a conclusion suggests that the oxidative addition may be far more complex than previously thought. The problem with previous studies is that they compare apples to oranges. The systems used in each case were similar, though not identical. Without comparing identical reactions under identical conditions it is difficult to predict or compare results between two systems. The unique chemical and physical properties of the compounds involved in each reaction can only be

generalized to a certain extent. A major flaw in the comparisons made previously is the aryl halide used in each of the cases. For one instance aryl bromides were used, in the other aryl iodies.[33,46] While this may not immediately be a striking difference, one must look at the reactivity of these species. It is known that for the Heck reaction aryl bromides will react much more slowly than will the aryl iodides.[1,66-70] With that in mind, one can easily imagine how subtle differences in the substrates could potentially have a bold impact on the reaction mechanism.

The nature of the alkene insertion

Coordination of the alkene to the palladium is recognized as the second step in the catalytic cycle. This step is considered both the regio and stereoselectivity-determining step. Studies in this area have yielded two possible pathways.[23] Similar to the oxidative addition step there is a possibility of either a neutral (as discussed by Overman)[72,73] or cationic species (as proposed by Ozawa, Hayashi, and Cabri).[74,75,76] Studies in this area have focused on determination between these two possibilities. This leaves the question of selectivity relatively unaddressed. It is important to consider the differences in electronics among different olefins and the effect that has on the selectivity between them. It is generally accepted that electron poor olefins react well in the Heck reaction. There have also been instances of highly electron rich olefins reacting, though often they require the use of silver or thallium salts to facilitate the reaction.[49,77] No studies have been conducted to distinguish the degree to which electronics governs this step. We do not know if an olefin that is more electron withdrawing will react faster, slower, or at the same rate as a more electron rich alkene.

One can imagine that if this is not the rate determining step of the reaction, the effect of olefin electronics may have little influence, so long as the olefin will coordinate to the palladium species. Conversely, condsidering reactions in which the alkene insertion step is rate determining, one can draw the conclusion that olefin electronics plays a pivotal role in influencing the outcome of the reaction by accelerating the rate. By determining the selectivity of this step, we will also gain a deeper understanding of asymmetric catalysis with regards to the Heck reaction. It is understood that electron rich alkenes will favor a higher amount of asymmetric induction by inducing a cationic pathway.[23,56] This is an important consideration, especially if electron poor alkenes react faster than electron rich alkenes. This relationship could provide headaches for many chemists who wish to harness the asymmetric Heck reaction. He or she must select an olefin that will be electron rich enough to insure asymmetric induction but is electron poor enough to facilitate the reaction. Those same chemists may come across situations in which multiple olefins are present in the same molecule and a Heck coupling would be an obvious choice for formation of their target. It would be helpful to know which alkene the reaction will be favored and to what extent the reaction will be favored for that alkene.

Mechanistic effects of new ligand developments

When considering the myriad of possible ligands for the Heck reaction, one must take into consideration why these individual ligands have the effect they do on the reaction. Such questions as, does a ligand accelerate the reaction, does it promote asymmetric amplification, is it more active towards particular substrates, and others must all be considered for each variation on ligand design. Subsequently, as varied as the effect the ligands have on those factors, one must also consider the same variations on the mechanism of the reaction. For instance, what makes a ligand active for aryl bromides when other ligands show no influence? Some ligands have been incorporated into mechanistic studies, especially in cases where asymmetry is evolved.[22,23,31,36] These generally are chiral ligands such as BINAP. New and exciting ligands have been produced that facilitate cross-couplings with aryl chlorides, and few studies on these systems have been done. [16,78] Participants in this class of ligands are alkylmonophosphine and sterically hindered carbene ligands.[79-98] One such alkylmonophosphine ligand, Dicyclohexyl phosphinobiphenyl (DCPB), has come from Buchwald.[44,87] DCPB and similar dialkyl phosphinobiphenyl ligands have been introduced as promising advances for coupling reactions such as Suzuki and Hartwig-Buchwald couplings.[16,22,78,44,45]

This revolutionary breakthrough has not yet been adapted to the Heck reaction though one could imagine the possibilities. Often, ligand research for the Heck reaction deals more with creating asymmetry and less with activating cheaper, less reactive substrates. Understanding the mechanism of this reaction could facilitate its adaptation to the Heck reaction. Also, knowing the effect of these ligands could provide motivation to develop ligands that were just as highly active for Heck reactions as for the other coupling reactions that can incorporate aryl chlorides into their scheme. Luckily, the first step of the Heck reaction and the reactions DCPB is active for are the same. Understanding the effect of these new ligands on the oxidative addition of the aryl halide would provide information not only about the mechanism of the Heck reaction but also information regarding the mechanisms of any of the coupling reactions discussed earlier.

CHAPTER III

APPROACH

Kinetic isotope effects

Kinetic isotope effects (KIEs) are differences in reaction rates between molecules differing only by isotopic substitution at a particular atom (isotopomers). The zero point energies (ZPE) of isotopomers will necessarily differ. ZPEs are a quantum mechanical value representing the lowest vibration state of a normal mode, and are related to the vibrational frequency by eq 1. The frequency is determined by the force constant of a harmonic oscillator, k, and the reduced mass, m, via eq 2

$$ZPE = (1/2)\, h\nu \qquad (1)$$

$$\nu = [1/(2\pi)](k/m)^{0.5} \qquad (2)$$

The difference between isotopomers is the mass. By changing m in eq 2 you change the value for ν, subsequently changing the value for the ZPE. The rate of a reaction depends upon the activation energy of a substrate towards a particular product. By using different isotopomers and varying the ZPE you also vary the activation energy (Figure 3-1). Heavier atoms will have a lower ZPE and therefore have a higher activation energy (i.e. more energy is required to reach a transition state when heavier isotopes are used). This, in effect, means that isotopomers with heavier isotopes will usually react more slowly.

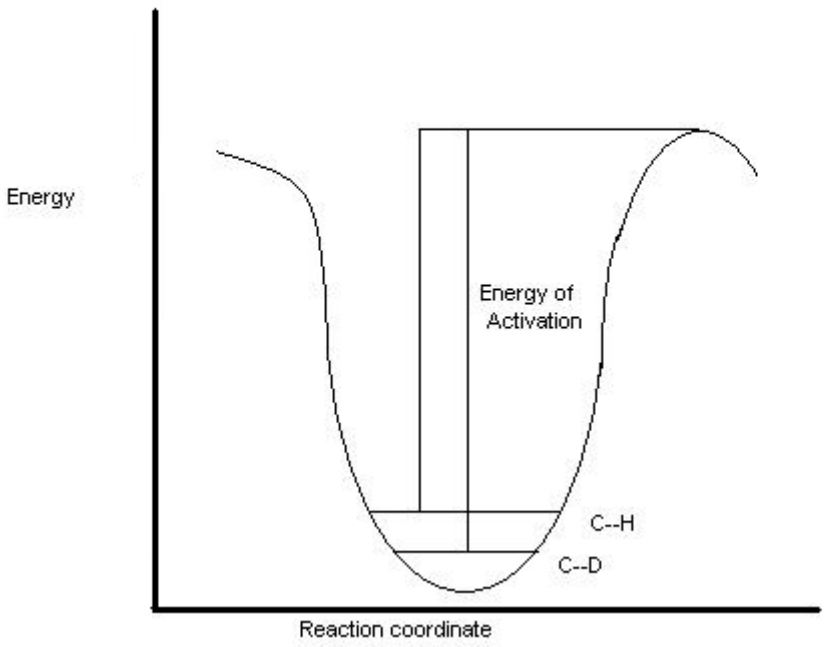


Figure 3-1. Reaction coordinate diagram of activation energy differences between deuterium and hydrogen. The C-D's lower zero point energy is a result of the higher mass of the deuterium relative to a proton. Having a lower ZPE dictates that a larger barrier must be overcome to facilitate the reaction. This difference in activation energy makes reactions with heavier isotopes go slower (i.e. more energy is required to attain the higher activation energy).

As a result of this relationship, elements with lower atomic weights will show greater KIEs. For instance, hydrogen/deuterium KIEs are in the range of 2-7 while ^{12}carbon/^{13}carbon typically ranges from 1.01-1.05. Additionally, KIEs are observed mostly on atoms involved in the rate-determining step of a reaction (primary KIEs). Secondary KIEs can be measured for some systems and can be either normal, $k_H/k_D > 1$,or inverse, $k_H/k_D < 1$. Primary KIEs give information about bond breaking and bond making during the rate-limiting step, while secondary KIEs give information about geometry changes at the transition state.

The measurement of kinetic isotope effects

There are two classes of KIE measurement, non-competitive and competitive. Non-competitive methods seek to determine KIEs by measuring rates of two separate reactions. One reaction is run with the most common isotope (hydrogen for example) and one reaction is run with a different isotope (deuterium for example). The rates of these two reactions are compared, and from this information KIEs can be determined. This method works well for large KIEs, but determination of the small KIEs for heavier atoms is plagued by the difficulty of obtaining sufficiently precise absolute rate constants. Also, the difficulty in obtaining properly enriched materials could prove bothersome. Competitive reactions avoid this problem by looking at the isotopic enrichment or depletion at specific locations in a molecule after a reaction is carried to partial conversion. The isotopic ratios will change in both starting material and product as a reaction proceeds and these changes can be measured. Also, this class of

KIE determination benefits from not requiring isotopic enrichment of substrates so long as the measurements are accurate enough.

Techniques for competitive kinetic isotope effect measurements

There are primarily three common techniques for carbon KIE determination, radio labeling, isotopic ratio mass spectroscopy (IRMS), and nuclear magnetic resonance (NMR) determination of isotopic ratios. Radiolabeling allows precise measurements of isotopic ratios. Since many elements have radioactive isotopes (tritium, ^{14}C) this technique can be applied to a wide range of atoms. The problem that arises with this method is the synthesis of the isotopically labeled material. Often such a task is challenging and the technique is sensitive to impurities. IRMS is also a powerful tool in KIE determination. Through this technique, KIEs can be determined at natural abundance thus eliminating the need for isotopically enriched materials. IRMS works by measuring the mass of the whole molecule-ion and comparing mass in the product versus mass in the starting material. The drawback of this technique is that because fragmentation can cause isotopic fractionation the molecule must be broken down into small pieces such as CO_2 and N_2, which can be impractical.

The Singleton group uses an NMR technique developed within the group several years ago for KIE determination. This technique seeks to avoid the problems related with the other methods of KIE determination. This technique is able to measure KIEs at natural abundance, and at multiple positions in a molecule simultaneously with high precision.[99] This technique works not by measuring the isotopic ratio directly, but rather measures the change in integration of peaks in NMR spectra versus an internal standard (an atom that is assumed to have a KIE of 1). By comparing spectra of starting material recovered from a reaction taken to high conversion against spectra of unreacted starting material, KIE data can be obtained. Here, we use the NMR technique for measuring KIEs in order to gain a better understanding of the oxidative addition of aryl halides into the palladium catalyst by using ligands that have shown catalytic activity for aryl chloride addition. The Heck reaction between *p*-iodotoluene and ethyl acrylate using dicyclohexylphospino biphenyl was chosen as a model for this reaction, as the olefin and aryl halide are typical of those used for Heck couplings.

Selectivity studies

We plan to study olefin selectivity in Heck reactions to gauge for changes in the selectivity determining step and to explore the nature of olefin selectivity in Heck reactions. In order to determine selectivity, pairs of olefins are reacted together with an aryl halide, and the ratio of products is determined. Such a study should give us an indication as to the effects of electronics upon olefin selectivity in the Heck coupling. The accepted conditions for the Heck reaction call for the use of an electron poor alkene.

Our study seeks to put into perspective how electron deficiency affects the reaction. More specifically, we want to know if more electron poor olefins react more quickly or are selected over olefins that are more electron rich. We have chosen a variety of synthetically common olefins for this study, with particular emphasis on methyl vinyl ketone versus ethyl acrylate. Emphasis on these two alkenes in particular is to assure that the system is as similar to our mechanistic studies as possible. Also, since these two olefins are very similar we can be fairly confident that electronics will be the deciding factor in selectivity between them.

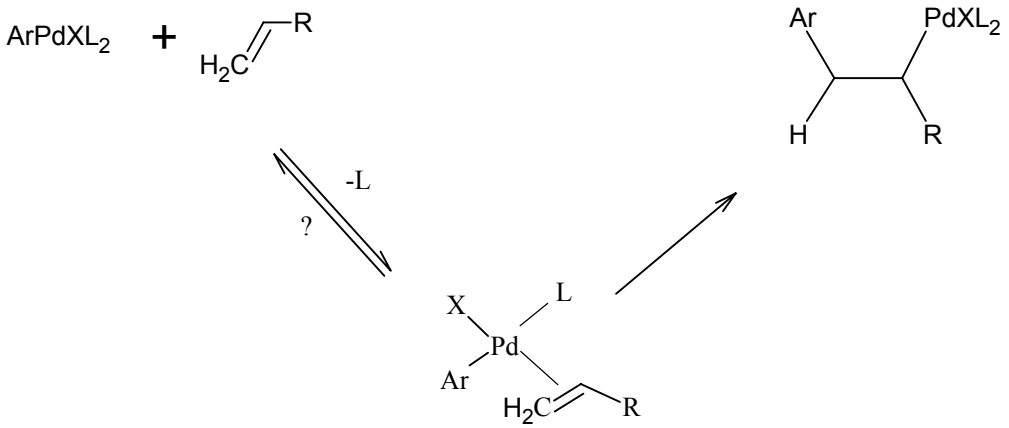
CHAPTER IV

RESULTS

Nature of selectivity based on electronic effects

This study was conducted to explore the impact of reaction conditions on the mechanism of the Heck reaction by studying selectivity of various pairs of olefins. By understanding how selectivity is affected we can understand if the mechanism changes during the various discrete stages of the catalytic cycle. Consistent selectivity from system to system will provide us with correlation between two systems as well as a basis to predict what the mechanism is. The work here focuses on the selectivity of the migratory insertion stage of the reaction (Scheme 11).

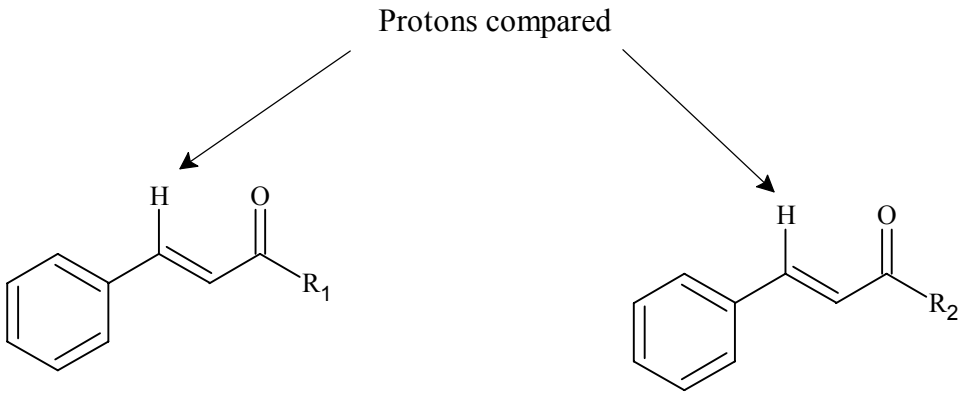
Scheme 11.



If, for example, the formation of the π-complex changes from reversible to irreversible, it seems likely that a change in olefin selectivity would be observed. Reactions of *p*-

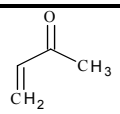
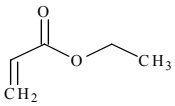
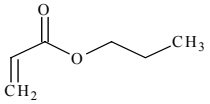
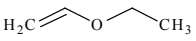
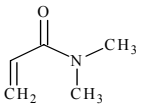
iodotoluene with olefins of varying electronics were chosen. Since it is understood that electron poor olefins work best for Heck reactions [12], we sought to study this phenomena by competitively reacting two different olefins simultaneously with *p*-iodotoluene. Successful couplings of *p*-iodotoluene with methyl vinyl ketone and any one of the following were observed using triphenylphosphine as the ligand: ethyl acrylate, dimethyl acrylamide, butyl acrylate, and ethyl vinyl ether. These reactions were conducted on a small scale at 25 ^{o}C, using DMF as the solvent (typically 20 mL) with 10 mol% of palladium acetate as the palladium source. Generally, one equivalent of each olefin was present for each half of an equivalent of iodotoluene. This allowed for all of the iodotoluene to react before any of the olefin was exhausted thus giving selectivity based solely upon chemical interactions rather than upon limiting reagents. The ratios of products from these reactions were determined by proton nuclear magnetic resonance (NMR) or gas chromatography (GC) and showed that electron poor alkenes were generally favored, though not exclusively. The NMR measurements were conducted by comparing analogous olefinic protons on the coupled products (Scheme 12).

Scheme 12.



The integration of these protons provided a ratio based upon concentration of each respective coupling product in relation to the other. Ratios obtained by GC were done by comparison of peak integrations for the respective products. NMR samples were prepared and analyzed by diluting aliquots of reaction mixture in deuterated solvent ($CDCl_3$). GC samples were prepared and analyzed by passing an aliquot of reaction mixture through a plug of silica gel to remove residual palladium, and collection of the chromatogram. In the cases of ethyl and butyl acrylates, the ratio of products favored those of methyl vinyl ketone by a ratio of 3:1. Ethyl acrylate was favored over ethyl vinyl ether by a ratio of 50:1. Reactions of methyl vinyl ketone with dimethyl acrylamide gave a ratio of 4:1 in favor of the dimethyl acrylamide. Results are summarized in Table 4-1.

Table 4-1. EA = ethyl acrylate, MVK = methyl vinyl ketone, BA = butyl acrylate, EVE = ethyl vinyl ether, DMA = dimethyl acrylamide (all ratios are within ± 0.5). *Ratio taken from reaction with DCPB. Deviations on experimental outcomes were universally ± 0.5 (for example the ratio obtained for EA / MVK ranged from 1 : 2.5 to 1 : 3.5.)

MVK  EA  BA  EVE  DMA  Olefins		Ratios
EA / MVK		1 : 3 ± 0.5
BA / MVK		1 : 3 ± 0.5
EA / EVE		50 : 1 ± 0.5
MVK / DMA		1 : 4 ± 0.5
EA / MVK		1 : 5 *± 0.5

These results are consistent with alkene insertion being the selectivity-determining step, and are also consistent with unpublished kinetic isotope effects from results obtained by Michael Szymanski of the Singleton group (Figure 4-1). These results suggest (based on ^{13}C KIEs) a bond a making or breaking process occurs at the two olefinic carbons during the first irreversible step of the insertion. The inverse ^{2}H KIEs

of the vinylic hydrogens is indicative of partial rehybridization of the olefinic centers from sp^2 to sp^3. These KIEs are much larger than would be expected for simple π-complex formation and are consistent with olefin insertion being the primary selectivity determining event of this mechanistic step. The KIEs also support the findings in this study, that olefin electronics will be important in the selectivity determining step of the insertion. Also, the KIEs correlate with the selectivity data by allowing us to conclude that olefin insertion is the primary mechanistic step of this stage of the reaction and that olefins of various electronics react at different rates although not necessarily through different mechanisms. It is evident from these results that alkene electronics plays a role in the selectivity of this step. If the migratory insertion were not selectivity determining then changes in electronics from alkene to alkene would have no effect on the selectivity. We would expect a 1:1 ratio of coupled olefins if there were no selectivity imparted by the electronics of the alkene. The selectivity of dimethyl acrylamide over methyl vinyl ketone is of particular interest as dimethyl acrylamide is not an electron poor alkene. It is unclear why dimethyl acrylamide is selective in this case and without further experimental evidence. However, coordination of the nitrogen to the palladium could play a role in increasing the selectivity of dimethyl acrylamide for two reasons. First, coordination of the nitrogen would saturate the palladium's coordination sites thus making coordination of methyl vinyl ketone impossible. Second, coordination to the palladium would make the olefin more electron poor and thus more favorable for the insertion. It is easy to imagine this scenario, especially if the nitrogen coordinates more readily than does an

electron poor alkene. Analogous reactions using dicyclohexylphosphino biphenyl as the phosphine were conducted with methyl vinyl ketone and ethyl acrylate. Reaction conditions were not identical between this reaction and those conducted with triphenylphosphine. Two sets of conditions were utilized in this study. First, a small-scale reaction similar to those described above was conducted using two equivalents of DCPB. In these reactions one equivalent of iodotoluene and one equivalent of each olefin was necessary to facilitate the reaction. The second set of conditions used was to conduct the reaction with all reagents scaled up by a factor of ten. These conditions afforded a smoother reaction with one equivalent of phosphine. The reactions furnished ratios of 5:1 in favor of the methyl vinyl ketone product (as determined by NMR). For both stoichiometries of DCPB, identical ratios were obtained suggesting that a palladium center containing only one DCPB ligated could be the active species. The selectivity of methyl vinyl ketone over that of ethyl acrylate is slightly enhanced in this system. This could be due to lower reactivity of the catalyst towards the Heck reaction combined with the increased reactivity of the electron poor alkenes thus showing a greater effect on selectivity.

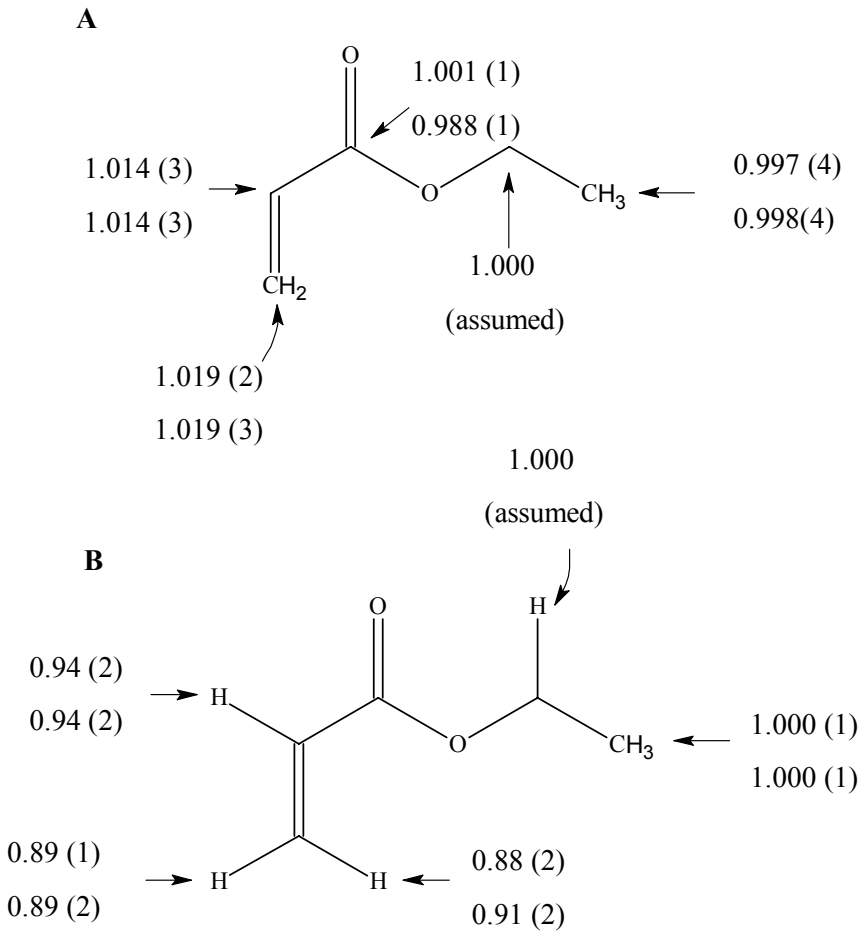


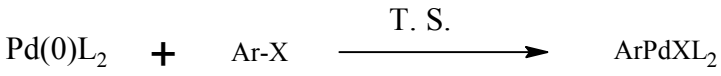
Figure 4-1. A. ^{13}C KIEs and B. ^{2}H KIEs for ethyl acrylate in its Heck reaction with iodobenzene. These are results obtained by Michael Szymanski of the Singleton group.[100]

Kinetic isotope effects of Heck reactions using dicyclohexylphosphino biphenyl as the phosphine ligand

The choice of *p*-iodotoulene for this study is twofold. First, the reactivity of aryl halides in Heck reactions increases as you move down the period thus affording a

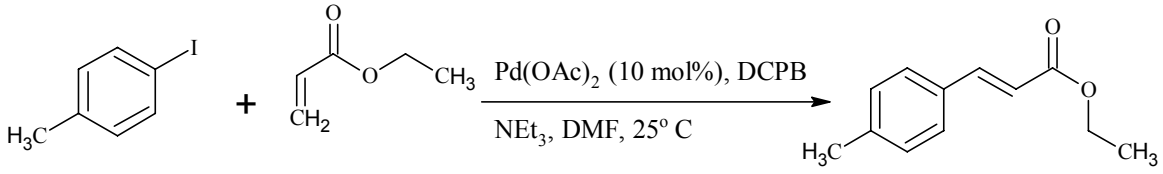
fairly easy reaction.[66-70] Second, the methyl group on the iodotoluene provides a good internal standard for KIE determination at natural abundance. It is assumed that due to its distal orientation to the presumed site of reaction, this methyl group does not directly participate in the reaction, and thus no isotopic changes will occur at this position. Kinetic isotope effects should provide us with information regarding the transition state during oxidative addition (Scheme 13).

Scheme 13.



The Heck reaction of *p*-iodotoluene with ethyl acrylate (Scheme 14) is a convenient example of a typical Heck reaction that is common among synthetic applications.

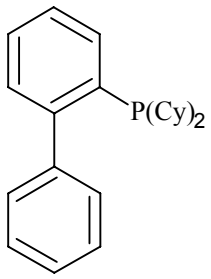
Scheme 14.



The difference between conventional Heck reactions and those performed in this study are the choice of phosphine. Typically triphenylphosphine is chosen to facilitate the formation of the active Pd(0) complex. In this study, however, we have

chosen to use dicyclohexylphosphino biphenyl (Scheme 15) since it presents interesting mechanistic implications due to its steric encumberance. For instance, it is believed to be responsible for the formation of an ArPdXL species as opposed to the traditional $ArPdXL_2$ after oxidative addition of the aryl halide (an example is shown by Buchwald from crystal structures in Scheme 16).[71]

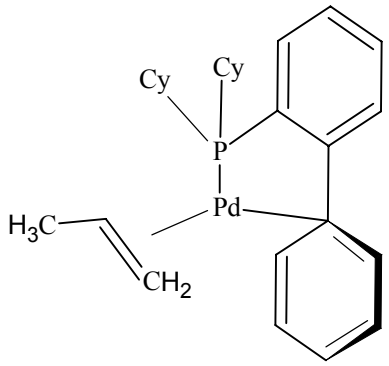
Scheme 15.



Reactions of ethyl acrylate and *p*-iodotoluene were taken to 84 ± 2% and 85 ± 2% respectively. Conversion was determined by integration of *ortho* protons on the iodotoluene starting material and cinnamate product. After an extractive work-up with water, unreacted iodotoluene was recovered via column chromatography on silica gel, using hexanes as an eluent, and analyzed by ^{13}C NMR. ^{13}C KIEs were determined via previously developed NMR methods.[99] ^{13}C NMR spectra were obtained for recovered starting material as well as a standard sample of original iodotoluene. Spectra were analyzed, and KIEs were calculated in the previously reported fashion.[18] Isotopic enrichment or depletion was determined using iodotoluene's *para* methyl as the internal standard and assuming the isotopic composition remains constant at that

position. Two sets of data were recorded for each sample. Figure 4-2 shows the results.

Scheme 16.



All KIEs in this experiment are within experimental error of each other. The substantial ^{13}C isotope effect at this C4 is larger than would be expected for a π - complex formation, and is indicative of a bond formation or breakage at this position during the first irreversible step for iodotoluene (i.e. oxidative addition). Studies by Michael Szymanski of the Singleton group show how this system compares to that of an anologous reaction using triphenylphosphine as the ligand (Figure 4-3). It is clear that the isotope effects do not change from system to system. This suggests that the dialkylphosphino biphenyl ligands do not change the oxidative addition stage of the Heck reaction and subsequenly have no overt effect on the mechanism of oxidative addition in any of the coupling reactions discussed in this thesis. This information gives us an understanding of the oxidative addition while allowing for conclusions to be drawn detailing the similarities between reactions carried out with this new class of

ligands and those with more traditional ligands. Since these studies prove the oxidative addition to be identical for both systems other possibilities must be considered for complete understanding of the mechanism by which aryl chlorides are activated using the dialkylphosphino biphenyl catalyst systems. Since it is possible that the active palladium species in the oxidative addition is different in its degree of chelation because DCPB is such a sterically encumbered molecule, it is possible that one ligand chelated to the palladium effectively blocks a coordination site on the metal center without having a bonding interaction.[71] However, a π-complex could also be formed between the palladium and the phenyl ring proximal to the phosphorus that is chelated to the metal. This would then make the active Pd catalyst more of an $ArPdXL_2$ species with the π-complex forced to fulfill the role generally reserved for chelating phosphines. This scenario would explain why identical KIEs are obtained for both triphenylphosphine and DCPB. In addition, difficulty in obtaining reactions of aryl chlorides in the Heck reaction with this system could be indicative of why oxidative addition is identical in the systems discussed. The other coupling reactions that are facilitated by the dialkylphosphino biphenyl ligands could potentially proceed via a different mechanism due to different reaction conditions such as solvent and temperature.

Indeed, as was discussed in the introduction to this thesis, variations on reaction conditions can have a substantial impact on the mechanism of individual steps (for example cationic versus neutral pathways).

While these results do not discount the formation of an initial π-complex between the aryl halide and palladium, they certainly show that formation of this complex is not rate determining. It is possible that formation of this complex only serves to initiate oxidative addition but merely by bringing the aryl halide within the coordination sphere of the palladium so that oxidative addition can then occur. Indeed, if the phosphine ligand can form π-complexes with the palladium, aryl halides certainly may as well. It may be that the π-complex is quite short lived such that it may not exist as a discreet species or that it is facile enough not to be of great importance to the selectivity of the reaction. It is important to consider the scenario of π-complex formation, especially since computational studies predict its formation.[51]

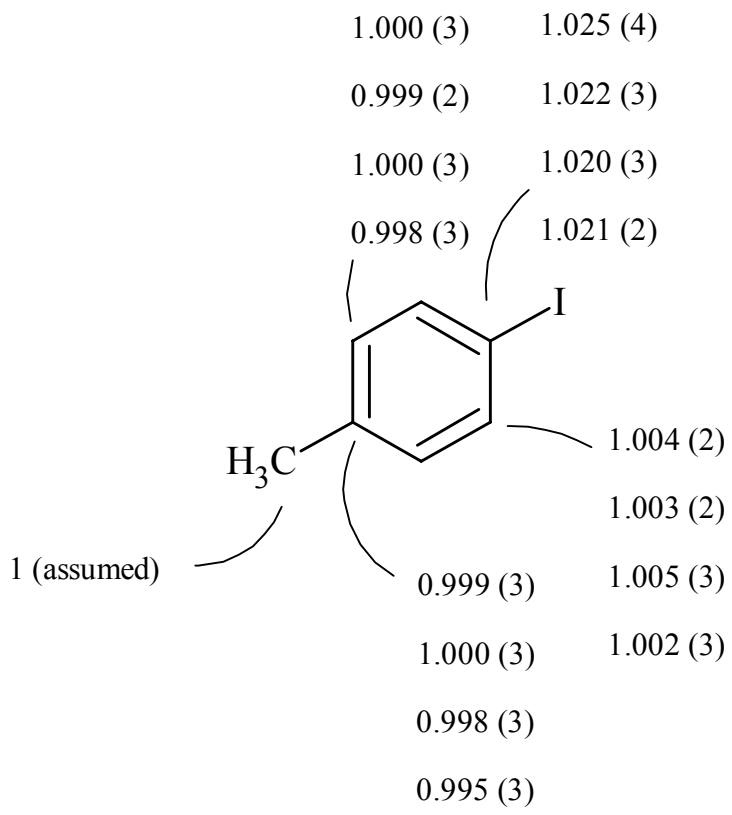


Figure 4-2. ^{13}C Isotope effects for the oxidative addition of *p*-iodotoluene in its Heck reaction with ethyl acrylate using dicyclohexylphosphino biphenyl as the chelating phosphine. The standard deviations for each reaction are shown in parenthesis.

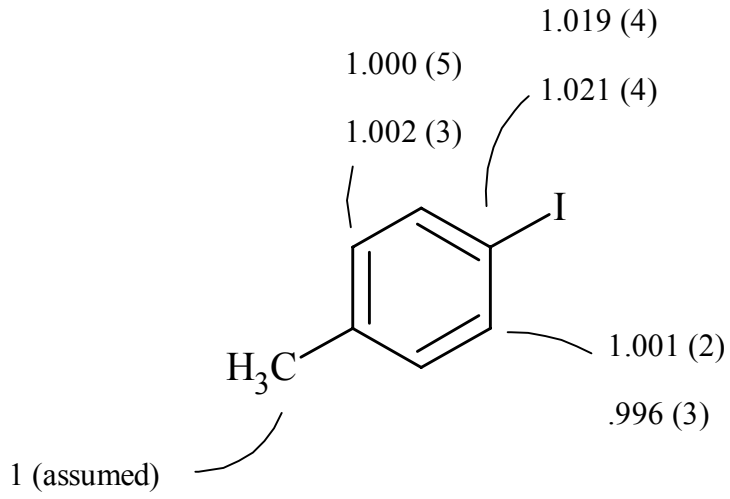
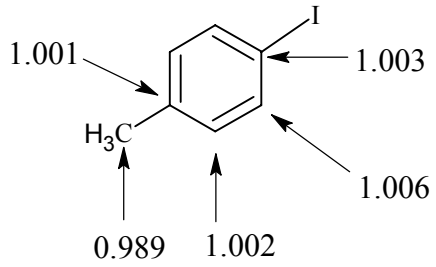


Figure 4-3. ^{13}C Isotope effects for the oxidative addition of *p*-iodotoluene in its Heck reaction with ethyl acrylate using triphenylphosphine as the chelating phosphine.

Computational prediction of isotope effects

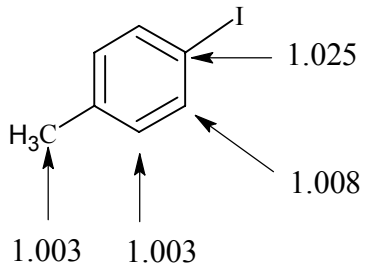
Ab initio calculations at the B3LYP 6-31g* level of theory on a Pd(DCPB) / iodotoluene system were preformed.[101] A transition state was found that, after examination of the stationary point and imaginary frequency, was determined not to be the transition state for oxidative addition (Figure 4-4). Rather the transition state was inversion of the substituents about the palladium atom. Predicted ^{13}C KIEs for the transition state found were significantly different than the experimental ^{13}C KIEs (Scheme 17).[101] Further disproving this transition state as that of the oxidative addition.

Scheme 17.



However, calculations previously conducted in the Singleton group on a simplified $Pd(PMe_3)_2$ / iodotoluene model predicted fairly accurate ^{13}C KIEs. (Scheme 18).

Scheme 18.



The predicted KIEs from these calculations correlate well with experimental KIEs for oxidative addition of iodotoluene from studies conducted in this thesis. That does not necessarily mean that the catalytic species has two DCPB bound to the Pd at the transition state. Rather, further computational investigations remain to be conducted into the nature of the transition state, including elucidation of the actual transition state for oxidative addition with only one phosphine bound to the metal.

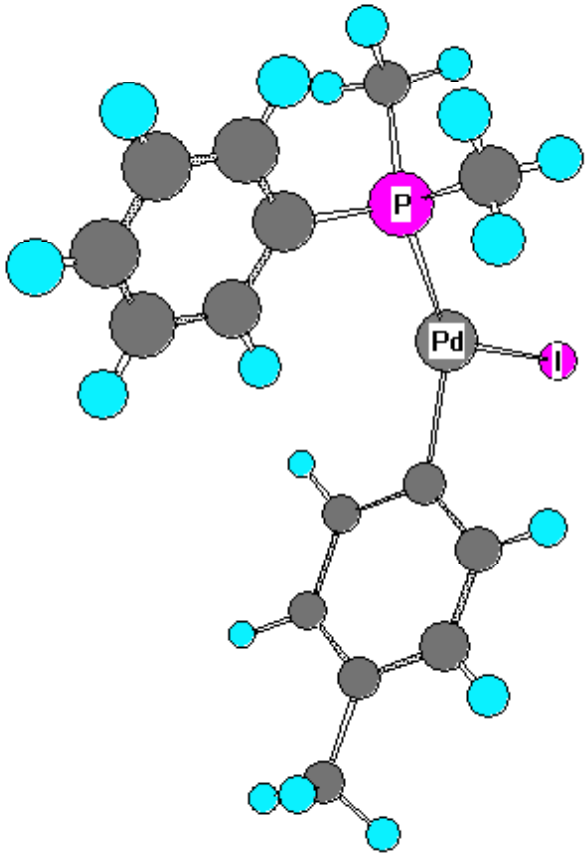


Figure 4-4. Calculated transition state structure for inversion about the Pd.

CHAPTER V

EXPERIMENTAL SECTION

General

Dimethyl formamide (Sigma-Aldrich), ethyl acrylate (Sigma-Aldrich), butyl acrylate (Sigma-Aldrich), palladium acetate (Sigma-Aldrich), Methyl vinyl ketone (Acros), *p*-iodotoluene (Acros), Triphenylphosphine (Fluka), and Dicyclohexyl phosphinobiphenyl (Strem) were all used without further purification. Triethyl amine (Sigma-Aldrich) was distilled under nitrogen before use.

Olefin selectivity

In Heck reactions employing triphenylphospine: Example procedure

A magnetically stirred mixture of 20 mL of dimethyl formamide and 1.9 g (5 mmol) of *p*-iodotoluene was sparged with nitrogen for 30 min. To the mixture was added 2.0 g (20 mmol) of triethylamine, 1.00 g (10 mmol) of ethyl acrylate, and 0.70 g (10 mmol) of methyl vinyl ketone, via syringe. To this solution was added 22 mg (0.1 mmol) of palladium acetate and 87 mg (0.3 mmol) of triphenylphosphine under a vigorous flow of nitrogen. The reaction mixture was allowed to stir for 72 h, at which time it was quenched with a stream of air. Low boiling starting materials were removed by vacuum distillation. The resulting dark red residue was analyzed by ^{1}H-NMR and the ratios of products were determined by comparing analogous olefinic proton integrations. An analogous reaction using methyl vinyl ketone and butyl acrylate was conducted under similar conditions.

In Heck reactions employing DCPB (2 eq.): Example procedure

A magnetically stirred mixture of 20 mL of dimethyl formamide and 2.18 g (10 mmol) of *p*-iodotoluene was sparged with nitrogen for 30 min. To the mixture was added 2.0 g (20 mmol) of triethylamine, 1.00 g (10 mmol) of ethyl acrylate, and 0.70 g (10 mmol) of methyl vinyl ketone, via syringe. To this solution was added 22 mg (0.1 mmol) of palladium acetate and 72 mg (0.15 mmol) of DCPB under a vigorous flow of nitrogen. The reaction mixture was allowed to stir for 72 h, at which time it was quenched with a stream of air. Starting materials and solvents were removed by vacuum distillation. The resulting dark red residue was analyzed by ^{1}H-NMR and the ratios of products were determined by comparing analogous olefinic proton integrations.

In Heck reactions employing DCPB (1 eq.): Example procedure

A mixture of 200 mL of dimethyl formamide and 21.8 g (0.100 mol) of *p*-iodotoluene was sparged for with nitrogen for 30 min. To this was added 20.2 g (0.200 mol) of triethylamine, 10.0 g (0.100 mol) of ethyl acrylate, and 7.00 g (0.100 mol) of methyl vinyl ketone. Nitrogen was allowed to gently bubble through this solution for 10 min then the flow was increased to a more vigorous rate. To the solution was added 0.22 g (0.01 mol) of palladium acetate and 0.35 g (0.01 mol) of dicyclohexylphosphino biphenyl. The reaction was kept at a positive pressure of nitrogen after addition of the catalyst. The reaction mixture was allowed to stir for 72 h, at which time it was quenched with a stream of air. A large aliquot was removed and starting materials and

solvent were removed by vacuum distillation. The resulting dark red residue was analyzed by ^{1}H-NMR and the ratios of products were determined by comparing analogous olefinic proton integrations.

Heck reaction for NMR sample preparation and recovery of starting material

p-Iodotoluene in the Heck reaction using DCPB as the phosphine ligand: Example procedure

A mixture of 200 mL of dimethyl formamide and 21.8 g (0.100 mol) of *p*-iodotoluene was sparged for with nitrogen for 30 min. To this was added 20.2 g (0.200 mol) of triethyl amine and 10.0 g (0.100 mol) of ethyl acrylate. Nitrogen was allowed to gently bubble through this solution for 10 min then the flow was increased to a more vigorous rate. To the solution was added 0.22 g (0.01 mol) of palladium acetate and 0.35 g (0.01 mol) of DCPB. The reaction was kept at a positive pressure of nitrogen after addition of the catalyst. The reaction was then carried out until the desired conversion (80-85%) was reached determined by NMR spectroscopy. After reaching an acceptable conversion (usually 24-36 h) the reaction was quenched by a stream of air and addition of 150 mL of deionized water. The resulting biphasic solution was decanted into a separatory funnel and the phases allowed to separate. The lower organic phase was removed and chromatographed on a 25 mm X 6 in. silica gel column using hexanes as the eluent. After chromatography, 2.16 g of iodotoluene was recovered at 85% conversion. Following NMR measurements, kinetic isotope effects were determined mathematically using isotopic ratios.

NMR measurements of kinetic isotope effects

NMR spectra were obtained on samples prepared by placing 0.44 g of fresh or recovered iodotoluene in a NMR tube and filling the tube to 5 cm depth with deuterated acetonitrile. A T_1 determination by the inversion-recovery method was carried out for each NMR sample, and the T_1's were found to remain constant from sample to sample. The spectra were obtained at 100.58 MHz with inverse gated decoupling. At a delay of 105 seconds between calibrated 90^0 pulses with an acquisition time of 6.00 seconds, 64 transients were taken, affording a high signal to noise ratio. Integrations were determined numerically using a constant region for each peak that was defined as the widest delta for a specific peak among all of the arrayed spectra (delta being the area from where the peak leaves the baseline to where it returns on the other side of the peak). A 0^{th} order baseline correction was generally applied but in no instance was a higher order correction applied.

NMR results

For the ^{13}C spectra of *p*-iodotoluene the integrations of the methyl group (C_5) were set at 1000. The average integrations for other carbons are shown in Table 5-1. Six spectra were recorded for each sample. Scheme 19 shows the numbering convention.

Scheme 19.

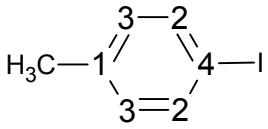


Table 5-1. Average ^{13}C integrations for *p*-iodotoluene.

% Conversion	C_1	C_2	C_3	C_4	C_5
Standard	992.0371	2013.303	2020.912	1006.208	1000
84 ± 1 %	990.5867	2028.098	2019.413	1052.87	1000
84 ± 1 %	984.45	2020.773	2011.243	1049.795	1000
85 ± 1 %	989.065	2029.75	2018.383	1045.557	1000
85 ± 1 %	991.3533	2023.917	2018.267	1043.74	1000

The values for R/R_0, calculated as the ratio of average integrations in Table 5-1 relative to standard, are shown in Table 5-2. The standard deviations were calculated from the formula:

$$\Delta R/R_0 = R/R_0 \times ((\Delta \text{ IntSample}/ \text{IntSample})^2 + (\Delta \text{ IntStandard}/ \text{IntStandard})^2)^{1/2} \quad (1)$$

Table 5-2. R/R_0 for ^{13}C.

R/R_0 and standard dev.	C_1	C_2	C_3	C_4	C_5
84 ± 1 % R/R_0	0.998543	1.007349	0.999259	1.046374	1
Standard Deviation	0.002807	0.00238	0.00287	0.0049249	0
84 ± 1 % R/R_0	0.990768	1.004765	0.99654	1.04367	1
Standard Deviation	0.002913	0.002527	0.002656	0.003069	0
85 ± 1 % R/R_0	0.995412	1.009228	1.000078	1.039457	1
Standard Deviation	0.002989	0.003113	0.002823	0.002452	0
85 ± 1 % R/R_0	0.999316	1.005272	0.998691	1.0373	1
Standard Deviation	0.002459	0.001587	0.001892	0.003036	0

The ^{13}C KIEs for *p*-iodotoluene were then calculated from eq. 2, with the standard deviations calculated from eq. 3, 4, and 5 and are shown in Table 5-3.[18]

$$KIE_{calcd} = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]} \quad (2)$$

$$\Delta KIE_F = \frac{\partial KIE}{\partial F}\Delta F = \frac{-\ln(R/R_0)}{(1-F)\ln^2[(1-F)R/R_0]}\Delta F \quad (3)$$

$$\Delta KIE_R = \frac{\partial KIE}{\partial (R/R_0)}\Delta(R/R_0) = \frac{-\ln(1-F)}{(R/R_0)\ln^2[(1-F)R/R_0]}\Delta(R/R_0) \quad (4)$$

$$\Delta KIE = KIE*((\Delta KIE_R/KIE)^2 + (\Delta KIE_F/KIE)^2)^{1/2} \quad (5)$$

Table 5-3. ^{13}C KIEs.

Sample	C_1	C_2	C_3	C_4	C_5
84±1%	0.9992(3)	1.004(2)	0.996(3)	1.025(4)	1
84±1%	0.9953(3)	1.003(3)	0.998(3)	1.022(3)	1
85±1%	0.9976(3)	1.005(3)	1.000(3)	1.021(2)	1
85±1%	0.9996(3)	1.003(2)	0.9993(2)	1.019(3)	1

CHAPTER VI

CONCLUSION

The KIEs observed above provide strong evidence for the mechanism of the oxidative addition step. These results clearly support the oxidative addition as being the primary mechanistic step in the multistep oxidative addition phase of the catalytic cycle. While formation of a π-complex cannot be ruled out, it is certain that the π-complex does not determine the outcome of the oxidative addition. These results assure us that this new class of ligands performs the oxidative addition in the same fashion as classical ligands do in the Heck olefination. Additionally, reaction conditions in which only one equivalent of phosphine was added has led us to believe that a XPdL species is the active catalyst as opposed to the generally accepted $XPdL_2$ in systems using conventional ligands. These exciting discoveries address some fundamental questions that were in need of clarification, while opening the door to a whole host of new possibilities. The selectivity studies show that the greater the electron deficiency of an olefin, the higher the reactivity towards this reaction. Both PPh_3 and DCPB show similar selectivities for the alkenes, which is indicative of similar mechanistic steps shared between the two systems. It is unclear what special property of DCPB makes it more active for aryl chlorides in other coupling reactions, since our data shows it behaves similarly to PPh_3 in many aspects.

Variables such as solvent, base, and temperature as well as the inherent differences in starting materials could be playing a mechanistic role in other systems that are not expressed in the Heck reaction. Elucidation of alkene selectivity could prove quite helpful for savvy synthetic chemists who hope to harness the power of the Heck reaction, but must contend with multiple alkenes within the same molecule. An understanding of the selectivity provides them with a tool to better decide if the Heck reaction is a viable option for their particular task. Surely if there were an alkene that was very electron poor and a relatively electron rich alkene as well, the synthetic chemist could be fairly confident that the electron poor alkene would emerge as the dominant reactant. These studies have provided a better understanding of the nature of selectivity in the Heck reaction with regards to both aryl halide and olefin. As well as a basis for understanding oxidative addition in this system compared to more traditional systems.

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APPENDIX

THEORETICAL CALCULATIONS

All calculations were carried out using Gaussian 03.[101]

Iodotoluene (starting material) B3LYP/6-31G*.

E(RB+HF-LYP) = -282.377558763

Zero-point correction=	0.117502 (Hartree/Particle)
Thermal correction to Energy=	0.125325
Thermal correction to Enthalpy=	0.126269
Thermal correction to Gibbs Free Energy=	0.082386
Sum of electronic and zero-point Energies=	-282.263494
Sum of electronic and thermal Energies=	-282.255671
Sum of electronic and thermal Enthalpies=	-282.254727
Sum of electronic and thermal Free Energies=	-282.298610

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	78.643	27.776	92.360

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.988081	0.003718	-0.002988
2	6	0	2.264546	1.203138	-0.003103
3	6	0	0.864841	1.213917	-0.001488
4	6	0	0.176646	0.002171	-0.000444
5	6	0	0.867661	-1.210788	-0.001572
6	6	0	2.264776	-1.198860	-0.003056
7	1	0	2.796898	2.151955	-0.004997
8	1	0	0.329601	2.157932	-0.002092
9	1	0	0.332526	-2.154886	-0.002242
10	1	0	2.798172	-2.147575	-0.004939
11	6	0	4.500090	-0.003279	0.004939
12	1	0	4.891259	-0.430887	0.937387
13	1	0	4.901809	-0.604609	-0.820132
14	1	0	4.904766	1.009665	-0.091210
15	53	0	-1.971979	-0.000787	0.000651

Transition state with Pd(dimethylphosphino phenyl)/iodotoluene complex B3LYP/ 6-31G* on all atoms except for Pd and I, SDD on Pd and I.

E(RB+HF-LYP) = -1063.20092103

Zero-point correction=	0.285717 (Hartree/Particle)
Thermal correction to Energy=	0.306707
Thermal correction to Enthalpy=	0.307651
Thermal correction to Gibbs Free Energy=	0.228931
Sum of electronic and zero-point Energies=	-1062.915388
Sum of electronic and thermal Energies=	-1062.894398
Sum of electronic and thermal Enthalpies=	-1062.893454
Sum of electronic and thermal Free Energies=	-1062.972175

	E (Thermal)	CV	S
	KCal/Mol	Cal/Mol-Kelvin	Cal/Mol-Kelvin
Total	192.462	73.670	165.682

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.130891	3.007880	-1.003530
2	6	0	-1.640692	1.696764	-1.080634
3	6	0	-1.473231	0.964666	0.097191
4	6	0	-1.888929	1.486947	1.326944
5	6	0	-2.377178	2.796792	1.380042
6	6	0	-2.501550	3.579857	0.221031
7	46	0	-0.291857	-0.609310	0.089108
8	15	0	2.136937	-1.191681	0.374252
9	53	0	-2.510546	-1.930958	-0.322017
10	6	0	-3.035451	4.993217	0.297344
11	1	0	-3.978102	5.036526	0.856797
12	1	0	-3.220036	5.404498	-0.700823
13	1	0	-2.327398	5.661890	0.805215
14	1	0	-2.683066	3.206693	2.341365
15	1	0	-1.832605	0.891020	2.233224
16	1	0	-1.395606	1.265343	-2.046653
17	1	0	-2.242765	3.582698	-1.921163
18	6	0	3.316536	0.166095	-0.030876
19	6	0	2.717128	-2.608691	-0.671554
20	6	0	2.662630	-1.729039	2.069519
21	1	0	3.726099	-1.991016	2.109476
22	1	0	2.468155	-0.923005	2.783699

23	1	0	2.069292	-2.600523	2.366093
24	6	0	2.810685	1.422469	-0.399050
25	6	0	3.676404	2.476466	-0.708685
26	6	0	5.058678	2.285641	-0.654266
27	6	0	5.574814	1.037489	-0.287884
28	6	0	4.709804	-0.013590	0.022055
29	1	0	1.735286	1.578765	-0.444752
30	1	0	3.267613	3.442846	-0.991862
31	1	0	5.732796	3.103412	-0.895692
32	1	0	6.650034	0.883282	-0.244088
33	1	0	5.130211	-0.975985	0.304969
34	1	0	3.773340	-2.845061	-0.499566
35	1	0	2.112224	-3.491666	-0.440096
36	1	0	2.572271	-2.363248	-1.727852

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