April 2015

An Evaluation of the C-H Activation Potential of Palladium Catalysts

Mark Alexander Mantell
Worcester Polytechnic Institute

Worcester Polytechnic Institute

Department of Chemistry and Biochemistry

An Evaluation of the C-H Activation Potential of Palladium Catalysts

A Major Qualifying Project submitted for review to the faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

Submitted by:

Mark Mantell

Project advisor:

Dr. Marion H. Emmert, WPI Department of Chemistry and Biochemistry

2015

Contents

Abstract

The breaking of a carbon – hydrogen bond, or C-H activation, is a very energetically intensive process, as the bond is almost entirely inert. Despite the difficulty of the process, understanding what drives efficient C-H activation can allow for the direct functionalization of aryl or alkyl C-H bonds. This direct functionalization has the potential to drive late-stage functionalization, which can aid in the synthesis of complex molecules without the need for pre-functionalized reactants. This project aimed to examine the C-H activation ability of various palladium catalysts by measuring their H/D exchange activity. H/D exchange is the exchange of a hydrogen atom for a deuterium atom on a hydrocarbon by breaking the original C-H bond. This can serve as a measure of efficiency for the C-H activation process, as the H/D exchange does not change the reactivity of the substrate molecule. This project examined several trends in H/D exchange ability of palladium catalysts, including the effects of sterically bulky ligands, ligands with varying electronic character, and the effect of varying the temperature of reaction.

Acknowledgements

I would like to thank Dr. Marion Emmert for her guidance and support throughout this project. I would also like to thank Dr. Dhammika Bandara and Dr. Kathleen Field for their aid in the project and in teaching me to be a better chemist. I also thank the rest of the Emmert lab, as they always were there to lend a helping hand when I needed it throughout this year and those previous that I worked in the lab.

1. Introduction

1.1 Motivation

Traditionally, the synthesis of complex molecules is conducted through the exchange of various functional groups.[1] This method, while effective for functionalizing smaller molecules, has several drawbacks for synthesis. The largest problem with traditional functionalization is the waste created by the exchange of functional groups.[2] When the substitution occurs, the leaving group becomes waste, which will quickly add up on the industrial scale.

One alternative to traditional functional group exchange is direct Carbon-Hydrogen (C-H) bond functionalization.[1] This process involves the breaking of the carbon-hydrogen bond selectively at the desired location and inserting a functional group in one step. Without the initial breaking of the carbon-hydrogen bond, or C-H activation, the rest of the C-H functionalization cannot continue. [3] This is the most energy intensive step of the reaction as carbon hydrogen bonds are among the strongest bonds in organic chemistry, which presents a hurdle for the overall functionalization.[3]

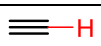
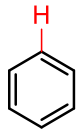
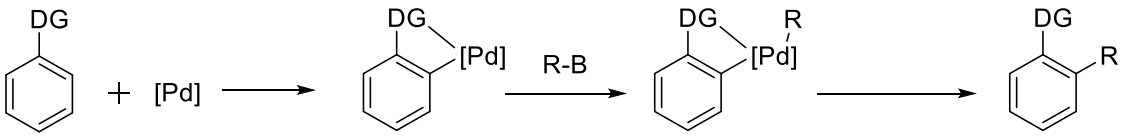
Bond Type	Bond Energy (kcal/mol)
	133
	113
	111
	105

Table 1: Chart of bond dissociation energies in (kcal / mol).

One method of driving this process is directed C-H functionalization.[4] This process utilizes a "directing group" (DG in Scheme 1), or a group on a substrate molecule whose purpose is to draw a catalytic center into close proximity to a C-H bond, allowing for more energetically favorable activation. The directing group then facilitates bonding of the center to the substrate carbon, and remains in place throughout the functionalization. While the directing group makes direct C-H activation less energetically intensive, the process leaves the directing group on the functionalized substrate molecule. This group may be unwanted on a final product, but can be difficult to remove on complex substrates, creating a substantial amount of waste in its removal.

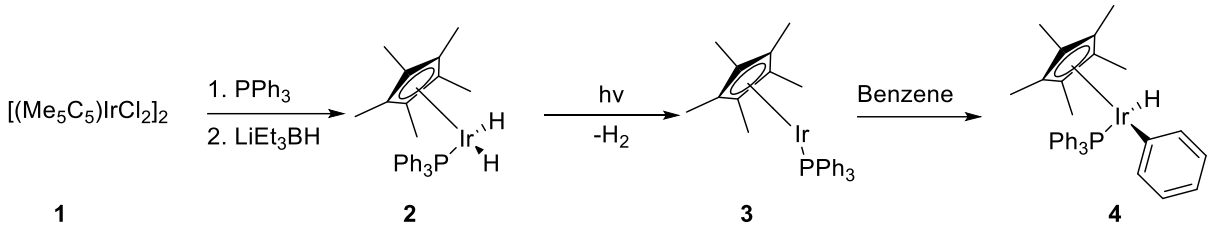


Scheme 1: General mechanism of directed C-H functionalization.

The other method of driving this process is non-directed C-H functionalization.[3] This process does not utilize a directing group, but is still able to break a C-H bond. These processes are less common than those that utilize directing groups, but they can still be both effective and stereo-selective. They also have the advantage of avoiding the use of a directing group, which means that non-directed C-H functionalization has the potential to selectively attack C-H sites on more complex substrates and it avoids the potential increased waste from the use of groups that are unwanted on the final product. This introduction will examine the first examples of non-directed C-H activation through stoichiometric methods, before moving on to more modern catalytic methods of driving this important reaction.

1.2 Stoichiometric C-H Activation

One of the first examples of successful inter-molecular C-H activation was published by the Bergman group.[5] This work detailed the formation of alkyliridium complexes from hydrido precursors. The proposed mechanism begins with the irradiation of the precursor compound to evolve gaseous hydrogen, leaving a coordinatively unsaturated compound. This transition state was then attacked by the solvent benzene, leading to the formation of compound **4**.



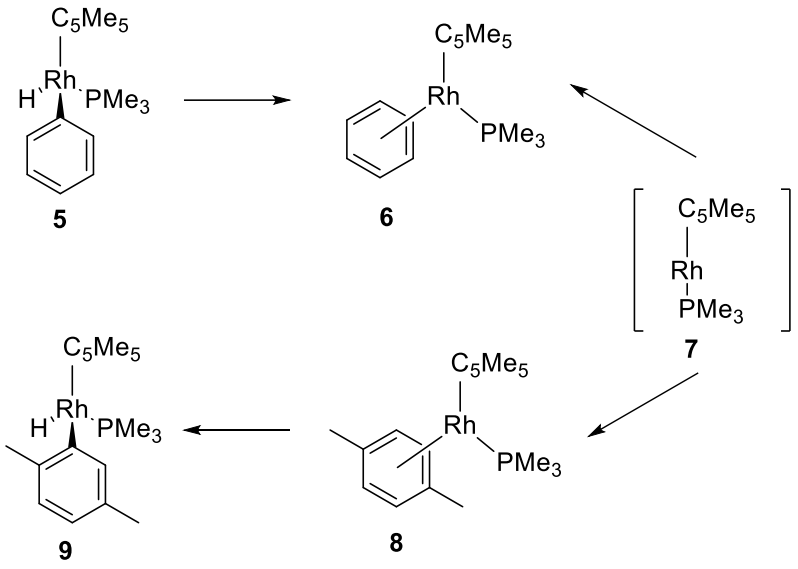
Scheme 2: Iridium catalyzed C-H activation reaction mechanism utilizing irradiation.

Although this is some of the earliest successful work on the subject, it was able to answer some important questions regarding the mechanism. First, the evolution of hydrogen gas from the solution after irradiation suggests the importance of the creation of compound **3**. The coordinatively unsaturated compound is necessary for the coordination of the solvent. The selectivity for primary or secondary C-H bond activation was also studied. Through the analysis of a solution containing a 50:50 mixture of cyclohexane and neopentane, it was found that the coordination of neopentane was favored, a compound with exclusively primary C-H bonds, as opposed to cyclohexane, a compound with exclusively secondary C-H bonds. This preference points to selectivity for primary C-H bonds. With a preference for primary C-H bonds, a mechanism involving organic radicals is more unlikely, as radical species would be more thermodynamically stable if the radical electron was situated on a secondary carbon.

Through a later study, the mechanism of the reaction was further examined.[6] Through several examinations of the reaction, it was concluded that while a radical process cannot be fully ruled out, it is most likely that the activation proceeds through the formation of a three-centered complex between the metal, carbon, and the alkyl hydrogen. The ratio of primary/secondary activation was also retested, and they found that the ratio was variable at the original reaction temperature. At an elevated temperature, however, the reaction was very

selective, and produced only the primary product. This shows a thermodynamic preference for the primary activation in addition to the kinetic preference shown in the previous study. Additionally, the study showed that the reaction can be used for functionalization, and demonstrated the ability of the complex to synthesize halogenated hydrocarbons.

A second example of stoichiometric C-H activation was published by the Jones group in 1984.[7] This example features a rhodium center, and focused mainly on the coordination of arenes.



Scheme 3: Rhodium catalyzed C-H activation reaction mechanism.

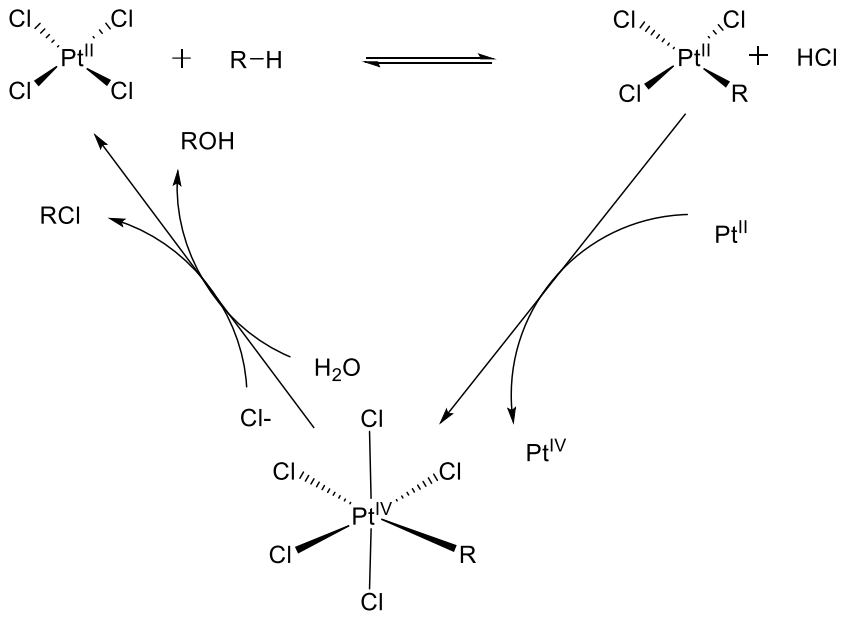
UV irradiation was utilized to provide enough energy to remove the hydride and aryl ligands from the rhodium center, yielding free benzene and compound **7** through reductive elimination. By demonstrating the formation of a bond between the rhodium center and an arene

molecule, it was suggested that the carbon-hydrogen bond was broken, allowing a free arene to coordinate with the now coordinatively unsaturated rhodium ion.

One important observation was the measurement of the free energy associated with the formation of the new metal-carbon complex. The free energy diagram of the reaction provided evidence for several conclusions. The most important of these conclusions is evidence for the formation of η-2 intermediate complexes which reacted further to form the desired complex and break the C-H bond, representing the rate-determining step for the reaction. This step proceeds differently for alkane activation, which requires the formation of a three-center transition state, as seen in previous research.

1.3 Catalytic C-H Activation

After the discovery of stoichiometric means of C-H activation, several groups began the evaluation of transition metal catalysts for C-H activation. One of the first discoveries was made by the Shilov group, which described the conversion of alkanes to alcohols using platinum (II) catalysts.[8] This reaction is proposed to proceed by a mechanism with three main steps; the C-H activation, the oxidative addition, and the reductive elimination. This catalytic mechanism is superior to stoichiometric C-H activation, as it allows for the functionalization of more substrate with a much smaller amount of metal complex.

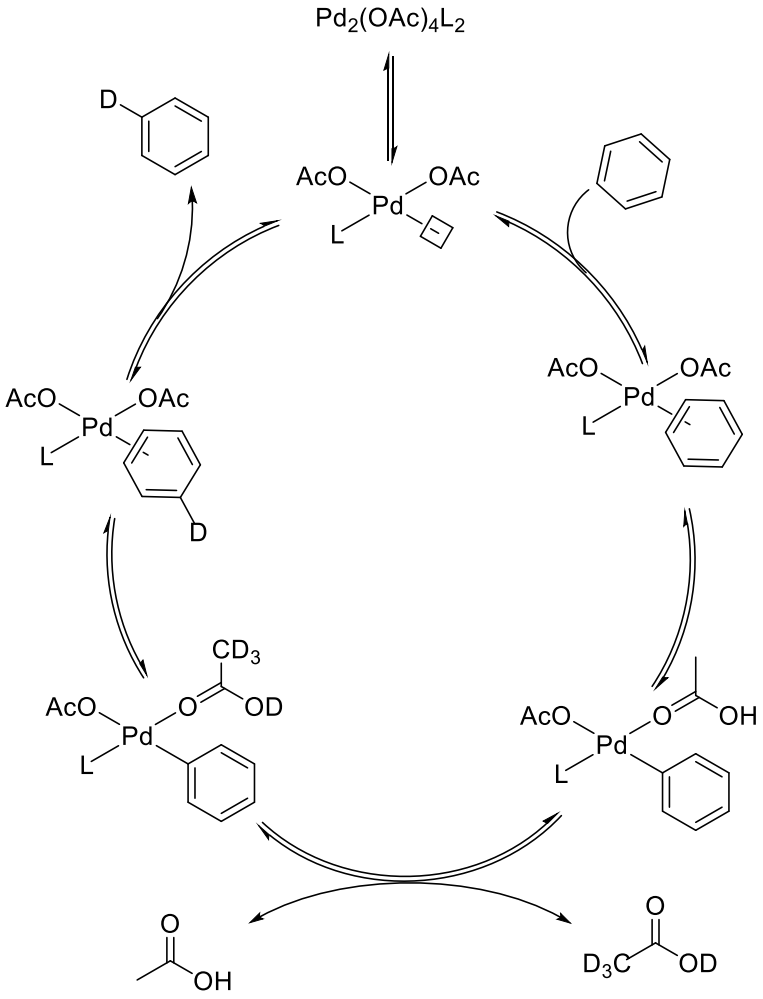


Scheme 4: An example of the Shilov platinum catalysis mechanism.

1.3.1 H/D Exchange Reactions

H/D exchange serves as a measureable quantity to the C-H activation potential of a catalyst, which in turn provides a parallel to the ability of a catalyst to drive C-H functionalization. When a C-H bond is broken, it allows for the bonding of other functional groups. Therefore, the measurement of the C-H bond breaking ability of a catalyst provides part of the picture of the efficiency of a reaction cycle which leaves a functionalized aryl or alkyl molecule in place of the C-H bond. H/D exchange describes the isotopic exchange of hydrogen for deuterium by exposing an alkyl or aryl C-H bond on a substrate molecule to catalytic conditions in a protic deuterated solvent (Scheme 4). In order for isotopic exchange to occur, the original C-H bond on the substrate must be broken. This process, however, does not change the reactivity of the substrate, meaning that the ability for a catalyst to drive the C-H activation would not change as

the reaction alters the substrate, giving a clear look at the ability of the catalyst to act on the C-H bonds of the substrate.



Scheme 5: Proposed mechanism of H/D exchange.

After the reaction, the percent deuterium incorporation onto the test molecule is measured using GC-MS (Gas Chromatography - Mass Spectroscopy) by analyzing the differences in abundance of the molecular weights of the test molecule, in this case benzene, with differing degrees of deuterium incorporation (Figure 1: Example of GC-MS spectrum for the H/D exchange of benzene. The peaks corresponding to benzene and deuterated benzene are outlined

in a yellow box.). The percent deuterium incorporation is calculated from the percent of each isotopolog of benzene containing deuterium multiplied by the number of hydrogen replaced by deuterium in the molecule. The percent deuterium incorporation is then divided by the molar amount of catalyst to give a turnover number (TON). This turnover number is then used as a comparison point for the C-H activation potential of each catalytic system, as it gives information of how many catalytic cycles, or number of C-H bonds broken, are attainable by each system in a standard amount of time.

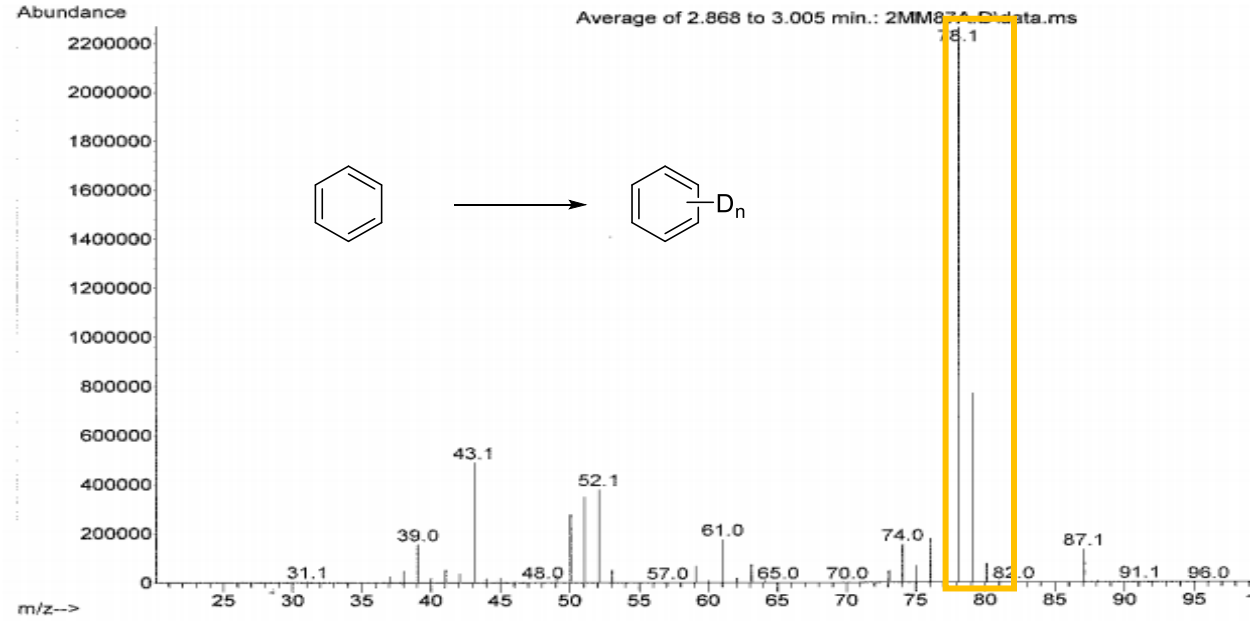


Figure 1: Example of GC-MS spectrum for the H/D exchange of benzene. The peaks corresponding to benzene and deuterated benzene are outlined in a yellow box.

In recent research by the Sanford Group, H/D exchange has been utilized to quantitatively measure the ability of a catalyst to promote C-H activation.[9] Using the above method, a systematic test of ten similar platinum catalysts in different reaction conditions was conducted to

determine their effect on H/D exchange. In these tests, three major trends in platinum catalyst design for efficient H/D exchange were determined. First and foremost was the superiority of bidentate ligands to simpler platinum salts.

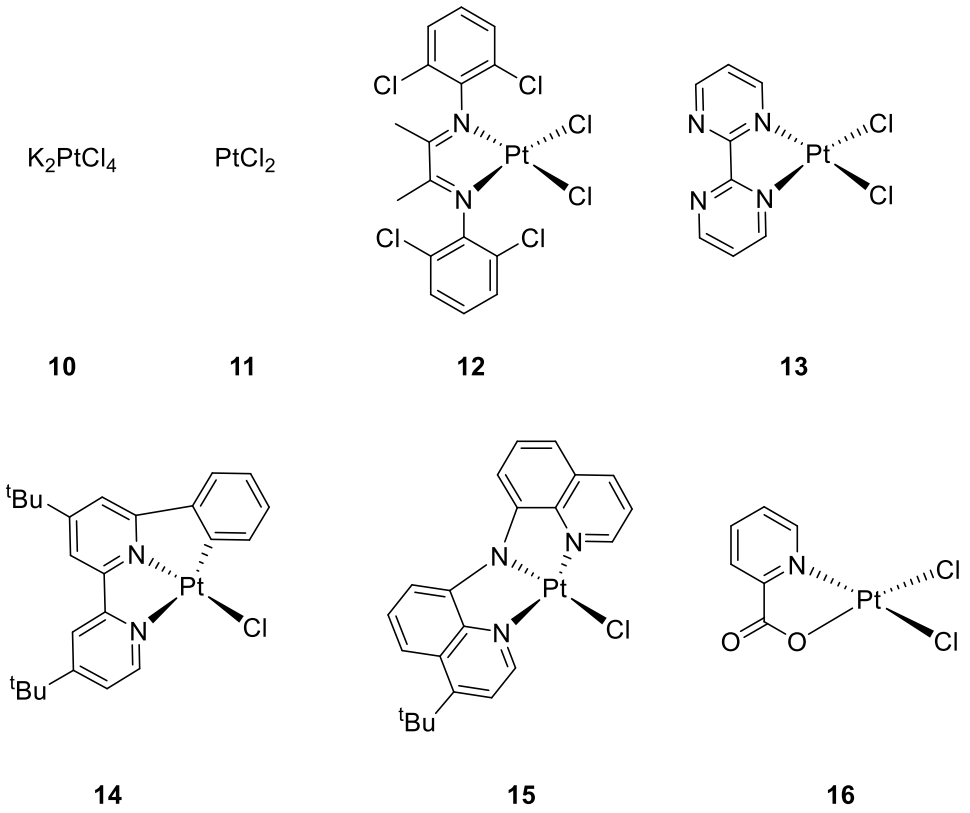
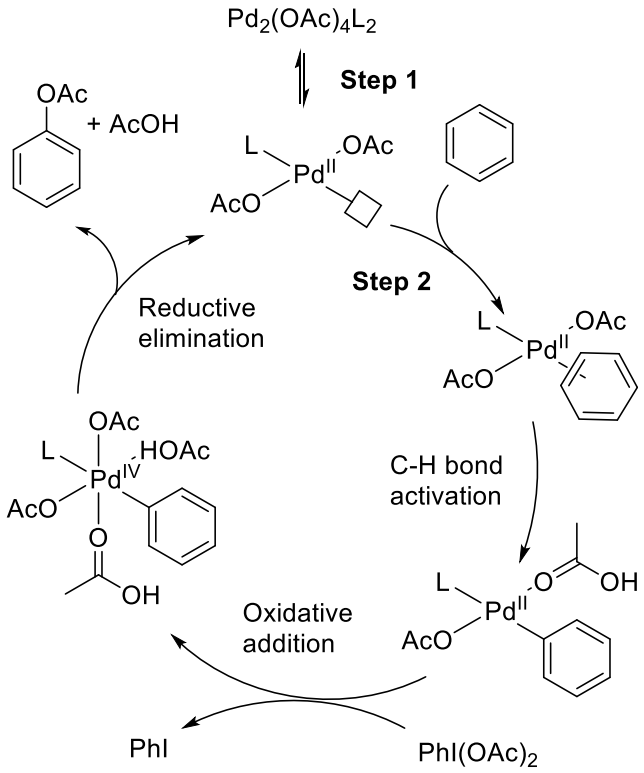


Figure 2: Catalysts tested by the Sanford Group.

The simple platinum salts **10** and **11** showed decomposition of the catalyst in the formation of a black precipitate, which was confirmed as platinum black, and yielded very low turnover numbers of 45 and 44 respectively. Catalysts with bidentate ligands on the other had showed much greater success, yielding turnover numbers of 207 and 202 for compounds **12** and **13** respectively. It was also concluded that bidentate ligands perform better than tridentate ligands,

which yielded turnover numbers of 53 and 46 for compounds **14** and **15** respectively. The third conclusion comes from the observation of catalyst decomposition even in the best example, which points to the necessity in further study to study methods of reducing decomposition pathways for the catalysts.

A temperature study was also conducted for each catalyst, examining temperatures in 25 °C intervals from 75 °C to the primary reaction temperature of 150 °C. In general, higher temperatures were able to provide better results, with complex **12** producing the best TON result at temperatures over 100 °C. Complex **16**, however, provides the best results for 75 °C and 100 °C with TON of 23 and 59 respectively. This complex sees relatively small improvements when the temperature was increased from here, and saw significant development of palladium black in the reaction mixture. This result leads to the conclusion that the complex has been decomposing significantly at higher temperatures, and that this represents the necessity of a balance between catalyst activity and catalyst stability. The activity of platinum catalysts is, while not exactly analogous, considered an indicator of the effectiveness of palladium catalysts as well. Platinum and palladium are in the same group in the periodic table, and thus have similar valence electron structures. This similarity allows for similar bonding activity between platinum and palladium, allowing study of one to give insight into the activity of the other.

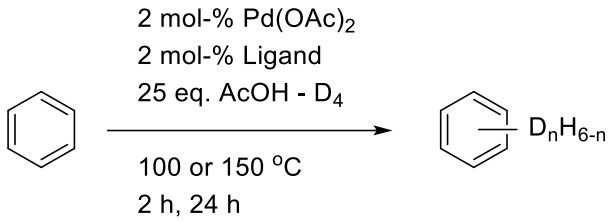


Scheme 6: Palladium catalyzed acetoxylation cycle as described by the Sanford Group.

1.4 Project Goals

The goal of this project is to investigate the C-H activation activity of Palladium catalysts for C-H activation of benzene through H/D exchange. Currently, the H/D exchange ability of palladium catalysts has not been studied in a systematic manner. This project aims to evaluate the H/D exchange ability of palladium catalysts in order to define trends in catalytic activity of C-H activation based on their success at H/D exchange when varying temperature, changing the steric bulk of the ligands, and varying electronic character of the ligands. The effect of these different types of ligands will be studied, as will the effect that temperature has on the H/D

exchange potential of each catalyst, and the amount of catalytic decomposition experienced in each system among other trends.



Scheme 7: Reaction conditions to be tested.

The measured H/D exchange provides a quantitative measurement of the C-H activation ability of the catalyst, which we hypothesize directly applies toward the overall goal of the one step functionalization of aryl molecules. The first step of these transformations is C-H activation, where the carbon hydrogen bond is inserted onto the metal center of the complex. This step is difficult to produce, as the C-H bond is relatively unreactive. Further adding to the difficulty, we intend to produce functionalization reactions without the use of a directing group. The ability to better understand the C-H activation step will allow for the development of more successful functionalization catalysts, which has the potential to make the synthesis of complex organic molecules considerably more efficient.

1.4.1 Approach

The planned investigation involves the varying of different ligands in identical H/D exchange reaction conditions, which are based upon the H/D exchange studies of the Sanford group.[12] These conditions provide an excess of the deuterium source, while keeping a low catalyst loading in relation to the benzene substrate, which allows for the catalyst's efficiency to be measured without needing to consider shortages of reagents. Two different temperature points are tested; 100 °C which gives a milder reaction environment and 150 °C for a harsher system. The 100 °C temperature point provides a potentially better system for complex substrates, which may decompose under harsh conditions. 150 °C, on the other hand, provides an environment with more energy, which may drive the reaction to perform better. Examining both systems will ensure that the catalysts are active in both conditions, which allows for more versatility. Reactions times of two hours and twenty four hours will be tested to yield information on both the initial activity of the catalyst and the stability of a catalyst as it reacts over a longer reaction time.

Both acridine and pyridine type ligands (Figure 2: Catalysts tested by the Sanford Group.) will be evaluated, which will draw information for two trends in ligand design. Sterically distinct ligands will be tested, examining the effect of both planar ligands of varying size and ligands which occupy more 3-D space around the catalytic center. Ligands with distinct electronic character will also be tested, which will give us a good understanding of the effects of ligands with electron donating or withdrawing groups on both the initial activity of a catalyst, and their effect on the long term stability of a catalyst.

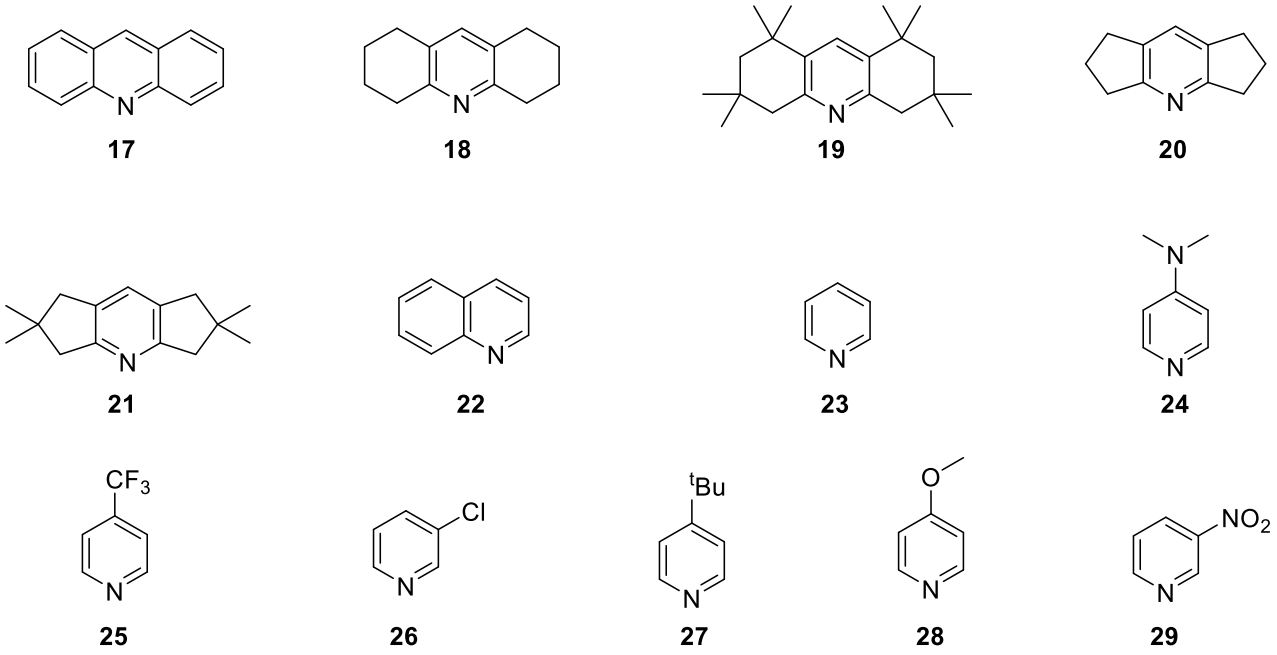


Figure 3: All ligands tested throughout catalytic studies.

2. Results and Discussion

2.1 Results

2.1.1 Temperature and Sterics Study

We first sought to examine the effects of temperature on the success of each catalyst both in initial rate of reaction and in longer term catalytic reactions. Overall, temperature was found to be a significant factor in the ability of a catalyst, as shown in Figure 4 and Figure 5, but had differing effects depending on the type of ligand. Some ligands, like ligands **19** and **23** showed improved reactivity at 150 °C, while others, like ligands **17** and **18** produced higher turnover numbers at 100 °C. The most successful ligand test was pyridine, which yielded a turnover number of 57.5 ± 1.0 after 24 h at 150 °C. This same study was also applied to the analysis of sterically distinct ligands. As described in the discussion, the analysis of these ligands is conducted on utilizing data gathered from the tests at 100 °C.

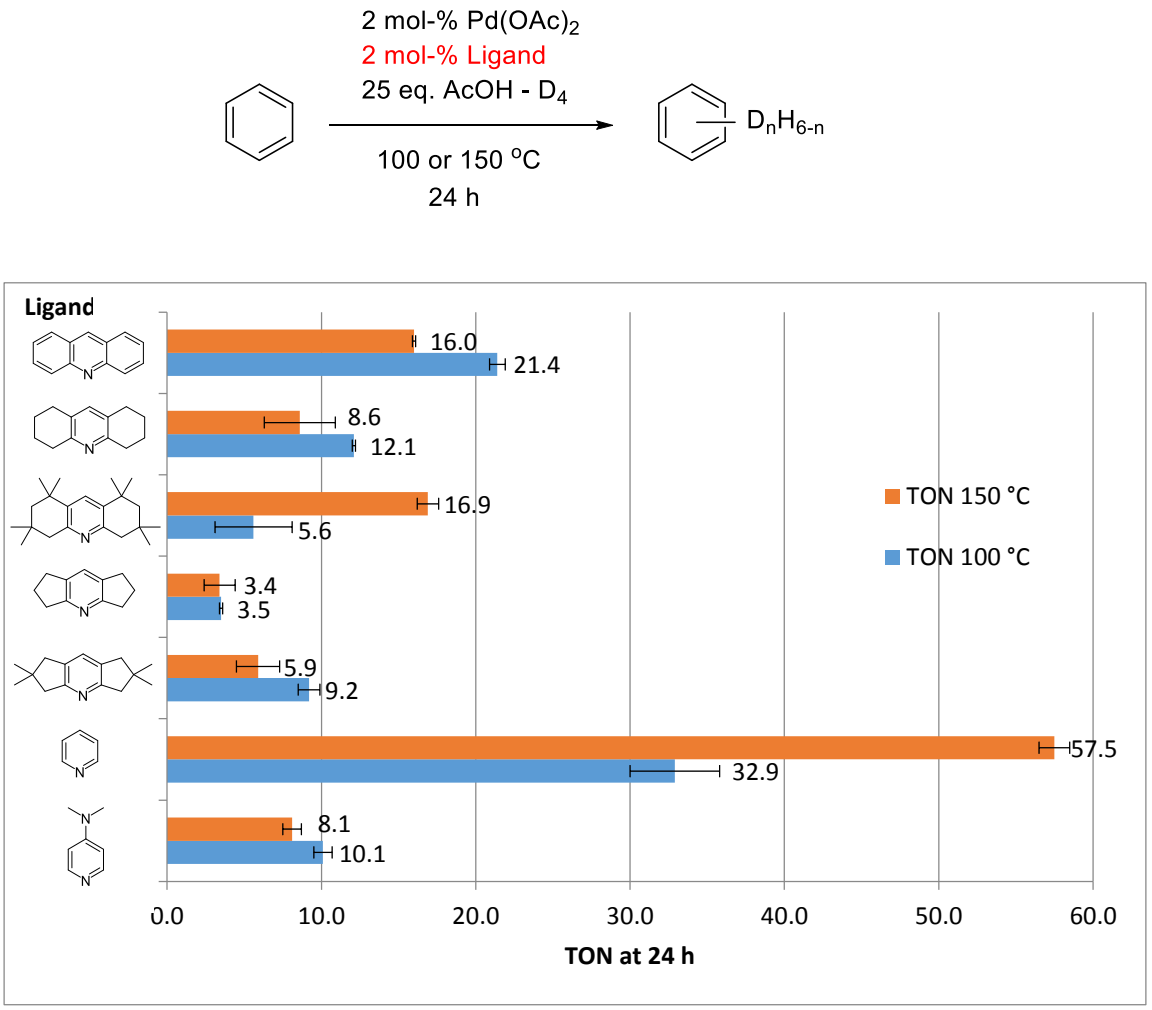


Figure 4: Graphical representation of H/D exchange results after 24h.

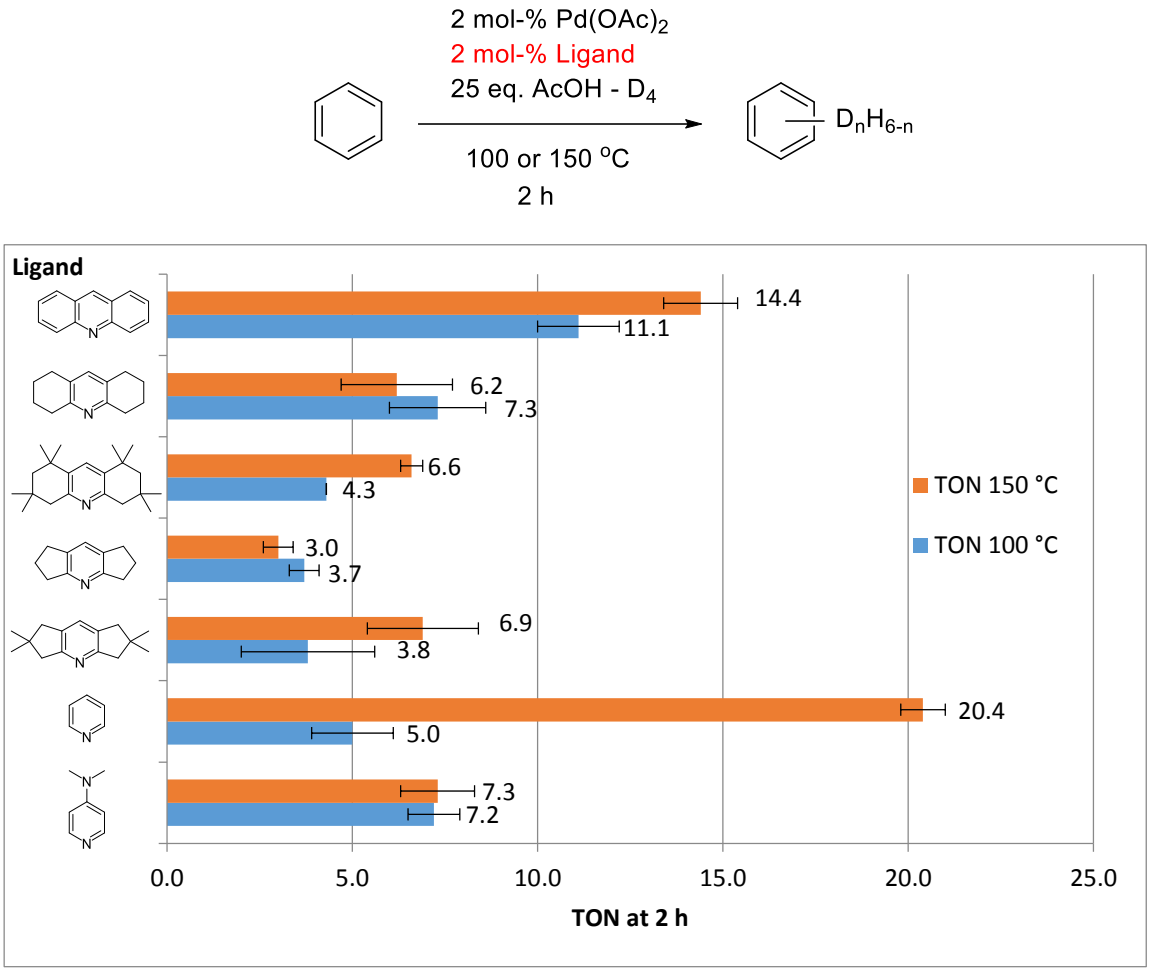


Figure 5: Graphical representation of H/D exchange results after 2 h.

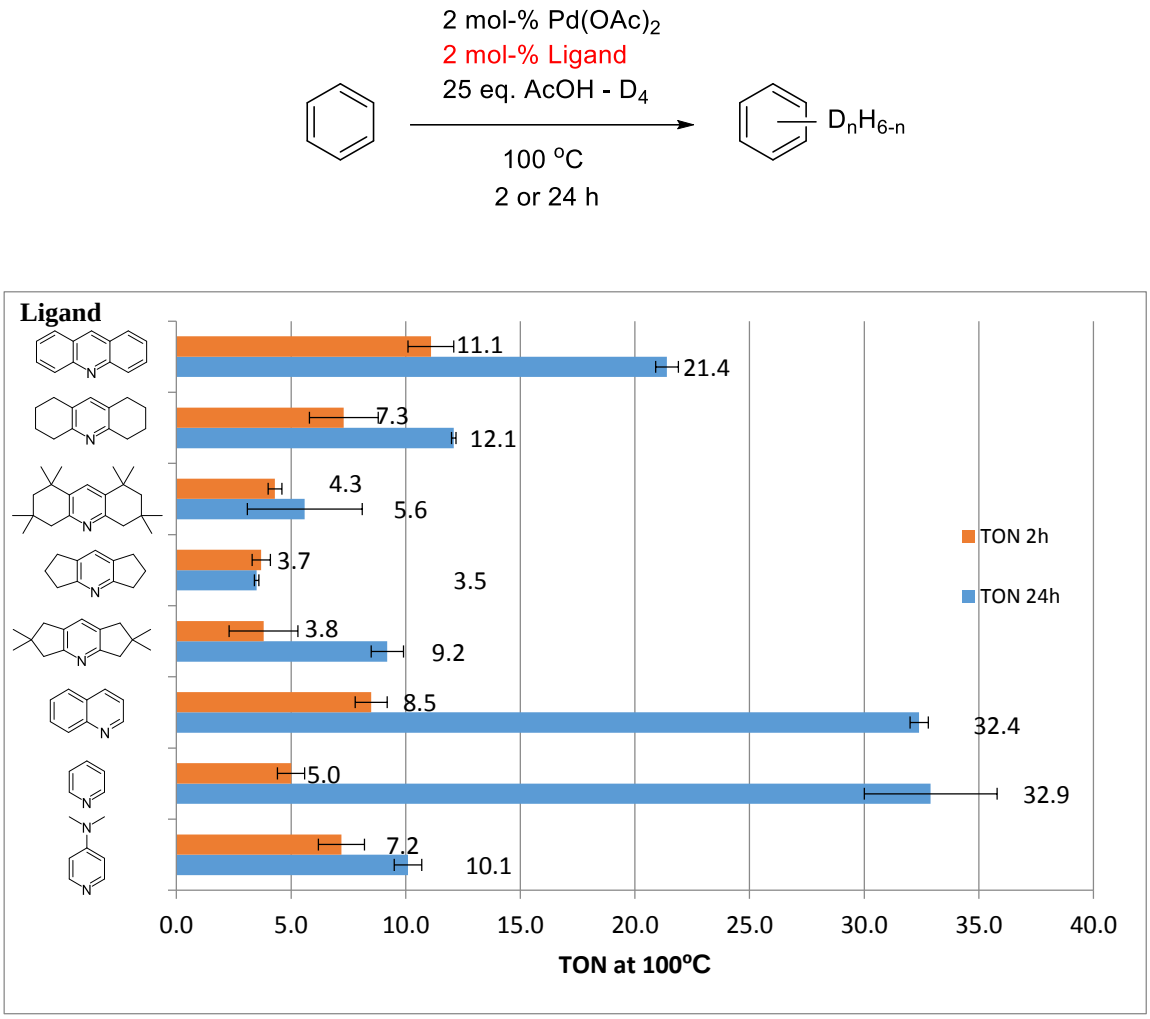


Figure 6: Graphical representation of H/D exchange results at 100 ºC. This data was used to analyze the effects of sterics on the catalyst system.

2.1.2 Electronic Character Study

After evaluating ligands for steric effects, the effects of ligands with distinct electronic character on the catalytic system were examined. This study was conducted at 100 °C to mirror the study of steric effects. By evaluating the TON achieved by ligands of varying electron withdrawing and donating character, we were able to draw trends in the activity of the catalysts,

which is discussed below. The most successful ligand at 2 h was (dimethylamino)pyridine which produced a TON of 7.2 ± 1.0, while pyridine produced the highest TON at 24 h, yielding a TON of 32.9 ± 2.9. Hammett plots were created to compare the TON produced by each ligand to its degree of electron donating or withdrawing character.

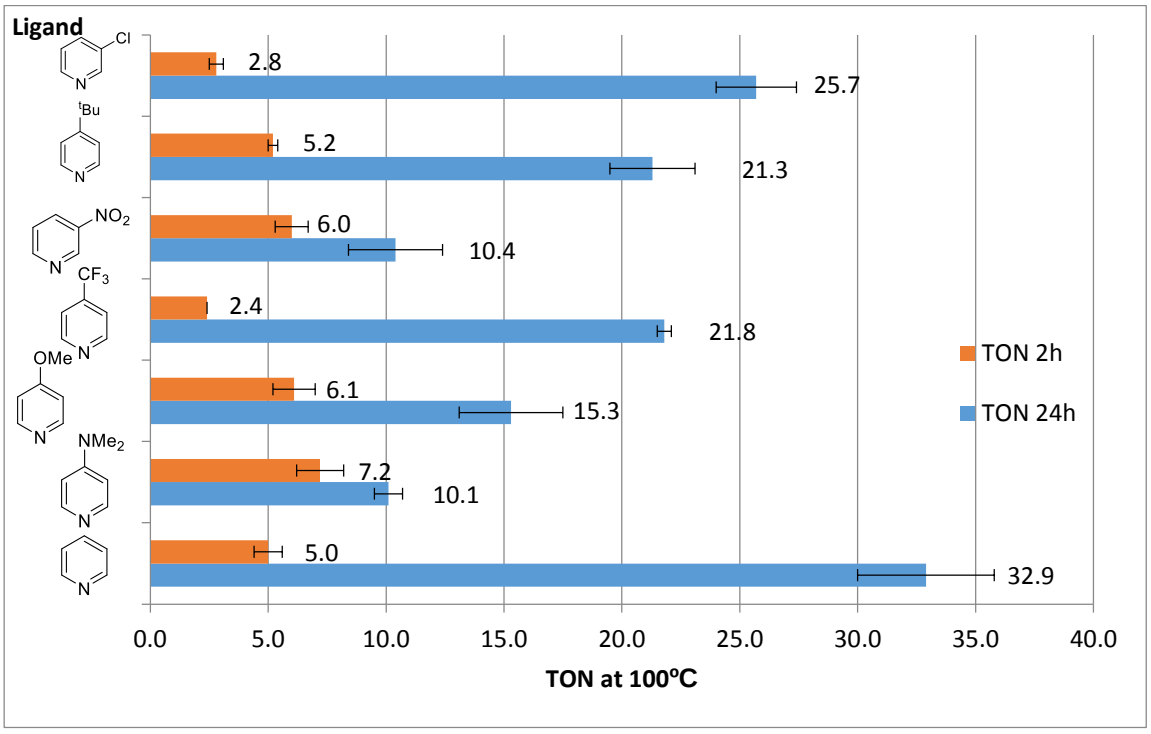


Figure 7: Graphical representation of H/D exchange results of ligands with distinct electronic character at 100 ºC.

2.2 Discussion

2.2.1 Effect of Temperature

Some ligands, such as ligands **19** and **23**, see significantly improved yields when the temperature is set at 150 °C. In these situations, the ligand is able to afford stability to the catalyst, and ensure that it proceeds with less significant decomposition. This allows the kinetic benefits of higher temperature prevail, allowing the catalyst to work more efficiently.

Other ligands, such as ligands **18** and **20,** produced higher TON at 100 °C. Those ligands afforded less stability to the catalyst, which allowed the reaction to proceed down a potential side pathway which causes the formation of biphenyl products. These products were observed through GC/MS in higher concentration in 150 °C samples, but were still observed in 100 °C samples. Ligands **18** and **20** also show a significant amount of palladium black formation in the reaction mixture, which is indicative of catalyst decomposition through the side pathway. In addition to the formation of the biphenyl products, at 100 °C, the formation of decomposition products of the ligand itself was observed through GC-MS.

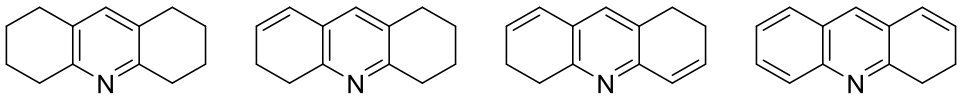


Figure 8: Ligand **18** is displayed to the left, with possible decomposition products are displayed to its right.

The reaction of ligand decomposition requires reduction on the part of the part of the catalyst to oxidize the ligand. This forces a change from Pd^{II} to Pd^{0}, leaving palladium black and killing

the catalyst. Therefore the ability to oxidize the ligand would create a less effective catalyst. The presence of these products was almost exclusively observed at 100 °C, which leads to the hypothesis that the oxidation conditions are better served at 100 °C, while the higher temperature point is too harsh for this formation.

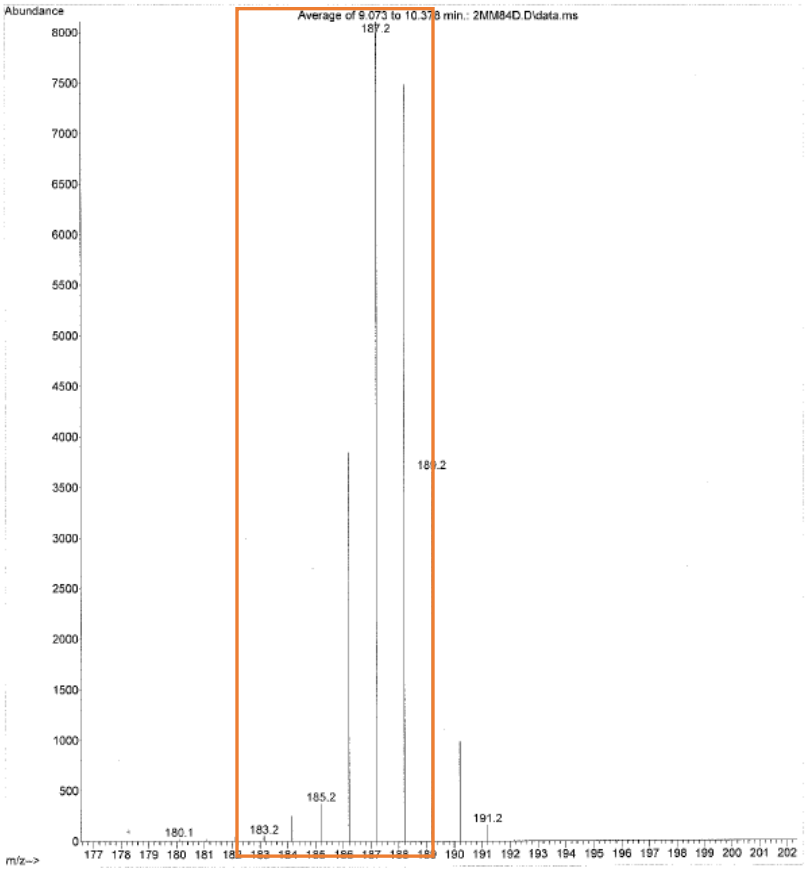


Figure 9: Example GC-MS spectrum showing the presence of decomposition products, which are outlined in an orange box.

For those ligands that afford the catalyst less stability, the 2 h data shows the same relationship, indicating that the trend is not limited to long term stability, but also to the initial

rates of reaction. Not all ligands that afforded stability, however, show the same relationship. Ligand A shows better TON at the 100 °C temperature point when reacted for 24 h, but at 2 h shows better initial reactivity at 150 °C.

2.2.2 Effect of Sterics

The most successful catalysts here are shown to be those that are relatively planar: Pyridine, quinoline, and acridine. The success of this catalytic system is dependent on the ability of a benzene substrate molecule to coordinate to the platinum center, without which C-H activation would not occur. It therefore stands to reason that a wider opening for approach would allow for increased catalytic success by allowing a more open angle for benzene to coordinate. Several density field theory (DFT) calculations were conducted which show the most energetically favorable conformation of a molecule, to help evaluate which catalysts would provide a wide opening.[10] As an example in Figure 10: Model of a ligand 22 coordinated palladium catalyst derived from DFT calculations.[10], a ligand **22** coordinated catalyst is displayed. Here it can be seen that when the acetate ligand opens an empty coordination site, the angle of approach would be relatively clear, as the quinoline does not significantly block the empty space.

Figure 10: Model of a ligand **22** coordinated palladium catalyst derived from DFT calculations.[10]

The model given by a more sterically bulky ligand, such as ligand **19**, tells a very different story. The image in Figure 11: Model of a ligand 19 coordinated palladium catalyst derived from DFT calculations.[10] shows the methyl-groups bonded to the outer rings of the ligand partially block the approach angle of a substrate benzene molecule, making the ligand altogether less effective at driving the catalytic reaction as it partially blocks the empty coordination site.

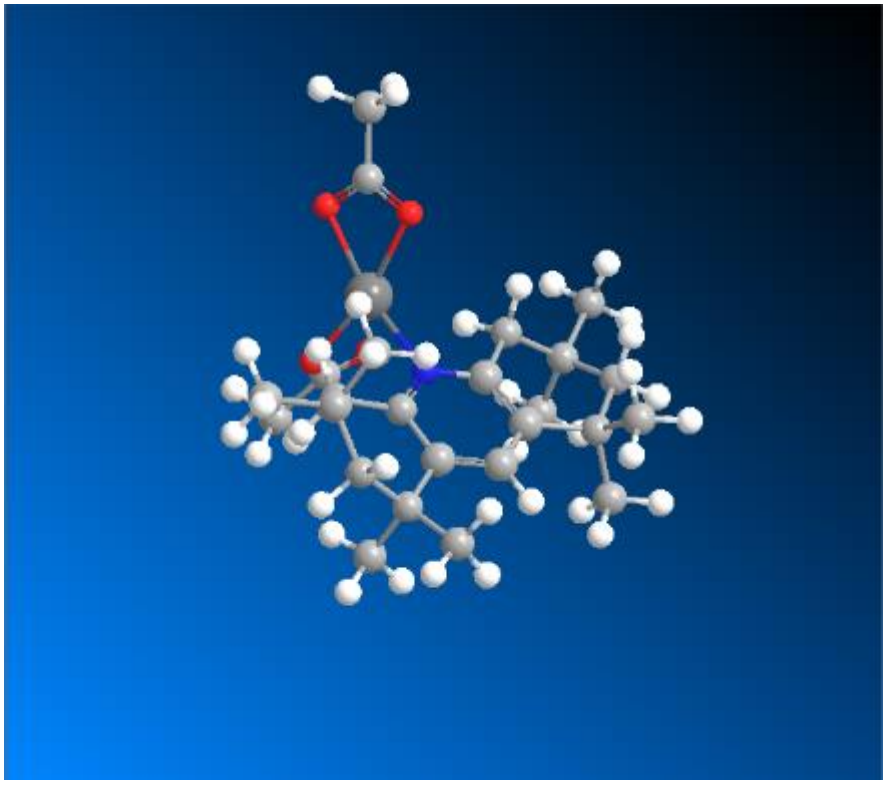


Figure 11: Model of a ligand **19** coordinated palladium catalyst derived from DFT calculations.[10]

While the effects of a sterically bulky ligand can be detrimental, they can also have some positive effects. Acridine, quinoline, and pyridine are each of a very different size, but each one remains planar, limiting the space they occupy. We examined each of these planar ligands through DFT calculations, and found that as the size of the planar ligand increases, so does the initial rate of reaction. This is shown through the activation energy for the change from a dimer to a monomer, as seen in Scheme 4, which is more favorable for the larger ligands to break into a monomer. While the results showed that it was more favorable for the larger ligands to break into the active monomer, this did not cause them to have increased activity on longer term

reactions. At the 24 h reaction time, less sterically bulky ligands showed the general trend of increased activity associated with occupying less space around the palladium center.

2.2.3 Effect of Electronic Character

After comparing the 24 h TON results of each ligand with its relative electron donating or withdrawing character, we created a Hammett plot to analyze the effect of the electronic character on the catalytic system. The data however, yielded two distinct trend lines, where in TON improves as σ values near 0, with pyridine yielding the best turnover number at Hammett σ value equaling 0.

This trend is well explained by a recent paper from the Sanford group, where the activity of catalysts with electron donating and withdrawing catalysts is applied to a similar system.[11] This study yielded a hypothesis regarding the activity of electron donating and withdrawing ligands on the catalytic cycle. Through the creation of a Hammett plot it was found that neither electron withdrawing nor donating ligands had a significant positive effect on the yield of the reaction when compared to pyridine. In a detailed look at the mechanism, it was hypothesized that where one type of ligand would aid in one step of the reaction, it would hinder another. As an example, it was hypothesized that an electron withdrawing ligand would hinder the separation of palladium centers from a dimer to the active catalytic monomer (Step 1 in Scheme 5), but would make the monomer more electron deficient, increasing its potential to attack the electron rich C-H bond in the substrate molecule (Step 2 in Scheme 5). Electron donating ligands were hypothesized to have an opposing effect, where Step 1 is promoted, and Step 2 hindered.

By the logic of the hypothesis, it stands to reason that a ligand that is neither strongly electron donating or withdrawing would yield the highest TON, as it avoids the negative effects

of strong electronic character. The data provides evidence for this, where the ligands that are strongly electronically active yield the worst turnover numbers over the full reaction time, and the less electronically active ligands improve the TON. This effect culminates with pyridine producing the highest turnover number, as it is the least electronically active.

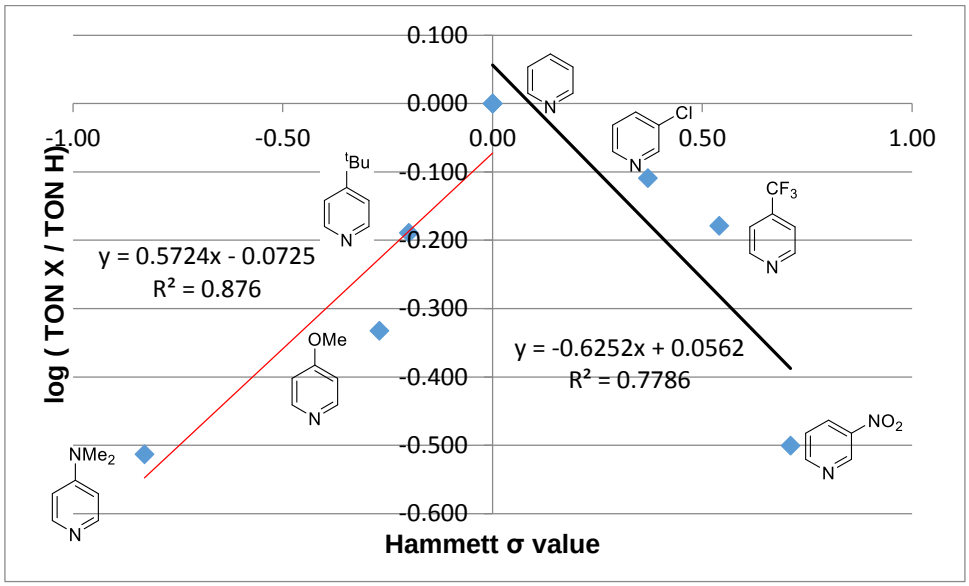


Figure 12: Hammett plot of 24 h data converted to the logarithmic product of the TON produced by the ligand divided by the TON of pyridine, the electronically neutral ligand. This provides a direct comparison to the Hammett plots referenced.[11]

The TON produced after 2 h also shows evidence for the same hypothesis, where electron donating ligands are yielding higher turnover numbers than electron withdrawing ligands. Having only reacted for 2 h, this data is much more indicative of the initial reactivity of the system. According to the hypothesis above,[11] electron donating ligands promote the breaking of the dimer into the reactive monomer, indicating that the first stages of the reaction would be promoted. The data supports this, as the initial TON yielded by the electron donating systems is

higher than that of the electron withdrawing systems, which would require more time to overcome the barrier of breaking the dimer.

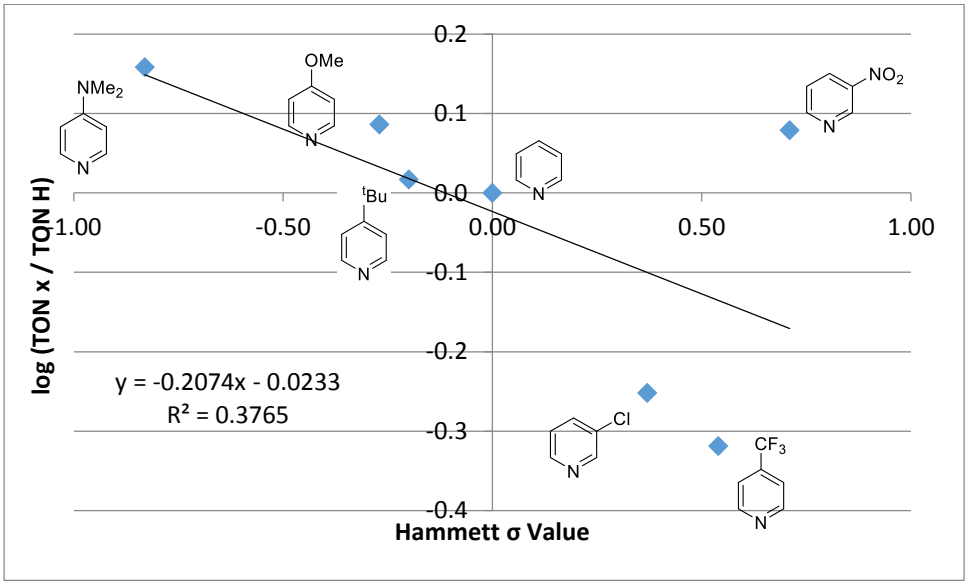


Figure 13: Hammett plot of 2 h data converted to the logarithmic product of the TON produced by the ligand divided by the TON of pyridine, the electronically neutral ligand. This provides a direct comparison to the Hammett plots referenced.[11]

3. Conclusions and Future Directions

Through the studies conducted, a trend was determined in the effects of temperature, the effects of sterics, and the effect of electronic character on the TON produced by the catalytic system. The data shows that where more stable ligands produce higher TON at higher temperature, ligands that afford the catalyst less stability will produce higher TON at lower temperature. This conclusion lead to the other tests being conducted and analyzed at a lower temperature. Sterics were found to have a significant effect on catalytic activity. Large non-planar ligands were found to produce lower TON than small planar ligands, due to the space occupied around the palladium center. Large planar ligands were also found to drive the initial reactivity higher than that of small planar ligands. Electron donating ligands were found to enhance the TON produced by the system in the initial stages of the reaction, while more electronically neutral ligands had greater success over the full length of the reaction.

To continue with the evaluation of ligands, it would first be interesting to examine the electronic effects of more sterically bulky ligands. While the tests on pyridine type ligands displayed electron donating ligands providing increased initial reactivity, it would be interesting to see if these trends remain when tested in acridine or quinoline type ligands as well. In addition, it was concluded that large planar ligands enhanced the breaking of the dimer into the active monomer, while electron withdrawing ligands would hinder this process. It would be interesting to examine a large planar electron withdrawing ligand, to determine if the effects would counteract one another, leaving the catalytic system with only the positive aspect of electron withdrawing ligands; the promotion of the attacking of the C-H bond.

The next big step in this project is to evaluate the selectiveness of this H/D exchange system by experimenting with substituted benzene derivatives as substrates. Using ^{1}H-NMR

spectroscopy, it is possible to determine which C-H bonds are most susceptible to activation. This test will help determine if the system is effective on sp^3 C-H bonds as well as the aryl sp^2 C-H bonds of benzene. With the knowledge of this catalytic system's selectivity and the degree to which it can be applied to a wide variety of substrates, it can be applied to the discovery of new routes to important synthetic targets.

In addition to testing selectivity of the system, it would be interesting to apply these trends to a synthetic system. While the trends were found effective in describing an H/D exchange system, a full functionalization cycle includes more than just the C-H activation step, which may counteract the positive effects of some ligands. Applying the defined trends to a synthetic system would also give more insight into the importance of the C-H activation step in relation to the other two proposed steps in the mechanism. Through the testing of new ligands, functionalized substrates, and full synthetic applications, there is a lot more to learn on the effect of differing ligands on palladium catalyzed C-H activation systems.

4. Experimental

4.1 General

All deuterated solvents used were at least 99.5% pure. All solvents were reactant grade. Benzene used for study was dried overnight over 4 Å molecular sieves that were activated by at least 24 h in a 120 °C oven. Unless otherwise noted, reagents were purchased and used without further purification.

4.2 Analytical Methods

4.2.1 GC/MS

GC/MS analysis was used to measure the relative abundances of isotopologs of benzene. All analysis was carried out on an Agilent 5977A MSD spectrometer.

4.2.2 Literature Search

Literature searches were completed by use of Scifinder and the WPI Library search function.

4.3 General Procedure

To a 4 mL resealable Schlenk tube was added $Pd(OAc)_2$ (1.1 mg, 5.0□mol, 2.0mol %), ligand (5.0 □mol, 2.0 mol %) as listed in Figure 3: All ligands tested throughout catalytic studies., and 0.37 mL of $[D_4]$AcOH was added, and the mixture was stirred for 1 min. Benzene (22.3 μL, 19.5 mg, 0.250 mmol, 1.00 equiv), stored over 4 Å molecular sieves, was added to the reaction vessel, which was subsequently sealed. The vessel was completely submerged in a preheated oil bath. At the end of the reaction, the vessel was cooled to room temperature. The reaction mixture

was then filtered over a plug of Celite to remove any particulates and rinsed with EtOAc (1 x 2 mL) into a 20 mL scintillation vial. A saturated aqueous solution of K_2CO_3 (9 M in deionized H_2O, 2 x 1 mL) was added to the vial to quench and separate the acid. The organic layer was carefully separated and diluted with additional EtOAc to give a 12.8 mM solution of benzene (~1 mg/mL) for analysis by GC-MS.

The % deuterium incorporation was defined as the percent of C–H bonds converted to C–D bonds. Background reactions (in the absence of any metal catalyst) at 150 °C and 100 °C are minimal with [D_4]AcOH (<0.5 TON) and are documented in the literature.[12]

Turnover numbers (TONs) are calculated as mole deuterium incorporated per mole of catalyst. The reported error is the standard deviation of at least two replicate trials.

4.4 H/D Exchange Studies

4.4.1 Reactions at 100 °C

Table 2: GC/MS yields are reported as turnover numbers with standard deviation. Reaction Conditions are as follows: $Pd(OAc)_2$ (1.1 mg, 5 µmol), ligand (5 µmol), benzene (0.25 mmol, 22.3 µL), deuterated acetic acid (6.25 mmol, 370 µL) reacted for two hours at 100 °C. The reported turnover number is the result of at least two trials.

Entry	Ligand	Amount (mg)	Turnover Number Achieved
2MM60A/B/C	**17**	0.9	11.1 ± 1.0
2MM61A/B/C	**18**	0.9	7.3 ± 1.5
2MM78A/B/C	**19**	1.5	4.3 ± 0.3
2MM62A/B/C	**20**	0.8	3.7 ± 0.4
2MM63A/B/C	**21**	1.1	3.8 ± 1.5
2MM71D/E/F/J/K/L	**22**	0.6	8.5 ± 0.7
2MM70D/E/F/J/K/L	**23**	0.4	5.0 ± 0.6
2MM74D/E/F	**24**	0.6	7.2 ± 1.0
2MM82D/E/F	**25**	0.7	2.4 ± 0.0
2MM91D/E/F	**26**	0.7	2.8 ± 0.3
2MM87D/E/F	**27**	0.7	5.2 ± 0.2
2MM81D/E/F	**28**	0.5	6.1 ± 0.9
2MM83D/E/F	**29**	0.6	6.0 ± 0.7

Table 3: GC/MS yields are reported as turnover numbers with standard deviation. Reaction Conditions are as follows: $Pd(OAc)_2$ (1.1 mg, 5 μmol), ligand (5 μmol), benzene (0.25 mmol, 22.3 μL), deuterated acetic acid (6.25 mmol, 370 μL) reacted for twenty-four hours at 100 °C. The reported turnover number is the result of at least two trials.

Entry	Ligand	Amount (mg)	Turnover Number Achieved
2MM54A/B/C	**17**	0.9	21.4 ± 0.5
2MM53A/B/C	**18**	0.9	12.1 ± 0.1
2MM78A/B/C	**19**	1.5	5.6 ± 2.5
2MM55A/B/C	**20**	0.8	3.5 ± 0.1
2MM56A/B/C	**21**	1.1	9.2 ± 0.7
2MM71A/B/C/G/H/I	**22**	0.6	32.4 ± 0.4
2MM70A/B/C/G/H/I/M/N/O	**23**	0.4	32.9 ± 2.9
2MM74A/B/C	**24**	0.6	10.1 ± 0.6
2MM82A/B/C	**25**	0.7	21.8 ± 0.3
2MM91A/B/C	**26**	0.7	25.7 ± 1.7
2MM87D/E/F	**27**	0.7	21.3 ± 1.8
2MM81A/B/C	**28**	0.5	15.3 ± 2.2
2MM83A/B/C	**29**	0.6	10.4 ± 2.0

4.4.2 Reactions at 150 °C

Table 4: GC/MS yields are reported as turnover numbers with standard deviation. Reaction Conditions are as follows: $Pd(OAc)_2$ (1.1 mg, 5 μmol), ligand (5 μmol), benzene (0.25 mmol, 22.3 μL), deuterated acetic acid (6.25 mmol, 370 μL) reacted for two hours at 150 °C. The reported turnover number is the result of at least two trials.

Entry	Ligand	Amount (mg)	Turnover Number Achieved
2MM57A/B/C	**17**	0.9	14.4 ± 1.1
2MM58A/B/C	**18**	0.9	6.2 ± 1.3
2MM79D/E/F	**19**	1.5	6.6 ± 0.0
2MM59A/B/C	**20**	0.8	3.0 ± 0.4
2MM65A/B/C	**21**	1.1	6.9 ± 1.8
2MM67A/B/C	**23**	0.4	20.4 ± 1.1
2MM72D/E/F	**24**	0.6	7.3 ± 0.7

Table 5: GC/MS yields are reported as turnover numbers with standard deviation. Reaction Conditions are as follows: $Pd(OAc)_2$ (1.1 mg, 5 µmol), ligand (5 µmol), benzene (0.25 mmol, 22.3 µL), deuterated acetic acid (6.25 mmol, 370 µL) reacted for twenty-four hours at 150 °C. The reported turnover number is the result of at least two trials.

Entry	Ligand	Amount (mg)	Turnover Number Achieved
2MM50A/B/C	**17**	0.9	16.0 ± 0.1
2MM64A/B/C	**18**	0.9	8.6 ± 2.3
2MM79A/B/C	**19**	1.5	16.7 ± 0.7
2MM51A/B/C	**20**	0.8	3.4 ± 1.0
2MM52A/B/C	**21**	1.1	5.9 ± 1.4
2MM66A/B/C	**23**	0.4	57.5 ± 1.0
2MM72A/B/C	**24**	0.6	8.1 ± 0.6

5. References

[1] Davies, H. M. L.; Manning, J. R. Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion, *Nature* **2008**, 451, 417-424

[2] Wencel-Delord, J.; Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of functional molecules, Nature Chemistry, 2013, 5, 369-375.

[3] Dick, A. R.; Sanford, M. S. Transition metal catalyzed oxidative functionalization of carbon–hydrogen bonds *Tetrahedron* **2006**, 62, 2439-2463

[4] Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions *Chem. Rev.*, **2010**, *110* (2), 1147–1169

[5]Janowicz, A.H.; Bergman R.G. C-H Activation in Completely Saturated Hydrocarbons: Direct Observation of M + R-H - M(R)(H) *J. Am. Chem. Soc.***1982**, *104*, 352-354.

[6]Janowicz, A.H.; Bergman R.G.Activation of C-H Bonds in Saturated Hydrocarbons on Photolysis of (q5-C5Me5)(PMe3)IrH2. Relative Rates of Reaction of the Intermediate with Different Types of C-H Bonds and Functionalization of the Metal-Bound Alkyl Groups *J. Am. Chem. Soc.***1983**, *105*, 3929-3939.

[7]Jones, W. D.; Feher F. J.The Mechanism and Thermodynamics of Alkane and Arene Carbon-Hydrogen Bond Activation in (C5Me5)Rh(PMe3)(R)H *J. Am. Chem. Soc.***1984**, *106*, 1650-1663.

[8] Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, 4th ed.; John Wiley & Sons Inc.: Hoboken, 2005

[9] Hickman A. J.; Villalobos, J. M.; Sanford, M.S. Quantitative Assay for the Direct Comparison of Platinum Catalysts in Benzene H/D Exchange*Organometallics***2009**, *28*, 5316–5322

[10] Field, K.; Emmert, M. H. Unpublished Results

[11] Cook, A.K.; Sanford, M.S. J. Am. Chem. Soc. **2015**, 137, 3109−3118

[12]Emmert, M. H.; Gary, J. B.;Villalobos, J. M.; Sanford,M. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5884-5886.