

Spring 2019

Development of Nickel Catalyzed Cross-Coupling Methodologies

Ryan J. Key

Follow this and additional works at: <https://scholarcommons.sc.edu/etd>

 Part of the [Chemistry Commons](#)

Recommended Citation

Key, R. J.(2019). *Development of Nickel Catalyzed Cross-Coupling Methodologies*. (Doctoral dissertation). Retrieved from <https://scholarcommons.sc.edu/etd/5324>

This Open Access Dissertation is brought to you by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact digres@mailbox.sc.edu.

DEVELOPMENT OF NICKEL CATALYZED CROSS-COUPPLING METHODOLOGIES

by

Ryan J. Key

Bachelor of Science
University of South Carolina Aiken, 2015

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

Chemistry

College of Arts and Sciences

University of South Carolina

2019

Accepted by:

Aaron K. Vannucci, Major Professor

Dmitry Peryshkov, Committee Member

Parastoo Hashemi, Committee Member

John R. Regalbuto, Committee Member

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

© Copyright by Ryan J. Key, 2019
All Rights Reserved.

DEDICATION

This work, along with the work and struggle of the past four years, is dedicated to my grandmother Frances “Mama” Key, who showed me that following God is more important than any work I can ever achieve and that “if I missed Heaven, I’ve missed it all”; and to my grandfather Lynwood “Pawpaw” Duggan, who’s courageous fight and unwavering faith showed me how to carry out his last words to me to “do well and be good.” I have done well and for that I dedicate this to you all.

ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge the reason I am here. Without the strength and perseverance of my Lord and Savior Jesus Christ, I would be incapable of achieving this goal. To Him to all Glory belongs and thus without Him I would easily have failed.

I would also like to acknowledge my lovely wife, DeShea, and my daughter, Savannah Grace. Without you, I wouldn't have been able to survive these four years. The love and support of my wife helped me overcome many of the obstacles I faced these few years. Honestly, if she was anymore supportive, she would literally be carrying me around. Thank you, my love. As for Savannah, everyday I am reminded of why I do what I do. Everything I am and everything I have achieved, including this work, pales in comparison to the blessing of being her daddy. I love you BooBoo.

Further acknowledgment must be extended to my family as well. Being the first Doctorate in the family can leave one feeling isolated and scared. However, being raised in the manner that my Mother and Father did allowed me to develop the skills and work ethic to achieve this massive goal. Without those lessons and that guidance, these goals would have never been achieved. For instilling these values and for your support, I thank you. This also includes my brother, Brandon, and his wife, Sierra, who always laughs at my jokes. Knowing you are behind me no matter where I go brings much comfort. Your impact upon this work is immeasurable.

I would also like to thank my research group and fellow graduate students. This path is not an easy one to take but knowing that there are others walking alongside me and supporting me makes it easier. All the conversations over coffee, frozen yogurt, and an excessive amount of Moe's burritos pushed me to my best and reminded me that I am not alone in this struggle. Without supporting each other, we would not be able to achieve our lofty goals.

Last, but not least, I want to thank my PhD committee, particularly Dr. Vannucci. Your guidance and patience with me have molded me into the chemist I am today. Even whenever I barged into your office during proposal writings, you still were willing to listen and provide insight to whatever questions I provided. Thanks to you, I focused on one project at a time rather than the scattershot I attempted in my first year. If not for your guidance in that matter, I would not be preparing for this defense. I am so thankful I chose to work with you and proud to say I am a graduate of the Vannucci Research Group.

ABSTRACT

In this work, we have addressed some of the issues surrounding catalytic cross-coupling reactions by using a nickel terpyridine catalyst, $[\text{Ni}(\text{tpy})(\text{py})(\text{CH}_3\text{CN})_2](\text{PF}_6)_2$ in the Buchwald-Hartwig amination reaction and a functionalized variant, $[(2,2':6',2''\text{-terpyridine-4'-benzoic acid})\text{Ni}(\text{II})]\text{Cl}_2$ on SiO_2 , in Suzuki coupling. These processes are unique in the approaches taken to achieve reactivity. In the Buchwald-Hartwig amination reaction, we used photoredox dual catalytic methods to achieve a sustainable approach to generate secondary and tertiary amines. This report is unique in many ways; most importantly, this method uses N-centered radicals to generate new C-N bonds. This report is also the first report to show generation of secondary and tertiary amines in the same reaction scaffold. For the Suzuki reaction, we developed a heterogeneous nickel catalyst by immobilization of a nickel terpyridine analogue on a solid oxide support. By doing so, we created a recyclable catalyst that can operate up to five reactions before suffering deactivation. The approach is more effective than homogeneous reactions, as the catalyst is easily reclaimed and simplifies both purification and analysis. We further developed this process by immobilizing the molecular catalyst using Atomic Layer Deposition. This approach allows for a physical barrier to be added to the catalyst motif that increases practical stability. Indeed, the immobilization worked effectively, allowing more than six reactions without any catalyst deactivation in aqueous solvents. After immobilization, activity was observed towards heteroaryl substrates, a useful moiety in pharmaceutical drug targets.

TABLE OF CONTENTS

Dedication	iii
Acknowledgements	iv
Abstract	vi
List of Tables	viii
List of Figures	ix
Chapter 1: Introduction	1
Chapter 2: Nickel Photoredox Dual Catalysis for the Synthesis of Aryl Amines	27
Chapter 3: A Molecular/Heterogeneous Nickel Catalyst for Suzuki-Miyaura Coupling	47
Chapter 4: Immobilization of a Nickel Molecular Catalyst on Solid Oxide Supports via Atomic Layer Deposition	65
Chapter 5: Conclusion and Future Work	76
References	81

LIST OF TABLES

Table 2.1 Optimization of Reaction Conditions	31
Table 3.1 Optimization of Suzuki-Miyaura Cross-Coupling.....	53
Table 3.2 Cross-coupled product yields from Recycled Catalyst.....	58
Table 4.1 Optimization of Suzuki reaction using ALD Catalyst	71

LIST OF FIGURES

Figure 1.1 Different classes of cross-coupling reactions	3
Figure 1.2 Conventional cross-coupling mechanism.....	4
Figure 1.3 Biaryl phosphane palladium catalyst.....	6
Figure 1.4 Basic structure of an N-heterocyclic carbene ligand.....	7
Figure 1.5 Proposed mechanism for the XEC reaction.....	15
Figure 1.6 Schematic representation of a reductive photoredox dual catalytic method	21
Figure 1.7 Coupling of α -carboxyl carbons with aryl halides reported by the MacMillan group.....	22
Figure 1.8 Proposed mechanism for the PARC reaction	25
Figure 2.1 Comparison of the proposed reactions for the formation of a Ni^{III} intermediate	29
Figure 2.2 Catalytic dual photoredox cross-coupling between <i>p</i> -methoxy aniline and aryl halides.....	33
Figure 2.3 Catalytic dual photoredox cross-coupling between aryl iodide and various aniline substrates.....	35
Figure 2.4 Stern-Volmer plot for the fluorescence of $\text{Ru}(\text{phen})_3$ in the presence of varying amounts of K_3PO_4	36
Figure 2.5 Stern-Volmer plot for the fluorescence of $\text{Ru}(\text{phen})_3$ in the presence of 4-methoxy-aniline	36
Figure 2.6 Stern-Volmer plot for the fluorescence of $\text{Ru}(\text{phen})_3$ in the presence of 4-methoxy-aniline and K_3PO_4	37
Figure 2.7 Stern-Volmer plot for the fluorescence $\text{Ru}(\text{phen})_3$ in the catalytic conditions	37

Figure 2.8 Proposed mechanism for dual photoredox C-N cross-coupling catalysis via an amine radical	38
Figure 3.1 Illustration of molecular/heterogeneous catalyst.....	50
Figure 3.2 Crystal structure of COOH-Ni	51
Figure 3.3 XRD Crystallographic Data before Catalytic Reaction.....	52
Figure 3.4 Catalytic Suzuki-Miyaura cross-coupling between aryl iodides and aryl boronic acids	56
Figure 3.5 Catalytic Suzuki-Miyaura cross-coupling between aryl boronic acids and aryl halides.....	57
Figure 3.6 XRD Crystallographic Data after Catalytic Reaction	59
Figure 4.1 Visual representation of immobilization of the nickel molecular catalyst	68
Figure 4.2 Reaction using the COOH-Ni SiO₂ TiO₂ catalyst in aqueous solvents	70
Figure 4.3 Comparison of the ALD and non-ALD catalyst.....	72
Figure 4.4 Suzuki coupling in aqueous solvents.....	73
Figure 5.1 Proposed Suzuki mechanism highlighting dualistic approach of ALD layers	79

CHAPTER 1:

INTRODUCTION

Ever since the Ullman coupling reported in 1901,¹ cross-coupling reactions have presented a litany of pathways to generate fine chemicals ranging from pharmaceuticals to agrochemicals to biofuels.²⁻⁵ The pharmaceutical industry in particular has benefitted greatly from cross-coupling reactions, allowing for faster and more effective drug discovery and application.³⁻⁵ In fact, the pharma industry has so embraced these organic pathways that in 2011 a publication in the Journal of Medicinal Chemistry found that 7315 medicinal syntheses reported at least one cross-coupling step in the process.⁶ With a current worldwide revenue reported in 2016 by the IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) of \$1.1 trillion and an expected revenue growth to \$1.4 trillion by 2021, the pharmaceutical industry has proven itself to be one of the largest industrial sectors in the world and this in part can be contributed to the chemistry of cross-coupling.

Cross-coupling reactions are reactions that can generate new C-Y (Y = C or heteroatoms including N, O, and S) bonds from pre-existing bonds.⁷⁻¹⁷ Though C-H bond activation reactions or functionalization reactions are not thought to be cross-coupling reactions, the mechanisms of C-H activation reactions are similar to cross-coupling reactions. The first reported coupling reaction is generally contributed to the copper catalyzed Ullman reaction, in which an aryl halide is homocoupled to form a biaryl

product.¹ The reaction presented a new methodology that received much attention. However, the inconsistent yields and heterogeneous nature of the reaction left something to be desired.

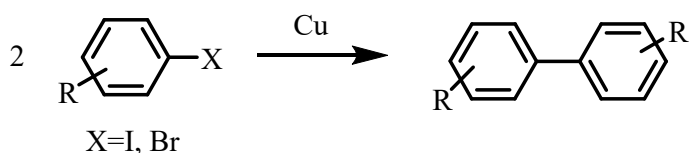
The field of catalytic cross-coupling started to experience renewed interest due to emergence of organometallics as a field, leading to a “renaissance” of catalytic cross-coupling reactions in the 1970’s.^{7, 18-20} It is during this decade that the Heck reaction and the Suzuki reaction were first developed. The Heck reaction was developed in the early 70’s and emphasized the first reaction to use non-activated organic substrates in a coupling reaction by using olefins and coupling them to aryl halides using a palladium catalyst.¹⁸⁻²⁰ These two reactions laid the foundation for the discovery of the Suzuki reaction in 1979, which quickly grew as one of the most effective C-C bond formation reactions.⁷⁻⁹ Using an organoboron compound as a nucleophile and a palladium catalyst, the Suzuki reaction is capable of generating new C-C bonds to form biaryls. Ever since the Suzuki and Heck reactions were developed in the 70s, the field of cross-coupling reactions have experienced a massive influx of research, money, and interest. So much so, that the Nobel Prize in 2010 for Chemistry was awarded to Richard Heck, Akira Suzuki, and Ei-ichi Negishi, who showed C-C bond formation using organozinc substrates.^{2, 21} Though not awarded the Nobel Prize, the Buchwald-Hartwig amination reaction has also greatly benefitted the pharmaceutical industry.²²⁻²⁴ By using a palladium catalyst, Buchwald and Hartwig independently reported the formation of C-N bonds between an amine and an aryl halide.^{22,}

25-27

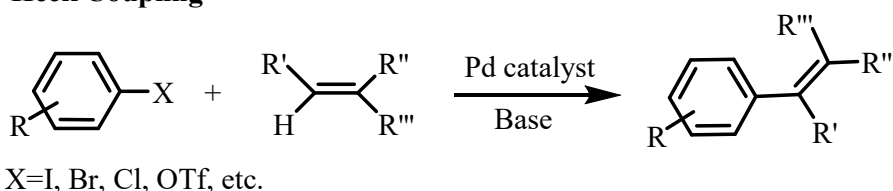
Most catalytic cross-coupling reactions follow a general coupling mechanism, as seen in Figure 1.2. Typically, this mechanism changes from reaction to reaction based upon

the feedstock for that reaction. Regardless of the feedstock, these conventional reactions generate new bonds, whether it be C-C or C-X (X=N, O, or S), from a nucleophile and an electrophile.

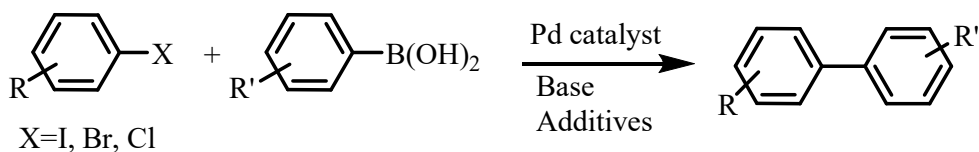
Ullman Coupling



Heck Coupling



Suzuki Coupling



Buchwald-Hartwig Amination

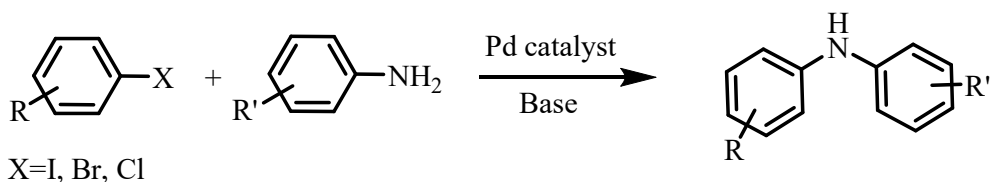


Figure 1.1. Different classes of cross-coupling reactions.

The conventional cross-coupling mechanism follows a three step process: 1) oxidative addition of an electrophile to the metal center, causing a formal oxidation state change from 0 to +2; 2) transmetalation, in which the nucleophile is activated by an additive and allows for a transfer of an organic functional group, such as an aryl group, to

the metal center; and 3) reductive elimination of the coupled product, producing a formal oxidation state change from +2 to 0, regenerating the catalyst.

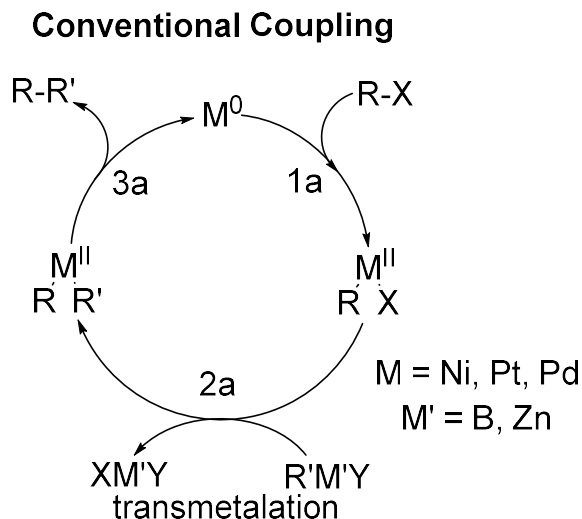


Figure 1.2. Conventional cross-coupling mechanism. The catalytic cycle consists of three steps: 1a) oxidative addition, 2a) transmetalation, and 3a) reductive elimination. Ligands on metal catalyst excluded for clarity.

Intermingled with these three steps are a variety of intermediates that have been isolated and characterized, giving valuable insight into how coupling processes operate.^{8, 28-32} Many intermediates are by-products of the catalytic activity centered on the metal catalyst and its oxidation state.²⁸ Indeed, the very nature of this mechanism is one of redox events, so preferred pathways and cycle killing by-products are to be expected. It is these characteristics that make this process an organometallic reaction rather than an organic reaction; thus, when conducting research into coupling reactions, understanding the organometallic characteristics of the reaction in question is imperative and must be addressed.

The traditional cross-coupling reaction utilizes palladium metal catalysts to achieve reactivity.⁷⁻⁹ Initial reactions used palladium phosphine catalysts, such as the tetrakisphosphinepalladium catalyst ($\text{Pd}(\text{PPh}_3)_4$) due to high thermal stability and versatility.^{8, 33} This catalyst was used in the first reported Suzuki coupling to produce biaryls and was amiable to a litany of catalytic conditions, both homogeneous and heterogeneous.^{8, 33} Later work showed that palladium salts were effective in the Suzuki reaction, leading to a simplified reaction. In certain cases, it was observed that non-coordinated palladium salts even outperformed the ligated palladium catalysts.⁸ In other cases, introduction of ligands to form *in situ* palladium catalysts provided an increase in reactivity.⁸⁻⁹ The phosphine ligands used in Suzuki coupling also provide a simplistic approach to affecting reactivity to certain substrates and reaction conditions by affecting the functionality of the ligands themselves. For example, the (*m*- $\text{NaO}_3\text{SC}_6\text{H}_4\text{PPh}_2$) ligand allows for reactivity in aqueous solvents, allowing for an environment friendly approach.⁸

Phosphine palladium catalysts are also widely used in amination reactions; in particular, a class of phosphine ligands called biaryl phosphane ligands are used throughout the Buchwald-Hartwig amination reactions (Figure 1.3).²²⁻²³ Palladium phosphane catalysts are suitable to these reactions due to the mechanism of the amination reaction. This mechanism varies slightly from the conventional cross-coupling mechanism seen in Figure 1.2; rather than having the transmetalation step, the second step of the mechanism involves the coordination of an amine to the metal center. The metal-amino bonds are rather strong, providing a significant thermodynamic barrier for the reductive elimination of the desired cross-coupling product.²³⁻²⁴ To combat this, biaryl phosphane ligands like XPhos or SPhos present a sterically demanding ligand that can effect this thermodynamic barrier

while at the same time provide a simplistic approach to varying the electronic nature of the ligand by simple organic synthesis.²³ There is also evidence that shows that the catalyst also aids in the electronic nature by binding to the palladium metal in a bidentate manner to the biaryl ring. This interaction allows for the formation of the Pd⁰ catalyst necessary for the catalytic cycle to continue. This would in turn further aid reductive elimination and the cleavage of the Pd-N bond.²³ Within the field of Buchwald-Hartwig amination reactions there has emerged another field, which is the development of the different type of phosphine catalysts and studying the various effects of functionalization of these ligands.²²⁻

24, 27

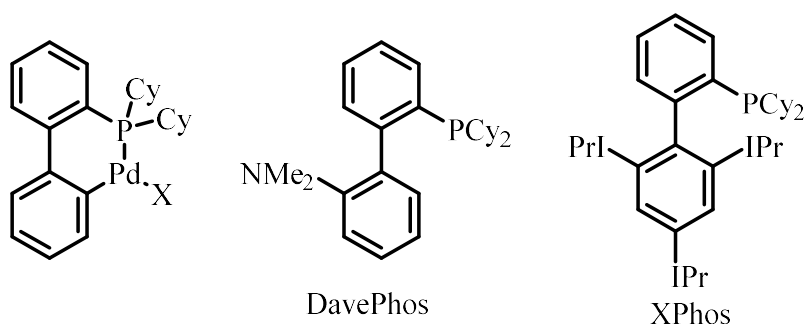


Figure 1.3. Biaryl phosphane palladium catalyst. This motif is commonly used in the Buchwald-Hartwig amination reactions. Pictured also is two common phosphane ligands, DavePhos and XPhos. Cy=cyclohexane.

Recently, the development of N-heterocyclic carbene ligands have gained the focus of cross-coupling research and has been replacing the typical phosphine catalysts initially used in these reactions.³⁴⁻³⁸ N-heterocyclic carbene (NHC) ligands provide a highly tunable alternative to phosphine catalysts, as the synthesis and functionalization of NHC ligands can be achieved by a variety of methods.^{34, 37-38} NHCs are defined as ligands with a carbene in a ring structure that contains at least one nitrogen, the most common of which is the

imidazole heterocycle as seen in Figure 1.4.³⁷⁻³⁸ The carbene is found to be in the singlet state, allowing for a strong σ -interaction with metals to form catalysts while also leading to relatively high stability for the formed organometallic catalyst.³⁷⁻³⁸ This characteristic arises from the π stabilization effect of the nitrogen adjacent to the carbene, leading to what can be conceptualized as an sp^2 hybridized carbon with an unoccupied π -orbital.³⁸ The electronic nature of the adjacent nitrogen also affects this characteristic and thus can be modified depending upon the N-substituent. In addition, the N-substituent also introduces steric effects that can increase reactivity. The electronic nature of NHCs allows for facile oxidative addition while the steric effects of the N-substituent aids in the reductive elimination step.³⁸

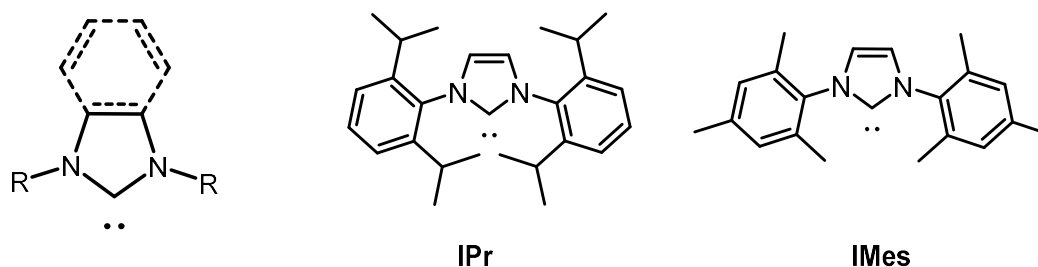


Figure 1.4. Basic structure of an N-heterocyclic carbene ligand. The structure presents highly tunable alternatives for ligand design, as the base structure can be imidazolium or benzimidazolium based. Further modality is introduced with the N-substituents and saturation of the ring structure. Pictured are two of the most common NHC ligands, IPr and IMes.

Since the 1995 report of the Herrmann group utilizing NHC catalysts in cross-coupling reactions, the field of NHC catalysts has grown rapidly.^{37, 39} These catalysts have become commonplace in organic synthesis and even in some cases have achieved previously difficult transformations, such as the IPr ligand being used to achieve Suzuki coupling with aryl chlorides or the functionalization of the NHC catalyst with sulfonate

functional groups to achieve aqueous transformations.^{37-38, 40-43} NHC-containing catalysts have also seen great strides in the application of Buchwald-Hartwig amination reactions, and have even shown potential for greater reactivity than the previously used phosphane catalysts.^{25, 42} Arguably, the greatest advancement in the field of N-heterocyclic carbenes would be the contribution of the Organ group in the mid-2000's. It is during this time that this group developed a widely applicable, general approach to catalytic cross-coupling catalysts termed PEPPSI, or Pyridine Enhanced Precatalyst, Preparation, Stabilization and Initiation.^{34, 38, 44} The PEPPSI catalysts have made a large impact on industrial processes, as the catalysts are easily prepared in ambient atmosphere and shows high stability. Furthermore, the catalysts are highly active in a myriad of cross-coupling reactions, presenting a general approach applicable to a wide range of reactions.^{34, 41} This general approach is a highly sought after characteristic in new catalyst design, as it presents a level of ease for industrial sectors, such as the pharmaceutical industry. Alongside the PEPPSI catalysts, NHC η^3 -allyl catalysts have also gained tremendous ground as well-defined, highly active cross-coupling catalysts.⁴¹⁻⁴²

In addition to the palladium catalysts used in the various coupling reactions, there are several additives used that are unique to each cross-coupling reaction. In general, the mechanism dictates which additives are necessary to ensure reactivity. For example, the Suzuki reaction requires the addition of a base to activate the boronic acid for transmetalation.⁸⁻⁹ This is due to the coordination of the negatively charged base to the boron, allowing for a ligand exchange to another positively charged metal center, such as the Pd^{II} intermediate generated after the initial oxidative addition.⁸ Commonly used bases in Suzuki coupling are usually insoluble heterogeneous carbonate and phosphate salts, such

as cesium carbonate, sodium carbonate, and potassium phosphate. However, organic bases have also shown to be effective, such as amine bases.⁸ These bases, however, present additional separation and purification challenges, as they are homogeneous. It is also common in Suzuki coupling reactions to see additional metal salts, such as CuCl, to aid in this transmetalation step.³⁰ In Buchwald-Hartwig amination, the base plays a large role in activating the amine substrate and is therefore imperative in the amination reaction scaffold.^{22-23, 27} These additives aid in producing the desired product selectively by producing alternative pathways that are thermodynamically favorable than competitive off-cycle reactions.⁴⁵ Along with these additives, most cross-coupling reactions use organic solvents to achieve reactivity. This is primarily due to the solubility of all the substrates and catalysts, but also has a part in off-cycle reactions as well. Recently, the Nova group published a review outlining the various effects of solvents, additives, and catalyst design to affect off-cycle reactions.⁴⁵ In general, when determining experimental design, the catalyst, additives, and solvents must all be evaluated to determine the most suitable approach, as well as other factors such as sustainability of the approach and cost.

It is in further evaluations that the shortcomings of the cross-coupling methods become apparent. Regarding the catalyst, palladium is still the most widely used metal in cross-coupling reactions. Palladium is expensive, meaning these catalysts can create a monetary problem in order to synthesize. In addition to cost, the palladium metal is toxic and, in some cases, such as with phosphine and phosphane ligands, the ligand increases the toxicity of the catalyst. In the case of pharmaceuticals, this toxicity presents a large problem as this necessitates extensive back-end purification and quality testing.³⁻⁵ Though this toxicity is inherent to organometallic processes, palladium presents a costly waste,

especially in cases which the catalyst cannot be reclaimed for further reactions.⁵ Palladium catalysts also have additional limitations associated with the chemical properties of palladium itself. For example, palladium is typically relegated to 2 e⁻ mechanisms that involve (0)/(II) oxidation state changes. Palladium catalysts are also prone to β -hydride elimination reactions, limiting the effectiveness of these catalysts with certain substrates like sp³ hybridized carbon substrates.^{8, 14, 27-28, 31, 46} Though these properties are unique to palladium, similar considerations must be taken for other organometallic catalysts. To further complicate matters, the ligand can also influence reactivity, causing more additives to be used and leading to more extensive and costly processes. Inherent reactivity trends at times hinder the reactions by limiting the available substrates. Developing new catalysts that introduce more favorable reactivity trends is a highly desired outcome of cross-coupling research.

Thorough evaluations of catalytic processes do not only look at the chemistry that is involved, but also at the practical aspects of the process itself. Typically, cost is the largest of these logistical characteristics, but there has emerged a new criterion by which to judge the efficacy of cross-coupling reactions. This criterion is known as green chemistry. In short, green chemistry is the approach that aims at maximizing efficiency while simultaneously minimizing the hazards associated with the process.⁴⁷ In terms of cross-coupling reactions, there are a few areas that green chemistry guides new research. One such area is that of the additives used in each reaction.³ Additives serve a supplemental role to the catalyst; their main use being limiting side reactions known as off-cycle reactions that may deactivate the cycle. The additives are thought to be integral to reactivity, such as the base in the Suzuki coupling reaction. However, removal of additives

creates a greener approach, as not only the efficiency of the reaction increases, but the process becomes simple. Furthermore, simplification of the process leads to more control and generality of a reaction. Ideally, the additives would be removed altogether. This goal is a lofty one, albeit a worthy goal.

The solvent used in coupling processes also present an area that green chemistry tries to address. Typically, catalytic cross-coupling reactions use organic solvents.^{3, 7-9, 18, 23, 27} A common organic solvent used is 1,4-dioxane, which is particularly toxic and carcinogenic. Other solvents, such as tetrahydrofuran (THF), toluene, or dichloromethane (DCM) are also used.^{2, 23, 28, 42} All these solvents can cause health problems, including cancer. This leads to stringent purification practices and quality testing, particularly in the pharmaceutical industry.³ However, replacing these unsafe solvents present a unique problem. Typically, solvents are chosen for the relative solubility of all components of the reaction. Recently, it was also found that the solvent also plays a part in off-cycle reactions instrumental to the activation of the catalyst. For example, the Melvin group recently outlined how alcohol-based solvents aid in the activation of Pd^{II} NHC η^3 -allyl catalyst, which have been shown to be highly reactive NHC catalysts.⁴⁸ In this work, it was shown that the solvent would displace a chloride ligand by activating the alcohol by deprotonation and coordination of the resulting negatively charged ion. This was seen to be rather important, as the alternative reaction was a comproportionation to form a Pd^I dimer using chloride as a bridging ligand is a cycle deactivation pathway. This pathway increased depending upon the ligand but did not proceed as effectively without the proper solvent. Therefore, when replacing the solvent to aid in safety and cost, the effects of the solvent upon the process must also be considered.

For industrial processes, the sustainability and cost of any new processes play a major part of implementation. For most conventional reactions, the primary energy source is heat. This type of energy input is inefficient and leads to reactions that can take up to a day to achieve reactivity. Furthermore, the additives and solvents previously discussed lead to harsh conditions, which in turn require extensive purifications and proper handling. All these previous considerations, along with the catalysts used, equate to high cost of cross-coupling reactions. Back-end purifications are extensive and time consuming, meaning quality testing constitutes a large portion of industrial lab settings. Any impurity can lead to failed production batches and cost the company money. Ensuring these impurities are not in the final product is costly. Although certain areas of industries like pharmaceuticals will always be necessary, simplifying analytical testing leads to streamlined performance and more revenue. The logical way of doing this is by simplifying the process and removing potential sources of contamination. Thus, lowering cost while increasing sustainability presents yet another goal of catalytic research and at times can even outweigh some of the previous limitations discussed.

Addressing the challenges rising from the catalysts used, the additives used, the solvent, the sustainability of the processes and the cost of cross-coupling reactions has guided research in both academic and industrial settings. Approaches that remove one or more of these problems are valuable to the field and provide advancements that push catalytic cross-coupling reactions like the Suzuki reaction and the Buchwald reaction further than initially imagined. In some cases, unique mechanisms arise, allowing for new reactivity and substrate classes to be accessed. The ideal cross-coupling reaction is a reaction that uses low catalyst loadings of an earth abundant catalyst in a green solvent like

water without any additional additives. Such a goal is difficult to achieve, but many advancements have been made towards this goal.

Recent work has been developed replacing the palladium catalyst. The goal of this development was initially to replace the palladium metal for cost reasons. Some earth abundant catalysts, like iron-based catalysts have been developed to lower costs. These catalysts provided an earth abundant option initially but was later to exhibit desirable reactivity trends. For example, iron catalysts were found to not be prone to β -hydride elimination reactions, which are cycle killing side-reactions common in palladium catalysts.⁴⁹ However there arises a new challenge, as the catalyst loading of most iron catalyzed cross-couplings are rather high, leading to waste and poor atom economy. Recently though the Szostak group was able to achieve cross-coupling between sp^2 - sp^3 carbons via a Grignard reagent at low iron catalyst loadings.⁴⁹ It was further impressive that these iron catalysts were able to operate at low temperatures and show promise for future work. However, a more common replacement to palladium catalysts in the Suzuki and Buchwald reactions are nickel catalysts.

Nickel-based catalysts have received much attention over the past few years due to their unique chemistry. Initially, nickel was thought to be a highly reactive, less selective analogue to palladium catalysts. It was discovered that this is due to the unique nature of nickel. Nickel catalysts can readily access various oxidation states ranging from 0 to +IV.^{29, 46, 50-51} These oxidation states show relatively high stability, as witnessed by the Sanford group who was able to provide electrocatalytic support for the generation of a nickel (IV) complex.⁵¹ Interestingly, the Sanford group went further and found that not only do these nickel (IV) catalysts, they are reactive to C sp^3 -X (X= O, N, and S) bond formation

reactions.⁵¹ Nickel catalysts are able to access these various oxidation states due to single-electron transfer (SET) processes. Palladium catalysts proceed through 2 electron processes, thus the 0/II oxidative addition and subsequent reductive elimination cycle. However, nickel was found to operate in a separate type of two electron process than palladium. Palladium catalysts typically follow a 0/II cycle due to thermodynamic factors. For nickel catalysts, it was found that nickel (II) intermediates are too stable for facile reductive elimination.⁵²⁻⁵³ Instead, oxidizing the nickel intermediates to the +3 oxidation state would allow for a facile reductive elimination cycle to occur to form a nickel (I) complex.⁵²⁻⁵⁴ However, achieving these nickel (III) intermediates is the challenge that can be answered using SET. Controlling these SET processes has allowed for numerous advancements in cross-coupling reactivity by achieving these required two electron processes, one of which is the cross-electrophile coupling.⁵⁵⁻⁵⁹

Cross electrophile coupling, or XEC, presented a very interesting development in the field of cross-coupling. Advanced by the Weix group, XEC processes present a way to couple two electrophiles, such as an alkyl halide and an aryl halide.⁵⁷ This is achieved by using a nickel catalyst and its propensity for SET processes. By generating an alkyl radical, a nickel (II) intermediate, such as the intermediate formed by oxidative addition of an aryl halide, can be oxidized to form a nickel (III) complex. In this state, reductive elimination can occur to form new a new sp^2 - sp^3 bond.⁵⁶⁻⁵⁸ These reactions are rather robust, producing yields in excess of 90% for some substrates.⁵⁶ The Weix group was also able to couple a wide range of electrophiles with relatively high functional group tolerance. Reactivity was also shown for heteroaryl compounds, which are difficult to access in the more

conventional approaches like Suzuki coupling.⁵⁶⁻⁵⁷ The mechanism for XEC can be seen in Figure 1.5 and exhibits why XEC reactions are so effective.

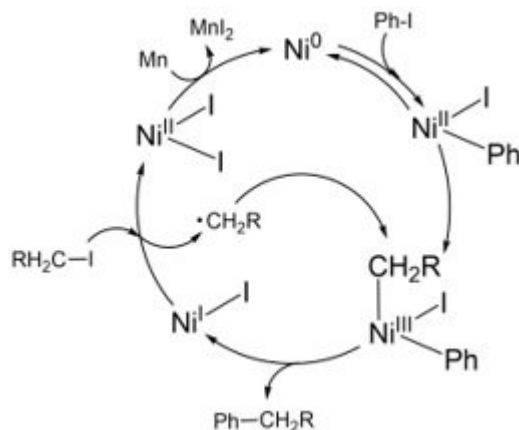


Figure 1.5. Proposed mechanism of the cross-electrophile coupling (XEC) reaction.⁵⁷ The necessary nickel (III) intermediate is generated by an alkyl radical that undergoes a radical rebound reaction that is in essence a one electron oxidative addition. The mechanism is still under investigation by the Weix group. Ligands are excluded for clarity.

The feedstock of the XEC reaction removes the need for the nucleophile, which can be a problematic aspect of conventional cross-coupling reactions. Typically, nucleophiles are unstable or unsafe to handle, such as the Grignard reagent. Furthermore, these substrates introduce unsustainable and unpredictable portions of the reaction. Replacing them with electrophiles, which are more readily available and much more stable introduce a decrease in cost and simplifies the system. However, XEC is not a perfect process. In order to achieve selectivity in XEC, an excess of the aryl halide must be present.⁵⁷ This is due to how readily some alkyl radicals form; this excessive reactivity leads to side reactions that kill the cycle, primarily homocoupling.⁵⁷ An excess of one reagent presents an avenue for further waste and exhibits poor atom economy. In addition, an external heterogeneous reductant, such as Zn or Mn, must be added to regenerate the active Ni^0 catalyst necessary

to continue the cycle.⁵⁵⁻⁵⁷ Not only does this present additional cost aspects, but also creates additional purification and quality testing for an additive that serves a singular role in the system. A more appealing approach is a redox neutral process that does not require additives such as Zn or Mn to produce the active catalyst, or at the very least an additive that serves multiple roles. However, the XEC reaction exhibits how the unique reactivity of nickel catalysts can be harnessed to develop new processes.

Though XEC uses a more favorable feedstock, the additives still present an area in which those reactions can improve. Removing these additives are a tricky goal. Recently, though, the Liotta group presented a clever way to remove the additives in the Suzuki reaction and achieve reactivity in aqueous solvents.⁶⁰ In fact, the reactivity was witnessed to increase in acidic conditions, reaching yields of 99%. By using a simple palladium salt with no ligands, pyridine substrates were reacted with boronic acids in an acetonitrile/water buffered solvent system. No extra base was used to achieve reactivity, which is exceedingly rare in the Suzuki reaction. This was achieved by including an additional amino functional group on the pyridine ring and by using a buffered solvent mixture to control pH. A clever work around, this allowed for a “base” to be included in the substrates itself and allowed for a dependency on pH to be shown.⁶⁰ Indeed, the highest yields exhibited were by the heteroaryl substrates with an additional amino functionality; moderate reactivity was witnessed for traditional pyridines, ranging from 29% to 82%.⁶⁰ In short, the Liotta group provided a method by which to remove additives in a conventional cross-coupling reaction by affecting the acid-base properties of the buffered solvent and including a basic site on the substrates. By affecting the pH of the buffered solvent, the boronic acid was activated via a separate method than the conventional Suzuki reaction; this was further aided by the

basic properties of the aryl halide substrate. Though the reaction showed reactivity without additives, a limited substrate scope was obtained, as the system only worked for pyridine substrates.⁶⁰ Still though, the approach presented a unique way of thinking about these additives and how other aspects of the system can replace the need for them. Another approach is to use additives that serve multiple roles to force selectivity and reactivity. In doing so, better atom economy is achieved, along with a simpler system to purify and test.

The field of alternative green solvents has grown over recent years. Green solvents are defined based on two properties: energy efficiency of the processes in that solvent and the environmental impact of the solvent.⁶¹ When determining which solvent to use in an industrial process, it is important to consider these properties. In 2016, the Sherwood group published a review outlining the considerations for choosing a solvent based upon the “greenness” of the solvent. This determination of the “greenness” of the solvent was based upon the EHS designations of each solvent in conjunction with the cost and usage the processes themselves, including the purification and waste disposal of the solvents. Following these guidelines, it was found that the commonly employed solvents like dichloromethane (DCM) and toluene present major health risks and thus should be replaced.⁶¹ On the other hand, it was found that certain solvents, like isopropanol and ethyl acetate, are more desirable in industrial processes as their EHS designations are less harsh and the costs of use is lower. Using the same criteria, a hierarchy can be developed that classify viable solvents into four primary categories: recommended, problematic, hazardous and highly hazardous with in-between categories existing between recommended and problematic and problematic and hazardous.⁶¹ This work is unique in the fact that these assessments were supplemented by solvent evaluations from leading

pharmaceutical companies, including GSK and Pfizer.⁶¹ Some interesting categorized solvents in this work are ethanol and water in the recommended tier, acetonitrile and 2-methyltetrahydrofuran in the problematic tier, dichloromethane in the in-between tier of problematic and hazardous, and DMF and 1,4-dioxane in the hazardous tier.⁶¹

Alternatively, developing new solvent systems present options that adhere to green chemistry principles. For example, in recent years a new solvent called Cyrene presented itself as a safe alternative to dipolar aprotic solvents like DMF.⁶²⁻⁶⁴ Derived from lignin biomass, cyrene is an environmentally benign solvent that has not shown any adverse health effects. This has made the solvent a popular replacement in cross-coupling reactions, as it mirrors the more commonly used solvents. Indeed, it was found that Suzuki coupling in Cyrene was capable of producing yields in excess of 90%.⁶⁴ Interestingly, it was found that in a mixed solvent system containing Cyrene and water, the yields produced for a reaction between bromotoluene and benzeneboronic acid using a palladium catalyst was comparable to reactions containing 1,4-dioxane and DMF in water.⁶⁴ With Cyrene being derived from biomass, the feedstock is relatively renewable as well. Cyrene does have its caveats as well; primarily from the lack of research concerning the new solvent. Though no health effects have been determined, environmental impact is still yet to be seen. However, the potential for the replacement of the more dangerous solvents like DMF makes Cyrene an appealing research area.

Other considerations for industrial practices concerning cross-coupling reactions is the cost of the process. Primarily, the cost of the process can be summed up in the previous points but can also be seen in the waste of resources. For example, an ideal catalytic process involves the reclamation and recycle of the expensive organometallic catalyst in

the system. Being unable to reclaim the catalyst does not only mean that it will not be reused, but also potential impurities can be present in the final product. Seeing as in the pharmaceutical industry the final product is going into the human body, being able to remove impurities and testing to ensure they are removed present a very costly aspect of the reaction. This trait is primarily due to the homogeneous nature of most cross-coupling reactions. A much more ideal scenario, especially from a cost standpoint, is using the traits of heterogeneous catalysis. Heterogeneous traits are scalable processes, easy separations, and recyclability. This is much easier said than done, as heterogeneous catalysts suffer from selectivity issues and are prone to deactivation reactions. Regardless, work has been conducted to develop heterogeneous catalysts, such as Pd nanoparticles, that can catalyze reactions like the Suzuki reaction or the Buchwald reaction.⁶⁵⁻⁷⁰

All the challenges outlined guide new catalytic cross-coupling research. An emerging field that attempts to address the challenges is photoredox chemistry. Photoredox dual catalysis has seen a marked growth over the recent years and achieves many goals, while presenting new challenges. Pioneered by the MacMillan, Yoon, and Stephenson groups, photoredox dual catalysis uses a photocatalyst in conjunction with a cross-coupling catalyst to achieve reactivity.^{16, 71-77} As stated earlier, cross-coupling reactions are governed by redox events occurring at a metal center. Using this characteristic, these reactions use the photocatalyst as an electron source for redox processes; upon excitation, the photocatalyst can either accept an electron or donate an electron, either acting as an oxidant or a reductant.⁷⁵⁻⁷⁶ In the ground state, photocatalysts do not have the necessary thermodynamic criteria to act in such a nature; however, upon excitation by a light source, the thermodynamic capabilities of the catalyst reach a level that would facilitate electron

transfer processes to other molecules, be it organic or organometallic.⁷⁶ Harnessing electron transfer processes is a specialty of nickel catalysts; therefore, the chemical properties of nickel make for an ideal candidate in photoredox reactions.⁴⁶ Furthermore, there are additional advantages to photoredox methods, such as sustainability from an energy standpoint and the lessening of the environmental impact.

Meeting the necessary thermodynamic criteria for an effective photocatalyst is a tricky goal. These criteria dictate that the catalyst must exhibit excited state redox properties capable of accessing other energy states on other molecules; in other words, the reduction and oxidation potentials must be substantial enough to oxidize or reduce another molecule. However, effective organic and organometallic photocatalysts have been developed that produce substantial redox properties to power the cross-coupling cycles.⁷⁶ The prototypical organometallic photocatalysts are ruthenium or iridium polypyridyl complexes, like Ru(bpy)₃ (bpy=bipyridine) or [Ir(ppy)₂(tbpy)](PF₆) (ppy= phenylpyridine; tbpy=tert-butyl bipyridine).⁷⁵ These photocatalysts have been successful in cross-coupling reactions due to their long excited state lifetimes and the overall redox windows being amicable to other catalysts.

Though organometallic photocatalysts are effective in these reactions, the metals used are rare-earth and are rather expensive. Instead, organic photocatalysts are becoming more popular for dual catalytic systems. Organic photocatalysts, however, suffer from short excited state lifetimes, limiting their reactivity.⁷⁵ Furthermore, the redox potential windows are usually much more lopsided than organometallic complexes; in other words, they are either very oxidative or very reductive, but not as strong on the opposite side.

There has, however, been a number that have been successfully employed in catalytic processes, such as Eosin Y and Mes-Acr.⁷⁷⁻⁷⁸

Figure 1.6 outlines the general mechanism for the activation of the cross-coupling catalyst in photoredox dual catalytic methods. The initiation of a cross-coupling mechanism is the activation of this precatalyst to form the active catalyst in the neutral oxidation state.

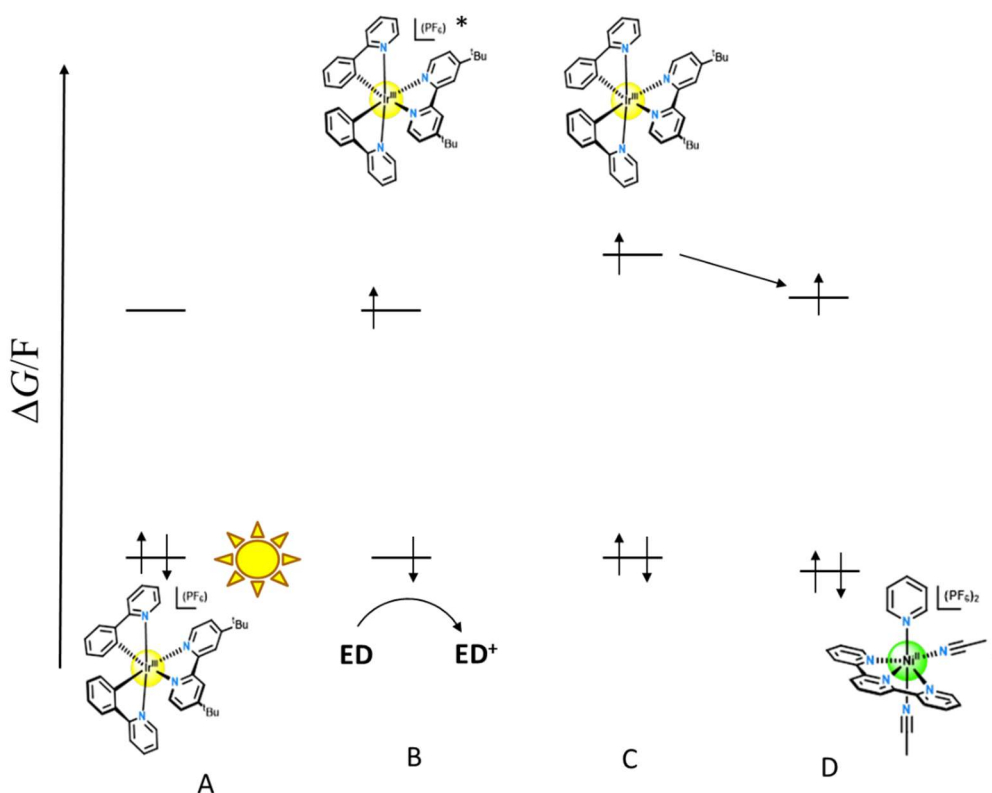


Figure 1.6. Schematic representation of a reductive photoredox dual catalytic method. A) a photocatalyst, such as the $[\text{Ir}(\text{ppy})_2(\text{tbp})](\text{PF}_6)$ photocatalyst pictured, is excited upon irradiation; B) an electron donor (ED) transfers an electron into the “hole” left by the excited electron; C) the now full ground state orbital causes electron repulsion to occur, strengthening the reductive capabilities of the catalyst; and D) the electron in the HOMO transfers to the cross-coupling nickel catalyst’s LUMO. This transfer is driven by inherent thermodynamic driving forces.

Once in the activated state, the cross-coupling catalyst proceeds through a more traditional mechanism, like the one outlined in Figure 1.2. However, recent research has shown that these photocatalysts can serve a dual role by activating both a substrate and the catalyst.⁷⁵ These redox neutral processes are a major advancement in the field of cross-coupling, as they present a method by which to remove additives and decrease energy input.

The MacMillan group has efficiently harnessed these characteristics to access many classes of substrates for cross-coupling reactions.⁷⁴⁻⁷⁵ One of the most powerful transformations was the coupling of α -carboxyl sp^3 carbons with aryl halides (Figure 1.7).⁷² Using a simple nickel salt with an iridium photocatalyst in DMF, successful coupling between amino acids and aryl halides was able to produce yields ranging from 60% to greater than 90%, regardless of the halide functional group.⁷² Mechanistic studies revealed that an important intermediate in the process is a carboxyl radical formed from the oxidation of the amino acid substrate, leading to a release of a CO_2 molecule and a subsequent radical rebound process to a nickel catalytic center. This one-electron oxidative addition produces the necessary Ni^{III} intermediate to facilitate the reductive elimination step.⁷² This discovery was significant, as using carboxylic acids as a cross-coupling feedstock presents a wide range of inexpensive and readily available substrates.

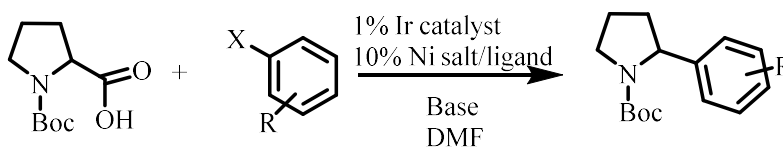


Figure 1.7. Coupling of α -carboxyl sp^3 carbons with aryl halides reported by the MacMillan group. Adapted from Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., Merging photoredox with nickel catalysis: Coupling of α -carboxyl sp^3 -carbons with aryl halides. *Science* **2014**, *345*, 437-440.

In conjunction with Stephen Buchwald, the MacMillan group was able to apply these photocatalytic methods to amination reactions as well.⁷⁴ Using a nickel catalyst with an iridium photocatalyst and a HAT catalyst like DABCO, these groups were able to generate aniline products from amines and aryl bromides. In this system, the photocatalyst is capable of reducing the nickel catalyst to activate the catalyst and later in the cycle allows for the oxidation of the catalyst to form the necessary Ni^{III} intermediate.⁷⁴ Yields in excess of 90% were also seen from this work; however, it was also noticed that the reaction only works in the presence of a base containing α -hydrogens.⁷⁴ This work also thoroughly investigated the photocatalyst and provided a database from which to choose a photocatalyst for amination reactions depending on the system. In terms of sustainability, it was found that the reaction was carried out in DMA, which is listed as a hazardous solvent.⁶¹ Additionally, there were aspects of the mechanism that still require research; however, photocatalytic coupling of amines using nickel in itself presents a major advancement in the field of Buchwald-Hartwig amination reactions.

Recently, the Vannucci group was capable of using photoredox dual catalysis to achieve XEC reactivity in a process dubbed Photoredox Assisted Reductive Coupling, or PARC.¹⁷ In this work, a nickel catalyst, [Ni(tpy)(py)(CH₃CN)₂](PF₆)₂, herein referred to as tpyNi, was used with an iridium photocatalyst to couple two electrophiles, such as an aryl iodide and an alkyl bromide. The system provided a simplified approach to C-C bond formation; other than the catalysts and the substrates, the only additive was triethanolamine, or TEOA, which acted as a sacrificial electron donor (SED).¹⁷ The mechanism for this process can be seen in Figure 1.8. The reaction is initiated by the reduction of the nickel precatalyst to form the active nickel species. An oxidative addition

of the aryl iodide occurs, creating a Ni^{II} intermediate. An alkyl radical, formed by another Ni^0 molecule, rebounds to the Ni^{II} intermediate, forming a Ni^{III} intermediate. In this oxidation state, the new C-C bond can be formed through reductive elimination and the subsequent Ni^{I} catalyst can be reduced by the photocatalyst. This reaction was found to be rather effective, producing yields in excess of 90% with limited side reactions, like homocoupling of the alkyl bromide. It was found through mechanistic experiments that the TEOA played a dual role in the reaction. Initially, the reaction was purely homogeneous. Throughout the reaction it was noticed that a solid would form. Upon isolation, it was found that the generated TEOA^+ was able to complex with the free Br^- formed during the alkyl radical formation.¹⁷ This would allow for the equilibrium to favor the formation of the alkyl radical, while simultaneously limiting side reactions. This dualistic role of the additive adds a higher level of sustainability to the process. Other mechanistic insights led to determining that the use of aryl iodides favored to mechanism for C-C bond formation. This is due to aryl iodides readily undergoing oxidative addition. It was found that if the alkyl halide formed a radical too quickly, only homocoupling product would be observed. Therefore, forcing the kinetics to favor oxidative addition by using aryl iodides allowed for the desired product to form.

Following this work, dual photocatalytic methods were developed for the Buchwald-Hartwig amination reaction and is thoroughly explored in Chapter 2. In these reactions, the nickel catalyst tpyNi was found to react in conjunction with a ruthenium photocatalyst to form new C-N bonds from electron rich anilines and aryl iodides. The system was rather simple to achieve these goals; the only additive was tribasic potassium phosphate and the catalyst loadings were only a meager 1%. With these conditions, new

C-N bonds were formed in acetonitrile, a more environmentally friendly solvent than previous works, and the method also worked to form tertiary amines. This work is the first such photocatalytic method to form tertiary amines in this type of manner.

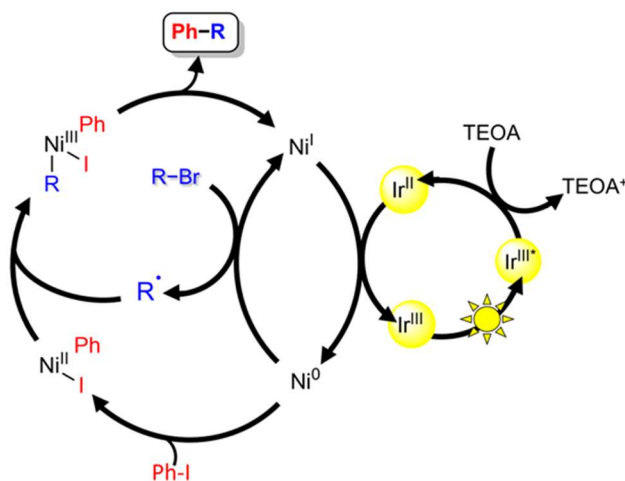


Figure 1.8. Proposed mechanism for the PARC reaction. Ligands are excluded for clarity.

Integral to the process was the formation of the N-centered radical, which led to similar reactivity seen in the PARC reaction. This was achieved by the photocatalyst and led to the process being redox-neutral, as no additional electron source was necessary. By replacing the common palladium catalyst, using light as an energy source, having a greener solvent than other works, and allowing for unique reactivity, this work shows a marked improvement in the field of cross-coupling reactions. This work was previously published in *Organometallics*.⁷⁹

Chapter 3 outlines further work using a functionalized version of the nickel terpyridine catalyst. By adding a benzoic acid moiety to the tpyNi catalyst, immobilization of the active catalyst onto a silica support was achieved, allowing for a heterogeneous catalyst to be developed. This catalyst was analyzed in a prototypical Suzuki reaction

scaffold and was found to be rather active, leading to moderate to high yields. The heterogeneity of the catalyst allowed for ease of separations and further allowed reactions up to 5 recycles. Further investigation showed that the catalyst is actively a molecular catalyst on an oxide support and does not act as nanoparticle on a surface, achieving the desired merger of heterogeneous and homogeneous catalysis. This work showed an advancement in cross-coupling reactions in this manner, by lowering the cost of the process and enabling easier separations. The ease of preparation, reactivity of the catalyst, and simplicity of the purification of the final products directed this work and is currently under review in *Organometallics*.

Chapter 4 signifies a continuation of Chapter 3, as the catalyst is further immobilized by Atomic Layer Deposition (ALD) to allow for reactivity in aqueous solvents. Previously, the catalyst was reactive in organic solvents. Upon immobilization with ALD, the reactivity not only persisted when placed in aqueous solvents but showed reactivity with heteroaryl substrates. Further recyclable reactivity was also witnessed, with recycle experiments exceeding 6 recycles. This highly recyclable nature of the catalyst, while operating in aqueous solvents to achieve rather remarkable reactivity shows a major advancement in the field of cross-coupling reactions. The unique preparation of this catalyst coupled with the robustness has pointed this work to journals such as *Green Chemistry*, *ACS Catalysis*, and *Journal of the American Chemical Society* and will be submitted to one of these journals upon completion.

CHAPTER 2:

NICKEL PHOTOREDOX DUAL CATALYSIS FOR THE SYNTHESIS OF ARYL AMINES¹

2.1 ABSTRACT

In this work, a new dual photoredox nickel catalysis system has been utilized for the synthesis of aryl amines. Previously, our group has shown that a nickel catalyst in conjunction with a photosensitizer and a sacrificial electron donor can cross-couple C–C bonds via photoredox-assisted reductive coupling. Here we have built upon that system to develop a redox neutral cross-coupling system for the formation of C–N bonds. The catalytic system is composed of just a nickel cross-coupling catalyst, a Ru photocatalyst, and base and is capable of coupling amines with aryl halides in good to excellent yields. Furthermore, it was found that these reactions are functional under ambient conditions with catalyst loadings of 1 mol%. Spectroscopic studies provide support that this amination mechanism proceeds via a nitrogen-based radical intermediate. This N-radical mechanism offers direct synthetic access to di- and tri-aryl amines from nickel photocatalysis and presents a new methodology to form C–N bonds, a highly desirable motif in pharmaceuticals.

¹ Key, R. J.; Vannucci, A. K., Nickel Dual Photoredox Catalysis for the Synthesis of Aryl Amines. *Organometallics* **2018**, 37 (9), 1468-1472. Reprinted here with permission from the American Chemical Society (publisher).

2.2 INTRODUCTION

Thermally-controlled cross-coupling reactions rely on ligand exchange mechanisms, such as transmetalation.⁸⁰⁻⁸¹ This synthetic approach has continued to advance, but some cross-coupling reactions and products have been limited under thermal control. The development of new cross-coupling methodologies, that may avoid ligand exchange mechanisms, have been achieved recently. These catalytic methodologies, such as reductive coupling⁵⁵⁻⁵⁷ and photoredox coupling^{73, 75}, have shown the ability to perform previously unachieved cross-coupling reactivity. These advances are in part due to the application of nickel catalysis and the use of SET protocols. Of specific importance to this report, dual photoredox catalysis enables routes for previously unattainable small molecule activations and bond forming reactions. Dual photoredox catalysis utilizes these single electron transfers to activate a secondary transition metal catalyst for small molecule activations and bond forming reactions.^{16, 72, 75}

Predominately, dual photoredox systems utilize nickel cross-coupling catalysts. Proposed mechanisms involve nickel catalysts in oxidation states that range from Ni^0 to Ni^{III} . At room temperature, it has been shown that the Ni^{III} oxidation state is necessary to promote product formation through reductive elimination.⁵²⁻⁵⁴ For dual photoredox cross-coupling from nickel-polypyridyl catalysts, multiple routes to form the important Ni^{III} oxidation state have been proposed. One proposed route is the oxidative addition of a carbon electrophile to a Ni^{I} intermediate (Figure 2.1a).^{52, 82-86} Another route proposes that the Ni^{III} intermediate is formed via photocatalyst oxidation of a Ni^{II} intermediate (Figure 2.1b).⁷³⁻⁷⁴ Both the Ni^{I} oxidative addition and the Ni^{II} oxidation routes tend to operate in mechanisms that rely on ligand exchange reactions to ultimately form the desired cross-

coupled product. Conversely, the Ni^{III} intermediate has been shown to form via a reaction between a carbon radical and a Ni^{II} intermediate, which was also observed in our lab (Figure 2.1c).¹⁷ This radical reactivity avoids ligand exchange mechanisms and can lead to previously unexplored product formation and reactivity.

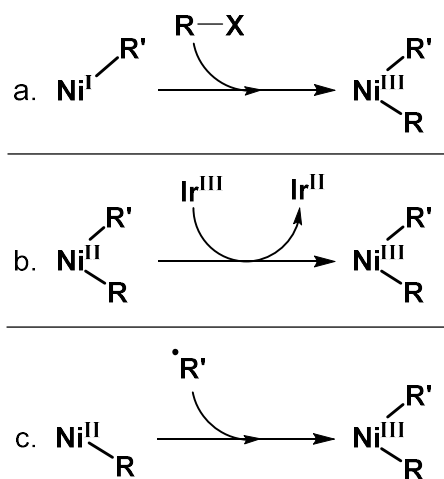


Figure 2.1. Comparison of the proposed reactions for the formation of a Ni^{III} oxidation state during dual photoredox catalysis.

Traditional amination pathways use palladium phosphane catalysts to form new C–N bonds and operate through $\text{Pd}^0/\text{Pd}^{\text{II}}$ oxidation states.^{22–23} The phosphane ligands require precise electron donating/withdrawing properties and steric encumbrance to promote product formation via reductive elimination from the Pd^{II} intermediate.²³ Utilizing dual photoredox nickel catalysis with simple ligand environments for the construction of C–N bonds, therefore, is highly desirable. In addition, the range of electrophiles amenable to nickel cross-coupling reactions should allow for a wide diversity of aminated products.^{23, 87–88} Reactions that construct new C–N bonds are also of great importance to pharmaceutical synthesis, constituting roughly 27% of pharmaceutical reactions.⁶

Recently dual photoredox nickel catalysis for the synthesis of aryl amines has been achieved.^{74, 86} Both studies were able to achieve aryl amine products using ligand-less nickel salts as the cross-coupling catalysts, which illustrates the advantages of dual photoredox cross-coupling compared to thermally-controlled reactions. For one of the studies, generation of the important Ni^{III} intermediate, was proposed to occur through oxidation of a Ni^{II} intermediate as illustrated in Figure 2.1b.⁷⁴ Formation of amine radicals was not proposed for this mechanism. For the second study, it was postulated that formation of the Ni^{III} intermediate occurred through oxidative addition of aryl halides to a Ni^{I} intermediate as shown in Figure 2.1a.⁸⁶ Computational insight into possible reaction mechanisms for these systems was also recently published.⁸⁹⁻⁹⁰ Comparison of these mechanisms to our work is discussed in further detail in this chapter.

2.3 RESULTS AND DISCUSSION

To optimize our dual photoredox catalytic system for the construction of C–N bonds and the synthesis of diaryl amines, cross-coupling between 4-methoxy-aniline and iodobenzene was chosen as a test reaction. Blue light irradiation of the coupling substrates in the presence of the $[\text{Ni}(\text{tpy})(\text{py})(\text{CH}_3\text{CN})_2](\text{PF}_6)_2$ cross-coupling catalyst (**tpyNi**),¹⁷ $\text{Ru}(\text{phen})_3^{2+}$ photocatalyst, and a potassium phosphate base in acetonitrile resulted in 76% yield of the desired cross-coupled diaryl amine product (Table 2.1, row 1). This reaction was set up on the benchtop without degassing, illustrating the ease of reaction set up for this approach. Variations of the reaction conditions are contained in Table 2.1. Using $\text{Ir}(\text{ppy})_2(\text{dtbpy})^+$ as the photocatalyst resulted in comparable yields compared to $\text{Ru}(\text{phen})_3^{2+}$, likely due to the similar excited state oxidation potentials of the two photocatalysts. Using the highly oxidizing, $\text{Ir}(\text{dF-CF}_3\text{-ppy})_2(\text{dtbpy})^+$ photocatalyst led to

drastically lower product yields. Attempting to perform the experiment with NiCl₂ and 2,2':6',2''-terpyridine ligand added instead of the preformed catalyst, did not produce product, as has been observed with this nickel salt/ligand combination.¹⁷ Lack of C–N cross-coupling from simple nickel salts is, however, a deviation from previously reported nickel dual photoredox C–N coupling.^{74, 86} Changing the base from K₃PO₄ to triethanolamine resulted in no product formation. Complete removal of any of the catalytic components – nickel catalyst, photocatalyst, base, or light – also led to the lack of product formation. Finally, the addition of water to the reaction mixture did not increase or negatively affect the product yield, hence the use of dried solvents is not necessary for this catalytic system.

Table 2.1. Optimization of Reaction Conditions

Variation	Yield	
none	76%	
no Ru(phen) ₃	0%	
Ir(ppy) ₂ (dtbpy) instead of Ru(phen) ₃	74%	
Ir(dF-CF ₃ -ppy) ₂ (dtbpy) instead of Ru(phen) ₃	9%	
no tpyNi	0%	
NiCl ₂ and tpy in situ instead of tpyNi	0%	
no base	0%	
TEOA instead of K ₃ PO ₄	0%	
no light	0%	
addition of 200 μL H ₂ O	76%	
1:1 amine:aryl halide	42%	

Base is K₃PO₄ unless otherwise stated. tpy is 2,2':6',2''-terpyridine; phen is 1,10-phenanthroline; (dF-CF₃-ppy) is 2-(2,4-difluorophenyl)-5-(trifluoromethyl)phenylpyridine; dtbpy is 4,4'-di-tert-butyl-2,2'-bipyridine. 24 hrs.

With the optimized reaction conditions in hand, we explored the substrate scope for this catalytic system. First, *p*-methoxy-aniline was used as a general and efficient amine coupling partner to examine the range of possible aryl coupling partners. Aryl iodides resulted in greater product yields compared to aryl bromides, which is consistent with previously reported nickel dual photoredox aryl amine synthesis.⁸⁶ Figure 2.2 shows that cross-coupling yields up to 93% can be achieved by varying the aryl iodide. In every case, further reactions of the diaryl amine products to form triaryl amines were not observed and no homocoupled biaryl products were observed. Leftover starting reactants, after the 24-hour reaction time were observed with GC/MS analysis of the reaction mixtures. Both electron donating and withdrawing groups are tolerated. Good yields were obtained regardless of functional group position, as seen with the *para* (**2**) and *meta* (**3**) positioned iodoaniline substrates. *Ortho*-substituted aryl iodides, such as 2-iodotoluene (**4**), however, exhibited lower yields than *para*-iodotoluene (**5**). It is suspected that these lower yields can be attributed to steric effects. This lower yield may also be a consequence of agostic effects with the *ortho* positioned methyl group, allowing for a stable intermediate unreactive towards reductive elimination. Coupling of heteroaryl iodides with 4-methoxy aniline was also successful (**7** and **8**).

A variety of amine coupling partners was also well tolerated by this catalytic system. Figure 2.3 shows that *ortho*- *meta*- and *para*-substitutions on aniline substrates all result in good yields (**1**, **10**, and **11**). Highly substituted aniline substrates were also successful (**12**). These reactions were also capable of coupling complex heterocycles, such as 3,4-methylenedioxyaniline, as amine coupling partners (**15**). Coupling of 4-chloro-aniline, which contains presence a synthetically useful chloro functional group, was

moderately tolerated (**16**). The possible C–C cross-coupled side product for that reaction was not observed.

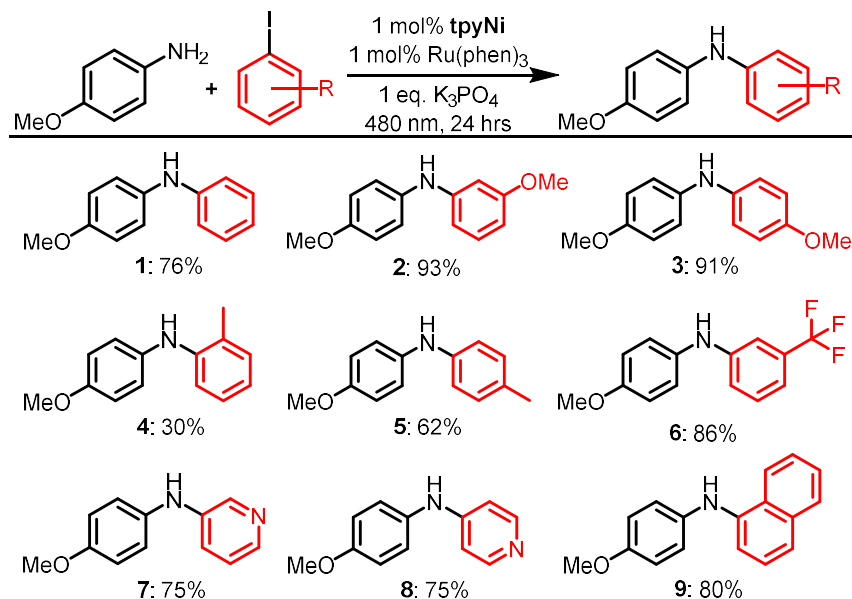


Figure 2.2. Catalytic dual photoredox cross-coupling between *p*-methoxy aniline and aryl halides. 100 mM aniline, 200 mM aryl halide in 5 ml of acetonitrile. mol% and % yields based on limiting reagent.

Cross-coupling involving sulfonamides was also successful (**17**). Furthermore, starting with secondary amines as coupling partners led to the formation of tertiary amine products as shown with products **18–21**. Products **18** and **19** show that amines containing both aryl groups and aliphatic groups are capable of being utilized in C–N coupling reactions. Triaryl amine, product **20**, can be formed with 71% yield starting with the diaryl amine. Lastly, dibenzyl amine was also a suitable cross-coupling partner forming the tri-substituted amine **21** in good yield. Thus, this is the first dual photoredox nickel catalysis system capable of the synthesis of both bi- and tri-aryl amine products

To gain insight into how our catalytic system successfully performs C–N cross-coupling reactions we examined the interaction between the amine substrates and the Ru-photoredox catalyst. As discussed in the introduction, gaining access to a Ni^{III} oxidation state is essential to forming cross-coupled products during room temperature dual photoredox catalysis. Three mechanistic routes for the formation of a Ni^{III} oxidation state have been proposed (Figure 2.1). In our previous work, we have observed that a carbon-based radical formed during photoredox cross-coupling catalysis was essential for mediating the oxidation state of the **tpyNi** catalyst.¹⁷ With this radical-based mechanism in mind, we set to examine the interaction between the amine substrates and the Ru-photoredox catalyst. Recently, during cyclization reactions, the Knowles group has shown that nitrogen-based radicals can be formed via photoredox oxidative proton-coupled electron-transfer (PCET).⁹¹ Thus we aimed to explore the possibility that forming amine radicals is a key step for our dual photoredox catalytic system.

Various fluorescence quenching experiments involving combinations of the Ru-photocatalyst in the presence of *p*-methoxy-aniline, K₃PO₄ base, and the entire catalytic reaction mixture were performed. A Stern-Volmer analysis showed that the base alone does not quench the photocatalyst (Figure 2.4). The *p*-methoxy-aniline substrate in both the absence and presence of base, however, did quench the photocatalyst (Figures 2.5, Figure 2.6). The Stern-Volmer plots exhibited a linear fit, indicating the quenching was first order with respect to the aniline substrate. This data suggests that electron transfer occurs directly between the aniline substrate and the photocatalyst, and that PCET does not appear to be the dominant pathway.

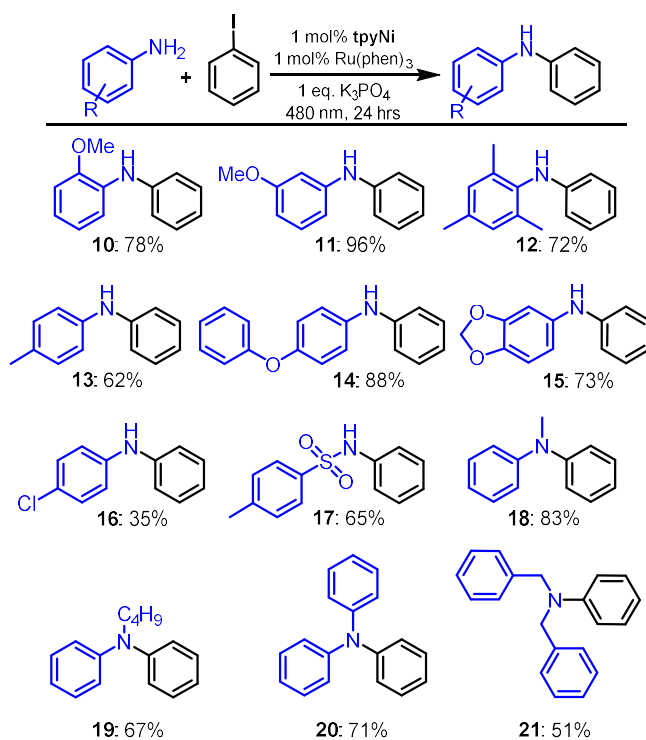


Figure 2.3. Catalytic dual photoredox cross-coupling between aryl iodide and various aniline substrates. 100 mM anilines, 200 mM aryl iodide in 5 ml of acetonitrile. mol% and % yields based on limiting reagent.

This data suggests that electron transfer occurs directly between the aniline substrate and the photocatalyst, and that PCET does not appear to be the dominant pathway. Instead, it is proposed that electron transfer between the aniline substrate and the photocatalyst occurs first, followed by deprotonation of the oxidized aniline by the added base. This electron-transfer followed by proton-transfer mechanism for the formation of nitrogen radicals has been previously reported.⁹²⁻⁹³

To test if quenching of the photocatalyst by the amine substrate was catalytically feasible, quenching experiments were performed using conditions identical to the optimized reaction conditions. Fluorescence quenching was once again observed under optimized reaction conditions (Figure 2.7). The slope of the Stern-Volmer plot for the

entire reaction mixture was nearly identical to the slope of the Stern-Volmer plot obtained from the photocatalyst in the presence of only the aniline substrate. The similarity in slopes indicates that quenching of the photocatalyst by the aniline substrate is catalytically feasible within the reaction mixture.

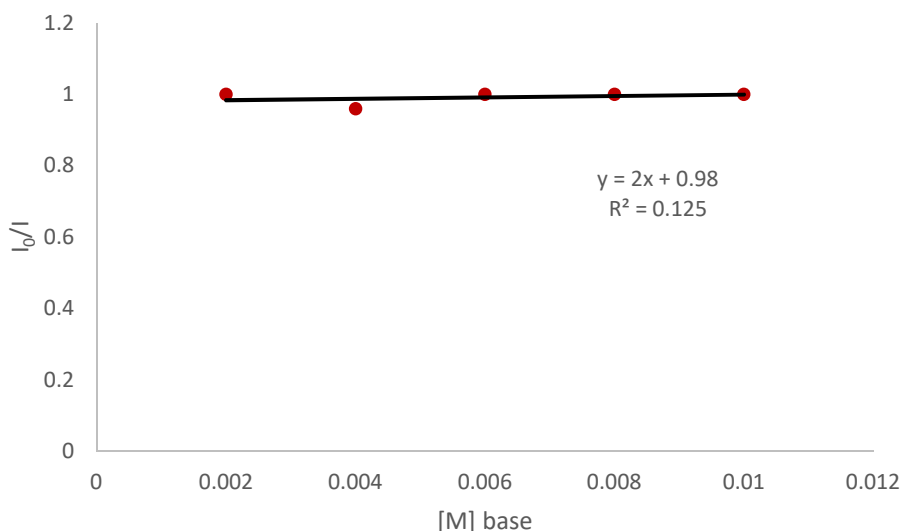


Figure 2.4. Stern-Volmer plot for the fluorescence of $\text{Ru}(\text{phen})_3$ in the presence of varying amounts of K_3PO_4 . As evidenced by the straight line with no slope, the K_3PO_4 base does not quench the $\text{Ru}(\text{phen})_3$ photocatalyst.

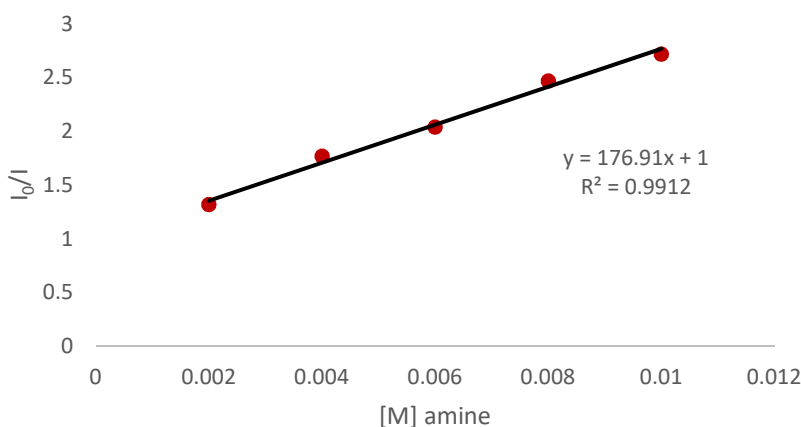


Figure 2.5. Stern-Volmer plot for the fluorescence quenching of $\text{Ru}(\text{phen})_3$ in the presence of varying amounts of 4-methoxy-aniline. The aniline substrate clearly quenches the $\text{Ru}(\text{phen})_3$ photocatalyst.

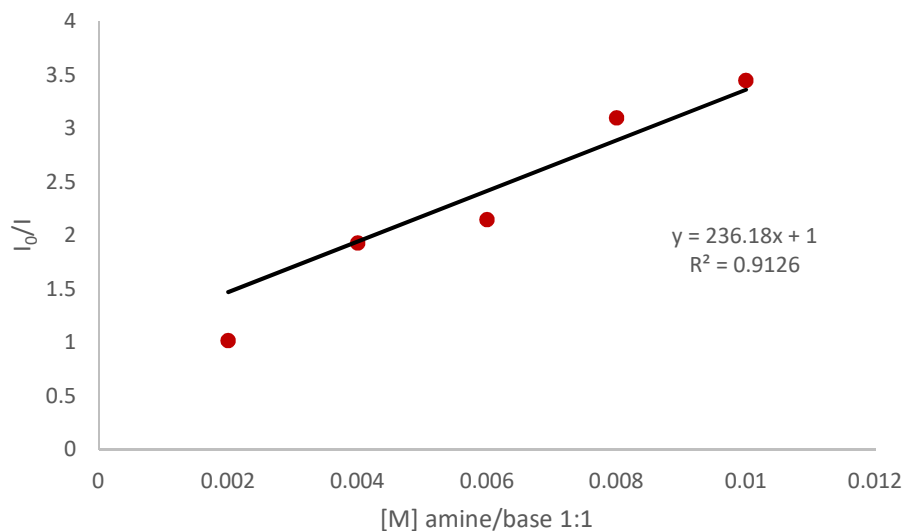


Figure 2.6. Stern-Volmer plot for the fluorescence quenching of Ru(phen)₃ in the presence of varying amounts of 4-methoxy-aniline and K₃PO₄. Addition of base does not have a measurable effect on the fluorescence quenching of Ru(phen)₃ by 4-methoxy-aniline.

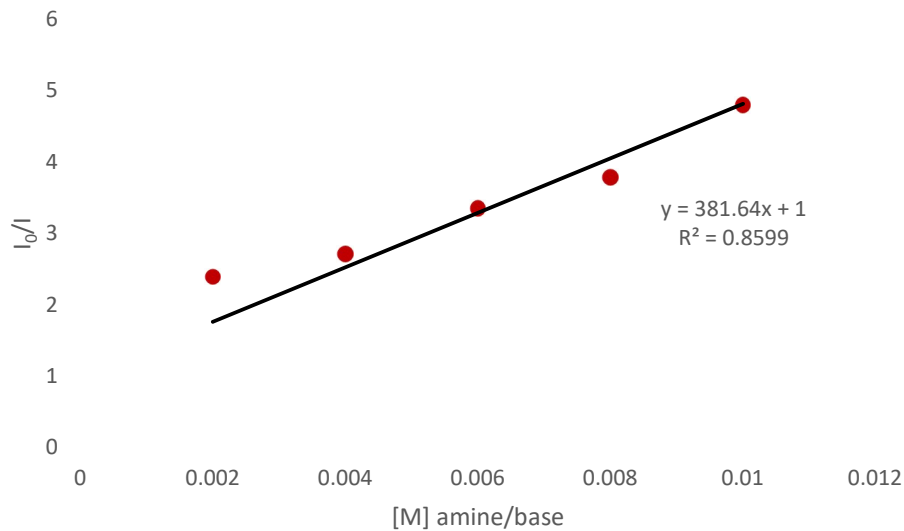


Figure 2.7. Stern-Volmer plot for the fluorescence quenching of Ru(phen)₃ in the presence of tpyNi catalyst, iodobenzene, and varying amounts of 4-methoxy-aniline and K₃PO₄. Addition of base does not have a measurable effect on the fluorescence quenching of Ru(phen)₃ by 4-methoxy-aniline in standard reaction conditions.

A likely mechanism for this catalytic system is shown in Figure 2.8. In cycle 1, the Ru-photocatalyst absorbs a photon of light to generate a long-lived excited state ($\text{Ru}^{\text{II}*}$). The excited state is reductively quenched by the aniline substrate to concurrently generate a reduced photocatalyst (Ru^{I}) and an oxidized amine. Formation of amine radicals is supported by the fluorescence quenching studies and was further supported by the fact that electron rich aniline substrates are more efficient coupling partners compared to electron deficient anilines. After oxidation of the aniline substrate, the acidity of the amine group increases, leading to subsequent deprotonation by the added base. The reduced photocatalyst, Ru^{I} , is then capable of reducing the nickel-catalyst to a Ni^0 oxidation state (step 2, Figure 2.8).¹⁷ Oxidative addition of an aryl iodide to Ni^0 in step 3 generates a Ni^{II} -Ph intermediate. Steps 2 and 3 the proposed steps are consistent with previously reported reactivity between **tpyNi** and aryl halides.¹⁷

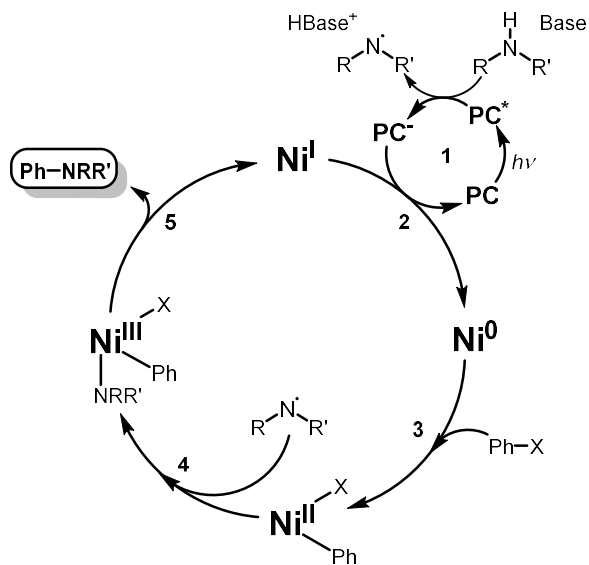


Figure 2.8. Proposed mechanism for dual photoredox C-N cross-coupling catalysis via an amine radical. Ligands excluded for clarity.

The Ni^{II} -Ph intermediate then reacts with the aniline radical to generate the important Ni^{III} intermediate in step 4, followed by reductive elimination in step 5 to form the desired C–N cross-coupled product. Step 4 in the proposed cycle is analogous to the reports summarized in Figure 2.1c.

This proposed mechanism differs from each of the previously proposed nickel dual photoredox mechanisms for the formation of biaryl amines. The MacMillan group reported that the formation of the important Ni^{III} intermediate occurred via oxidation of a Ni^{II} -amido complex by an iridium photocatalyst, as shown in Figure 2.1b.⁷⁴ That mechanism relied on ligand exchange between the amine substrates and halide groups of the nickel-center, and did not propose the formation of an amine radical. In addition, the formation of aryl-amines was only observed when amines containing α -hydrogens were present. Recent computational work gave insight into the requirement for α -hydrogen containing heterocycles.⁹⁰ In that paper, the authors propose that the hydrogen atom transfer reagent DABCO generates a pyrrolidine radical that helps generate a Ni^0 intermediate capable of activating aryl-halides.⁹⁰ The catalytic system reported in this manuscript does not require substrates containing α -hydrogens or the addition of hydrogen atom transfer reagents. Instead this catalytic system was able to directly synthesize bi- and tri-aryl amines with only the addition of a common base to the dual photoredox catalysts. This reaction was also active in acetonitrile as opposed to DMA, which is listed as a hazardous chemical.⁶¹

In another study by researchers at AstraZeneca,⁸⁶ fluorescence quenching studies provided evidence for the formation of amine radicals during dual photoredox biaryl synthesis, as was observed in this study. The authors, however, proposed that the amine radical reacted directly with the Ni^0 intermediate to generate a Ni^{I} -amine intermediate. It

was then proposed that the Ni^{I} intermediate was capable of activating aryl halides in a reaction as shown in Figure 2.1a. Radical reactivity with Ni^0 complexes and aryl halide activation by Ni^{I} intermediates has been supported by computational work.⁸⁹ In addition, fluorescence quenching of their photocatalyst also occurred in the presence of the triethyl amine base used in their study, which is commonly seen with this amine base.¹⁷ While our proposed mechanism and the proposed mechanism differ just slightly, the mechanistic differences once again lead to a difference in accessible products. The previous study reports an inability to synthesize triphenyl amine and only a 9% yield for the formation of *N*-methyl-*N*-phenylaniline, whereas the catalytic system reported in this paper was able to synthesize those products with 71% and 83% yield respectively.

In conclusion, the differing aspects of the three reports on nickel dual photoredox catalysis for the formation of aryl amines shows both the versatility and range of chemistries that can be achieved using this approach. The catalytic system in this report utilizes a Ru-photocatalyst to generate amine radicals for cross-coupling reactions with aryl iodide substrates. This approach is amenable to a variety of both aryl iodide and amine coupling partners and can be set-up and performed under ambient conditions. Both biaryl and tertiary amine products can be accessed using this approach, which operates with only added base and 1 mol% catalyst loadings. This process addresses a litany of the goals in pharmaceutical cross-coupling research, as it utilizes an earth abundant metal in low loadings for a cost effective, sustainable process.

2.4 EXPERIMENTAL

2.4.1 Instrumental. All separations were conducted on a Reveleris X2 Flash Chromatography system using a 40 μM Silica column or via preparative scale TLC.

Solvents used for purification were ethyl acetate and hexane, ACS Grade or better ($\geq 99\%$), and were used without further purification.

^1H NMR spectroscopy was performed using a 300 MHz instrument using deuterated chloroform as the solvent with a calibrated peak at 7.26 ppm. ^{13}C NMR was conducted on a 300 MHz instrument set to a frequency of 100 MHz using chloroform as the solvent and a calibrated solvent peak at 77.33 ppm. The light source used for all experiments is a blue LED light exciting at 480 nm.

Emission spectra were acquired on an Edinburgh FS5 fluorescence spectrometer equipped with a 150 W Continuous Wave Xenon Lamp source for excitation. Emission measurements on degassed solution samples were collected on solutions of appropriate materials inside a 1.0 cm quartz cuvette using the SC-05 standard cuvette module.

2.4.2 General Procedure for Photoredox-Assisted Amination Reactions. In a 12 mL glass vial with a TFE/SIL O/T cap, $[\text{Ni}(\text{tpy})(\text{py})(\text{MeCN})_2]\text{PF}_6$ (0.005 mmol, 1% loading), $\text{Ru}(\text{phen})_3^{2+}$ (0.005 mmol, 1% loading), amine (0.5 mmol), aryl iodide (1.0 mmol), and base (0.5 mmol) was added and dissolved in 5 mL acetonitrile. The vial was then placed in front of the blue LED light source on a stir plate and was irradiated for 24 hours with stirring. After 24 hours, the solution was then separated via flash chromatography using ethyl acetate and hexanes. The isolated products were then analyzed via ^1H NMR and ^{13}C NMR to confirm purity.

2.4.3 Stern-Volmer Experiments. Fluorescence quenching experiments were performed with N_2 purged solution of 5×10^{-6} M $\text{Ru}(\text{phen})_3^{2+}$ in acetonitrile at room temperature. The

solutions were irradiated at 480 nm and fluorescence was measured at 598 nm. Each peak intensity is the average of three experimental spectra.

2.4.4 Product Confirmation

4-methoxy-N-phenylaniline (1): Yield: 0.066 g, 76%. ^1H NMR (300 MHz, CDCl_3) δ : 7.14 (t, 2H), 7.09 (d, 2H), 6.96-6.72 (m, 5H), 5.39 (br s, 1H), 3.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 152.8, 145.3, 139.9, 132.2, 128.0, 117.5, 116.4, 114.8, 55.7. Spectra match previous reports.⁹⁴

3-methoxy-N-(4-methoxyphenyl)aniline (2): Yield: 0.107 g, 93%. ^1H NMR (300 MHz, CDCl_3) δ : 7.19 (t, 1H), 6.94 (d, 2H), 6.84 (d, 2H), 6.80-6.77 (m, 2H), 6.50 (d, 1H), 5.35 (br s, 1H), 3.69 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 160.1, 155.2, 138.4, 130.8, 129.9, 123.0, 117.8, 113.8, 55.4, 55.3. Spectra match previous reports.²⁵

bis(4-methoxyphenyl)amine (3): Yield: 0.105 g, 91%. ^1H NMR (300 MHz, CDCl_3) δ : 7.5 (d, 4H), 6.61 (d, 4H), 6.59 (s, 1H), 3.70 (s, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 159.5, 138.2, 124.4, 114.2, 55.6 ppm. Spectra match previous reports.⁹⁵

N-(4-methoxyphenyl)-2-methylaniline (4): Yield: 0.035 g, 30%. ^1H NMR (300 MHz, CDCl_3) δ : 7.19 (d, 1H), 7.15-6.97 (m, 4H), 6.95-6.73 (m, 3H), 5.18 (br s, 1H), 3.81 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 161.6, 147.1, 138.9, 129.8, 128.2, 127.4, 124.4, 119.5, 114.2, 55.6, 28.1. Spectra match previous reports.⁹⁶

4-methoxy-N-(p-tolyl)aniline (5): Yield: 0.066 g, 62%. ^1H NMR (300 MHz, CDCl_3) δ : 7.81 (d, 2H), 7.20 (d, 2H), 7.04-6.87 (m, 4H), 5.40 (s, 1H), 3.75 (s, 3H), 2.10 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 156.2, 146.0, 134.3, 131.9, 131.5, 123.5, 117.8, 115.5, 55.6, 16.9 ppm. Spectra match previous reports.²⁵

N-(4-methoxyphenyl)-3-(trifluoromethyl)aniline (6): Yield: 0.110 g, 86%. ¹H NMR (300 MHz, CDCl₃) δ: 7.21-7.19 (t, 1H), 7.04-7.00 (m, 5H), 6.84-6.81 (d, 2H), 5.57 (br s, 1H), 3.75 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 156.1, 146.0, 134.3, 131.9, 131.5, 129.8, 123.5, 117.8, 115.6, 115.5, 111.3, 55.6 ppm. Spectra match previous reports.²⁴

N-(4-methoxyphenyl)pyridin-3-amine (7): Yield: 0.075 g, 75%. ¹H NMR (300 MHz, CDCl₃) δ: 7.81 (d, 1H), 7.60 (d, 1H), 7.23 (dd, 1H), 7.05-7.00 (m, 1H), 7.05 (d, 2H), 6.93 (d, 2H), 5.85 (br s, 1H), 3.80 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): 161.6, 139.4, 137.5, 130.3, 127.7, 127.5, 124.4, 114.2, 55.6 pm. Spectra match previous reports.²⁵

N-(4-methoxyphenyl)pyridin-4-amine (8): Yield: 0.075 g, 75%. ¹H NMR (300 MHz, CDCl₃) δ: 8.45 (d, 2H), 7.92 (d, 1H), 6.80 (m, 1H), 6.70 (d, 2H), 6.50(d, 2H), 5.82 (br s, 1H), 3.72 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 155.7, 144.5, 139.9, 125.3, 120.8, 120.5, 116.4, 114.8, 114.1, 55.4 ppm. Spectra match previous reports.⁹⁷

N-(4-methoxyphenyl)naphthalen-1-amine (9): Yield: 0.100 g, 80%. ¹H NMR (300 MHz, CDCl₃) δ: 7.96 (d, 2H), 7.64 (d, 1H), 7.38-7.04 (m, 6H), 7.00 (d, 2H), 5.60 (br s, 1H), 3.68 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 161.6, 147.2, 134.4, 129.3, 128.7, 128.0, 126.9, 126.8, 126.6, 126.4, 125.9, 124.5, 114.3, 55.6 ppm. Spectra match previous reports.⁹⁸

2-methoxy-N-phenylaniline (10): Yield: 0.078g, 78%. ¹H NMR (300 MHz, CDCl₃) δ: 7.35-7.29 (m, 3H), 7.25-7.18 (m, 2H), 6.99 (t, 1H), 6.74-6.69 (m, 3H), 6.35 (br s, 1H), 3.89 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 147.3, 136.1, 130.9, 129.8, 121.0, 120.8, 118.4, 118.2, 115.0, 110.4, 55.4. Spectra match previous reports.⁹⁹

3-methoxy-N-phenylaniline (11): Yield: 0.096 g, 96%. ¹H NMR (300 MHz, CDCl₃) δ: 7.35-7.30 (m, 2H), 7.18 (m, 1H), 7.12-7.06 (m, 2H), (6.92 m, 1H) 6.38 (m, 2H), 6.35 (m,

1H), 6.00 (br s, 1H), 3.79 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 160.7, 147.7, 142.7, 130.1, 129.3, 121.2, 118.0, 107.9, 103.9, 101.1, 55.1. Spectra match previous reports.⁹⁶

2,4,6-trimethyl-N-phenylaniline (12): Yield: 0.076 g, 72%. ¹H NMR (300 MHz, CDCl₃) δ: 7.18 (t, 2H), 6.90 (s, 2H), 6.84-6.72 (m, 1H), 6.67 (d, 2H), 5.09 (s, 1H), 2.35 (s, 3H), 2.17 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ: 148.6, 137.6, 135.4, 135.3, 130.1, 121.0, 120.7, 22.0, 20.0. Spectra match previous reports.⁹⁶

4-methyl-N-phenylaniline (13): Yield: 0.057 g, 62%. ¹H NMR (300 MHz, CDCl₃) δ: 7.19 (t, 2H), 6.90 (d, 2H), 6.60 (m, 4H), 6.52 (t, 1H), 5.30 (br s, 1H), 2.17 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 143.8, 140.2, 131.1, 129.7, 129.1, 127.8, 116.2, 115.3, 20.4. Spectra match previous reports.²⁵

4-phenoxy-N-phenylaniline (14): Yield: 0.114 g, 88%. ¹H NMR (300 MHz, CDCl₃) δ: 7.23-6.86 (m, 14H) 3.51 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 158.9, 148.6, 142.6, 130.0, 129.6, 129.5, 122.0, 121.1, 120.9, 117.2, 116.2. Spectra match previous reports.¹⁰⁰

N-phenylbenzo[d][1,3]dioxol-5-amine (15): Yield: 0.077 g, 73%. ¹H NMR (300 MHz, CDCl₃) δ: 7.57-7.52 (m 2H), 6.96-6.94 (m, 3H), 6.69-6.60 (m, 2H), 6.32-6.30 (m, 1H), 6.00 (s, 2H), 5.89 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 148.2, 141.4, 140.4, 120.9, 116.7, 111.9, 108.6, 101.7, 101.0 ppm. Spectra match previous reports.¹⁰¹

4-chloro-N-phenylaniline (16): Yield: 0.038 g, 35%. ¹H NMR (300 MHz, CDCl₃) δ: 7.31 (m, 2H), 7.10-7.13 (d, 2H), 6.93-7.01 (d, 2H), 6.68-6.76 (m, 3H), 5.34 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 143.9, 143.6, 129.3, 128.0, 122.1, 118.9, 115.1. Spectra match previous reports.⁹⁶

4-methyl-N-phenylbenzenesulfonamide (17): Yield: 0.075 g, 65%. ¹H NMR (300 MHz, CDCl₃) δ: 7.69 (d, 2H), 7.33-7.28 (m, 4H), 7.09-7.06 (m, 3H), 2.02 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 171.0, 139.8, 139.3, 137.4, 130.2, 127.4, 30.8. Spectra match previous reports.¹³

N-methyl-N-phenylaniline (18): Yield: 0.076 g, 83%. ¹H NMR (300 MHz, CDCl₃) δ: 7.25 (t, 4H), 6.80 (dd, 4H), 6.70 (dd, 2H), 2.90 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ: 149.4, 129.2, 117.3, 112.4, 30.7. Spectra match previous reports.²⁵

N-butyl-N-phenylaniline (19): Yield: 0.075 g, 67%. ¹H NMR (300 MHz, CDCl₃) δ: 7.26-7.01 (m, 10H), 3.04-3.02 (t, 2H), 1.60-1.40 (m, 4H), 0.91-0.88 (t, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 146.7, 128.4, 127.3, 125.6, 41.8, 29.8, 18.4, 12.0. Spectra match previous reports.¹⁰²

Triphenylamine (20): Yield: 0.087 g, 71%. ¹H NMR (300 MHz, CDCl₃) δ: 7.33-6.80 (m, 15H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 143.2, 129.3, 122.1, 118.1, 117.8 ppm. Spectra match previous reports.⁶⁷

N,N-dibenzylaniline (21): Yield: 0.070 g, 51%. ¹H NMR (300 MHz, CDCl₃) δ: 7.43-7.37 (m, 12H), 7.34-7.28 (m, 3H), 3.87 (s, 4H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 156.8, 140.4, 128.5, 128.3, 128.2, 126.9, 116.7, 112.4, 53.2. Spectra match previous reports.¹⁰³



Title: Nickel Dual Photoredox Catalysis for the Synthesis of Aryl Amines

Author: Ryan J. Key, Aaron K. Vannucci

Publication: Organometallics

Publisher: American Chemical Society

Date: May 1, 2018

Copyright © 2018, American Chemical Society

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

Copyright © 2019 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#)

[Terms](#) [and](#) [Conditions.](#)
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 3:

A MOLECULAR/HETEROGENEOUS NICKEL CATALYST FOR SUZUKI-MIYaura COUPLING²

3.1 ABSTRACT

A molecular/heterogeneous catalyst motif based on an earth abundant nickel catalyst and SiO₂ support has been designed and synthesized. Characterization and catalytic testing indicates that the molecular nickel catalyst [(2,2':6',2''-terpyridine-4'-benzoic acid)Ni(II)]Cl₂ attached to a high surface area SiO₂ support is the active cross-coupling catalyst. This molecular/heterogeneous motif is easily separated from reaction mixtures and can be recycled for multiple catalytic reactions. The catalyst is active for Suzuki-Miyaura catalysis at catalyst loadings as low as 0.1 mol% and turnover numbers nearing 2000 have been achieved. This method shows high applicability and presents a cost-effective, recyclable approach to Suzuki coupling reactions.

3.2 INTRODUCTION

Transition-metal catalyzed cross-coupling reactions, especially those catalyzed by palladium, are extensively used in a variety of synthesis routes.^{81, 104} Of these reactions, the Suzuki-Miyaura cross-coupling reaction is the most widely used for the formation of C–C

² Key, R.J.; Smith, M. D.; Vannucci, A. K. Submitted to *Organometallics*, 2/7/19.

bonds.^{8, 105-106} While palladium catalyzed Suzuki-Miyaura coupling reactions have become text book,¹⁰⁷ development of new cross-coupling catalysts based on abundant first row transition metals is a continual growing research area.¹⁰⁸⁻¹¹¹ In particular, over the past decade interest has grown and great progress has been made in the field of nickel catalyzed cross-coupling reactions.⁴⁶ Furthermore, the ACS Pharmaceutical Round Table has called for increased use of nickel catalysts and encouraged the development of catalyst immobilization techniques.¹¹²

Nickel-based cross-coupling catalysts offer many advantages over palladium catalysts beyond nickel being a less expensive/more sustainable metal. Nickel catalysts have shown the ability to activate less reactive carbon electrophiles such as aryl chlorides,¹¹³⁻¹¹⁵ unactivated alkyl electrophiles,^{17, 116} tertiary alkyls,¹¹⁷⁻¹¹⁸ and various C–O bonds.¹¹⁹⁻¹²¹ Stereoselective Suzuki-Miyaura coupling with nickel catalysts bearing inexpensive ligands has also been achieved.¹²²⁻¹²³ High-valent nickel complexes have even been isolated, showing that nickel has the redox range typically only observed with palladium catalysts.^{51, 124-125} Mechanistic insight on nickel catalyzed C–C cross-coupling has supported high-valent nickel intermediates in cross-coupling reactions.^{32, 126} Furthermore, innovative routes for nickel catalyzed cross-coupling have been reported. Reductive coupling between two carbon electrophiles has expanded the scope of sp^2 - sp^3 C–C coupling reactions.^{55, 57, 127} Nickel catalysts have also found a prevalent role in photoredox cross-coupling catalysis.^{72, 128-130}

While nickel catalysts offer clear advantages, controlled reactivity and catalyst stability can still present issues. Compared to palladium catalysts, nickel catalysts exhibit a high degree of sensitivity to the choice of solvent and base during Suzuki cross-

couplings.¹³¹ In addition, Suzuki couplings typically require upwards of 5 - 10 mol% of catalyst loadings for efficient product formation.⁴⁶ Higher catalyst loadings not only decreases sustainability, but can increase the rate of bimolecular decomposition pathways for nickel catalysts. Nickel dimers formed during bimolecular decomposition pathways have been shown to be inactive species formed during nickel catalyzed Suzuki coupling reactions.³² Increased concentrations of catalyst can also lead to unwanted metal poisoning of products which is a major concern for pharmaceutical development, leading to extensive purifications and quality analytical testing.⁵ In addition, the vast majority of nickel catalyzed cross-coupling reactions are performed in a homogeneous solution which makes post reaction separations and catalyst recycling difficult.

To attempt to address the issues of high catalyst loading in homogeneous solution (bimolecular deactivation, product contamination, and difficult catalyst recycling) we have designed and synthesized a molecular/heterogeneous nickel-based catalyst system. This catalyst system starts with the molecular catalyst [(2,2':6',2''-terpyridine-4'-benzoic acid)Ni(II)]Cl₂, which is a direct analog of our previously reported (2,2':6',2''-terpyridine)Ni(II) catalyst that was shown to be an efficient catalyst for C–C and C–N photoredox cross-coupling.^{17, 79} The addition of the carboxylic acid moiety to the terpyridine ligand allows for this catalyst to be attached to solid metal oxide supports for the generation of a molecular/heterogeneous catalyst motif. This motif, illustrated in Figure 3.1, simplifies catalyst separation from post reaction mixtures and leads to good catalyst recyclability. This molecular/heterogeneous catalyst has been characterized and performs Suzuki-Miyaura cross-coupling catalysis at catalyst loadings as low as 0.1 mol%.

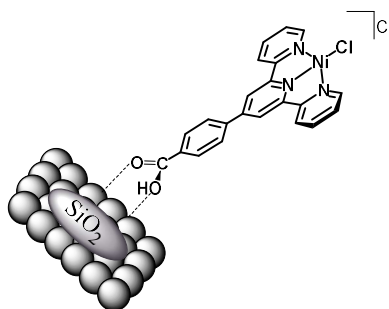


Figure 3.1. Illustration of molecular/heterogeneous catalyst **COOH-Ni/SiO₂**.

3.3 RESULTS AND DISCUSSIONS

The previously unreported complex [(2,2':6',2''-terpyridine-4'-benzoic acid)Ni(II)]Cl₂ (COOH-Ni) was synthesized by dissolving a 1:1 ratio of the 2,2':6',2''-terpyridine-4'-benzoic acid ligand and nickel dichloride in ethanol and allowing the solution to stir at reflux for 4 hours. Post reflux, the green solid was washed with diethyl ether and dried. Crystals suitable for X-ray crystal analysis were grown by slow evaporation of dichloromethane. Elemental Analysis: Calculated for NiC₁₆H₁₁N₃O₂Cl₂: C 54.71%; H 3.13%; N 8.70%. Found: C 53.81%; H 3.03%; N 8.32%.

COOH-Ni crystallizes in the monoclinic system and is shown in Figure 3.2. The pattern of systematic absences in the intensity data was consistent with the space group *P*2₁/*n*. The asymmetric unit consists of one NiCl₂(H₂O)(C₂₂H₁₅O₂) complex and one non-coordinated, partially occupied water molecule. Around the nickel center, the chloride and coordinated water ligands are disordered. Two sites were modeled as a disordered mixture of Cl⁻/H₂O; the third anion site was modeled with a split chloride position. The distance between the nickel center and the middle nitrogen atom of the (2,2':6',2''-terpyridine-4'-benzoic acid) ligand is 1.99 Å and the distance from the nickel center to the two nitrogen atoms in the equatorial plane are 2.08 Å each. The average distance to the chloride atoms

is 2.38 Å. These distances are all within 0.02 Å when compared to the previously reported crystal structure for the (2,2':6',2''-terpyridine)Ni(II) complex,¹⁷ indicating the benzoic acid moiety does not significantly alter the electronic structure or geometry of the nickel metal center.

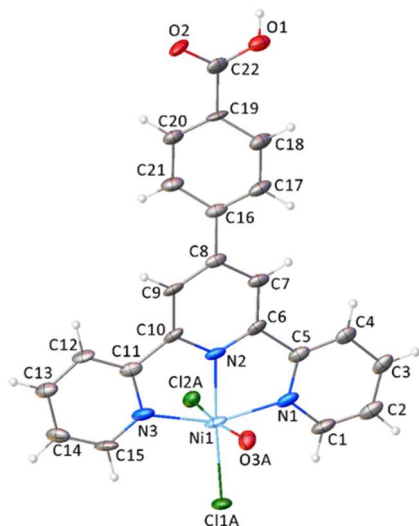


Figure 3.2. Crystal structure of **COOH-Ni**. Displacement ellipsoids drawn at the 40% probability level.

Functionalization of high surface area SiO₂ particles with the molecular catalyst was achieved by soaking the SiO₂ particles in a methanol solution containing the catalyst. This catalyst loading procedure is analogous to previously reported metal oxide derivatization by molecular complexes.¹³² After soaking, the particles were filtered from solution, rinsed with cold methanol, dried, and then characterized. The resulting molecular/heterogeneous catalyst (**COOH-Ni|SiO₂**) was characterized with ICP-MS and XRD. The paramagnetic nature of the nickel complex prevented accurate characterization through solid-state NMR spectroscopy. ICP-MS analysis indicated that **COOH-Ni|SiO₂** contained 0.56 weight% nickel. This equates to 3.9x10⁻⁸ moles of catalyst per m² of silica

support. X-ray diffraction analysis of **COOH-Ni|SiO₂** (Figure 3.3) did not show any evidence for crystalline nickel particles when compared to fresh SiO₂ particles. This result suggests that the molecular nickel catalyst, and not metallic nickel particles, are present on the SiO₂ support. It is worth noting that the detection limit of the XRD instrument used is 1.0 nm crystalline particles.¹³³⁻¹³⁴

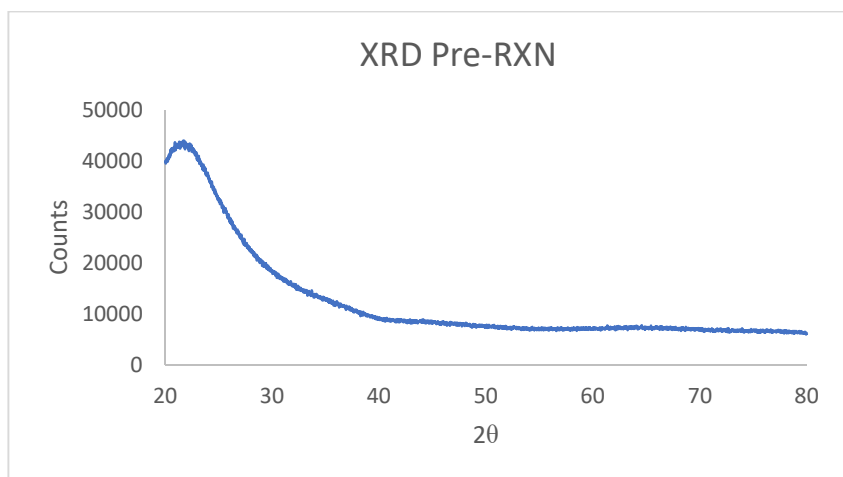
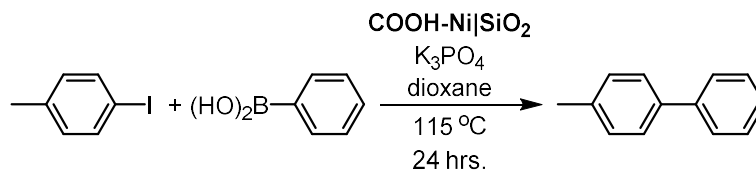


Figure 3.3. XRD Crystallographic Data for **COOH-Ni|SiO₂** before Catalytic Reaction

Further characterization of the **COOH-Ni|SiO₂** catalyst was carried out through the catalytic optimization reactions summarized in Table 3.1. The Suzuki-Miyaura coupling between 4-iodotoluene and benzenboronic acid was chosen as the test reaction. Common reactions conditions – equivalents of substrates, base used, and solvent – were chosen for a general comparison to literature. The chosen standard reaction conditions (row 1 Table 3.1) contained 100 mg of **COOH-Ni|SiO₂**, which is equivalent to 1.2×10^{-6} mol of the molecular **COOH-Ni** catalyst. A 24-hour reaction in dioxane solvent heated to reflux resulted in a 75 % yield of the desired cross-coupled product. Reactions of 6 and 18 hours

resulted in 20 and 51 % yields respectively, while reactions performed for longer than 24 hours did not result in a significant increase in product yield.

Table 3.1. Optimization of Suzuki-Miyaura Cross-Coupling



Deviation from Standard Conditions ^a	% Yield ^b
none	75
6 hrs.	20
18 hrs	51
0.1 mol% COOH-Ni homogeneous	0
10 mol% COOH-Ni homogeneous	25
SiO ₂ no Ni catalyst	0
SiO ₂ + 0.1 mol% COOH-Ni <i>in situ</i>	0
Rainey Ni, 10 mol%	1
COOH-Ni TiO₂	5
COOH-Ni ZrO₂	0
COOH-Ni Al₂O₃	0

^aStandard conditions: 100 mg **COOH-Ni|SiO₂** (1.2×10^{-6} mol **COOH-Ni**), 0.68 mmol iodotoluene, 0.82 mmol. benzene boronic acid, 1.7 mmol K₃PO₄, 20 ml dioxane. ^bYields determined by GC-MS. ^ctpy is 2,2':6',2''-terpyridine.

To examine the possible benefit of utilizing the molecular/heterogeneous catalyst **COOH-Ni|SiO₂**, homogeneous catalytic reactions were performed using **COOH-Ni** as the catalyst in solution. A reaction performed with 0.1 mol% **COOH-Ni**, roughly equivalent to the catalyst loading for **COOH-Ni|SiO₂**, did not result in any observed cross-coupled product. Increasing the homogeneous catalyst loading to 10 mol% did result in a 25 % yield of cross-coupled product, but unwanted dimerizations of the substrates were also observed.

These results indicate a clear advantage is obtained by using the molecular/heterogeneous **COOH-Ni|SiO₂** catalyst. In order to examine if SiO₂ has any direct reactivity with the substrates, a reaction was performed with just SiO₂ added to the reaction solution. No cross-coupled products or dimer formation was observed. Furthermore, a mixture of fresh SiO₂ particles and 0.1 mol% **COOH-Ni** catalyst did not result in any cross-coupled product formation, once again indicating that the preformed **COOH-Ni|SiO₂** catalyst is necessary for efficient Suzuki-Miyaura cross coupling.

It is proposed that the **COOH-Ni|SiO₂** catalyst isolates individual **COOH-Ni** molecules and helps prevent bimolecular decomposition of the catalyst. As mentioned previously, nickel dimers formed from monomeric nickel catalysts have been shown to be inactive for Suzuki cross-couplings.³² Potential nickel catalyst decomposition products were thus tested for possible catalytic activity. The $[(\mu\text{-Cl})\text{Ni}(\text{tpy})]_2^{2+}$ dimer was examined in homogeneous solution, but no cross-coupled product was observed. In addition, $[\text{tpy}_2\text{Ni}]\text{Cl}_2$ was also examined, and no cross-coupled products were obtained, however, deborylation products were observed. Rainey nickel was tested to examine if metal nickel particles exhibited catalytic activity. The metallic nickel produced little to no desired cross-coupled products, but some homocoupled product of the boronic acid substrate was observed. Thus, the monomeric **COOH-Ni** catalyst appears to be the only active Ni species for the desired Suzuki coupling, and preventing of the decomposition of this catalyst is essential for prolonged catalytic activity.

Lastly, we examined various metal oxides beyond SiO₂. The **COOH-Ni** molecular catalyst loaded onto TiO₂, ZrO₂, and Al₂O₃ individually all lead to poor product formation. These results are likely attributed to how the metal oxide reacts to the dioxane solvent.

Upon heating, the TiO_2 particles immediately clumped up into rock-like particles that could not be broken up with vigorous stirring. These clumps greatly decreased the exposed surface area of the particles, thus limiting catalysis. Similar results were observed for Al_2O_3 particles which immediately adhered to the walls of the round bottom flask. Lastly, ZrO_2 oxide particles formed a milky solution that turned yellow upon heating, indicating ZrO_2 is not stable in hot dioxane.

With evidence showing the molecular/heterogeneous catalyst **COOH-Ni|SiO_2** is uniquely capable of Suzuki-Miyaura cross-coupling reactions, the substrate scope for this catalyst was examined. Figure 3.4 shows that coupling of 4-*tert*-butyl-benzeneboronic acid with 4-iodotoluene gave comparable yields to the coupling of benzeneboronic acid with 4-iodotoluene. A strong electron donating methoxy group on the boronic acid increased yields of the cross-coupled product up to 92%. This catalyst was also amenable to coupling boronic acids with an electron withdrawing CF_3 group. The coupling reaction involving 4-fluorobenzeneboronic acid resulted in 80% yield, showing this catalyst exhibits functional group tolerance to pharmaceutically important fluorine atoms. No coupling at the fluoroposition was observed. Boronic acids with a functional group *ortho*- to the acid were also successfully coupled as product 6 was obtained in 50% yield. Naphthylboronic acids and aryl iodides were also tolerated as evidenced by products 7 and 8.

Next, the cross-coupling of various aryl halides with aryl boronic acids was examined. Entry 9 shows the general trend of reactivity for **COOH-Ni|SiO_2** towards aryl halides. Aryl iodides were generally more efficient coupling partners compared to aryl bromides, while no reactivity was observed with aryl chlorides.

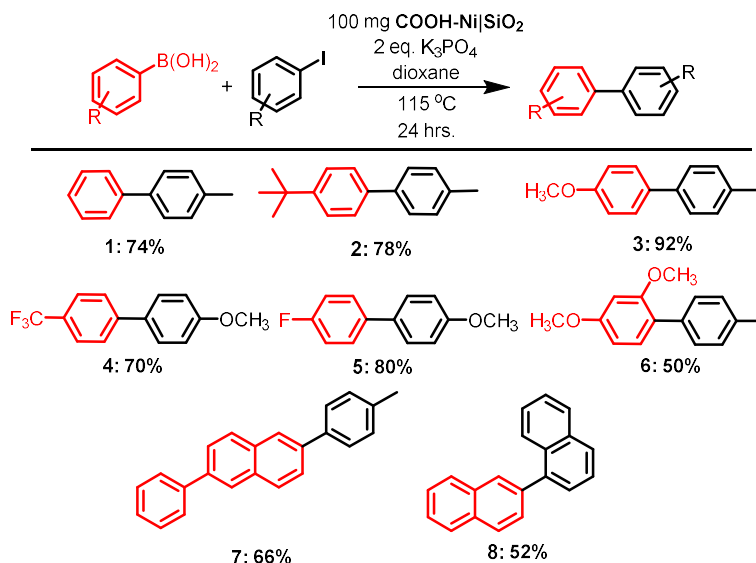


Figure 3.4. Catalytic Suzuki-Miyaura cross-coupling aryl iodides and aryl boronic acids. 34 mM aryl iodide, 41 mM boronic acid in 20 ml of 1,4-dioxane. % yields are isolated yields and based on limiting reagent.

This reactivity trend is consistent with previously reported nickel catalysts containing tridentate polypyridyl ligands.¹⁷ Good yields were, however, obtained from aryl bromide coupling partners with electron withdrawing groups in both the *para*- and *meta*- positions (entries 10, 11, and 12). Aryl iodides containing the electron donating methoxy group were also successfully coupled to form products 13 and 14. Although, electron donating groups on the boronic acid are more tolerated by this catalyst compared to electron donating groups on the aryl halide. Product 13 was only obtained in 58% yield starting with phenylboronic acid and 4-methoxy-iodobenzene, while a closely related product, (entry 3, Figure 3.2) was obtained in 92% yield through coupling of 4-methoxy-phenylboronic acid and 4-iodotoluene. Coupling involving iodonaphthalene was also successful (product 15).

Figures 3.4 and 3.5 show that COOH-Ni|SiO_2 exhibits good functional group tolerance, however, the main goal of designing this molecular/heterogeneous catalyst was

to increase the ease of catalyst separation from product mixtures and to increase the recyclability of cross-coupling catalysts.

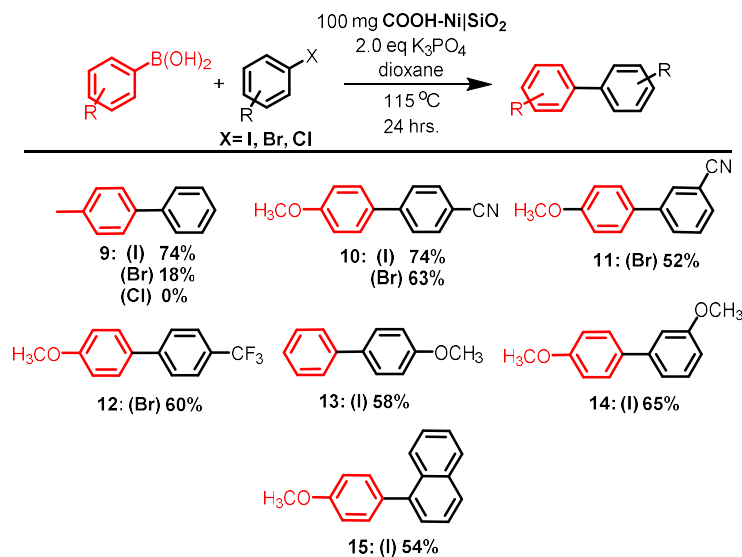
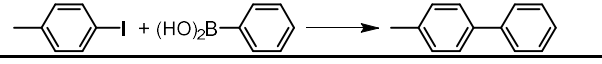


Figure 3.5. Catalytic Suzuki-Miyaura cross-coupling aryl boronic acids and aryl halides. 34 mM aryl halide, 41 mM boronic acid in 20 ml of 1,4-dioxane. % yields are isolated yields and based on limiting reagent.

In relation to the first goal, the solid COOH-Ni|SiO_2 catalyst was easily separated from product mixtures through filtration without need for column chromatography. To test the recyclability, the used, filtered catalyst was rinsed, dried and added to a fresh reaction solution. This procedure was repeated for multiple reactions and Table 3.2 shows the results of those trials. The molecular/heterogeneous COOH-Ni|SiO_2 catalyst exhibited consistent catalyst activity and product formation over the course of four consecutive reactions. The percent yields reported in Table 3.2 equate to 1700 catalytic turnovers before catalyst deactivation is observed in the fifth reaction. These experiments were repeated, and catalyst deactivation was once again observed during the fifth reaction. We hypothesize that loss of nickel catalyst from the surface of the SiO_2 support over the course

of five reactions and filtrations hits a critical point by the fifth reaction and product formation begins to drop due to low nickel catalyst loadings.

Table 3.2. Cross-coupled product yields from consecutive reactions using recycled **COOH-Ni/SiO₂**.

	
Experiment ^a	% Yield
1	76
2	74
3	72
4	72
5	37

^astandard conditions used as described in Table 3.1.

Post reaction analysis of the molecular/heterogeneous **COOH-Ni/SiO₂** catalyst was performed with ICP-MS and XRD. Once again, XRD patterns showed no evidence of Ni nanoparticle formation on the surface of the SiO₂ support, as seen in Figure 3.6. This result, in conjunction with the result from Table 3.1 showing that metallic Ni is inactive for this cross-coupling reactivity, support that the molecular **COOH-Ni** catalyst attached to the SiO₂ support is responsible for the observed catalytic activity. ICP-MS analysis of the used catalyst showed that only 78 mg/g of the original 687 mg/g of nickel remained on the SiO₂ support. This leaching of the catalyst is not ideal and is the likely cause for eventual catalyst deactivation. Though this result also corroborates that the molecular catalyst on the SiO₂ support is the active catalyst and molecular nickel catalyst in homogeneous solution quickly deactivates.

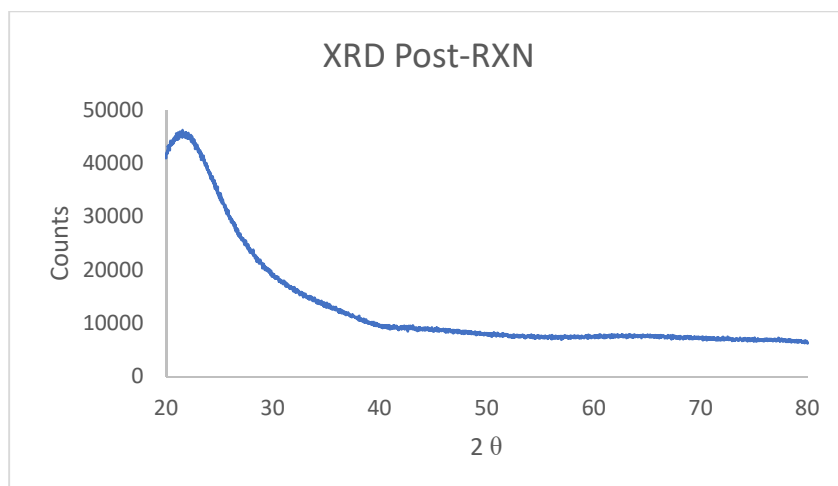


Figure 3.6. XRD Crystallographic Data for COOH-Ni|SiO₂ after Catalytic Reaction

3.4 CONCLUSIONS

A molecular/heterogeneous catalyst system for Suzuki-Miyaura cross-coupling has been designed, synthesized, and characterized. The catalyst is composed of an earth-abundant Ni molecular catalyst and inexpensive amorphous SiO₂ support. The catalyst exhibits activity at low catalyst loadings (roughly 0.2 mol% based on the molecular nickel catalyst) and good functional group tolerance. Eventual catalyst leaching from the surface of the support leads to catalyst deactivation, though the catalyst is easily recycled and turnover numbers of 1700+ were observed before deactivation. This loss of the molecular catalyst from the solid support shows the need to design new molecular/heterogeneous systems with stronger immobilization of the catalyst onto the support.¹³⁵ A successful attempt at this goal is seen in Chapter 4, in which another method allows for a more stable catalyst. Obtaining good yields of cross-coupled products from a low-loading of a non-precious metal catalyst, however, shows promise for future studies for this catalyst motif for cross-coupling reactions.

3.5 EXPERIMENTAL

3.5.1 Materials. All reagents were used as received from the manufacturer and were used without any further purification. $[(\mu\text{-Cl})\text{Ni}(\text{tpy})]_2$ was prepared by previously reported methods.¹⁷ Silica oxide support used throughout was Aerosil 300 (A300, Evonik). A300 is amorphous SiO_2 with 300 m^2/g surface area and an average particle size of 20 nm.

3.5.2 Instrumentation. X-ray diffraction (XRD) analysis was carried out with a benchtop powder X-ray diffractometer (Rigaku Miniflex-II with a silicon strip detector, D/teX Ultra – capable of detecting nanoparticles down to 1.0 nm) with $\text{Cu K}\alpha$ radiation ($\lambda = 1.5406 \text{ \AA}$), operated at 15 kV and 30 mA. Powder samples were loaded on a zero-background holder and scans were made from the $20^\circ - 80^\circ 2\theta$ range, with a scan rate of $3.0^\circ 2\theta/\text{min}$. Inductively Coupled Plasma-mass spectrometry (ICP-MS, Finnigan ELEMENT XR double focusing magnetic field) analysis was used for the analysis of nickel present on silica with rhenium as internal standard. Quartz torch and injector (Thermo Fisher Scientific) and 0.2 mL/min Micromist U-series nebulizer (GE, Australia) were used for sample introduction. GC-MS (Shimadzu QP-2010S) analysis was performed with a 30-meter-long Rxi-5ms (Restek) separation column with a 0.25 mm id and the oven temperature program was 40°C for 0.5 minutes followed by a $10^\circ\text{C}/\text{min}$ ramp to 280°C and held for 2 minutes. Mass spectrometer electron ionization was at 70 eV and the spectrometer was scanned from 1000 to 50 m/z at low resolution. NMR spectroscopy was performed using a Bruker Advance III HD 300. Data were processed using Bruker TopSpin software. ^1H NMR spectroscopy was performed using a 300 MHz instrument using deuterated chloroform or deuterated methylene chloride as the solvent with a calibrated peak at 7.26 ppm or 5.32 ppm respectively. ^{13}C NMR was conducted on a 300 MHz

instrument set to a frequency of 75 MHz using chloroform or methylene chloride as the solvent and a calibrated solvent peak at 77.33 ppm or 54.00 ppm. Details of the single crystal X-ray crystallography can be found in the supporting information.

3.5.3 Synthesis of [(2,2':6',2''-terpyridine-4'-benzoic acid)Ni(II)]Cl₂. To a round bottom flask, 0.100 g (0.28 mmol) of 2,2':6',2''-terpyridine-4'-benzoic acid was dissolved in 100 mL of ethanol and heated to 60°C. To this solution, 0.067 g of NiCl₂·6 H₂O (0.28 mmol) was added and stirred for 3 hours. The solution was then placed on the rotary evaporator and evaporated to dryness. The solid was washed several times with ethanol and diethyl ether. The resulting green solid was then isolated and dried in an oven overnight. Yield: 0.125 g, 0.113 mmol. Elemental Analysis: Calculated: C: 54.71%; H: 3.13%; N: 8.70%. Actual: C: 53.81%; H: 3.03%; N: 8.32%.

3.5.4 Synthesis of tpy₂Ni. To a round bottom flask, 150 mg of (2,2':6',2''-terpyridine)Ni was dissolved in 20 mL of acetonitrile. To this solution, 23 mg of potassium *tert*-butoxide was added and the solution was stirred at room temperature for 24 hours. The resulting brown solution was dried on the rotary evaporator to produce a brown solid. Yield: 0.105 g, 0.20 mmol. ESI MS two most prominent peaks 166 m/z (C₁₇H₁₄N₄Ni²⁺, tpyNi(MeCN)) and 262 m/z (C₃₀H₂₂N₆Ni²⁺, tpy₂Ni²⁺).

3.5.5 Preparation of COOH-Ni|SiO₂. To a 500 mL media bottle, 1.00 g of Aerosil A300 SiO₂ and 100 mL of methanol was mixed. To this solution, 0.100 g of 2,2':6',2''-terpyridine-4'-benzoic acid and 0.067 g of NiCl₂·6 H₂O were dissolved. The solution was allowed to settle overnight. The solid was then vacuum filtered, rinsed with methanol, and dried before characterization or catalytic reactions.

3.5.6 General Catalytic Reaction Scheme. In a round bottom flask, 0.100 g of COOH-Ni|SiO₂, 0.68 mmol aryl halide, 0.82 mmol boronic acid, and 1.7 mmol of K₃PO₄ were added to 20 mL of dioxane. This solution was heated to 115°C and kept at reflux for 24 hours. The resulting solution was concentrated and the product isolated by preparative scale TLC.

For recycle experiments, the solid catalyst was collected post reaction via suction filtration, rinsed with hexanes and dried. The collected catalyst was then placed in a new reaction following the general procedure described above.

3.5.7 Product Confirmation

4-methyl-1,1'-biphenyl (Products 1 and 9) ¹HNMR (300 MHz, CDCl₃) δ: 2.44 (s, 3H), 7.28 (d, 2H), 7.34 (t, 1H), 7.51 (t, 2H), 7.61 (d, 2H), 7.66 (d, 2H).

¹³CNMR (75 MHz, CDCl₃) δ: 21.13, 127.00, 127.02, 127.2, 127.3, 128.7, 128.8, 129.5, 131.2, 137.0, 137.2, 138.4, 141.2. All peaks match previous reports.¹³⁶

4-(t-butyl)-4'-methyl-1,1'-biphenyl (Product 2) ¹HNMR (300 MHz, CDCl₃) δ: 1.29 (s, 9H), 2.32 (s, 3H), 7.18 (d, 2H), 7.47 (m, 6H). ¹³CNMR (75 MHz, CDCl₃) δ: 21.1, 31.4, 34.5, 125.7, 126.6, 126.9, 129.4, 131.2, 136.7, 137.2, 138.3. All peaks match previous reports.¹³⁷

4-methoxy-4'-methyl-1,1'-biphenyl (Product 3) ¹HNMR (300 MHz, CD₂Cl₂) δ: 2.28 (s, 3H), 3.73 (s, 3H), 6.87 (d, 2H), 7.13 (d, 2H), 7.41 (d, 2H), 7.45 (d, 2H). ¹³CNMR (75 MHz, CD₂Cl₂) δ: 20.7, 114.1, 126.3, 127.8, 129.4, 133.5, 136.5, 137.7, 159.1. All peaks match previous reports.¹³⁸

4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl (Products 4 and 12) ^1H NMR (300 MHz, CD_2Cl_2) δ : 3.77 (s, 3H), 6.93 (d, 2H), 7.50 (d, 2H), 7.60 (s, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 55.3, 114.1, 114.4, 125.6, 126.8, 127.5, 128.3, 160.2. All peaks match previous reports.¹³⁹

4-fluoro-4'-methoxy-1,1'-biphenyl (Product 5) ^1H NMR (300 MHz, CD_2Cl_2) δ : 3.87 (s, 3H), 7.00 (d, 2H), 7.16 (t, 2H), 7.50 (m, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 55.3, 114.2, 115.3, 115.6, 127.9, 128.1, 128.2, 132.6, 137.0, 159.2, 163.7. All peaks match previous reports.¹³⁶

2,4-dimethoxy-4'-methyl-1,1'-biphenyl (Product 6) ^1H NMR (300 MHz, CD_2Cl_2) δ : 2.28 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 6.47 (m, 2), 7.12 (m, 3H), 7.25 (d, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 20.8, 55.3, 55.4, 98.8, 100.3, 104.6, 106.0, 128.6, 129.3, 129.8, 131.0, 135.5, 136.1, 157.5, 160.3, 161. All peaks match previous reports.¹³⁸

2-phenyl-6-(*p*-tolyl)naphthalene (Product 7) ^1H NMR (300 MHz, CD_2Cl_2) δ : 2.34 (s, 3H), 7.22 (d, 2H), 7.28 (d, 1H), 7.45 (t, 2H), 7.57 (d, 2H), 7.67 (t, 4H), 7.88 (d, 2H), 8.00 (s, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 21.2, 125.2, 126.0, 127.2, 127.3, 127.4, 128.7, 128.9, 129.6. All peaks match previous reports.¹⁴⁰

1,2'-binaphthalene (Product 8) ^1H NMR (300 MHz, CD_2Cl_2) δ : 7.22-7.27 (t, 2H), 7.61-7.63 (m, 2H), 7.65-7.69 (m, 2H), 7.83-7.85 (d, 2H), 7.89-7.96 (m, 2H), 8.15-8.18 (m, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 109.3, 117.7, 123.6, 126.3, 126.7, 126.8, 127.6, 127.7, 128.6, 129.0, 132.0, 134.3, 137.5, 164.8. All peaks match previous reports.¹⁵

4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (Product 10) ^1H NMR (300 MHz, CD_2Cl_2) δ : 3.80 (s, 3H), 6.92 (d, 2H), 7.49 (d, 2H), 7.60 (d, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ : 55.6,

110.0, 114.4, 114.7, 115.9, 119.0, 127.0, 128.3, 131.3, 132.5, 145.0, 149.9, 153.5, 160.3.

All peaks match previous reports.¹⁴¹

4'-methoxy-[1,1'-biphenyl]-3-carbonitrile (Product 11) ¹HNMR (300 MHz, CD₂Cl₂) δ: 3.86 (s, 3H), 6.97-7.07 (m, 2H), 7.54-7.68 (m, 4H), 7.78-7.88 (m, 2H). ¹³CNMR (75 MHz, CD₂Cl₂) δ: 55.3, 113.4, 114.5, 128.1, 129.5, 130.0, 130.1, 130.8, 136.6, 160.2. All peaks match previous reports.¹⁴²

4-methoxy-1,1'-biphenyl (Product 13) ¹HNMR (300 MHz, CD₂Cl₂) δ: 3.75 (s, 3H), 6.91 (d, 2H), 7.21 (t, 1H), 7.32 (t, 2H), 7.43 (m, 4H). ¹³CNMR (75 MHz, CD₂Cl₂) δ: 55.2, 114.1, 126.5, 126.6, 127.9, 128.6, 140.6. All peaks match previous reports.¹³⁶

3,4'-dimethoxy-1,1'-biphenyl (Product 14) ¹HNMR (300 MHz, CD₂Cl₂) δ: 3.81 (s, 6H), 6.91 (d, 2H), 7.00 (t, 2H), 7.35 (d, 4H). ¹³CNMR (75 MHz, CD₂Cl₂) δ: 55.4, 94.2, 113.7, 123.0, 129.7, 130.8, 160.2. All peaks match previous reports.¹⁴³

1-(4-methoxyphenyl)naphthalene (Product 15) ¹HNMR (300 MHz, CD₂Cl₂) δ: 3.79 (s, 3H), 6.94 (d, 2H), 7.30-7.45 (m, 6H), 7.80-7.83 (m, 3H). ¹³CNMR (75 MHz, CD₂Cl₂) δ: 55.3, 113.7, 125.4, 125.7, 125.9, 126.7, 126.8, 127.2, 127.7, 128.2, 128.6, 129.0, 131.0, 131.8, 131.9, 132.9, 133.8, 139.8, 159.0. All peaks match previous reports.³⁵

CHAPTER 4:

IMMOBILIZATION OF A NICKEL MOLECULAR CATALYST ON SOLID OXIDE SUPPORTS VIA ATOMIC LAYER DEPOSITION³

4.1 ABSTRACT

In this work, the ideas utilized in Chapter 3 are continued by stabilizing the single-site molecular catalyst by using Atomic Layer Deposition. By using this technique, a new heterogeneous catalyst using a single-site molecular catalyst was developed and was capable of carrying out the Suzuki coupling reaction in aqueous solvents, thus removing the dangerous organic solvent used in Chapter 3. The catalyst is capable of being recycled beyond 6 reactions and is hypothesized to react beyond 10 recycles without losing product conversion. The catalyst was also able to couple heteroaryl compounds, a highly sought-after process in Suzuki coupling, in high yields with only 0.1% catalyst loading. This process, therefore, addresses several goals in cross-coupling reactions, such as the catalyst design, solvents used, and cost.

4.2 INTRODUCTION

Catalytic cross-coupling reactions have become a large part of organic synthesis, both in the academic lab^{8, 30-32, 69} and the industrial sector^{4, 69, 87} and have witnessed some

³ Key, R. J.; Losego, M. D.; Vannucci, A. K. To be submitted to the *Journal of the American Chemical Society*.

astonishing advances over the past decade, such as reductive coupling^{17, 55-56} and photoredox coupling.^{73, 75, 77} Throughout these advances, the Principles of Green Chemistry⁴⁷ have been the guiding light for the development of more sustainable and effective chemical processes. With ideas such as waste prevention, safer chemicals and solvents, and less hazardous chemical synthesis, “green chemistry” continues to provide guidance to improve catalytic cross-coupling reactions.^{14, 47}

Perhaps the most widespread cross-coupling reaction is the Suzuki coupling reaction between an organoboron compound and an aryl halide.⁸ These reactions have been one of the many cross-coupling reactions that have benefitted from the implementation of “green chemistry,” as recent advances have shown more energy efficient reactions, such as microwave reactions¹⁴⁴⁻¹⁴⁷, or the use of “green” solvents, such as water.^{14, 36, 60, 148} These reactions tend to use toxic and expensive palladium catalysts and are not always amenable to all desired substrates; therefore, even with the current innovations seen throughout all these advances, there is still room to improve in the Suzuki coupling reactions.

Recently, nickel catalysts have received a renewed interest due to the reactivity of the nickel metal and the low cost of the metal precursors.^{31, 46} Nickel catalysts are typically “harder” catalysts as compared to palladium catalysts, which allows for more facile oxidative addition and better activation of electrophiles.^{32, 46, 149} Furthermore, nickel catalysts are not susceptible to β -hydride elimination, which is considered an off-cycle reaction in palladium catalyzed reactions.^{28, 149} Though these particular properties make nickel an attractive alternative to palladium catalysts, there exists a inherent difference that makes the palladium-to-nickel transition difficult. Palladium catalysts proceed through mechanisms that require 2 electron transfers whereas nickel catalysts prefer SET

processes.^{46, 149} Though this particular trait has been manipulated to produce a variety of reactions like photoredox methods, it creates a limitation in application of previous reactions in which palladium was used, such as the Suzuki reaction.^{16, 31, 46, 71, 73-75, 79} Replacing the palladium with the cost-effective nickel can create new pathways using Suzuki coupling and is an area of intense research in both academic and industrial settings.^{31-32, 50, 150-152}

Another approach to creating more “green” processes is the heterogenization of homogeneous catalysts on supports to create single-site molecular catalysts, or SSMC.^{65-70, 153} In doing so, the process becomes more “green” as the ease of separation and recyclability of heterogeneous catalysis is combined with the increased reactivity and selectivity of homogeneous catalysts.⁶⁸ These catalysts would prove to be a major advancement in industrial processes as well, as heterogeneous processes are easier to scale-up to production than homogeneous reactions. However, to achieve this goal, stable catalysts must be developed that are robust enough to match the efficacy of homogeneous catalysts that are currently used.^{44, 65-66, 68-69} Previous work conducted in our lab shows how the heterogenization of a molecular catalyst can create or improve reactivity, providing convincing support to these methods.

The development of SSMC’s for Suzuki coupling has been achieved in recent years and has shown the potential to overcome the current homogeneous techniques.^{65, 69, 154-155} These developments, however, center around using palladium catalysts rather than nickel catalysts. Furthermore, not all the catalysts can work in “green” solvents. To this end, a more desirable approach would be the development and implementation of a nickel catalyst in a similar manner. To further make the process “greener” use of aqueous solvents and

low catalyst loading would be ideal. At the writing of this manuscript, only 34 references appear in a SciFinder search, with only 2 publications directly related to aqueous Suzuki coupling using nickel catalysts.

In this work, we have successfully synthesized and heterogenized a nickel molecular catalyst capable of carrying out aqueous Suzuki coupling in high yields once immobilized on an oxide support. The instability of the nickel catalyst on the surface of these oxide supports presented a problem in previous reports. To combat this instability, layers of another metal oxide is cemented around the molecular catalyst. This is achieved by Atomic Layer Deposition (ALD), a method that allows for the formation of metal oxide monolayers to be added sequentially in cyclical manner. Figure 4.1 shows a visual representation of the catalyst after the ALD process. This new catalyst motif achieves several goals for industrial cross-coupling reactions, including greener solvents, simplistic purifications, and a nickel catalyst in the place of palladium catalysts.

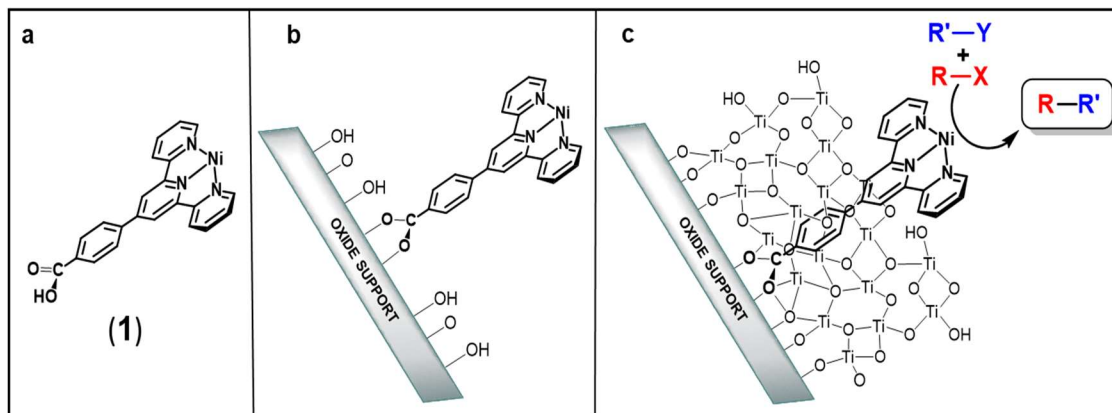


Figure 4.1 Visual representation of immobilization of the nickel molecular catalyst. The mounting of Catalyst (1) produces the heterogenized catalyst, as seen in Chapter 3. Upon immobilization, the proposed catalytic system can operate as seen in the figure. The nickel catalyst is present as a Ni^{II} catalyst with chloride ligands excluded for clarity.

4.3 RESULTS AND DISCUSSION

In order to allow heterogenization of a molecular catalyst, the terpyridine ligand was functionalized with a benzoic acid moiety. In Chapter 3, we have shown that doing so allowed for effective immobilization of the nickel catalyst onto a silica support with a nickel weight percentage of 0.56%. This catalyst was indeed effective but was not able to react beyond 5 recycles. Furthermore, the catalyst was not active in water for the coupling of iodotoluene and benzenboronic acid and could only work effectively in less desirable organic solvents. We hypothesized that the basic conditions and relatively high heat created harsh enough conditions to cause the molecular catalyst to dissociate from the surface of the SiO₂ particles. We further hypothesized that forming a physical barrier would stabilize the catalyst by protecting the binding site from these harsh conditions. To achieve this, Atomic Layer Deposition presented an alluring alternative with some work in the past showing that this method can stabilize catalysts and increase reactivity.¹³⁵

Atomic Layer Deposition is a cyclical, self-limiting process that allows for metal monolayers to form from metal precursors. The process starts with the introduction of a metal precursor, in our case TiCl₄, to a solid oxide, such as the COOH-Ni|SiO₂ catalyst. This precursor can only react with the available SiO₂ sites not occupied with molecular catalyst; in addition, the precursor is unreactive to itself, forcing the monolayer to form. The excess precursor is removed by a vacuum purge. After this purge, an oxidant is used to form TiO₂ layers. In our case, the oxidant is water and the by-product HCl is removed by a simple vacuum purge. This cycle is repeated depending upon the desired depth of the TiO₂ layer, forming the desired ALD immobilized catalyst **COOH-Ni|SiO₂|TiO₂**. The ALD process was carried out by the Losego group at Georgia Tech and was found to

effective for the desired catalyst. Upon immobilization by this method, the catalyst was found to be reactive at 90% yield for the reaction between iodotoluene and benzenboronic acid in water, as seen in Figure 4.2.

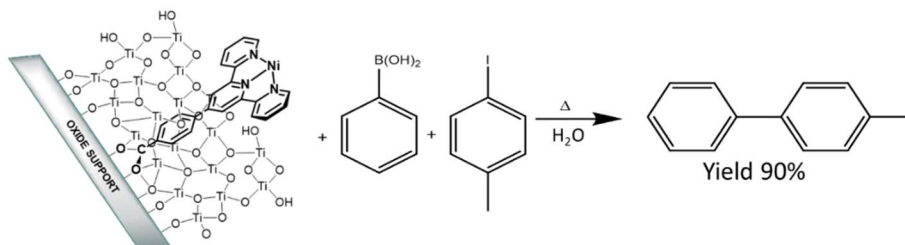
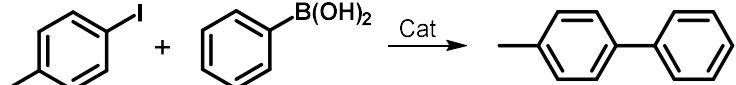


Figure 4.2. Reaction using the **COOH-Ni|SiO₂|TiO₂** catalyst in aqueous solvents. The nickel catalyst is present as a Ni^{II} catalyst with chloride ligands excluded for clarity.

This reaction was further studied, both in reactivity of the cross-coupling reaction and the effect of the ALD layers upon reactivity. The optimization results can be found in Table 4.1. Since the heterogenized catalyst was already studied in Chapter 3, the focus of these optimization reactions was on the effect of the ALD on the catalytic activity. The unmounted nickel catalyst was unreactive in aqueous solvents, similar to the reactivity observed in dioxane. Upon immobilization, the yields did increase slightly to 25%. This lower yield can be attributed to the harsh conditions of the reaction itself and thus show the importance of the ALD immobilization practice. ICP-MS was conducted on a batch of the immobilized catalyst before and after the ALD process and was found to be similar, showing no significant decrease in nickel concentration on the surface of the oxide support. In order to show that the reactivity is not solely attributed to the TiO₂ layers, a control reaction with TiO₂ was ran and yielded only 12%. We also tested for the *in-situ* generation of the catalyst with TiO₂ particles, which yielded no product. This provides support that it is the molecular catalyst that is carrying out this reactivity rather than dissociating and

forming the molecular catalyst in a homogeneous manner. In addition to the general control reactions, the depth of the ALD layers was analyzed for the effect on reactivity. It was found that 1.0 nm produced an ideal yield at 90% whilst 0.5 nm produced 32% and 1.5 nm produced 2%. We suspect that the 1.5 nm depth led to the catalyst being buried beneath the ALD layers, preventing access to the nickel catalyst and lowering reactivity. This also supports the hypothesis that the ALD layers are unreactive towards for the Suzuki reaction in this reaction scheme, as an excess would lead to more formation of desired product.

Table 4.1. Optimization of Suzuki reaction using ALD catalyst



Rxn.	Cat	Yield
1	COOH-Ni	0%
2	COOH-Ni on SiO ₂ (COOH-Ni SiO ₂)	25%
3	COOH-Ni on TiO ₂	38%
4	COOH-Ni on SiO ₂ with 0.5 nm TiO ₂ ALD	32%
5	COOH-Ni on SiO ₂ with 1.0 nm TiO ₂ ALD (COOH-Ni SiO ₂ TiO ₂)	90%
6	COOH-Ni on SiO ₂ with 1.5 nm TiO ₂ ALD	2%
8	Only TiO ₂	12%
9	COOH-Ni + SiO ₂ <i>in situ</i>	0%
10	COOH-Ni + TiO ₂ <i>in situ</i>	14%
11	NiCl ₂ + SiO ₂ <i>in situ</i>	0%

Conditions: 0.82 mmol phenylboronic acid, 0.68 mmol iodotoluene 1.7 mmol K₃PO₄ in 20 ml 1:1 ethanol/water 115 °C 24 hr. Catalyst loading 0.1 mol% based on Ni and iodotoluene.

An additional advantage of this immobilization technique is an increase in the stability of the catalyst, allowing for more recyclability. The catalyst was tested to see how much reactivity would be retained after the initial reaction. The COOH-Ni|SiO₂|TiO₂

catalyst was recycled by vacuum filtering and placed into the same reaction conditions to test robustness. Indeed, these catalysts are highly durable and recyclable, as six reactions were successfully completed without a drop-off in yields. We hypothesize the catalyst can endure over 10 recycles, leading to a highly active and cost-efficient alternative to traditional homogeneous catalysts.

Further analysis of this recyclable nature leads to TON in excess of 3000, showing a significant improvement over the previously utilized non-ALD catalyst used in Chapter 3. Figure 4.3 shows the difference in the TON in relation to recycles of the catalyst between the ALD and non-ALD catalyst. As seen in the figure, the ALD layers significantly increased catalyst lifetime, thus leading to a higher TON.

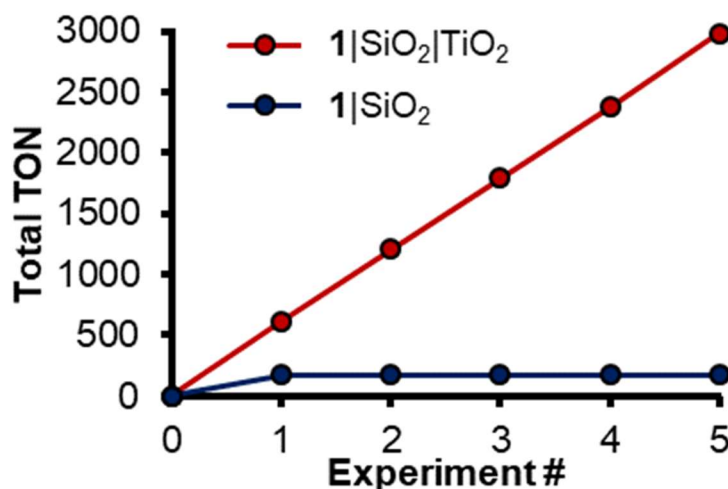


Figure 4.3. Comparison of the ALD and non-ALD heterogeneous catalyst.

With support that the TiO₂ ALD layer enhances product yield, we then assessed the viable substrates for Suzuki cross-coupling reactions in aqueous solutions. Figure 4.4 shows the current substrate scope; additional substrates are under investigation. Though not included in the figure, the initial product produced in the optimization reactions

between 4-iodotoluene and benzenboronic acid was capable of producing yields of 90%, a marked increase from the 76% in dioxane seen in Chapter 3. Additional substrates were tested that were similar to previous experiments and show comparable, if not improved, yields. Of note is this system can access heteroaryls, as seen in the coupling of furan-3-boronic acid with iodotoluene. This was unattainable with non-ALD catalysts in organic solvents. Furthermore, more complex substrates like 3,4-methylenedioxybenzene boronic acid was capable of coupling. These two substrates present a very alluring substrate class; heteroaryls are a difficult substrate to access even using traditional palladium catalysts in the Suzuki reaction. For this unique catalyst motif to access heteroaryls in aqueous solutions using a non-rare earth metal presents a major outcome in this research and is currently under further investigation to test the extent of this coupling. In short, not only has the immobilization by ALD led to increased stability, but unique and very interesting reactivity has resulted.

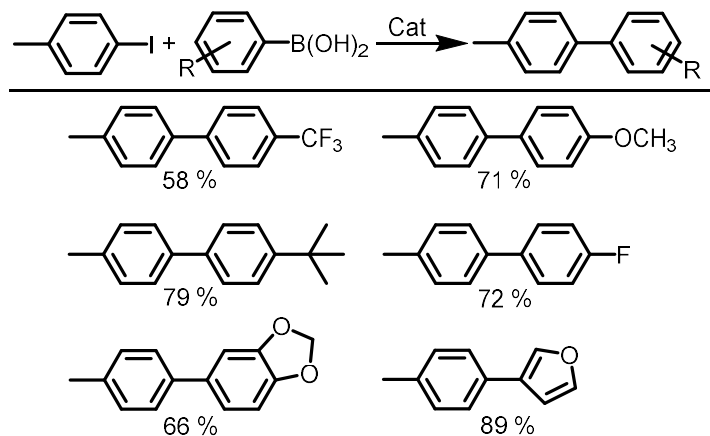


Figure 4.4. Substrate scope using COOH-Ni[SiO₂]/TiO₂ catalyst in aqueous solutions. Conditions: 0.82 mmol boronic acid, 0.68 mmol iodotoluene 1.7 mmol K₃PO₄ in 20 ml 1:1 ethanol/water 115 °C 24 hr. Catalyst loading 0.1 mol% based on Ni and iodotoluene. Yields are GC-MS yields.

4.4 EXPERIMENTAL

4.4.1 Materials. All reagents were used as received from the manufacturer and were used without any further purification. Silica oxide support used throughout was Aerosil 300 (A300, Evonik). A300 is amorphous SiO₂ with 300 m²/g surface area and an average particle size of 20 nm. The ALD preparation was conducted by the Losego group at Georgia Tech followed a previously published procedure.¹³⁵

4.4.2. Instrumentation. Inductively Coupled Plasma-mass spectrometry (ICP-MS, Finnigan ELEMENT XR double focusing magnetic field) analysis was used for the analysis of nickel present on silica with rhenium as internal standard. Quartz torch and injector (Thermo Fisher Scientific) and 0.2 mL/min Micromist U-series nebulizer (GE, Australia) were used for sample introduction. GC-MS (Shimadzu QP-2010S) analysis was performed with a 30-meter-long Rxi-5ms (Restek) separation column with a 0.25 mm id and the oven temperature program was 40°C for 0.5 minutes followed by a 10°C/min ramp to 280°C and held for 2 minutes. Mass spectrometer electron ionization was at 70 eV and the spectrometer was scanned from 1000 to 50 m/z at low resolution.

4.4.3 General Catalysis Reaction Scheme. In a round bottom flask, 0.100 g of COOH-Ni|SiO₂|TiO₂, 0.68 mmol aryl halide, 0.82 mmol boronic acid, and 1.7 mmol of K₃PO₄ were added to 20 mL of a 1:1 mixture of water and ethanol. This solution was heated to 115°C and kept at reflux for 24 hours. The organic products were then extracted with pentane and placed on a gas chromatograph equipped with a mass spectrometer as the detector.

For recycle experiments, the solid catalyst was collected post reaction via suction filtration, rinsed with hexanes and dried. The collected catalyst was then placed in a new reaction following the general procedure described above.

4.5 CONCLUSIONS

Immobilization of a molecular catalyst onto a solid oxide support provided an effective way of producing a recyclable, efficient, and frugal approach to Suzuki coupling as seen in Chapter 3. However, these catalysts suffered from deactivation after extended reactions and further showed lower reactivity in more desirable solvents like water. To combat this, we have successfully immobilized a molecular catalyst using Atomic Layer Deposition to “cement” the nickel catalyst in a TiO_2 layer. In doing so, we have significantly increased recyclability, reaching beyond six recycles in aqueous solvents without seeing a drop-off in the 90% product conversion in the optimization reaction. A substrate scope also exhibited the applicability of this catalyst in aqueous Suzuki coupling, yielding product yields with heteroaryl compounds. This reactivity shows how this approach of stabilization by ALD immobilization can create a catalyst that is effective in greener solvents while also presenting a cost-effective nickel catalyst. Such an advancement bears a large impact on the field of catalysis and is in further development.

CHAPTER 5:

CONCLUSION AND FUTURE WORK

The field of cross-coupling reactions have undoubtedly changed several industries, such as the pharmaceutical industry. However, there exist many areas that these reactions can be improved. Those areas center around the catalysts used, the additives in the reaction, the solvents being used, the sustainability of the reactions, and the cost of the reactions. This work has outlined advancements that address these areas of potential impact.

In Chapter 2, it was demonstrated that the nickel terpyridine catalyst utilized in the PARC reactions was also active in amination reactions. These reactions differed from the PARC reactions insomuch that the additives used were a simple heterogeneous base that is cheap and easily isolated from the final mixture and the process was redox-neutral, not requiring the addition of a sacrificial electron donor. These characteristics, along with the energy input being photonic energy from readily available light sources made this reaction a significant advancement in the field of amination reactions. We also found this methodology to be rather effective, showing reactivity to a wide range of substrates and even generating tertiary amines from secondary amine feedstocks. These characteristics make this new reaction scaffold address the challenges in cross-coupling reactions: the nickel catalyst presents a cost-effective alternative to palladium catalysts, the potassium phosphate base is less dangerous and easily isolable as compared to other additives, the energy input is photonic rather than thermal, reducing energy

consumption, and the acetonitrile solvent is a more desirable solvent than the commonly used DMF solvents.

Further work is being conducted on these photocatalytic processes, primarily in terms of the mechanism involved. There are several proposed mechanisms as to how these radicals react in these reactions, ranging from the proposed 1-electron oxidative addition to a Ni^{II} catalyst proposed in Chapter 2 to oxidative addition to a Ni^{I} catalyst proposed by groups like the Molander group.^{85, 89, 129} Other mechanisms exclude the radical, such as the one proposed by MacMillan and Buchwald.⁷⁴ Understanding the mechanisms at play allows the manipulation of the reaction conditions to better suit substrate classes. In order to develop more effective coupling reactions, these mechanisms must be understood. We have starting to work on understanding these mechanisms by attempting to synthesize our proposed intermediates and reacting them in the catalytic conditions. Currently, we have seen that the photocatalyst has been capable of reducing the Ni^{II} precatalyst to the Ni^{I} oxidation state. We have isolated this compound and attempted to obtain an NMR spectra. Unfortunately, the catalyst is paramagnetic, leading to broadened signals. However, this shows promise as the Ni^{II} catalyst can produce an NMR signal, leading us to believe accessing this one electron reduced state is easily attainable in our redox conditions. We were also able to establish an EPR signal with the compound, further supporting the generation of a Ni^{I} catalyst as no signal would appear in an EPR experiment for a Ni^{II} compound. Further plans involve reacting this compound in the system utilized in Chapter 2 to test for reactivity. Other complexes to be synthesized are the Ni^0 activated catalyst, the Ni^{II} -aryl complex (proposed intermediate after 2 electron aryl halide oxidative addition), the Ni^{II} -amido complex (proposed off-cycle by-product that “kills” the cycle), and the

unstable Ni^{III} intermediate. The Ni^{III} intermediate may not be fully isolable due to its high reactivity; therefore, *in-situ* techniques such as NMR or cyclic voltammetry may have to be utilized to support the existence of this catalytic intermediate.

In Chapter 3, we were able to immobilize a nickel terpyridine analogue to a solid oxide support to develop an active heterogeneous catalyst. This process allowed for a molecular catalyst that was not initially very reactive in the Suzuki coupling reaction to achieve moderate reactivity. Not only did this motif allow for increased reactivity, but allowed for a recyclable, easily isolable catalyst for up to four reactions. We believe that after these initial four reactions that enough catalyst has dissociated from the silica support to deactivate the catalyst. However, the easy preparation and isolation, along with the recyclability of the catalyst presents valuable insight into overcoming the current goals and limitations found in cross-coupling reactions.

In order to address the limitations of the previous catalyst, Chapter 4 outlines work into using Atomic Layer Deposition to stabilize the catalyst for further reactivity. We hypothesized that the high basicity and relatively high temperatures created an environment that led to dissociation of the catalyst in Chapter 3. We overcame this problem by creating a physical barrier between the attachment point and the harsh conditions to stabilize the catalyst. We were able to use this catalyst to carry out the Suzuki coupling reaction in aqueous solvents, a difficult solvent in which to achieve reactivity. Not only was this catalyst active in this troublesome, but highly desirable solvent, but was also recyclable for six reactions as tested and did not show any signs of deactivation, leading one to believe that the reactivity can persist much longer. Such a method to increase stability is unique and holds the potential to address long-standing issues in cross-coupling reactivity. As it

stands, Chapter 4 answers the challenges presented herein: by using a heterogeneous nickel catalyst, a recyclable catalyst in the greenest of solvents is achieved that lowers cost, creates easy separations, and can access difficult and desirable substrates.

The development of this catalytic motif is ongoing. Some interesting results were found throughout the development of this process. For example, the control reaction using just TiO_2 with no nickel catalyst did lead to some product conversion. This points to some form of activation pathway involving TiO_2 . We hypothesize that the ALD layers can serve a dual role: by activating the boronic acid and by increasing stability of the catalyst. By doing so, we can propose a mechanism as seen in Figure 5.1.

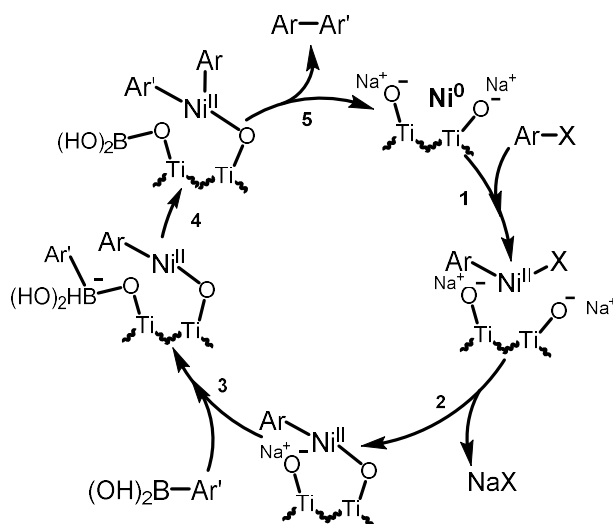


Figure 5.1. Proposed Suzuki mechanism highlighting dualistic approach of ALD layers. Ligands excluded for clarity.

To support this theory, additional ALD layers can be tested. If the ALD layers acted in this manner, the acid-base properties would dictate the effectiveness of the catalyst. Playing with various ALD precursors can help develop a deeper understanding of how these layers behave in these reactions. Furthermore, these layers can be varied be mixed

oxides. Further experimentation can lead to a preferred composition that can affect reactivity.

One other consequence of these layers being involved in reactivity is the removal of the base. Ever since the initial development of the Suzuki reaction, the base has played an integral role in reactivity. Primarily, it is believed that the base activates the boronic acid for the transmetalation step. However, the proposed mechanism in Figure 5.1 shows how the ALD oxide layer can activate the boronic acid. Therefore, if the layer was behaving in such a way, the base would not be needed. Even lowering the concentration of the base would lead to a better reaction, as that particular additive is typically in excess of the substrates, creating more waste. To test this, an initial reaction without added base was performed. The reaction between 4-iodotoluene and benzeneboronic acid without added base led to roughly 20% conversion to desired product. This is rather astonishing, as the reaction yielded 0% conversion without added base when no ALD layers were present in Chapter 3.

The provided examples show how nickel catalysts can change current cross-coupling methodologies. Indeed, the unique chemistry of the nickel catalyst coupled with the typically lower production cost show how these catalysts can replace traditional cross-coupling catalysts. Whether it be in photoredox methods, or a new approach to traditional methods, nickel catalysis shows high promise and deserves to be fully explored by industrial entities.

REFERENCES

1. Ullman, F.; Bielecki, J., Synthesis in the Biphenyl Series. *Ber. Dtsch. Chem. Ges* **1901**, *34*, 2174-2185.
2. Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F., Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66* (34), 8914-8934.
3. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y., Key green chemistry research areas—a perspective from pharmaceutical manufacturers. *Green Chemistry* **2007**, *9* (5), 411-420.
4. Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A., Organic synthesis provides opportunities to transform drug discovery. *Nature Chemistry* **2018**, *10* (4), 383-394.
5. Jo, J.; Tu, Q.; Xiang, R.; Li, G.; Zou, L.; Maloney, K. M.; Ren, H.; Newman, J. A.; Gong, X.; Bu, X., Metal Speciation in Pharmaceutical Process Development: Case Studies and Process/Analytical Challenges for a Palladium-Catalyzed Cross-Coupling Reaction. *Organometallics* **2019**, *38* (1), 185-193.
6. Roughley, S. D.; Jordan, A. M., The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *Journal of Medicinal Chemistry* **2011**, *54* (10), 3451-3479.7. Miyaura, N.; Yamada, K.; Suzuki, A., A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Letters* **1979**, *20* (36), 3437-3440.
8. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chemical Reviews* **1995**, *95* (7), 2457-2483.
9. Suzuki, A., Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995–1998. *Journal of Organometallic Chemistry* **1999**, *576* (1-2), 147-168.
10. Beletskaya, I. P.; Cheprakov, A. V., The heck reaction as a sharpening stone of palladium catalysis. *Chemical Reviews* **2000**, *100* (8), 3009-3066.

11. Littke, A. F.; Dai, C.; Fu, G. C., Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *Journal of the American Chemical Society* **2000**, *122* (17), 4020-4028.
12. Gao, C. Y.; Yang, L. M., Nickel-catalyzed amination of aryl tosylates. *J Org Chem* **2008**, *73* (4), 1624-7.
13. Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T., CuO Nanoparticles Catalyzed C–N, C–O, and C–S Cross-Coupling Reactions: Scope and Mechanism. *The Journal of Organic Chemistry* **2009**, *74* (5), 1971-1976.
14. Vivek, P.; Audrey, D.; Christophe, L.; Aziz, F., Suzuki–Miyaura Cross-Coupling Reactions in Aqueous Media: Green and Sustainable Syntheses of Biaryls. *ChemSusChem* **2010**, *3* (5), 502-522.
15. Chen, H.; Huang, Z.; Hu, X.; Tang, G.; Xu, P.; Zhao, Y.; Cheng, C. H., Nickel-catalyzed cross-coupling of aryl phosphates with arylboronic acids. *J. Org. Chem.* **2011**, *76* (7), 2338-44.
16. Noble, A.; McCarver, S. J.; MacMillan, D. W. C., Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *Journal of the American Chemical Society* **2015**, *137* (2), 624-627.
17. Paul, A.; Smith, M. D.; Vannucci, A. K., Photoredox-Assisted Reductive Cross-Coupling: Mechanistic Insight into Catalytic Aryl–Alkyl Cross-Couplings. *The Journal of Organic Chemistry* **2017**, *82* (4), 1996-2003.
18. Heck, R. F.; Nolley, J. P., Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *The Journal of Organic Chemistry* **1972**, *37* (14), 2320-2322.
19. Dieck, H. A.; Heck, R. F., Organophosphinepalladium complexes as catalysts for vinylic hydrogen substitution reactions. *Journal of the American Chemical Society* **1974**, *96* (4), 1133-1136.
20. Tsutomu, M.; Kunio, M.; Atsumu, O., Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bulletin of the Chemical Society of Japan* **1971**, *44* (2), 581-581.
21. Kobayashi, M.; Valente, L. F.; Negishi, E. I.; Patterson, W.; Silveira, A., Jr., Selective carbon-carbon bond formation via transition metal catalysis; 15. Controlled carbometallation; 6. A selective and efficient synthesis of (E)-4-methyl-3-alken-1-ols via zirconium-catalyzed carboalumination of terminal alkynes. *Synthesis* **1980**, (12), 1034-5.

22. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L., Rational development of practical catalysts for aromatic carbon– nitrogen bond formation. *Accounts of Chemical Research* **1998**, *31* (12), 805-818.
23. Surry, D. S.; Buchwald, S. L., Biaryl phosphane ligands in palladium-catalyzed amination. *Angew Chem Int Ed Engl* **2008**, *47* (34), 6338-61.
24. Biscoe, M. R.; Fors, B. P.; Buchwald, S. L., A new class of easily activated palladium precatalysts for facile C– N cross-coupling reactions and the low temperature oxidative addition of aryl chlorides. *Journal of the American Chemical Society* **2008**, *130* (21), 6686-6687.
25. Shen, Q.; Ogata, T.; Hartwig, J. F., Highly reactive, general and long-lived catalysts for palladium-catalyzed amination of heteroaryl and aryl chlorides, bromides, and iodides: scope and structure-activity relationships. *J Am Chem Soc* **2008**, *130* (20), 6586-96.
26. Paul, F.; Patt, J.; Hartwig, J. F., Palladium-catalyzed formation of carbon-nitrogen bonds. Reaction intermediates and catalyst improvements in the hetero cross-coupling of aryl halides and tin amides. *J. Am. Chem. Soc.* **1994**, *116* (13), 5969-70.
27. Yang, B. H.; Buchwald, S. L., Palladium-catalyzed amination of aryl halides and sulfonates. *Journal of Organometallic Chemistry* **1999**, *576* (1), 125-146.
28. Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W., On the nature of the active species in palladium catalyzed Mizoroki-Heck and Suzuki-Miyaura couplings - Homogeneous or heterogeneous catalysis, a critical review. *Advanced Synthesis & Catalysis* **2006**, *348* (6), 609-679.
29. Hu, X., Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chemical Science* **2011**, *2* (10), 1867-1886.
30. Carrow, B. P.; Hartwig, J. F., Distinguishing Between Pathways for Transmetalation in Suzuki–Miyaura Reactions. *Journal of the American Chemical Society* **2011**, *133* (7), 2116-2119.
31. Han, F.-S., Transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions: a remarkable advance from palladium to nickel catalysts. *Chemical Society Reviews* **2013**, *42* (12), 5270-5298.
32. Payard, P.-A.; Perego, L. A.; Ciofini, I.; Grimaud, L., Taming Nickel-Catalyzed Suzuki-Miyaura Coupling: A Mechanistic Focus on Boron-to-Nickel Transmetalation. *ACS Catalysis* **2018**, *8* (6), 4812-4823.

33. Miyaura, N.; Yamada, K., 3437.(c) Miyaura, N.; Yanagi, T.; Suzuki. *A. Synth. Commun* **1981**, *11*, 513.
34. O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G., Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC=N-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chemistry – A European Journal* **2006**, *12* (18), 4743-4748.
35. Kuroda, J.-i.; Inamoto, K.; Hiroya, K.; Doi, T., N-Heterocyclic carbene derived nickel-pincer complexes: Efficient and applicable catalysts for Suzuki-Miyaura coupling reactions of aryl/alkenyl tosylates and mesylates. *Eur. J. Org. Chem.* **2009**, (14), 2251-2261.
36. Godoy, F.; Segarra, C.; Poyatos, M.; Peris, E., Palladium Catalysts with Sulfonate-Functionalized-NHC Ligands for Suzuki–Miyaura Cross-Coupling Reactions in Water. *Organometallics* **2011**, *30* (4), 684-688.
37. Herrmann, W. A., N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angewandte Chemie International Edition* **2002**, *41* (8), 1290-1309.
38. Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F., An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485.
39. Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J., Metal Complexes of N-Heterocyclic Carbenes—A New Structural Principle for Catalysts in Homogeneous Catalysis. *Angewandte Chemie International Edition in English* **1995**, *34* (21), 2371-2374.
40. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F., An N-Heterocyclic Carbene Ligand with Flexible Steric Bulk Allows Suzuki Cross-Coupling of Sterically Hindered Aryl Chlorides at Room Temperature. *Angewandte Chemie International Edition* **2003**, *42* (31), 3690-3693.
41. Fortman, G. C.; Nolan, S. P., N-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chemical Society Reviews* **2011**, *40* (10), 5151-5169.
42. Marion, N.; Nolan, S. P., Well-Defined N-Heterocyclic Carbenes–Palladium(II) Precatalysts for Cross-Coupling Reactions. *Accounts of Chemical Research* **2008**, *41* (11), 1440-1449.
43. Roy, S.; Plenio, H., Sulfonated N-Heterocyclic Carbenes for Pd-Catalyzed Sonogashira and Suzuki–Miyaura Coupling in Aqueous Solvents. *Advanced Synthesis & Catalysis* **2010**, *352* (6), 1014-1022.

44. Marquard, A. N.; Slaymaker, L. E.; Hamers, R. J.; Goldsmith, R. H., Investigation of activity, stability, and degradation mechanism of surface-supported Pd-PEPPSI complexes for Suzuki-Miyaura coupling. *Molecular Catalysis* **2017**, 429, 10-17.
45. Balcells, D.; Nova, A., Designing Pd and Ni Catalysts for Cross-Coupling Reactions by Minimizing Off-Cycle Species. *ACS Catalysis* **2018**, 8 (4), 3499-3515.
46. Ananikov, V. P., Nickel: The “Spirited Horse” of Transition Metal Catalysis. *ACS Catalysis* **2015**, 5 (3), 1964-1971.
47. Anastas, P.; Eghbali, N., Green Chemistry: Principles and Practice. *Chemical Society Reviews* **2010**, 39 (1), 301-312.
48. Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A., Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type (η^3 -allyl)Pd(L)(Cl) and (η^3 -indenyl)Pd(L)(Cl). *ACS Catalysis* **2015**, 5 (9), 5596-5606.
49. Bisz, E.; Kardela, M.; Piontek, A.; Szostak, M., Iron-catalyzed C(sp²)–C(sp³) cross-coupling at low catalyst loading. *Catalysis Science & Technology* **2019**.
50. Junichiro, Y.; Kei, M.; Kenichiro, I., Recent Progress in Nickel-Catalyzed Biaryl Coupling. *European Journal of Organic Chemistry* **2013**, 2013 (1), 19-30.
51. Camasso, N. M.; Sanford, M. S., Design, synthesis, and carbon-heteroatom coupling reactions of organometallic nickel(IV) complexes. *Science* **2015**, 347 (6227), 1218-1220.
52. Han, R.; Hillhouse, G. L., Carbon–Oxygen Reductive-Elimination from Nickel(II) Oxametallacycles and Factors That Control Formation of Ether, Aldehyde, Alcohol, or Ester Products. *Journal of the American Chemical Society* **1997**, 119 (34), 8135-8136.
53. Lin, B. L.; Clough, C. R.; Hillhouse, G. L., Interactions of Aziridines with Nickel Complexes: Oxidative-Addition and Reductive-Elimination Reactions that Break and Make C–N Bonds. *Journal of the American Chemical Society* **2002**, 124 (12), 2890-2891.
54. Koo, K.; Hillhouse, G. L., Carbon-Nitrogen Bond Formation by Reductive Elimination from Nickel(II) Amido Alkyl Complexes. *Organometallics* **1995**, 14 (9), 4421-4423.
55. Biswas, S.; Weix, D. J., Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J Am Chem Soc* **2013**, 135 (43), 16192-7.

56. Weix, D. J., Methods and Mechanisms for Cross-Electrophile Coupling of Csp(2) Halides with Alkyl Electrophiles. *Acc Chem Res* **2015**, *48* (6), 1767-75.
57. Everson, D. A.; Weix, D. J., Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *The Journal of Organic Chemistry* **2014**, *79* (11), 4793-4798.
58. Johnson, K. A.; Biswas, S.; Weix, D. J., Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chemistry – A European Journal* **2016**, *22* (22), 7399-7402.
59. Anka-Lufford, L. L.; Huihui, K. M. M.; Gower, N. J.; Ackerman, L. K. G.; Weix, D. J., Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents. *Chemistry – A European Journal* **2016**, *22* (33), 11564-11567.
60. Li, Z.; Gelbaum, C.; Fisk, J. S.; Holden, B.; Jaganathan, A.; Whiteker, G. T.; Pollet, P.; Liotta, C. L., Aqueous Suzuki Coupling Reactions of Basic Nitrogen-Containing Substrates in the Absence of Added Base and Ligand: Observation of High Yields under Acidic Conditions. *The Journal of Organic Chemistry* **2016**, *81* (18), 8520-8529.
61. Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J., Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chemical Processes* **2016**, *4* (1), 7.
62. Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H., Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents. *Chemical Communications* **2014**, *50* (68), 9650-9652.
63. Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P., Green and Sustainable Solvents in Chemical Processes. *Chemical Reviews* **2018**, *118* (2), 747-800.
64. Wilson, K. L.; Murray, J.; Jamieson, C.; Watson, A. J. B., Cyrene as a Bio-Based Solvent for the Suzuki–Miyaura Cross-Coupling. *Synlett* **2018**, *29* (05), 650-654.
65. Byun, J.-W.; Lee, Y.-S., Preparation of polymer-supported palladium/N-heterocyclic carbene complex for Suzuki cross-coupling reactions. *Tetrahedron Letters* **2004**, *45* (9), 1837-1840.
66. Avelino, C.; Hermenegildo, G., Silica-Bound Homogenous Catalysts as Recoverable and Reusable Catalysts in Organic Synthesis. *Advanced Synthesis & Catalysis* **2006**, *348* (12-13), 1391-1412.

67. Hirai, Y.; Uozumi, Y., Heterogeneous Aromatic Amination of Aryl Halides with Arylamines in Water with PS-PEG Resin-Supported Palladium Complexes. *Chemistry – An Asian Journal* **2010**, 5 (8), 1788-1795.
68. Copéret, C.; Comas-Vives, A.; Conley, M. P.; Estes, D. P.; Fedorov, A.; Mougél, V.; Nagae, H.; Núñez-Zarur, F.; Zhizhko, P. A., Surface Organometallic and Coordination Chemistry toward Single-Site Heterogeneous Catalysts: Strategies, Methods, Structures, and Activities. *Chemical Reviews* **2016**, 116 (2), 323-421.
69. Ibrar, H.; Jaworski, C.; A., Y. M., Synthesis of Biaryls via Ligand-Free Suzuki–Miyaura Cross-Coupling Reactions: A Review of Homogeneous and Heterogeneous Catalytic Developments. *Advanced Synthesis & Catalysis* **2016**, 358 (21), 3320-3349.
70. Chen, Z.; Vorobyeva, E.; Mitchell, S.; Fako, E.; Ortuño, M. A.; López, N.; Collins, S. M.; Midgley, P. A.; Richard, S.; Vilé, G.; Pérez-Ramírez, J., A heterogeneous single-atom palladium catalyst surpassing homogeneous systems for Suzuki coupling. *Nature Nanotechnology* **2018**.
71. Prier, C. K.; Rankic, D. A.; MacMillan, D. W., Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem Rev* **2013**, 113 (7), 5322-63.
72. Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., Merging photoredox with nickel catalysis: Coupling of α -carboxyl sp^3 -carbons with aryl halides. *Science* **2014**, 345, 437-440.
73. Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C., Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **2015**, 524, 330.
74. Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W., Aryl amination using ligand-free Ni(II) salts and photoredox catalysis. *Science* **2016**, 353 (6296), 279-83.
75. Shaw, M. H.; Twilton, J.; MacMillan, D. W., Photoredox Catalysis in Organic Chemistry. *J Org Chem* **2016**, 81 (16), 6898-926.
76. Skubi, K. L.; Blum, T. R.; Yoon, T. P., Dual Catalysis Strategies in Photochemical Synthesis. *Chem Rev* **2016**, 116 (17), 10035-74.
77. Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J., Visible Light Photocatalysis: Applications and New Disconnections in the Synthesis of Pharmaceutical Agents. *Organic Process Research & Development* **2016**, 20 (7), 1134-1147.

78. Du, Y.; Pearson, R. M.; Lim, C. H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; Damrauer, N. H.; Miyake, G. M., Strongly Reducing, Visible-Light Organic Photoredox Catalysts as Sustainable Alternatives to Precious Metals. *Chemistry - A European Journal* **2017**, *23* (46), 10962-10968.
79. Key, R. J.; Vannucci, A. K., Nickel Dual Photoredox Catalysis for the Synthesis of Aryl Amines. *Organometallics* **2018**, *37* (9), 1468-1472.
80. Terao, J.; Kambe, N., Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π -Carbon Ligand(s). *Accounts of Chemical Research* **2008**, *41* (11), 1545-1554.
81. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. *Chem Rev* **2011**, *111* (3), 1417-1492.
82. Jouffroy, M.; Primer, D. N.; Molander, G. A., Base-Free Photoredox/Nickel Dual-Catalytic Cross-Coupling of Ammonium Alkylsilicates. *Journal of the American Chemical Society* **2015**, *138*, 475-478.
83. Patel, N. R.; Molander, G. A., Phenol Derivatives as Coupling Partners with Alkylsilicates in Photoredox/Nickel Dual Catalysis. *The Journal of Organic Chemistry* **2016**, *81*, 7271-7275.
84. Macgregor, S. A.; Neave, G. W.; Smith, C., Theoretical studies on C-heteroatom bond formation via reductive elimination from group 10 $M(PH_3)_2(CH_3)(X)$ species ($X = CH_3, NH_2, OH, SH$) and the determination of metal-X bond strengths using density functional theory. *Faraday Discussions* **2003**, *124* (0), 111-127.
85. Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A., Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp^3 - sp^2 Cross-Coupling. *Accounts of Chemical Research* **2016**, *49*, 1429-1439.
86. Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W., Highly Chemoselective Iridium Photoredox and Nickel Catalysis for the Cross-Coupling of Primary Aryl Amines with Aryl Halides. *Angew Chem Int Ed Engl* **2016**, *55* (42), 13219-13223.
87. Ruiz-Castillo, P.; Buchwald, S. L., Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem Rev* **2016**, *116* (19), 12564-12649.
88. Park, N. H.; Teverovskiy, G.; Buchwald, S. L., Development of an air-stable nickel precatalyst for the amination of aryl chlorides, sulfamates, mesylates, and triflates. *Org Lett* **2014**, *16* (1), 220-3.

89. Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C., Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *Journal of the American Chemical Society* **2015**, *137* (15), 4896-4899.
90. Qi, Z.-H.; Ma, J., Dual Role of a Photocatalyst: Generation of Ni(0) Catalyst and Promotion of Catalytic C–N Bond Formation. *ACS Catalysis* **2018**, *8* (2), 1456-1463.
91. Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R., Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer. *Journal of the American Chemical Society* **2015**, *137* (42), 13492-13495.
92. Chen, J. R.; Hu, X. Q.; Lu, L. Q.; Xiao, W. J., Visible light photoredox-controlled reactions of N-radicals and radical ions. *Chem. Soc. Rev.* **2016**, *45*, 2044-2056.
93. Xiong, T.; Zhang, Q., New amination strategies based on nitrogen-centered radical chemistry. *Chem. Soc. Rev.* **2016**, *45*, 3069-3087.
94. Noël, T.; Naber, J. R.; Hartman, R. L.; McMullen, J. P.; Jensen, K. F.; Buchwald, S. L., Palladium-catalyzed amination reactions in flow: overcoming the challenges of clogging via acoustic irradiation. *Chemical Science* **2011**, *2* (2), 287-290.
95. McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A., A Pronounced Anionic Effect in the Pd-Catalyzed Buchwald–Hartwig Amination Reaction Revealed in Phosphonium Salt Ionic Liquids. *European Journal of Organic Chemistry* **2007**, *2007* (9), 1423-1428.
96. Ackermann, L.; Sandmann, R.; Song, W., Palladium- and Nickel-Catalyzed Aminations of Aryl Imidazolylsulfonates and Sulfamates. *Organic Letters* **2011**, *13* (7), 1784-1786.
97. Kore, N.; Pazdera, P., New Stable Cu(I) Catalyst Supported on Weakly Acidic Polyacrylate Resin for Green C–N Coupling: Synthesis of N-(Pyridin-4-yl)benzene Amines and N,N-Bis(pyridine-4-yl)benzene Amines. *Molecules* **2017**, *22*, 2-12.
98. Reddy, B. V. S.; Reddy, N. S.; Reddy, Y. J.; Reddy, Y. V., Indium/Cu(II)-mediated one-pot synthesis of unsymmetrical diaryl amines from aryl boronic acids and azides. *Tetrahedron Letters* **2011**, *52* (20), 2547-2549.
99. Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F., Solvent Free Amination Reactions of Aryl Bromides at Room Temperature Catalyzed by a (π -Allyl) palladium Complex Bearing a Diphosphinidenecyclobutene Ligand. *The Journal of organic chemistry* **2004**, *69* (19), 6504-6506.

100. Kim, B. R.; Cho, S.-D.; Kim, E. J.; Lee, I.-H.; Sung, G. H.; Kim, J.-J.; Lee, S.-G.; Yoon, Y.-J., Efficient palladium-catalyzed amination of aryl chlorides using di(dicyclohexylamino)phenylphosphine as a PN₂ ligand. *Tetrahedron* **2012**, *68* (1), 287-293.
101. Xie, X.; Zhang, T. Y.; Zhang, Z., Synthesis of Bulky and Electron-Rich MOP-type Ligands and Their Applications in Palladium-Catalyzed C–N Bond Formation. *The Journal of organic chemistry* **2006**, *71* (17), 6522-6529.
102. Shamim, T.; Kumar, V.; Paul, S., Silica-Functionalized CuI: An Efficient and Selective Catalyst for N-Benzylolation, Allylation, and Alkylation of Primary and Secondary Amines in Water. *Synthetic Communications* **2014**, *44* (5), 620-632.
103. Zhang, Y.; Qi, X.; Cui, X.; Shi, F.; Deng, Y., Palladium catalyzed N-alkylation of amines with alcohols. *Tetrahedron Letters* **2011**, *52* (12), 1334-1338.
104. Gildner, P. G.; Colacot, T. J., Reactions of the 21st Century: Two Decades of Innovative Catalyst Design for Palladium-Catalyzed Cross-Couplings. *Organometallics* **2015**, *34* (23), 5497-5508.
105. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V., Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51* (21), 5062-5085.
106. Martin, R.; Buchwald, S. L., Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41* (11), 1461-1473.
107. Negishi, E., *Handbook of Organopalladium Chemistry for Organic Synthesis*. John Wiley & Sons Inc.: New York, 2002.
108. Netherton, M. R.; Fu, G. G., Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides and Pseudohalides with Organometallic Compounds. *Adv. Synth. Catal.* **2004**, *346*, 1525-1532.
109. Crockett, M. P.; Tyrol, C. C.; Wong, A. S.; Li, B.; Byers, J. A., Iron-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions between Alkyl Halides and Unactivated Arylboronic Esters. *Org. Lett.* **2018**, *20* (17), 5233-5237.
110. Anderson, T. J.; Jones, G. D.; Vicic, D. A., Evidence for a NiII Active Species in the Catalytic Cross-Coupling of Alkyl Electrophiles. *J. Am. Chem. Soc.* **2004**, *126* (26), 8100-8101.
111. Sherry, B. D.; Fürstner, A., The Promise and Challenge of Iron-Catalyzed Cross Coupling. *Acc. Chem. Res.* **2008**, *41* (11), 1500-1511.

112. Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J., Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chemistry* **2018**, *20* (22), 5082-5103.
113. Liu, N.; Wang, L.; Wang, Z.-X., Room-temperature nickel-catalysed cross-couplings of aryl chlorides with arylzincs. *Chem. Commun.* **2011**, *47* (5), 1598-1600.
114. Jones, K. D.; Power, D. J.; Bierer, D.; Gericke, K. M.; Stewart, S. G., Nickel Phosphite/Phosphine-Catalyzed C–S Cross-Coupling of Aryl Chlorides and Thiols. *Org. Lett.* **2018**, *20* (1), 208-211.
115. Gatien, A. V.; Lavoie, C. M.; Bennett, R. N.; Ferguson, M. J.; McDonald, R.; Johnson, E. R.; Speed, A. W. H.; Stradiotto, M., Application of Diazaphospholidine/Diazaphospholene-Based Bisphosphines in Room-Temperature Nickel-Catalyzed C(sp²)–N Cross-Couplings of Primary Alkylamines with (Hetero)aryl Chlorides and Bromides. *ACS Catal.* **2018**, *8* (6), 5328-5339.
116. Xi, Z.; Liu, B.; Chen, W., Room-Temperature Kumada Cross-Coupling of Unactivated Aryl Chlorides Catalyzed by N-Heterocyclic Carbene-Based Nickel(II) Complexes. *J. Org. Chem.* **2008**, *73* (10), 3954-3957.
117. Zultanski, S. L.; Fu, G. C., Nickel-catalyzed carbon-carbon bond-forming reactions of unactivated tertiary alkyl halides: Suzuki arylations. *J. Am. Chem. Soc.* **2013**, *135* (2), 624-7.
118. Serrano, E.; Martin, R., Nickel-Catalyzed Reductive Amidation of Unactivated Alkyl Bromides. *Angew. Chem. Int. Ed.* **2016**, *55* (37), 11207-11211.
119. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V., Nickel-Catalyzed Cross-Couplings Involving Carbon–Oxygen Bonds. *Chem. Rev.* **2011**, *111* (3), 1346-1416.
120. Quasdorf, K. W.; Tian, X.; Garg, N. K., Cross-Coupling Reactions of Aryl Pivalates with Boronic Acids. *J. Am. Chem. Soc.* **2008**, *130* (44), 14422-14423.
121. Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K., Suzuki-Miyaura cross-coupling of aryl carbamates and sulfamates: experimental and computational studies. *J. Am. Chem. Soc.* **2011**, *133* (16), 6352-63.

122. Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R., Functional-group-tolerant, nickel-catalyzed cross-coupling reaction for enantioselective construction of tertiary methyl-bearing stereocenters. *J. Am. Chem. Soc.* **2013**, *135* (24), 9083-90.
123. Zhang, S.-Q.; Taylor, B. L. H.; Ji, C.-L.; Gao, Y.; Harris, M. R.; Hanna, L. E.; Jarvo, E. R.; Houk, K. N.; Hong, X., Mechanism and Origins of Ligand-Controlled Stereoselectivity of Ni-Catalyzed Suzuki–Miyaura Coupling with Benzylic Esters: A Computational Study. *J. Am. Chem. Soc.* **2017**, *139* (37), 12994-13005.
124. Bour, J. R.; Camasso, N. M.; Meucci, E. A.; Kampf, J. W.; Canty, A. J.; Sanford, M. S., Carbon–Carbon Bond-Forming Reductive Elimination from Isolated Nickel(III) Complexes. *J. Am. Chem. Soc.* **2016**, *138* (49), 16105-16111.
125. Camasso, N. M.; Canty, A. J.; Ariaferd, A.; Sanford, M. S., Experimental and Computational Studies of High-Valent Nickel and Palladium Complexes. *Organometallics* **2017**, *36* (22), 4382-4393.
126. Lipschutz, M. I.; Tilley, T. D., Carbon–Carbon Cross-Coupling Reactions Catalyzed by a Two-Coordinate Nickel(II)–Bis(amido) Complex via Observable NiI, NiII, and NiIII Intermediates. *Angew. Chem. Int. Ed.* **2014**, *53* (28), 7290-7294.
127. Amatore, C.; Jutand, A., Rates and mechanism of biphenyl synthesis catalyzed by electrogenerated coordinatively unsaturated nickel complexes. *Organometallics* **1988**, *7* (10), 2203-2214.
128. Shields, B. J.; Kudisch, B.; Scholes, G. D.; Doyle, A. G., Long-Lived Charge-Transfer States of Nickel(II) Aryl Halide Complexes Facilitate Bimolecular Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140* (8), 3035-3039.
129. Tellis, J. C.; Primer, D. N.; Molander, G. A., Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014**, *345*, 433-436.
130. Lim, C.-H.; Kudisch, M.; Liu, B.; Miyake, G. M., C–N Cross-Coupling via Photoexcitation of Nickel–Amine Complexes. *J. Am. Chem. Soc.* **2018**, *140* (24), 7667-7673.
131. Ge, S.; Hartwig, J. F., Highly Reactive, Single-Component Nickel Catalyst Precursor for Suzuki–Miyaura Cross-Coupling of Heteroaryl Boronic Acids with Heteroaryl Halides. *Angew. Chem. Int. Ed.* **2012**, *51* (51), 12837-12841.
132. Vannucci, A. K.; Chen, Z.; Concepcion, J. J.; Meyer, T. J., Nonaqueous Electrocatalytic Oxidation of the Alkylaromatic Ethylbenzene by a Surface Bound RuV(O) Catalyst. *ACS Catal.* **2012**, *2* (5), 716-719.

133. O'Connell, K.; Regalbuto, J. R., High Sensitivity Silicon Slit Detectors for 1 nm Powder XRD Size Detection Limit. *Catal. Lett.* **2015**, *145* (3), 777-783.
134. Liu, Q.; Samad, J.; Copple, J. E.; Eskandari, S.; Satterwhite, C.; Regalbuto, J. R., A pinch of salt to control supported Pt nanoparticle size. *Catal. Today* **2017**, *280*, 246-252.
135. Vannucci, A. K.; Alibabaei, L.; Losego, M. D.; Concepcion, J. J.; Kalanyan, B.; Parsons, G. N.; Meyer, T. J., Crossing the divide between homogeneous and heterogeneous catalysis in water oxidation. *Proc. Natl. Acad. Sci.* **2013**, *110*, 20918-20922.
136. Marset, X.; De Gea, S.; Guillena, G.; Ramón, D. J., NCN-Pincer-Pd Complex as Catalyst for the Hiyama Reaction in Biomass-Derived Solvents. *ACS Sustainable Chemistry & Engineering* **2018**, *6* (5), 5743-5748.
137. Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y., A General Palladium Catalyst System for Suzuki-Miyaura Coupling of Potassium Aryltrifluoroborates and Aryl Mesylates. *J. Org. Chem.* **2010**, *75* (15), 5109-5112.
138. Hoshi, T.; Honma, T.; Mori, A.; Konishi, M.; Sato, T.; Hagiwara, H.; Suzuki, T., An active, general, and long-lived palladium catalyst for cross-couplings of deactivated (hetero)aryl chlorides and bromides with arylboronic acids. *J. Org. Chem.* **2013**, *78* (22), 11513-24.
139. Razler, T. M.; Hsiao, Y.; Qian, F.; Fu, R.; Khan, R. K.; Doubleday, W., A preparatively convenient ligand-free catalytic PEG 2000 Suzuki-Miyaura coupling. *J. Org. Chem.* **2009**, *74* (3), 1381-4.
140. Zhang, L.; Luo, Y.; Wu, J., Transition-metal-catalyzed cross-couplings of aryl tosylates or mesylates with organoindium reagents. *Synlett* **2010**, (12), 1845-1848.
141. Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P., Preparation of solid salt-stabilized functionalized organozinc compounds and their application to cross-coupling and carbonyl addition reactions. *Angew. Chem., Int. Ed.* **2011**, *50* (39), 9205-9209, S9205/1-S9205/68.
142. Papoian, V.; Minehan, T., Palladium-catalyzed reactions of arylindium reagents prepared directly from aryl iodides and indium metal. *J. Org. Chem.* **2008**, *73* (18), 7376-9.
143. Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B. M.; Percec, V., Ni(COD)₂/PCy₃ catalyzed cross-coupling of aryl and heteroaryl neopentylglycolboronates with aryl and heteroaryl mesylates and sulfamates in THF at room temperature. *J. Org. Chem.* **2011**, *76* (24), 9946-9955.

144. Larhed, M.; Lindeberg, G.; Hallberg, A., Rapid microwave-assisted Suzuki coupling on solid-phase. *Tetrahedron Letters* **1996**, 37 (45), 8219-8222.
145. Leadbeater, N. E., Fast, easy, clean chemistry by using water as a solvent and microwave heating: the Suzuki coupling as an illustration. *Chemical Communications* **2005**, (23), 2881-2902.
146. R., B. I.; M., G.-J. C.; V., L. S.; K., T. G., Microwave-Assisted Suzuki Coupling Reactions with an Encapsulated Palladium Catalyst for Batch and Continuous-Flow Transformations. *Chemistry – A European Journal* **2006**, 12 (16), 4407-4416.
147. Akiyama, T.; Taniguchi, T.; Saito, N.; Doi, R.; Honma, T.; Tamenori, Y.; Ohki, Y.; Takahashi, N.; Fujioka, H.; Sato, Y.; Arisawa, M., Ligand-free Suzuki–Miyaura coupling using ruthenium(0) nanoparticles and a continuously irradiating microwave system. *Green Chemistry* **2017**, 19 (14), 3357-3369.
148. Arvela, R. K.; Leadbeater, N. E., Suzuki Coupling of Aryl Chlorides with Phenylboronic Acid in Water, Using Microwave Heating with Simultaneous Cooling. *Organic Letters* **2005**, 7 (11), 2101-2104.
149. Tasker, S. Z.; Standley, E. A.; Jamison, T. F., Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, 509, 299-309.
150. Christian, A. H.; Müller, P.; Monfette, S., Nickel Hydroxo Complexes as Intermediates in Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling. *Organometallics* **2014**, 33 (9), 2134-2137.
151. Li, X.-J.; Zhang, J.-L.; Geng, Y.; Jin, Z., Nickel-Catalyzed Suzuki–Miyaura Coupling of Heteroaryl Ethers with Arylboronic Acids. *The Journal of Organic Chemistry* **2013**, 78 (10), 5078-5084.
152. Nazari, S. H.; Bourdeau, J. E.; Talley, M. R.; Valdivia-Berroeta, G. A.; Smith, S. J.; Michaelis, D. J., Nickel-Catalyzed Suzuki Cross Couplings with Unprotected Allylic Alcohols Enabled by Bidentate N-Heterocyclic Carbene (NHC)/Phosphine Ligands. *ACS Catalysis* **2018**, 8 (1), 86-89.
153. Szeto, K. C.; Jones, Z. R.; Merle, N.; Rios, C.; Gallo, A.; Le Quemener, F.; Delevoye, L.; Gauvin, R. M.; Scott, S. L.; Taoufik, M., A Strong Support Effect in Selective Propane Dehydrogenation Catalyzed by Ga(i-Bu)₃ Grafted onto γ -Alumina and Silica. *ACS Catalysis* **2018**, 7566-7577.
154. Das, T.; Uyama, H.; Nandi, M., Pd-bound functionalized mesoporous silica as active catalyst for Suzuki coupling reaction: Effect of OAc⁻, PPh₃ and Cl⁻ ligands on catalytic activity. *Journal of Solid State Chemistry* **2018**, 260, 132-141.

155. Veisi, H.; Gholami, J.; Ueda, H.; Mohammadi, P.; Noroozi, M., Magnetically palladium catalyst stabilized by diaminoglyoxime-functionalized magnetic Fe₃O₄ nanoparticles as active and reusable catalyst for Suzuki coupling reactions. *Journal of Molecular Catalysis A: Chemical* **2015**, 396, 216-223.