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Effects on Altering Reaction Conditions in Suzuki Cross Coupling Reactions Using the Microwave

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EFFECTS ON ALTERING REACTION CONDITIONS IN SUZUKI CROSS COUPLING

REACTIONS USING THE MICROWAVE

A Thesis

by

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Submitted to the Graduate College of
The University of Texas Rio Grande Valley
In partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

December 2018

Major Subject: Chemistry

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December 2018

ABSTRACT

Perez, Javier Alejandro, <u>Effects on Altering Reaction Condition in Suzuki Cross Coupling Reactions Using the Microwave.</u> Master of Science (MS), December, 2018, 45 pages, 3 table, 27 figures, 29 references.

Over the last few decades, Suzuki cross coupling has become the preferred method of choice for the synthesis of intermediates in pharmaceutical and industrial applications. The parameters of this reaction were investigated using palladium and cerium as catalysts. The reactants consisted of phenylboronic acid at 1 mMol and of either 4-bromoanisole, 4-bromotoluene, bromobenzene, 4-bromonitrobenzene or 4-bromochlorobenzene at 1.5 mMol with 5 mol % of the catalyst. All reactions under a palladium catalyst extensively favored the cross-coupled product. The reactions were performed under microwave conditions using a CEM discover microwave reaction unit at different temperatures in 5mL propanol. Characterization of reaction products were analyzed using gas chromatography flame ionization detector (GC-FID) and gas chromatography mass spectroscopy (GC-MS) to identify and quantify cross and homo coupled products.

DEDICATION

Me gustaria dedicar esta tesis principalmente a mis padres Francisco Javier Perez Pena y Luz Esthela Olivares Sainz por ser el mejor ejemplo de gente exitosa, ejemplar, muy trabajadora. Todo lo que he logrado es gracias a ellos, por el inmenso apoyo economicamente y mucho mas importante emocionalmente. Gracias por todo lo que han hecho por mi, por siempre han estar ahi para apoyarme, para hacerme entrar en razon cuando estoy mal y para inculcarme de una manera ejemplar, es lo mas valioso que me pueden ensenar. Tambien agradezco a toda mi familia (mis abuelos, tios, novia y amigos) que me han apoyado a lo largo del camino, todos han sido de gran ayuda. Agradezo todo el amor y el carino de ellos hacia mi.

I would like to dedicate this mainly to my parents Francisco Javier Perez Pena and Luz Esthela Olivares Sainz who are the best example of successful, hard working and kind people. I thank them because everything I have achieved is mainly because of them. They have been supporting me extensively in the economic and more important emotionally, showing their love and their caring for me. Thank you for your lessons in life, it is the most valuable thing you can teach me. For overall, teaching me how to be the person that I am now. Also, I would like to dedicate this to my family (grandparents, uncles, aunts, girlfriend and friends) I thank you all for your support and your love.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Suzuki cross coupling reactions

There are many different syntheses that performed in organic chemistry but some specific transformations are considered crucial to this field; the carbon-carbon bond forming reactions is one of these crucial organic chemistry reactions. This type of reactions yields many significant molecules that range from extremely simple molecules to complex systems, for example materials, polymers, pharmaceuticals, and etc[1,2].

During the last few decades, metal catalyzed cross coupling reactions have been utilized extensively in the synthesis of organic materials. These reactions have been the most common method for the formation of carbon-carbon bonds due to their significant advantages over different protocols. This approach has been optimized and perfected over the last few decades to produce efficient and reliable synthetic routes to compounds. Some examples of the well-known common cross coupling methods include the Kumada, Negishi, Stille, Heck and Suzuki coupling reactions[2].

Prior to the development of these methods, the Ullman reaction was the most popular way to produce biaryls[3]. The generation of biaryls are very important reactions in organic chemistry since they are important intermediates in the production of a wide range of compounds

with crucial pharmacological activity. The Ullman reaction involves the coupling of aryl halides with the aid of finely divided copper. The reason the Ullman reaction has lost popularity is more than obvious; better approaches have been discovered with time, the fact of comparing the limitations of the Ullman reaction with the new reactions has made this old method obsolete. This reaction requires significantly high temperatures (up to 200 °C) which limits the use of thermally sensitive substrates. Also, this reaction requires very high quantities of copper (stoichiometric amounts) which results in an enormous amount of waste. Large amounts of waste results in significant damage and pollution to the environment over time and its production is economically unfavorable[3].

To alleviate the negative effects on the environment and to generate synthetic routes using temperature sensitive starting materials, there was a need for a better method to produce new methods for the synthesis of carbon-carbon bonds.

Due to the current demand to produce biaryl compounds that will be useable in the pharmaceutical and industrial applications, the Suzuki-Miyaura cross coupling reaction has been developed. The Suzuki cross coupling reactions has proven to meet these needs by improving reaction yields and revamping reaction parameters commonly not applied into old cross coupling reactions. For such reason, the Suzuki reaction has gained widespread popularity among researchers working in academia and industry[3]. Researchers have been focusing in this reaction over the last few decades, many scientific articles have been published on this specific reaction. Since its discovery, this reaction has become the method of choice for the formation of new carbon-carbon bond for biaryl compounds in many synthetic strategies.

Early Suzuki Cross Coupling Reactions

The very first successful Suzuki cross-coupling reaction was employed by Akira Suzuki and his team in 1979[4]. Their reaction protocol coupled alkenyl boranes along with alkenyl halides or alkynyl halides by using a palladium catalyst and in presence of a base to produce conjugated dienes or enynes.
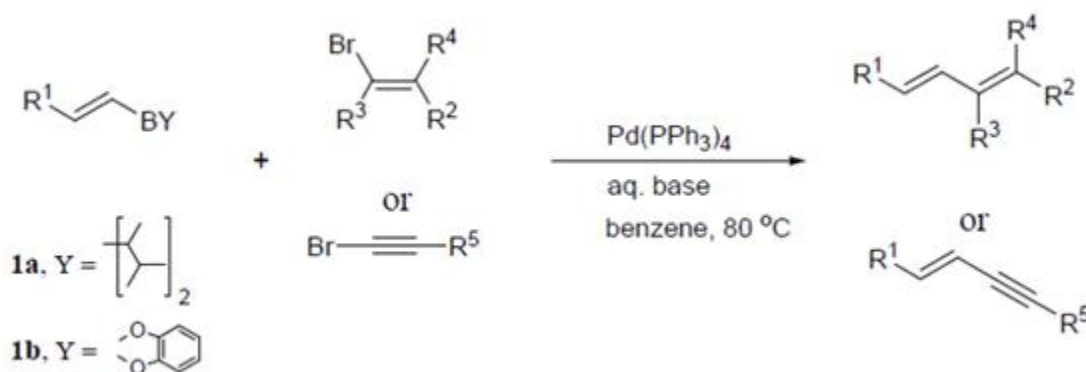
Figure 1: First Suzuki cross-coupling reaction of (E)-1-alkenylboranes with 1-alkenyl or 1-alkynyl bromides[4].

Even though the reaction involved alkenyl and alkynyl reagents initially, Suzuki rapidly extended its scope by including the coupling of carbons in aryl, heteroaryl and alkyl groups under different conditions.

The first Suzuki cross coupling reaction towards the production of biaryls was reported by Akira Suzuki and Norio Miyaura in 1981[5], the conditions employed are shown below:
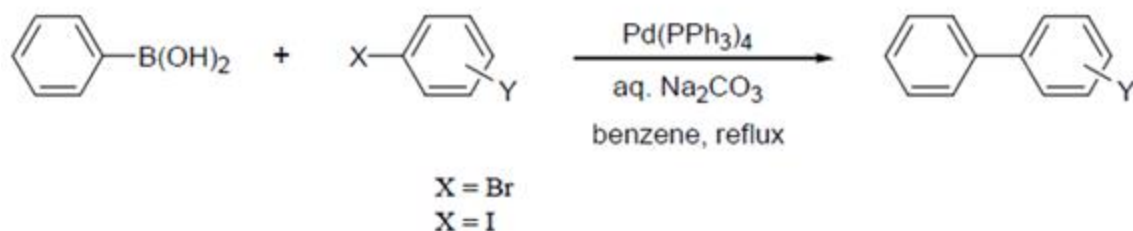
Figure 2: First Suzuki cross-coupling reaction towards biaryl products[5].

The reaction was performed using aqueous Na_2CO_3 as a base (homogeneous conditions). Furthermore, the reaction was also tested under heterogeneous conditions and good product yields were observed.

However, it has been reported that many bases (mild and strong) have been tested for the Suzuki cross coupling reaction, for example; K_3PO_4, Tl_2CO_3, $CsCo_3$ and K_2CO_3, all of them giving the product expected with good yields. Other bases such as $Ba(OH)_2$, NaOH and TlOH achieved better results for more challenging biaryl (sterically hindered) cross coupling reactions[6]. In addition, other bases such as KF and CsF have been utilized, which have milder conditions and have been successful in synthesizing biaryls containing base-sensitive functional groups. It is suggested that the ideal base for this type of reactions depends on the type of substrates that are being used and the conditions.

Advantages of the Suzuki Cross Coupling Reaction

The discovery of the Suzuki coupling reaction has had a great impact on academic research and manufacturing. Over the last few decades, Suzuki cross coupling reaction has undoubtedly become one of the most popular and preferred methods to produce biaryls or substituted aromatic compounds[4].

Throughout the last few decades, it has been shown that Suzuki cross coupling has many advantages compared to other protocols. A summary of such advantages is stated as follows:

- The Suzuki cross coupling reaction usually produces very high yields (about 95-98 %) and good selectivity under the right conditions applied to the substrates[4,7].

- Suzuki cross coupling works excellent either with symmetrical or unsymmetrical reactions[4,8].

- The reaction demonstrates high tolerance for different functional groups, either on the organometallic partner or in the electrophile. The protocol being very flexible is a huge advantage because it demonstrates many synthetic routes and very high yields[4,6,9].

- A significant benefit is that the organoboron reagent (boronic acid) is thermally stable and inert to oxygen and water, which enables working with this reagent without special precautions[8,10].

- The starting materials (esters and boronic acids) are commercially available and not expensive[9-11].

- The starting materials are non-toxic, meaning that they are not a hazard to the environment or humans. Also, the inorganic by-product formed in the reaction is not a hazard and can be separated from the reaction very easily[4,10,12].

- The reaction is usually performed at a mild temperature, demonstrating the green chemistry[13].

- Water can be used as a solvent or cosolvent, it doesn't affect the reaction of the substrates[7].

- This reaction requires very low amounts of the ligand or ligandless catalyst (palladium) to perform the reaction efficiently[7,10,14].

- Heterogeneous catalysts are easily removed from the mixture and can be recycled for further use[7].

Limitations of the Suzuki Cross Coupling Reaction

Even though Suzuki coupling reactions brings many advantages to the organic synthesis there are a few unfavorable aspects associated with the protocol:

- Some mixtures such as boroxines can be hard to remove from the boronic acid starting materials, making it difficult to purify them. Boroxines don't interfere with the coupling mechanism but interfere with the stoichiometric calculations[14].

- The hetero coupling product can be contaminated with another coupled reagent containing the aryl group originating from the phosphine ligand (ligand scrambling)[12,15].

- Deboronation side reaction either hydrolytic or protolytic can be an issue. This is the case with highly hindered substrates[8,9,16].

- Reagents showing a very high degree of steric hindrance (bearing three or four ortho substituents) are difficult to couple even though a lot of progress has been shown in the recent years[14,17].

If the previous mentioned advantages are analyzed, it can easily be concluded that the benefits that this reaction entails far outweigh the limitations. Therefore, it is not surprising to notice that the Suzuki cross coupling reaction has being exploited so much since its discovery. It has become one of the most utilized protocols for the carbon-carbon bond formation and it has been used in the laboratory for research purposes, at the industrial level for the synthesis of

large-scale processes[7]. The Suzuki cross coupling reaction has some important applications in the construction of ligands and polymers and plays a very important role in the synthesis of natural products such as vancomycin, ellipticine and michellamine,

General catalytic cycle

Just as in the other type of coupling reactions, the mechanism for Suzuki cross coupling is not strictly defined, instead there is a catalytic cycle that has been accepted for this type of reactions. The catalytic cycle mainly involves three steps; (i) oxidative addition, (ii) transmetallation, and (iii) reductive elimination[4]. The complete catalytic cycle for the Suzuki cross coupling reaction is shown below:
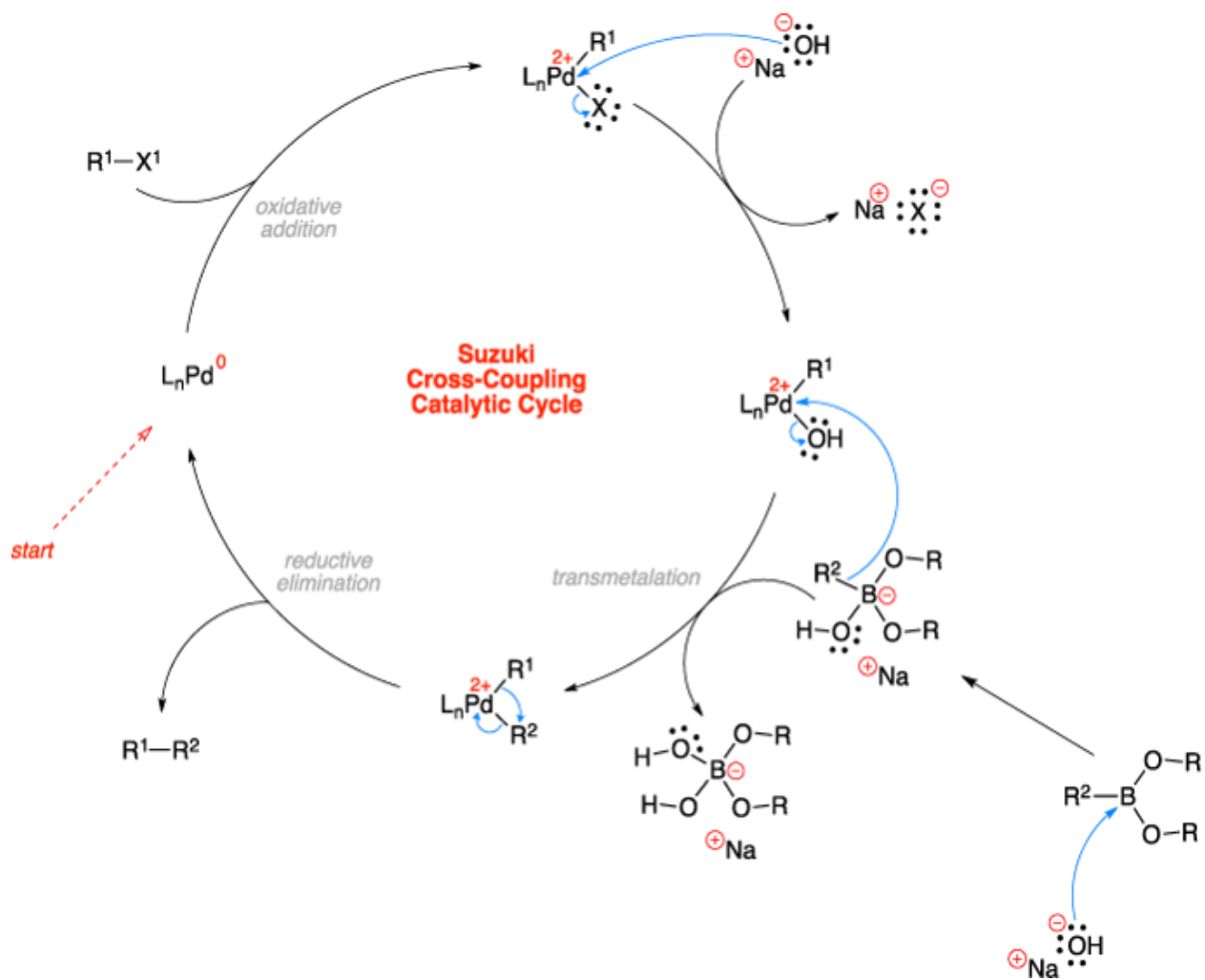
Figure 3: General catalytic cycle for the Suzuki cross coupling reaction[6].

The oxidative addition step is often the rate limiting step for many reactions, although many studies into these reactions have shown that one of the other steps might actually be the rate determining step depending on the substrates and the conditions employed[16].

$$Pd(0)L_n \quad + \quad Ar-X \longrightarrow \quad L_nPd(II) \underset{X}{\overset{Ar}{\diagup}}$$
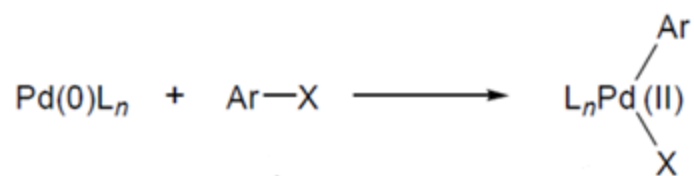
Figure 4: Oxidative addition of palladium into an Ar-X bond[16].

Oxidative addition

In this step, the transition metal (palladium) is inserted into the Ar-X bond producing a cleavage of the sigma bond and the formation of two new sigma bonds[16,17,18].

As seen above, the name, oxidative addition, is given to this step is because of the oxidation state increase of the catalyst, going from a 0 charge to a 2+ charge. In addition, the coordination number is increased, creating a new coordination species arranged in the cis configuration. Therefore, in order for this step to take place, the catalyst of choice needs to be in a coordinatively unsaturated state and in a low oxidation state[3]. Higher electron densities at the center of the metal are known to facilitate the oxidative addition step, some sigma donor ligands such as tertiary phosphines have been proven to increase the electron density[19].

The catalytic cycle is believed to be slightly different depending on the nature of the organohalide substrate that is being employed. The cycle can proceed via one of the two methods: The first catalytic cycle scenario (shown below) is very similar to a simple nucleophilic aromatic substitution reaction, in which the nucleophile is the metal catalyst.
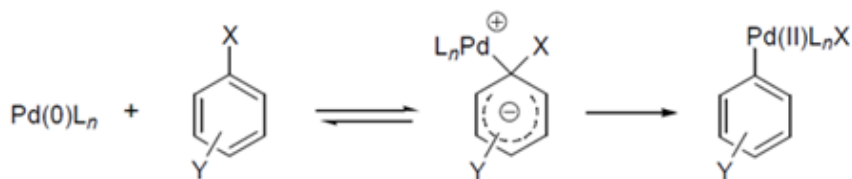
Figure 5: S_NAr-type mechanism of oxidative addition[16].

Data collected from different studies were shown to follow this mechanism, it has been observed that the cleavage of the carbanion intermediate bond with the aryl halide is the rate-determining step[2]. This can be confirmed based on the reactivity shown by aryl halides towards oxidative addition, increasing the strength of the aryl halide bond decreases reactivity. In addition, another feature characteristic of SNAr reactions is shown. The considerably enhanced rate of oxidative addition observed when electron withdrawing groups are attached on the aromatic ring[5,7].

The other possible pathway that the mechanism can take is a concerted process with the attack of the catalyst at the aryl halide bond, forming a three-centered transition state.
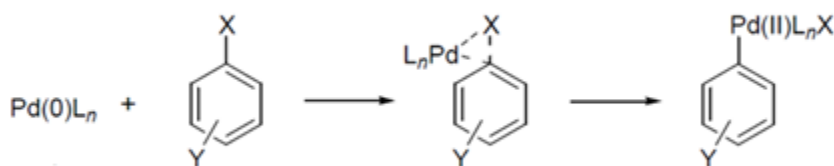
Figure 6: Concerted mechanism of oxidative addition[16].

This mechanistic pathway for the oxidative addition was the most common in most of the data seen in different investigations.

Transmetallation and the role of the base

This process initiated with the reaction of an organometallic species with the oxidative complex previously formed, creating a new complex consisting of both organic groups added to the palladium complex. This step of the mechanism is known to be a key feature in Suzuki couplings[4,18,20].

Before the transmetallation step takes place, the halide ion is displaced from the oxidative adduct by the base (either alkoxy or hydroxy group).
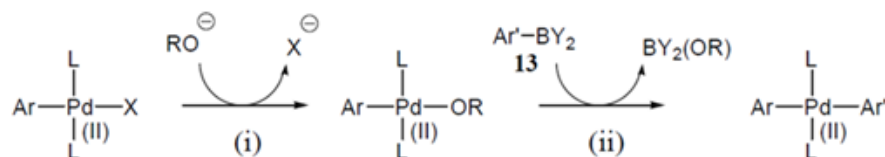
Figure 7: Alternative pathway proposed for the transmetallation step[18].

After the displacement of the halide ion (i), the aryl group is removed from the arylboron substrate and is transferred to the (oxo) palladium (II) complex. The reactivity of the latter is thought to be higher towards this step since the polarity of the palladium-oxygen bond is very high and the center is more electrophilic[4,21].

The addition of a base is crucial since it facilitates the transmetallation step. It is believed that the base not only has one specific role but rather performs multiple roles during the whole mechanism, simultaneously[22].

Reductive elimination

The reductive elimination is the last step of the catalytic cycle and is seen as the opposite of the oxidative addition. In this step, the palladium(II) species is reduced to a palladium(0) complex. It is considered as a unimolecular process in which the new carbon-carbon bond is formed by simultaneous elimination from the palladium complex. Also, homogeneous catalysts can be recycled, and the catalytic cycle can begin again. Reductive elimination is known to be facilitated by a reduced electron density and steric hindrance at the center of the palladium complex (the opposite of oxidative addition)[4,6,23]. It can be concluded that if less electron rich, bulky ligands are utilized in these reactions, then the oxidative addition step would be more difficult to perform but the reductive elimination step would be more facilitated.

$$L_nPd \underset{(II)}{\overset{Ar}{\diagdown_{Ar'}}} \longrightarrow Pd(0)L_n + Ar-Ar'$$
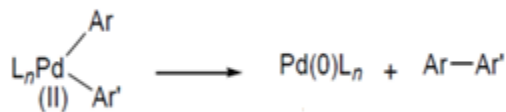
Figure 8: General description of the reductive elimination step[18].

Catalysts

A several catalysts, catalyst derivatives and ligands have been employed in the Suzuki cross coupling reaction, but only one type of catalyst have been proven to work efficiently for the last decades; a palladium catalyst complex.

Palladium is such a great catalyst because it has important features in reactions such as hydrogenation, carbonylation, hydrogenolysis, cycloisomerization, etc. Palladium aids in the formation of carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur bonds[24,25]. Also,

the protocols that employ palladium as a catalyst are usually performed under mild conditions, and for the most part, produce very high yields and show excellent levels of stereo-, regio-, and chemo-selectivity.

In the Suzuki coupling reactions homogeneous catalysts are a very common choice. Thus, those catalysts that dissolve in the solvent are often sought after for this purpose. The choice can be either Pd(0) catalysts or Pd(II) precatalysts. The redox interchange between the oxidation states of Pd(0) and Pd(II) is spontaneous and has been represented as a key factor responsible for the very high catalytic efficiency of palladium in the catalytic cycle[26].

Also, heterogeneous catalysts are also a good choice, especially for those involved in the industry they have some advantages; these catalysts can be recycled, can be removed easily from the mixture and water is used either as a solvent or co-solvent. In this case, there need to use hydrophilic ligands or catalysts such as palladium on carbon (Pd/C) which is a solid-supported catalyst in imperative. The Pd/C has gained a lot of popularity and is has been used extensively since no contamination of the hetero-coupling product is observed and separation from the mixture is instantaneous.

For this reason, ligand-less and phosphine-free catalysts have been in the focus of researchers. They offer a huge advantage since the "ligand scrambling" is avoided, there are no side reactions. Also, there is no need of further purification procedures since there are no phosphine species in the products[27,28].

On the other hand, cerium has been attractive to researchers in the field of catalysis. Cerium has some interesting properties, it is known to be the most abundant rare earth metal, it has a very good storage capacity of oxygen and it shows high mobility and facile exchange of oxidation states between Ce(III) and Ce(IV). Therefore, it has been thought to be an effective

alternative of the noble metal catalysts in different applications. Cerium catalysts can be synthesized easily in lab, there are many simple ways to work with cerium, it is commercially available and less expensive than all other effective catalysts. These properties make cerium a low-cost highly effective catalyst[29]. Although no cerium data has been shown in the Suzuki cross coupling reactions, it is believed to be efficient in such type of reactions.

Therefore, it is with the intent of investigating the capacities of cerium and palladium as a potential candidate catalyst for the Suzuki reactions that the research documented in this thesis was performed.

CHAPTER II

MATERIALS AND METHODS

CEM discover microwave

Suzuki cross coupling reactions were performed using a CEM discover microwave. Working parameters included a fixed temperature (variable), 5 minutes and 300 W of power. Microwaves are known to accelerate reaction yields when polar solvents are employed[24]. Therefore, this approach was used as a rapid testing method to check the effectiveness of the reactions.

Reaction Equivalence

The Suzuki cross coupling reactions employed in this study used 5 mol % of either a $PdCl_2$ or a $Ce(OH)_4$ catalyst that was synthesized in lab. For this study, a number of bases were investigated ($NaOH$, Na_2CO_3, K_3PO_4, $NaNO_3$, $NaHCO_3$) for the coupling of boronic acid with various organohalides using 5mL of iso-propanol as a solvent. The reactants consisted of phenylboronic acid at a constant concentration of 1 mMol and of either 4-bromoanisole, 4-bromotoluene, bromobenzene, 4-bromonitrobenzene or 4-bromochlorobenzene at 1.5 mMol. All reactions were performed in a period of 5 minutes using the CEM discover microwave with a variable temperature of 40, 50, 60, and 70 °C. Reactions were performed in triplicates, the average results were analyzed based on the GC-MS and GC-FID data.

Reaction synthesis

In the first reaction, 1 mMol of phenylboronic acid is coupled with 1.5 mMol of 4-bromoanisole (an electron donating group) to yield the hetero coupling product (4-methoxybiphenyl) and the homo coupling product (biphenyl). Product yields were compared based on the chromatogram from either the GC-MS or GC-FID.

Figure 9: Reaction of phenylboronic acid with 4-bromoanisole.

In the second reaction, 1 mMol of phenylboronic acid was coupled with 1.5 mMol of 4-bromotoluene (an electron donating group) to yield the hetero coupling product (4-methylbiphenyl) and the homo coupling product (biphenyl). Product yields are compared based on the chromatogram from either the GC-MS or GC-FID.

Figure 10: Reaction of phenylboronic acid with 4-bromotoluene.

In the third reaction, 1 mMol of phenylboronic acid was coupled with 1.5 mMol of 4-bromonitrobenzene (an electron withdrawing group) to yield the hetero coupling product (4-nitrobiphenyl) and the homo coupling product (biphenyl). Product yields are compared based on the chromatogram from either the GC-MS or GC-FID.

Figure 11: Reaction of phenylboronic acid with 4-bromonitrobenzene.

17

In the fourth reaction, 1 mMol of phenylboronic acid was coupled with 1.5 mMol of 4-bromochlorobenzene (an electron withdrawing group) to yield the hetero coupling product (4-chlorobiphenyl) and the homo coupling product (biphenyl). Product yields are compared based on the chromatogram from either the GC-MS or GC-FID.

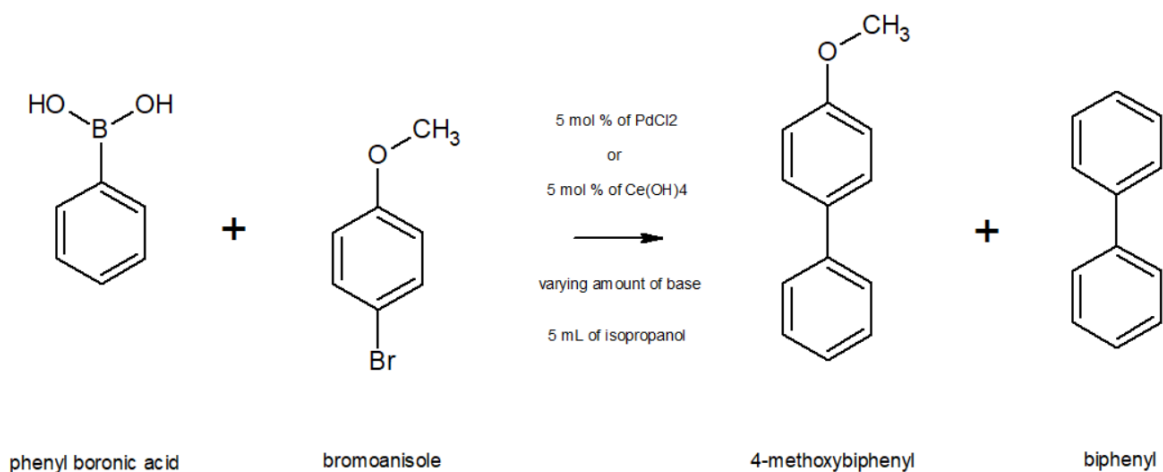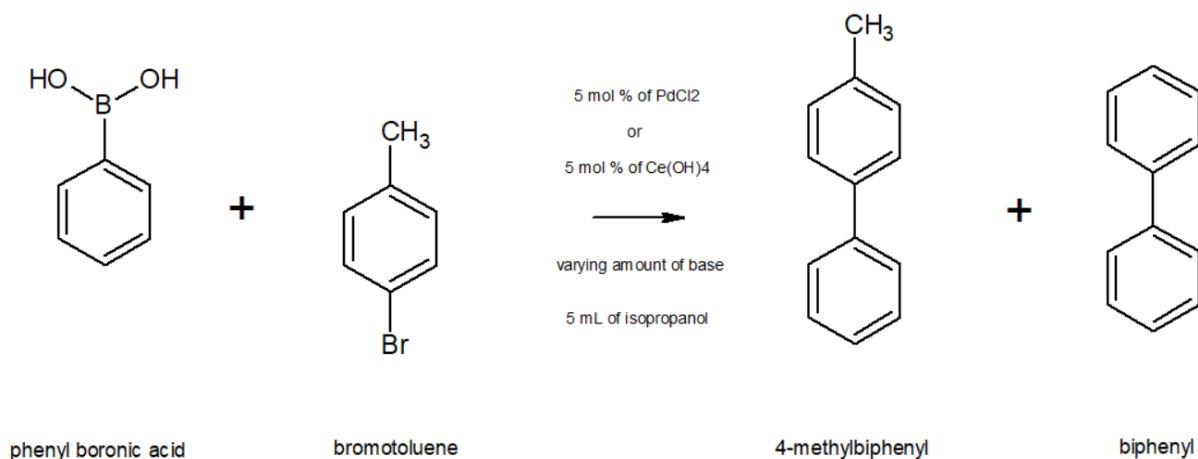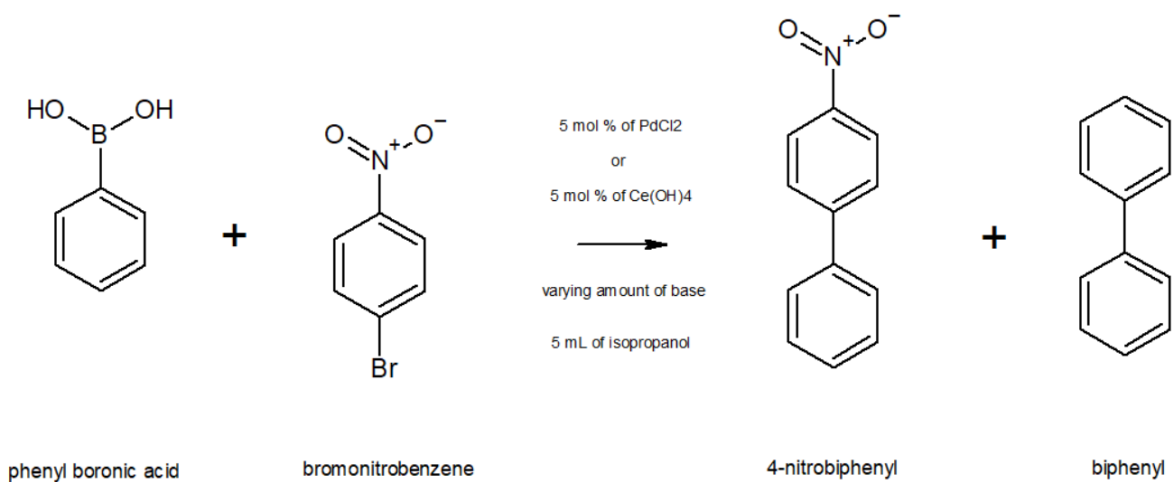phenyl boronic acid   bromochlorobenzene   4-chlorobiphenyl   biphenyl
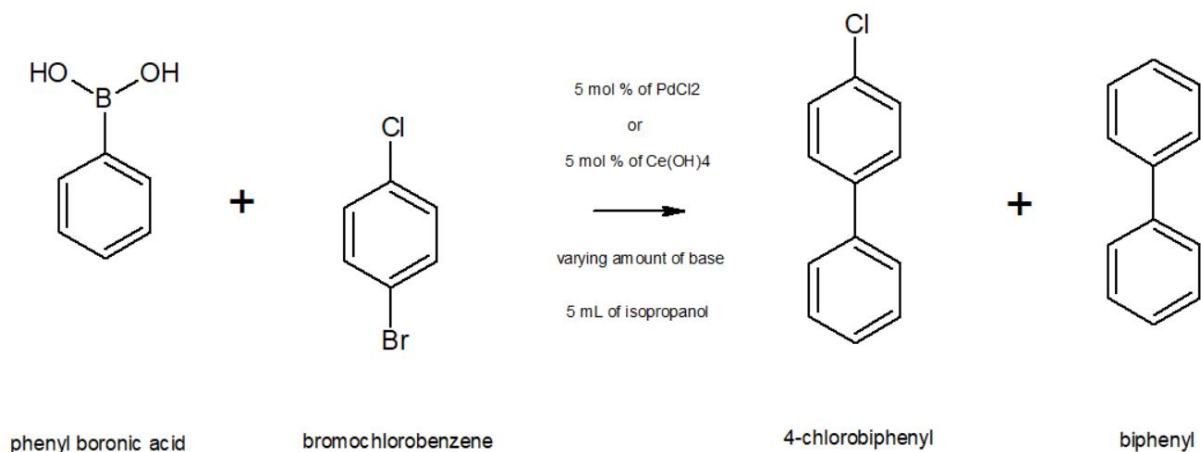
Figure 12: Reaction of phenylboronic acid with 4-bromochlorobenzene.

In the fifth reaction, 1 mMol of phenylboronic acid was coupled with 1.5 mMol of 4-bromobenzene to yield only the homo coupling product (biphenyl). The product yields are compared against starting materials to determine the percent completion.
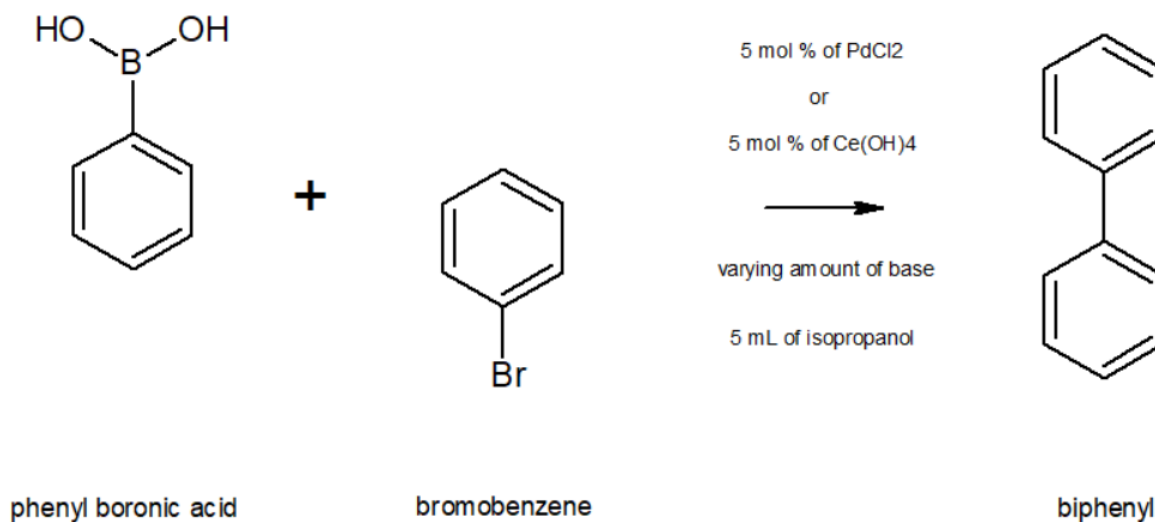
Figure 13: Reaction of phenylboronic acid with 4-bromobenzene.

Synthesis of Cerium Hydroxide

Cerium hydroxide was synthesized in lab by following a titration procedure. Using a pump-variable flow, 1 M NaOH solution was titrated to a beaker containing a previously made 30 mmol Ce(NO$_3$)$_2$ solution stirring on a hot plate. After the titration was complete, the solution was heated at 60 °C for a period of 2 hours. After heating, the solution was left in the oven overnight at a temperature of 40 °C. The product was a light-yellow powder and it was employed for the Suzuki cross coupling reactions.

Characterizations

Characterization of the products were performed using a gas chromatography flame ionization detector (GC-FID) and/or gas chromatography mass spectroscopy (GC-MS) to study the effects that altering reaction conditions have in the products, as well to compare the ratios of the hetero-coupling product and the homo-coupling product and to analyze the product completion compared to starting materials.

GC-FID Analysis

A Perkin Elmer gas chromatograph with a flame ionization detector was used to compare the ratios of the hetero coupling and homo coupling products as well with starting materials. Working parameters included 0.5 μL injections with 250°C injection temperatures. The oven was heated from 100°C to 250°C at a ramp rate of 20°C per minute. Carrier gas flow contained helium and the FID operating gases were 450ml of air and 45ml of hydrogen gas. The resulting chromatograms were integrated to determine product yields.

GC-MS Analysis

A Perkin Elmer Autosystem XL gas chromatograph with a TurboMass Gold mass spectrometer detector was used to identify reaction products and product yields. Operating conditions included injections of 0.5 μL with injection temperatures of 260°C. The oven was heated from 60°C to 260°C with a pressure of 10 psi of the helium carrier gas flowing through the column. The resulting chromatograms were integrated using TurboMass software to determine the ratio of the hetero coupling product compared with the homo coupling product as well with starting materials.

CHAPTER III

SUZUKI CROSS COUPLING REACTIONS RESULTS AND DISCUSSION

XRD Results

The phase and composition of the synthesized catalyst were determined using powder X-Ray diffraction (XRD). Cerium hydroxide, $Ce(OH)_4$, catalyst was synthesized using cerium (IV) nitrate as the cerium source, Figure 14 shows the powder XRD pattern of the synthesized $Ce(OH)_4$.
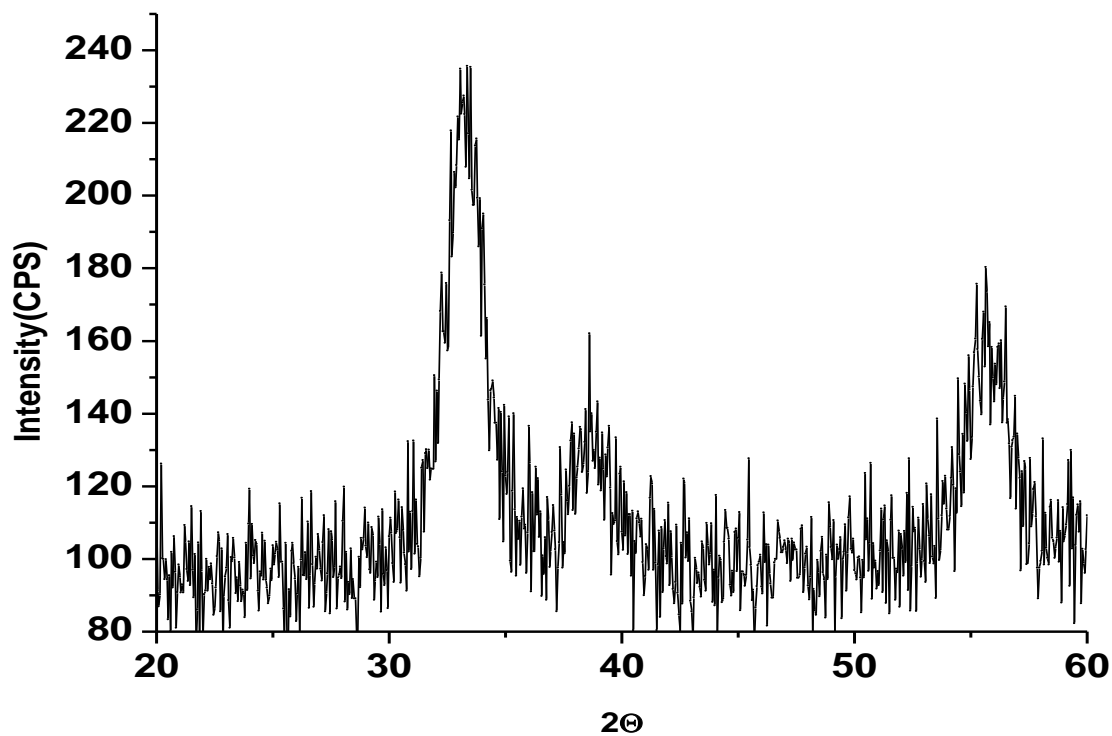
Figure 14: Diffraction pattern of the synthesized Ce(OH)4.

GC-MS/GC-FID Results

Products from the Suzuki cross coupling reactions were identified using GC-MS analysis, and the NIST mass spectroscopy database. The data analysis consisted of comparing the amount of homo-coupled product to hetero-coupled products. In addition, a comparison between the amount of product with the starting materials was performed in the reaction of bromobenzene with phenylboronic acid.

The parameters of the GC-MS are shown in table 1, these parameters were employed with all the reactions performed in this study.

Gas chromatography / mass spectrometry	
parameters	Settings
Sample volume	1 uL
Oven Ti	60 ˚C
Oven Tf	260 ˚C
Ramp	20 ˚C/min
Source temperature	250 ˚C
Internal temperature	250 ˚C
Pressure	10 psi
Flow	0.75 sand/min
Gap	Helium

Table 1: GC-MS parameters.

The reaction of phenylboronic acid with 4-bromoanisole using $PdCl_2$ was performed following the conditions in the methodology. Reaction products were characterized using either GC-MS or GC-FID. The NIST database was used to identify products obtained from each reaction. Figure 15 shows the GC-MS chromatogram obtained from the reaction of phenylboronic acid with 4-bromoanisole using $PdCl_2$. The peak observed at time 5.68 corresponds to the starting material (4-bromoanisole), the one observed at 6.69 correspond to biphenyl and the last peak at 8.26 correspond to 1,1' biphenyl 4 methoxy.
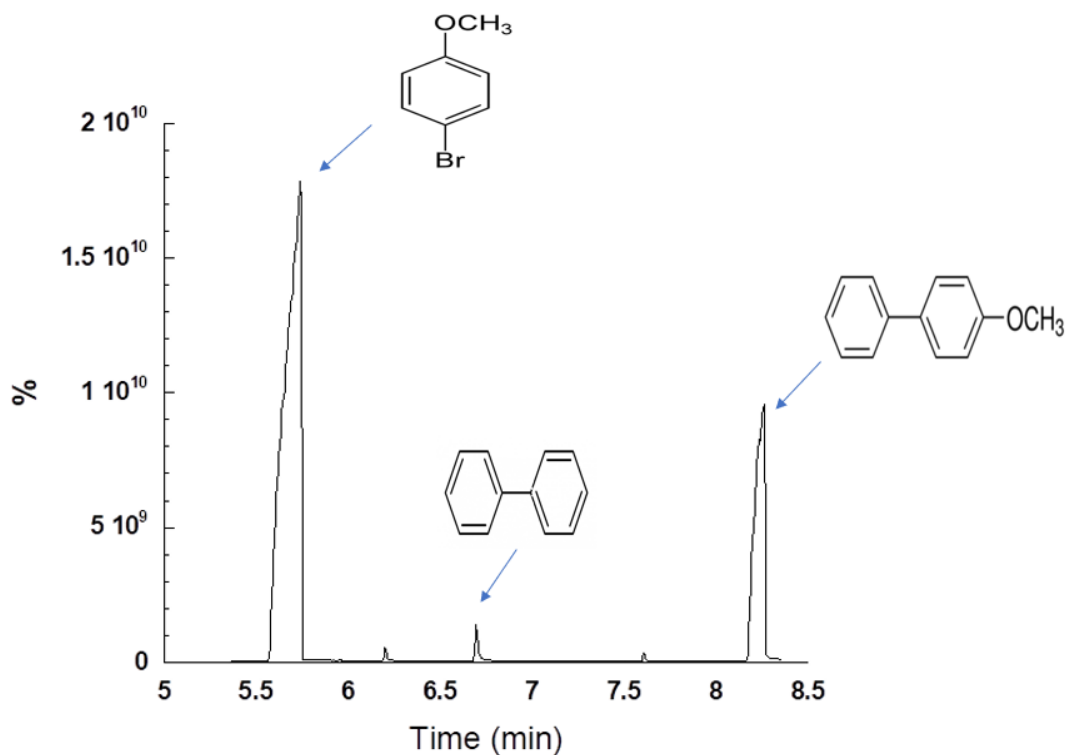
Figure 15: Chromatogram of the reaction of phenylboronic acid with 4-bromoanisole.

Once the products were identified, the average of the homo-coupling product obtained was compared with the average of the hetero-coupling product solving for the ratio of formation of each product was performed. Figure 16 shows the averages of the triplicate reactions performed for this reaction in which the ratio of the hetero-coupling product compared to the homo-coupling product was determined.

Figure 16: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromoanisole.

The hetero-coupling product ratio was very high in this reaction (95-98%) with the highest being 99.2 %. However, this reaction was not very constant, it was hard to find a trend. Also, the highest ratio of the hetero-coupling product was observed at 40 °C which was something unexpected. The reaction does occur to work better at higher base concentrations for the most part and at lower temperatures.

The reaction of phenylboronic acid with 4-bromotoluene using $PdCl_2$ was performed previously mentioned. Reaction products were characterized using either GC-MS or GC-FID.

The NIST database was used to identify products obtained from each reaction. Figure 17 shows

the GC-MS chromatogram obtained from the reaction of phenylboronic acid with 4-

bromotoluene using PdCl2. The peak observed at time 6.69 correspond to biphenyl while the

peak at 7.40 correspond to 1,1' biphenyl 4 methyl.
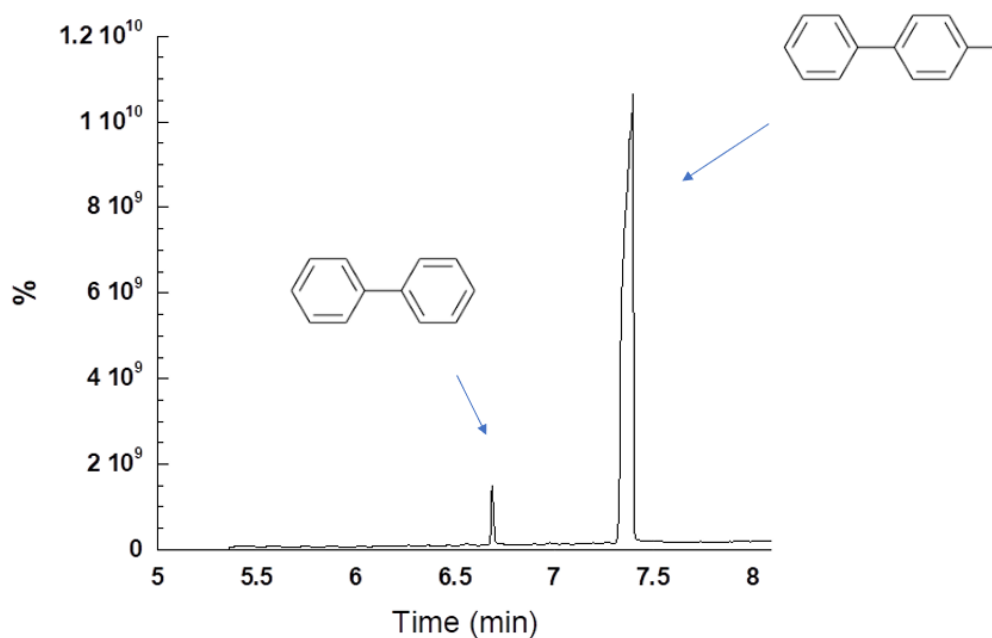
Figure 17: Chromatogram of the reaction of phenylboronic acid with 4-bromotoluene.

The average of the homo-coupling product obtained was compared with the average of

the hetero-coupling product solving for the ratio of formation of each. Figure 18 represents the

averages of the triplicate reactions where the ratio of the hetero-coupling product compared to

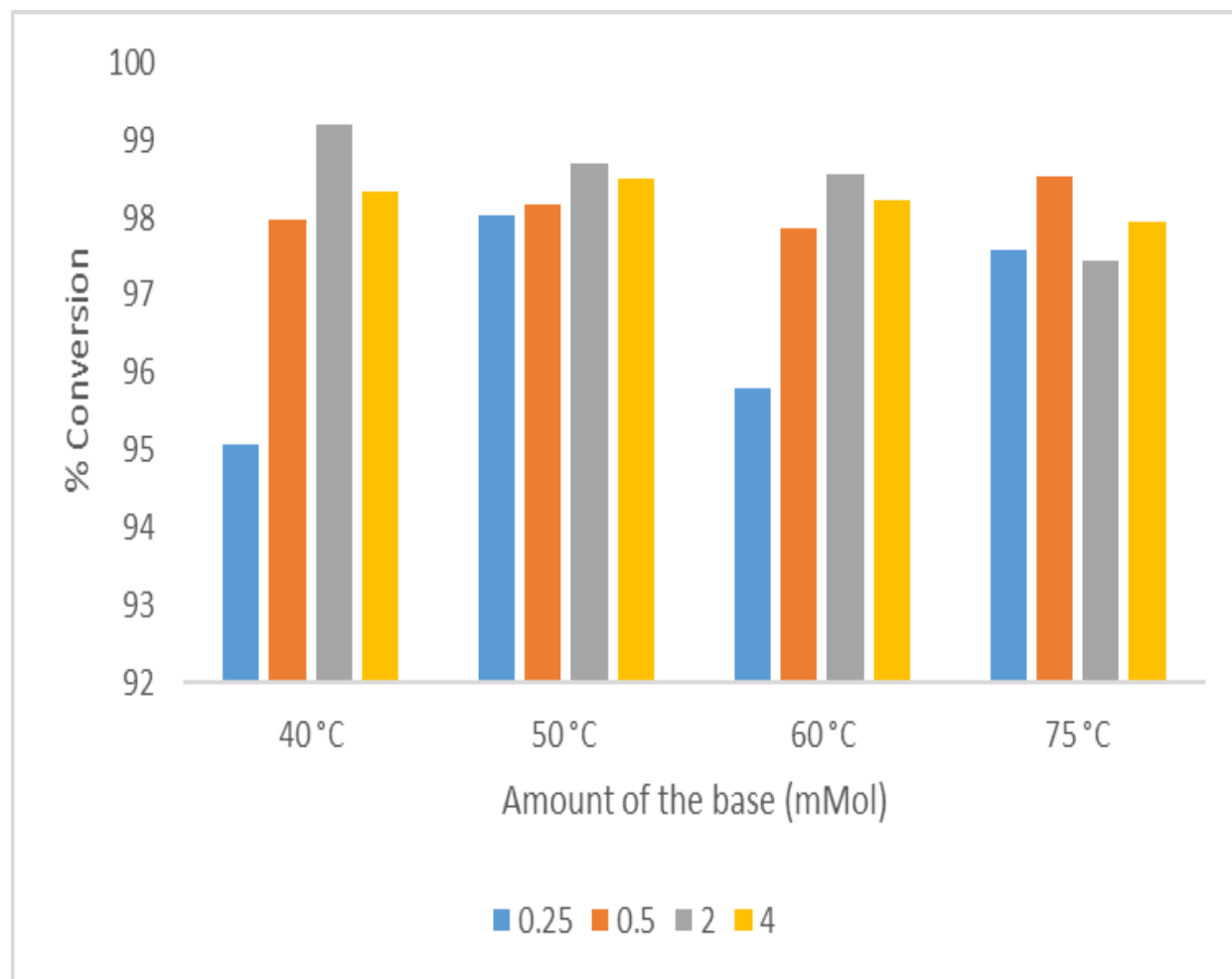the homo-coupling product was determined.

Figure 18: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromotoluene.

The hetero-coupling product ratio again was very high for this reaction (92-95%) with the highest being 96.3 %. This reaction was constant, finding a trend very easily. Also, the highest ratio of the hetero-coupling product was observed at 60 °C. It can be expected to see the highest amount of product at the highest temperature but since the boiling point of the solvent employed is very close to that temperature, some product may be lost. In addition, the data also indicate that the higher the amount of base used in the reaction favors the production of product.

After analyzing the comparison between both products, the Arrhenius equation was employed to determine the activation energy of the reaction. This was performed to understand

27

how the reaction parameters influence in the reaction products (temperature and amount of

catalyst). Figure 19 shows the Arrhenius equation plot for the activation energies for the reaction

of phenylboronic acid with 4-bromotoluene. As can be seen there is a direct correlation between

the reaction rate and temperature.
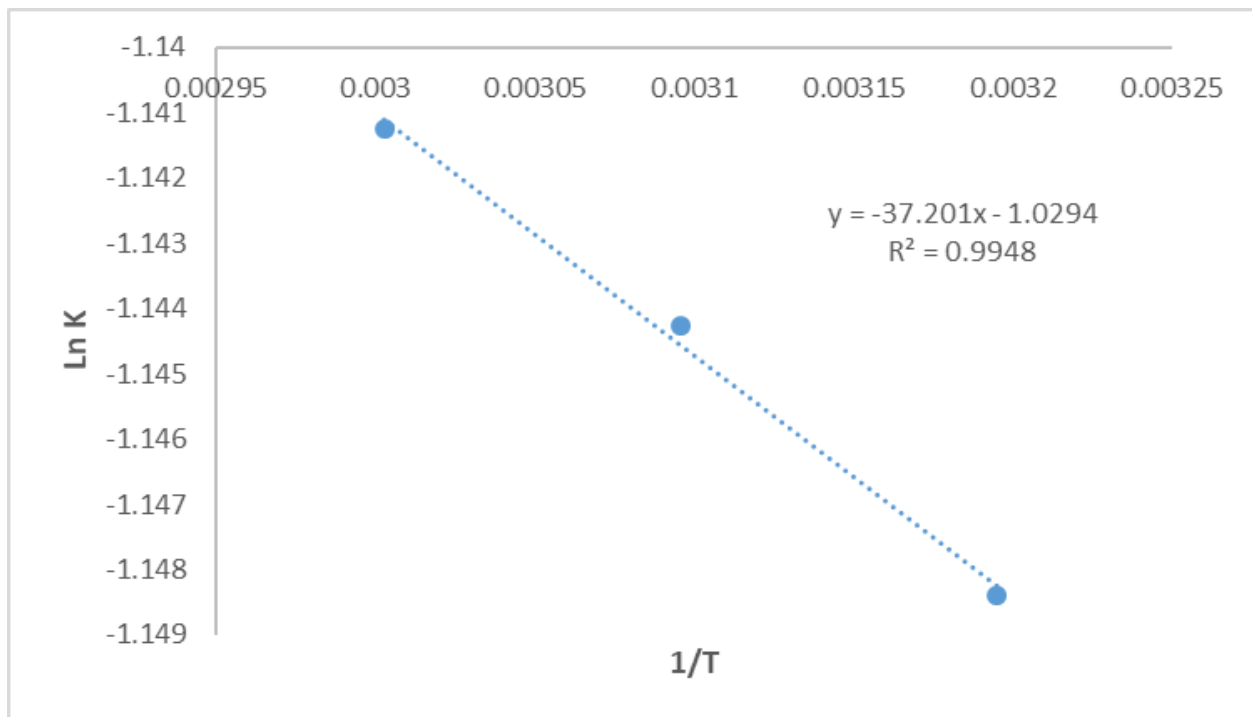
Figure 19: Plot of the Ln K vs 1/T for the reaction of phenylboronic acid with 4-bromotoluene.

4-Bromotoluene	
Conditions	Ea (in Kj)
0.25	1.03
0.50	0.49
2.00	0.77
4.00	0.31

Table 2: Activation energies for the reaction of phenylboronic acid with 4-bromotoluene using PdCl$_2$.

As can be seen in the data in table 2, the activation energy for the reaction decreases with increasing amount of base present in the reaction. This indicates that the base plays an important role in the reaction kinetics.

The reaction of phenylboronic acid with 4-bromobenzene using PdCl$_2$ was performed previously mentioned. Again the reaction products were characterized using either GC-MS or GC-FID. The NIST database was used to identify products obtained from each reaction. Figure 20 shows the GC-MS chromatogram obtained from the reaction of phenylboronic acid with 4-bromobenzene using PdCl$_2$. The peak observed at 3.48 correspond to the starting material (4-bromobenzene) while the peak at 6.72 correspond to biphenyl.
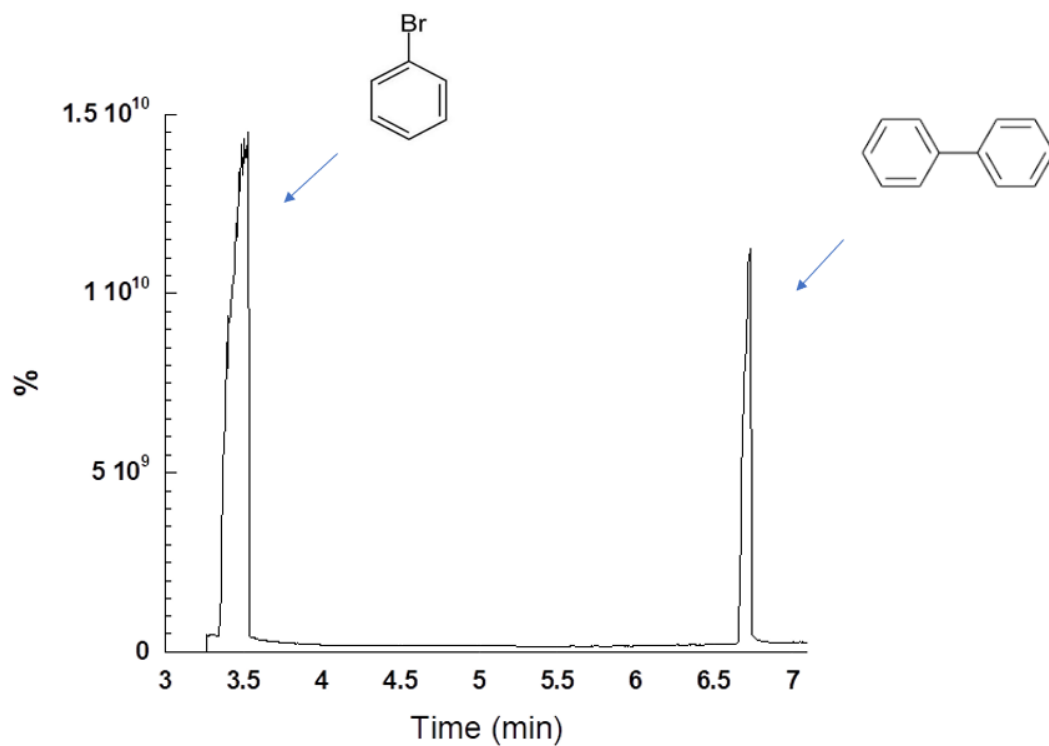
Figure 20: Chromatogram of the reaction of phenylboronic acid with 4-bromobenzene.

The product biphenyl was identified and compared against starting materials to determine

percent completion of the reaction. Figure 21 represents the averages of the triplicate reactions
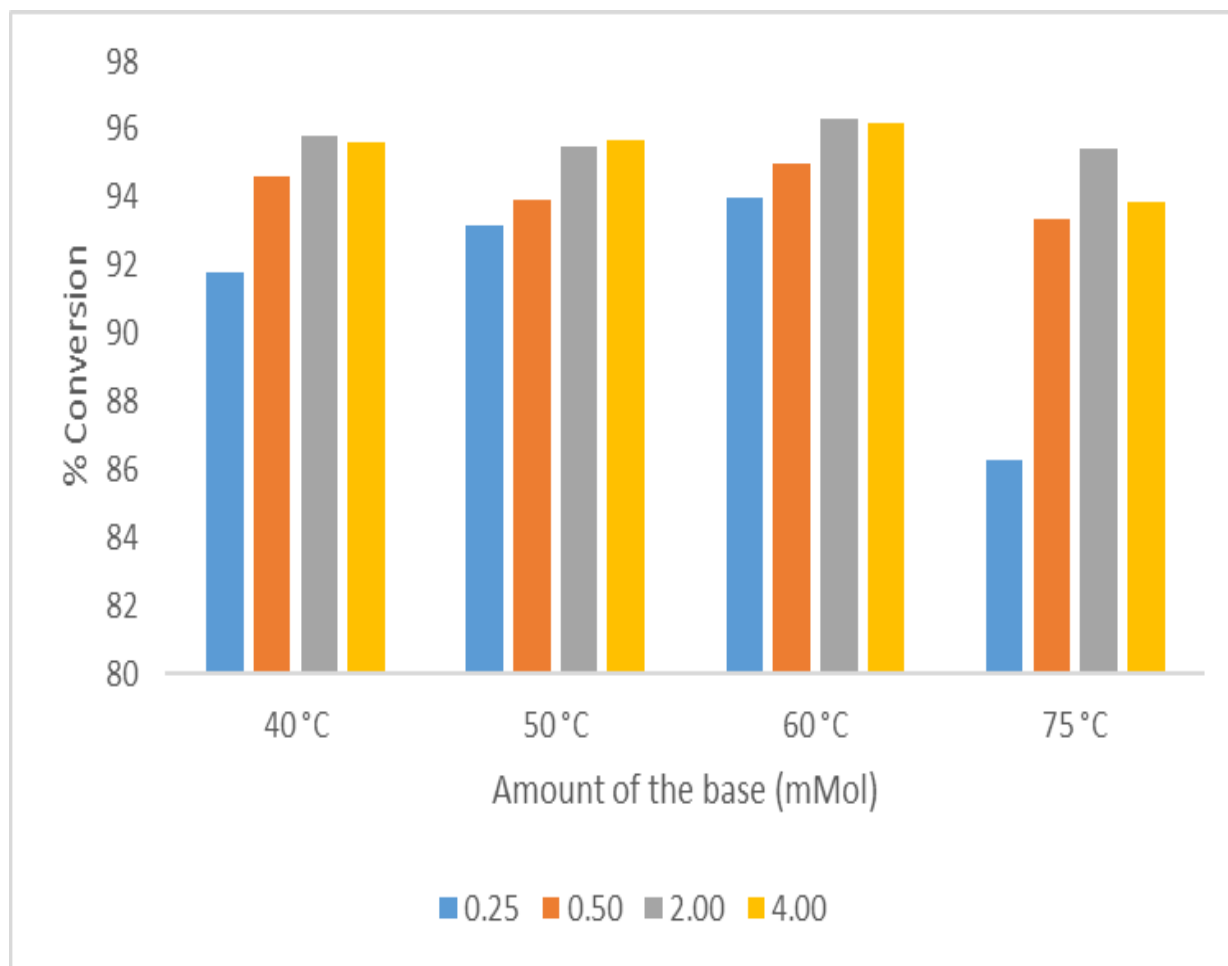
performed for this particular reaction.
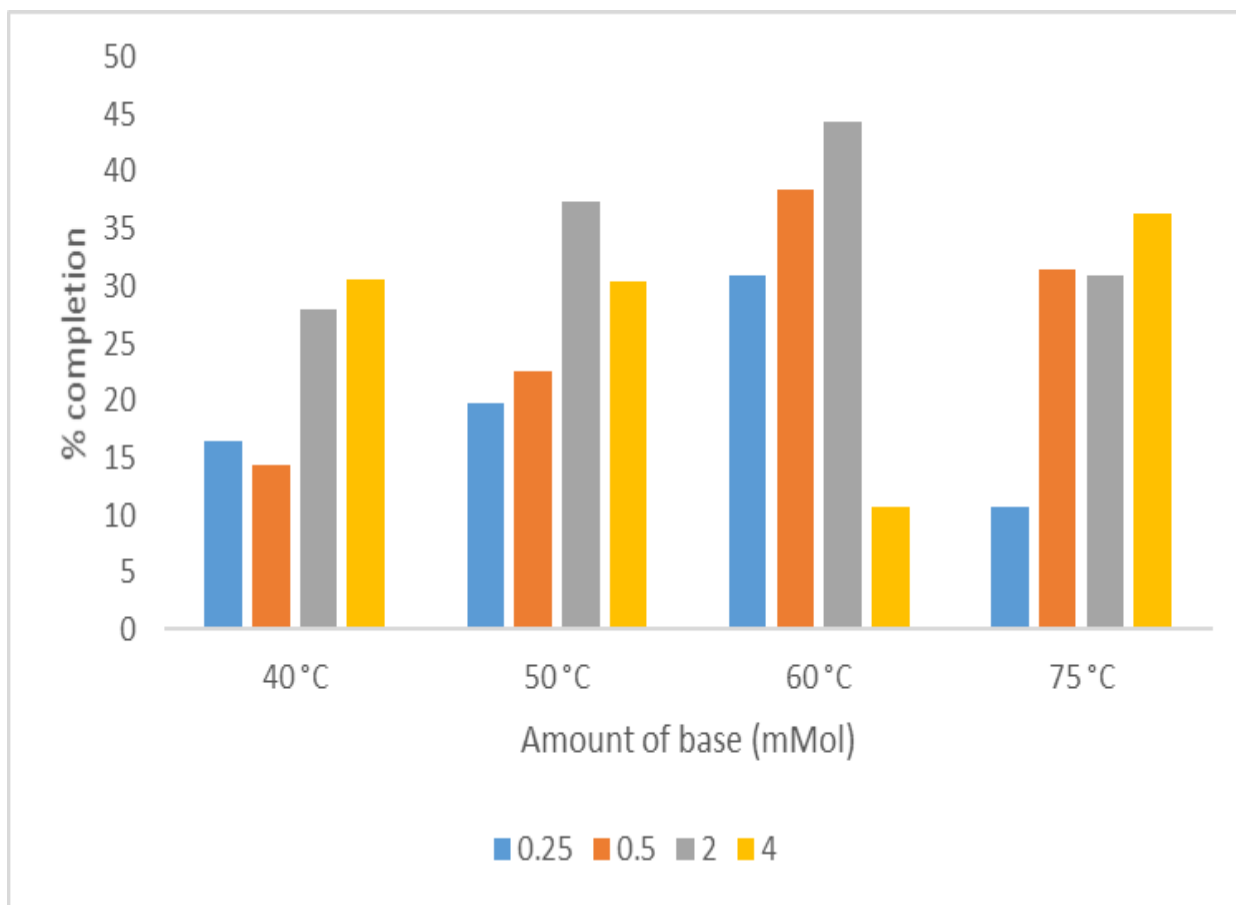
Figure 21: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromobenzene.

In this reaction, there is only one product (biphenyl). In this case, the product formation was compared against the starting materials. It was found that the amount of product was high compared to the starting materials (25-40%) with the highest being 44.3 %. However, this reaction was not very constant, making it hard to find a trend. For the most part the reactions appear to increase with increasing temperature, up to 60°C. At 75°C there was a decrease in the amount of product produced, which may be due to the boiling of the solvent or loss of reactants. The high base reaction 4 mMol was the only reaction that did not follow the trend, it decreases with increased temperature and was observed to work best at 40°C. The high base reaction may

have caused deboronation of the phenylboronic acid at higher temperature preventing the formation of the biphenyl.

After analyzing the comparison between both products, the Arrhenius equation was employed to find the activation energy of the reaction. This was performed to understand the reaction parameters influence in the reaction (temperature and amount of catalyst). Figure 22 shows the Arrhenius equation plot for the activation energies of the reaction of phenylboronic acid with bromobenzene. Again a linear relationship was observed for the reaction rate and temperature was observed. The highest activation energy was observed for the reaction performed with the 0.5 mMol of base.
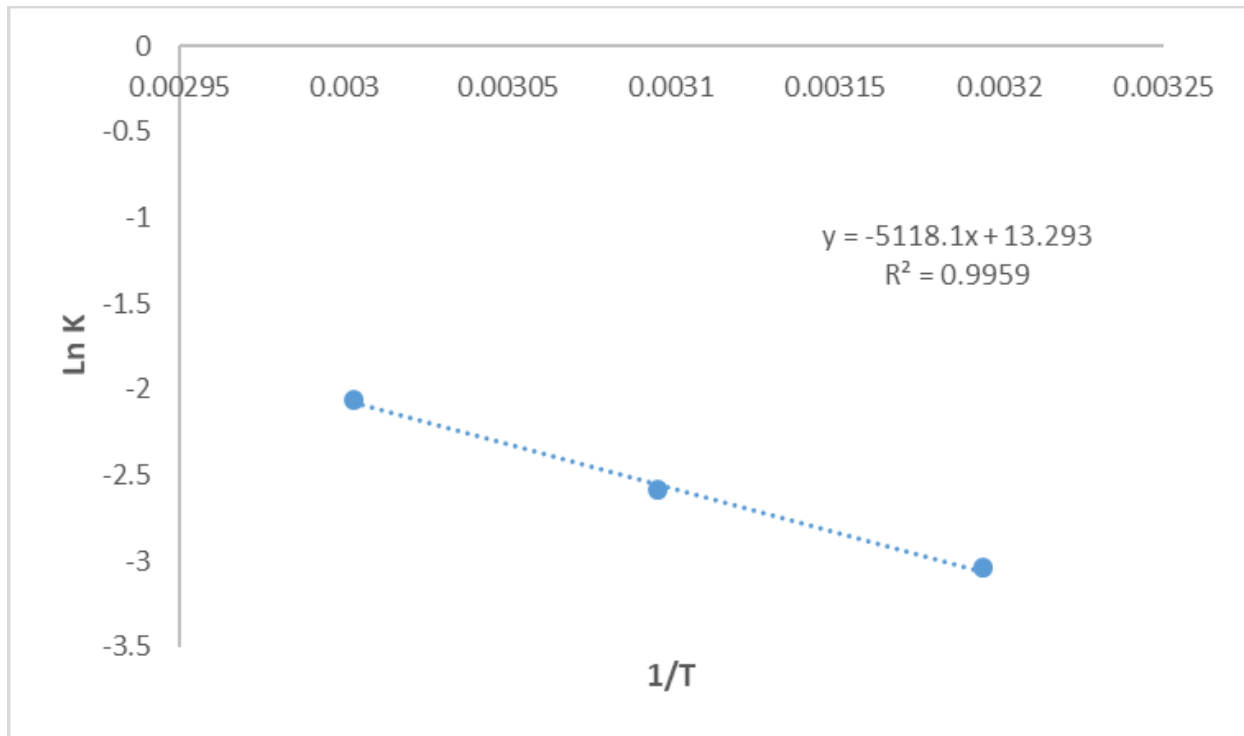
Figure 22: Plot of the Ln K vs 1/T for the reaction of phenylboronic acid with 4-bromobenzene.

Bromobenzene	
Conditions	Ea (in Kj)
0.25	27.27
0.50	42.55
2.00	20.03

Table 3: Activation energies for the reaction of phenylboronic acid with 4-bromobenzene using PdCl$_2$.

The reaction of phenylboronic acid with 4-bromochlorobenzene using PdCl$_2$ was performed following the previously mentioned reaction conditions. Figure 23 represents the averages of the triplicate done for this reaction. The ratio of the hetero-coupling product compared to the homo-coupling product was determined.

Figure 23: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromochlorobenzene using PdCl2.

The hetero-coupling product ratio was very high in this reaction (91-94%) with the highest being 98.2 %. This reaction was constant, a trend was very easily observed. Also, the highest ratio of the hetero-coupling product is found at 65°C.

After analyzing the comparison between both products, the Arrhenius equation was employed to find the activation energy of the reaction. This was done to understand how the reaction conditions influence in the reaction products (temperature and amount of catalyst). Figure 24 shows the Arrhenius equation plot for the activation energies of the reaction of phenylboronic acid with bromobenzene.
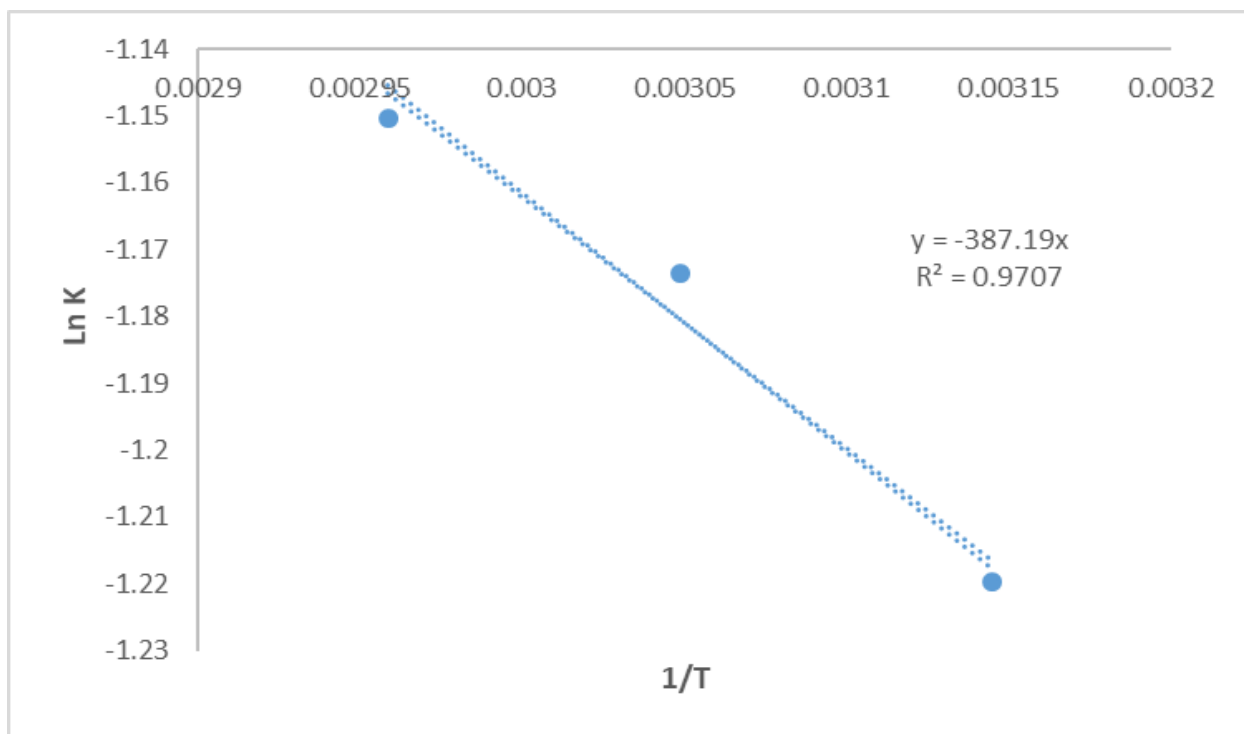
Figure 24: Plot of the Ln K vs 1/T for the reaction of phenylboronic acid with 4-bromochlorobenzene using PdCl$_2$.

The reaction of phenylboronic acid with 4-bromochlorobenzene using Ce(OH)$_4$ was performed using the same conditions. Figure 25 represents the averages of the triplicate performed for this reaction. The ratio of the hetero-coupling product compared to the homo-coupling product was determined.
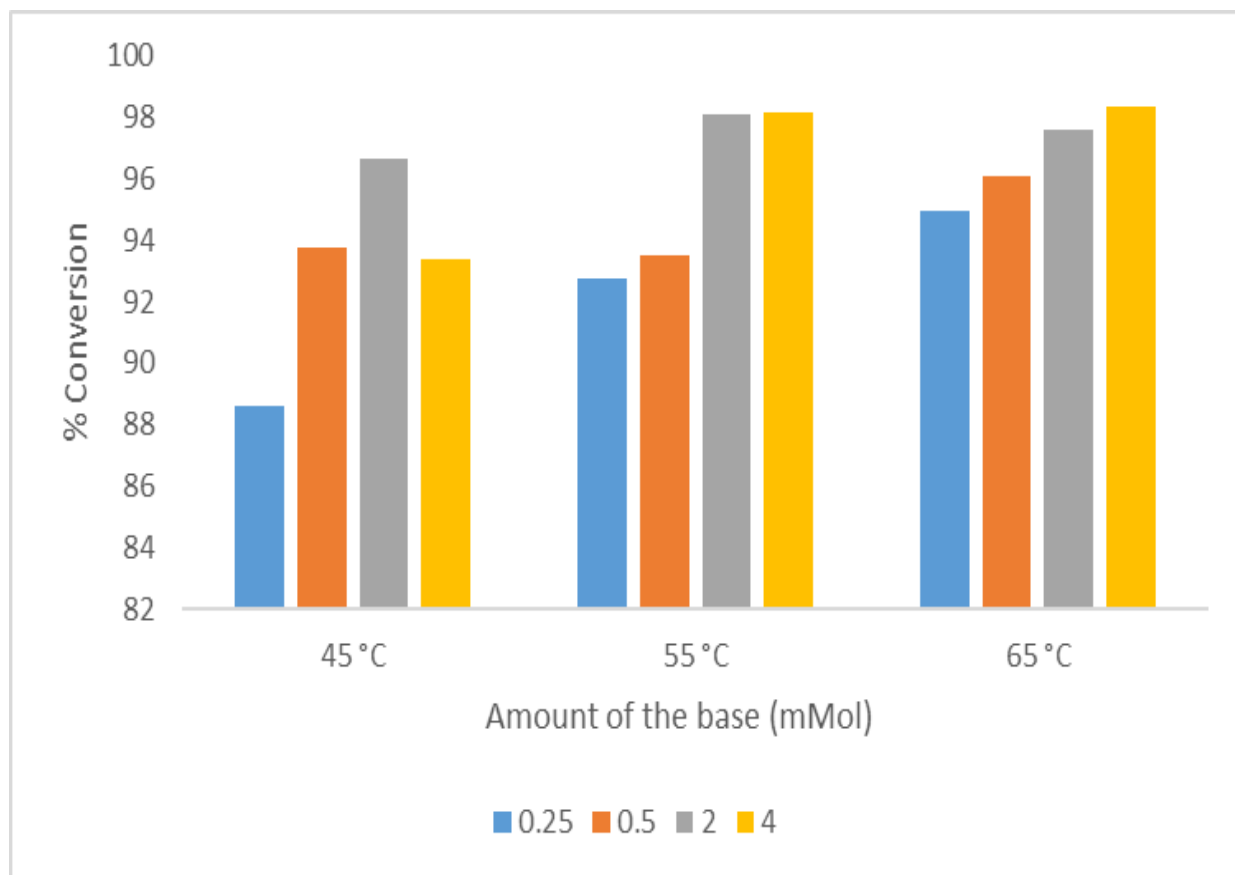
Figure 25: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromochlorobenzene using Ce(OH)$_4$.

The hetero-coupling product ratio was very high in this reaction for being performed using Ce(OH)$_4$ as the catalyst (75-85%) with the highest being 91.5 % found at 65 °C. This reaction was fairly constant, at all temperatures performed. Also, the reactions performed at 55 °C with 2 and 4 mMol did not give any observable products in the GC or MS spectra.

The reaction of phenylboronic acid with 4-bromonitrobenzene using Ce(OH)$_4$ was performed using the previously mentioned conditions. Reaction products were characterized using either GC-MS or GC-FID. The NIST database was used to identify products obtained from each reaction. Figure 26 is a GC-MS chromatogram obtained from the reaction of phenylboronic acid with 4-bromonitrobenzene using PdCl$_2$. The peak observed at 6.74 correspond to the

starting material (4-bromonitrobenzene) while the other peak at 9.25 correspond to 1,1'-

biphenyl, 4-nitro.
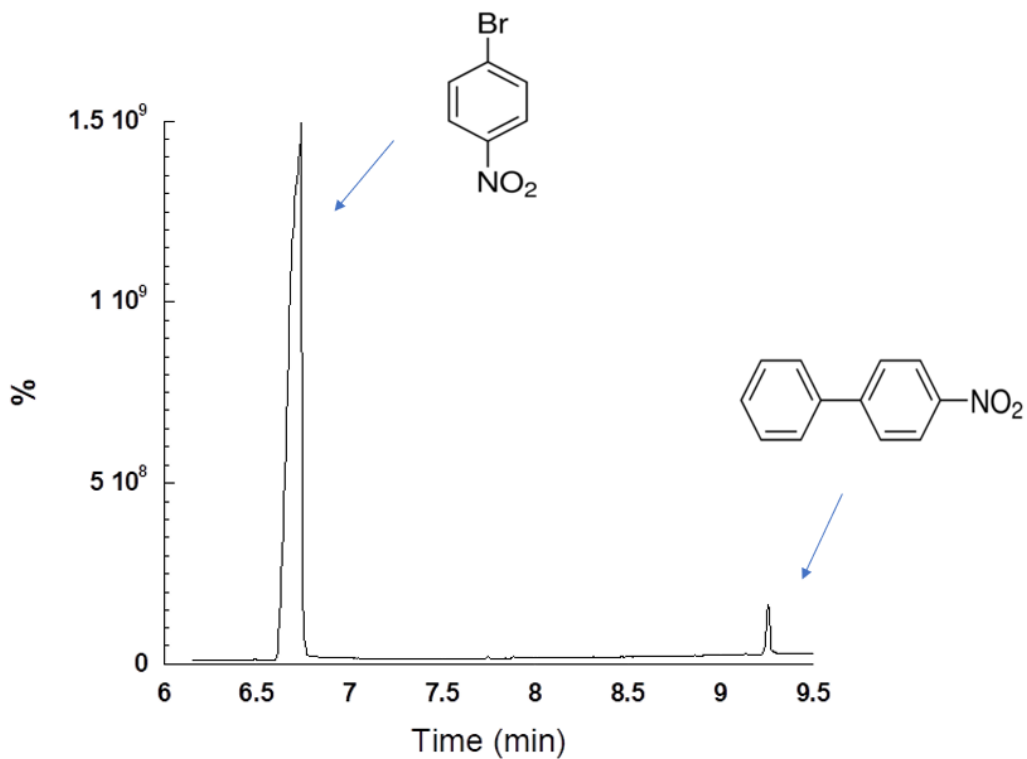
Figure 26: Chromatogram of the reaction of phenylboronic acid with 4-

bromonitrobenzene.

Figure 27 represents the averages of the triplicate done for this reaction in which the ratio

of the hetero-coupling product compared to the homo-coupling product was determined.
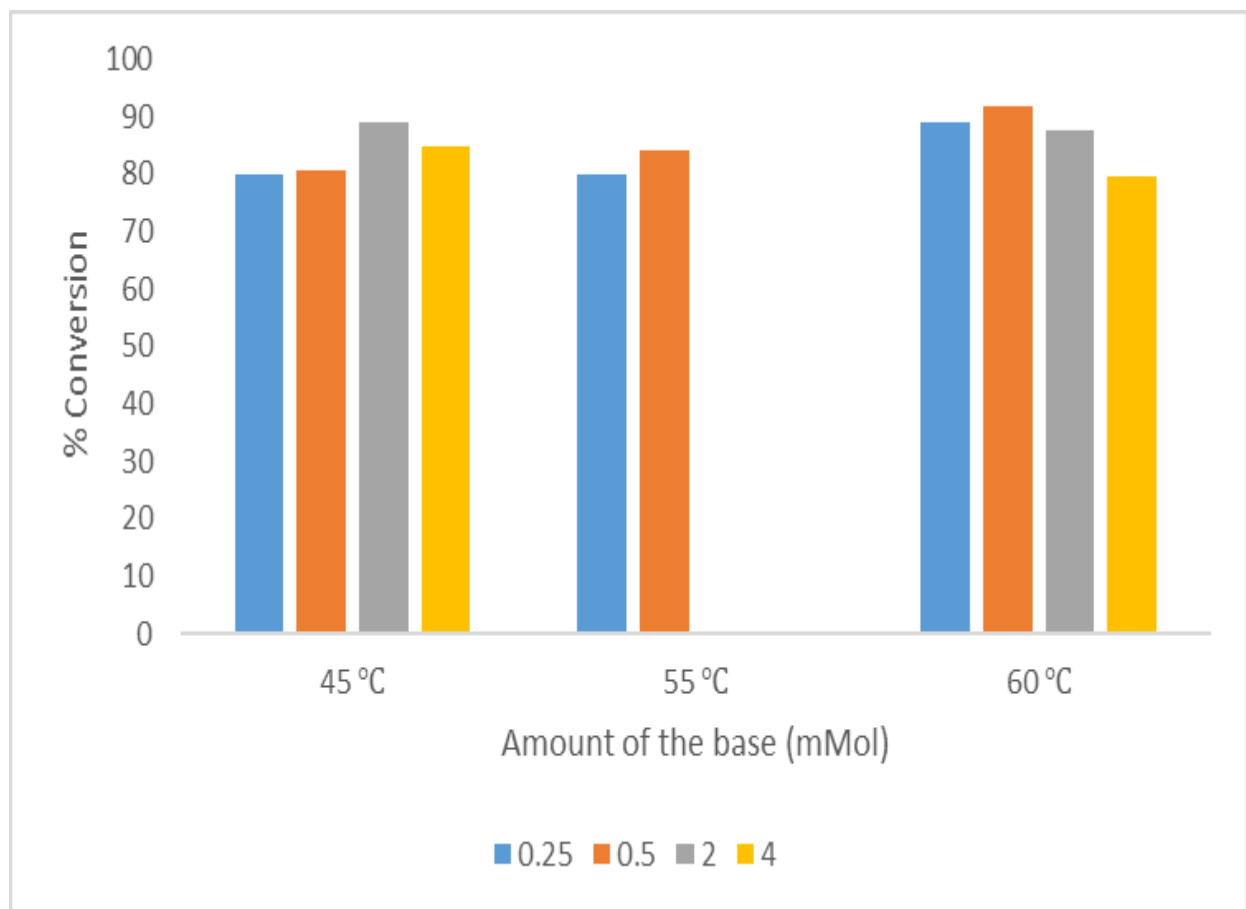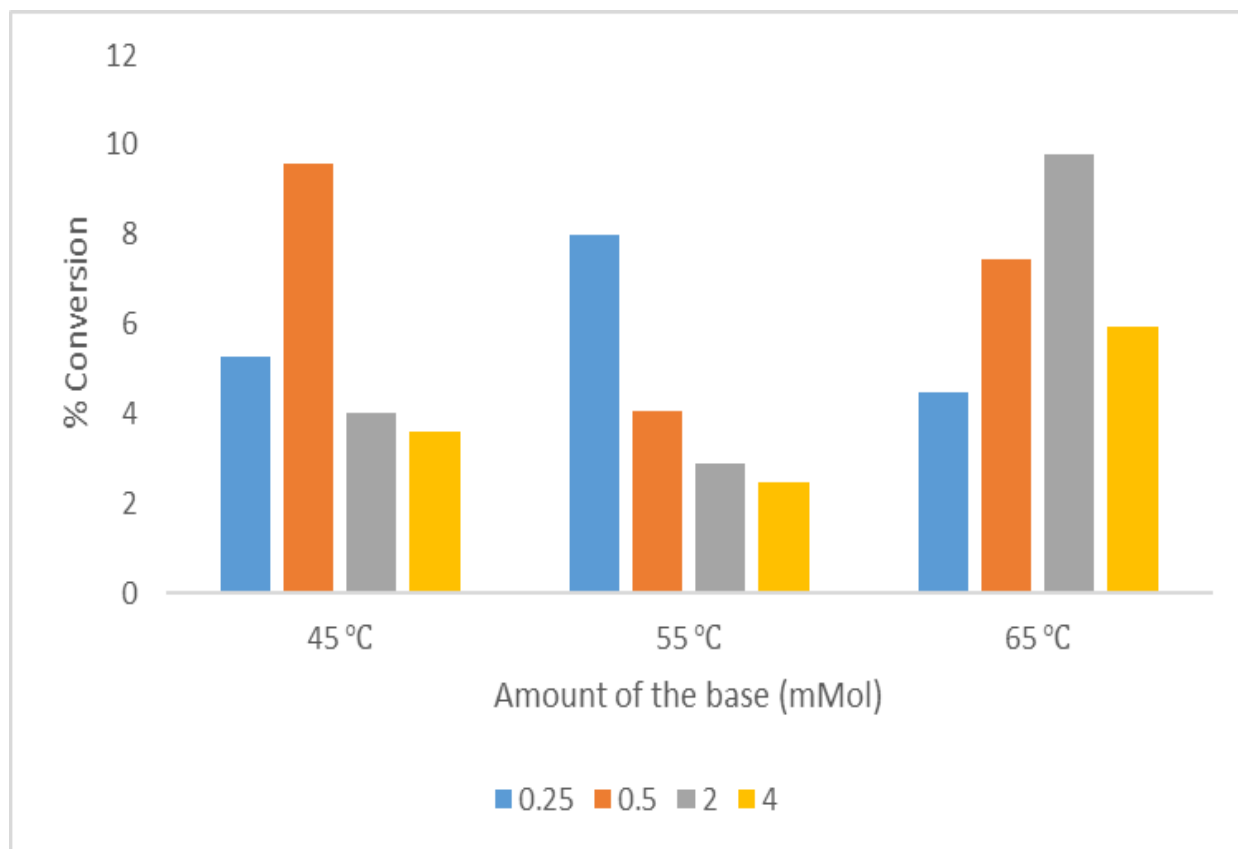
Figure 27: Averages of the triplicate reactions performed for the reaction of phenylboronic acid with 4-bromonitrobenzene using $Ce(OH)_4$.

The hetero-coupling product ratio was extremely low in this reaction where $Ce(OH)_4$ was employed as the catalyst (4-8%) with the highest being 9.9 % found at 65 °C. This reaction did not work as well as the 4-bromochlorobenzene, which can be tied to the presence of the nitro group which is a strong electron withdrawing group, whereas in the previous reaction the halides are only weak electron withdrawing gropus.

CHAPTER IV

CONCLUSION

Suzuki cross coupling reactions have been exploited extensively for industrial and pharmaceutical applications. They have been the preferred method of choice for the formation of the C-C bonds because these reactions have many advantages, compared to different methods. These types of reactions have been studied extensively by a high number of researchers since their discovery. However, there is still room for improvement for these reactions. There are many ways that these reactions can be performed, a very common way for fast testing of these reactions is using microwave irradiation. The microwave is known to accelerate conditions when using polar solvents, for example alcohols which also happen to be safe for the environment, conserving the green chemistry.

Therefore, this research study was made using microwave conditions and isopropanol as the solvent. Suzuki cross coupling reactions are typically performed using a palladium complex as a catalyst. In addition, it is believed that cerium may be useful as a catalyst since both metals have similar properties. The optimum conditions on the nature of these reactions were analyzed. For the catalysts, $PdCl_2$ and $Ce(OH)_4$ were employed in the reactions. The $PdCl_2$ catalyst source was used straight from the reagent bottle, while the $Ce(OH)_4$ catalyst was synthesized in lab, this catalyst was further characterized using XRD. Among the reactants, 4-bromotoluene and 4-bromoanisole were employed as the reactants having EDG while 4-bromonitrobenzene, 4-bromochlorobenzene and 4-bromobenzene were employed as the reactions having EWG. For the

39

base and temperature, 0.25, 0.5, 2 and 4 mMol of the base were employed with temperatures of 40, 50, 60 and 70 ˚C. For the reactions performed using $PdCl_2$ as the catalyst, it was found that the optimum conditions are when 2-4 mMol of the base and 50-60 ˚C temperatures are employed.

The base that worked the best in this project was Na_2CO_3. Since the role of the base in these reactions is to help by facilitating the oxidative addition step in the mechanism of the reaction, it was expected that as the amount of the base increases, the activation energy would be lower and therefore producing more yields. However, it was noticed that by using only 2 mMol, the product yield was slightly higher than when using 4 mMol. This is due to the fact that using too much base, can cause a deboronation reaction. The product yields when using either 2 and 4 mMol were very close to each other.

It was also expected that as the temperature increases there are more collisions in the reaction producing higher reaction yields. However, this was also not observed in this project. Using isopropanol as a solvent, the boiling point is 82.6 ˚C which was very close to the highest temperature employed in the reactions which may have inhibited the reaction.

Tangent to this analysis, for the reactions performed using $Ce(OH)_4$ as the catalyst, it was found that they were very consistent at all temperature not much changing in the amount of product produced in the presence of a halide. Which is something very important since cerium is not typically a catalyst that works well on these reactions. However, the addition of a strong electron withdrawing group such as the nitro group inhibited the cross coupling reaction, only very small yields of products were observed.

The use of microwave reaction conditions which are rapid reactions (5 min), using isopropanol as the solvent which is uncommon in these reactions (most people use hexane,

toluene, ethyl acetate) and using palladium or cerium as the catalyst good yields of the amount of hetero-coupling product were observed, with weak electron withdrawing groups.

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BIBLIOGRAPHICAL SKETCH

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