Title
Pi Ligand Effect in Copper-Mediated C-N Oxidative Coupling Reactions

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Pi Ligand Effect in Copper-Mediated C-N Oxidative Coupling Reactions

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Chemistry

by

Gerhard Frederick Kummerow

2014

ABSTRACT OF THE THESIS

Pi Ligand Effect in Copper-Mediated C-N Oxidative Coupling Reactions

by

Gerhard Frederick Kummerow

Master of Science in Chemistry

University of California, Los Angeles, 2014

Professor Craig A. Merlic, Chair

The effect of π ligands, 3-hexyne and 1,2-cyclononadiene, in the Chan-Lam modification of the Ullmann reaction was investigated. Reaction conditions were optimized to give the highest yields in this copper(II) mediated oxidative coupling of boronic acids and arylamines. Pyridine proved to be a more efficient base than triethylamine for the substrates screened. It was found that 3-hexyne and 1,2-cyclononadiene had a beneficial effect on most of the substrates screened. The yields ranged from modest to excellent. A small self-ligating effect from olefin-substituted phenyl boronic acids was observed.

The thesis of Gerhard Frederick Kummerow is approved.

Miguel A. Garcia-Garibay

William M. Gelbart

Craig A. Merlic, Committee Chair

University of California, Los Angeles

2014

To my parents Evelyn and Gerardo Kummerow,

for all their love and support.

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ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor Professor Craig Merlic for believing in me and allowing me to be part of group. His intellectual support and guidance have allowed me to grow immensely as a scientist and make tremendous progress in my research. He is an incredible teacher and continues to inspire and guide me to one day be a fraction of the chemist he is.

To all the members of the Merlic lab, you are a pleasure to work with. I would like to make special mention to Rob Tobolowsky for providing me with 9,9-dibromobicyclo[6.1.0]nonane and Brett Cory for a sample of *para*-tert-butyl pinacol boronic ester.

To my sister Selma, my brother Gerald, and my parents Evelyn and Gerardo who have always been there for me through all the ups and downs. Without their support and encouragement I would not be where I am today. I love you guys.

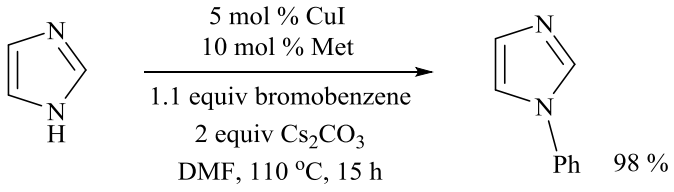
Finally, and most importantly, I would like to acknowledge Jake Joseph. He is my first love and has believed in me since day one. He is my voice of reason and my pillar of strength. I am grateful for his contagious optimism about everything in life.

I. INTRODUCTION

1.1 Overview of Copper Mediated Cross Coupling Reactions

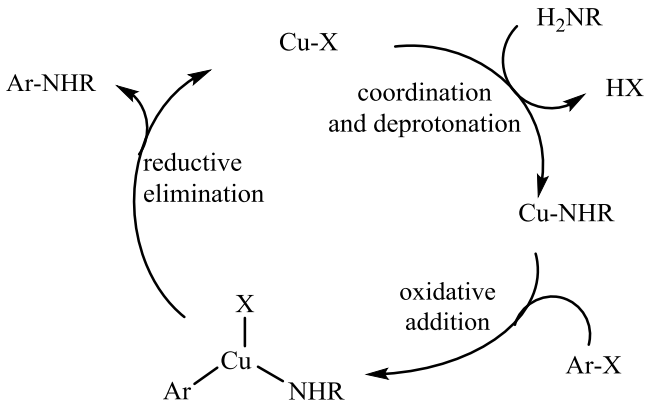
N-arylation of amines is an extremely important reaction for synthetic organic chemists and has allowed the production of pharmaceuticals, commodity chemicals, pesticides, and many other compounds.[1,2] One of the earliest carbon-heteroatom bond forming reactions using copper was reported by Ullmann and Goldberg in 1903 and 1906, respectively.[3,4] This coupling reaction, known as the Ullmann condensation, uses aryl halides as the electrophile, arylamines as the nucleophile, a source of copper(I), and heating at temperatures as high as 160 ^{o}C.[2,3] The reaction was also applied to O-arylation of phenols to prepare aryl ethers. Recently, the arylation of imidazoles with aryl halides using homogeneous CuI/metformin complex was reported with good yields, but required heating at 110 ^{o}C (Scheme 1.1-1).[4] Metformin (Met) serves as a ligand and helps to solubilize copper(I) iodide. The methodology was extended to O-arylation of substituted phenols to afford biaryl ethers in good yields and required heating at 60 ^{o}C.

Scheme 1.1-1: Copper(I) Catalyzed Arylation of Imidazole



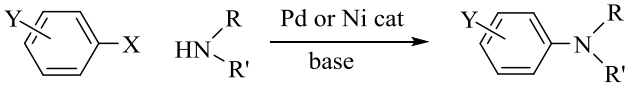
Although the exact oxidation states of the copper intermediates in the Ullmann reaction have not been well established, it is proposed to begin with copper(I) undergoing coordination with the amine to copper. This step is then followed by oxidative addition to the aryl halide. Reductive elimination from the aryl-copper(III) amine complex gives the arylamine product, and regenerates the copper(I) catalyst (Figure 1.1).[2]

Figure 1.1: Proposed Mechanism for Copper(I) Catalyzed Cross Couplings



Although the focus of this thesis is on copper(II) mediated oxidative cross-coupling reactions, it is worth making brief mention of a complimentary reaction for the synthesis of arylamines and aryl ethers. The Buchwald-Hartwig cross-coupling reaction (Scheme 1.1-2) has been known since the mid 1990's, and has received significant attention since its inception.[6] This reaction uses nickel or palladium catalysts that are typically expensive in addition to being air and moisture sensitive. The coupling partners involved are amines or alcohols with aryl halides. Furthermore, strong bases, high reaction temperatures, and complex phosphine ligands are often required.

Scheme 1.1-2: Buchwald-Hartwig Cross-Coupling

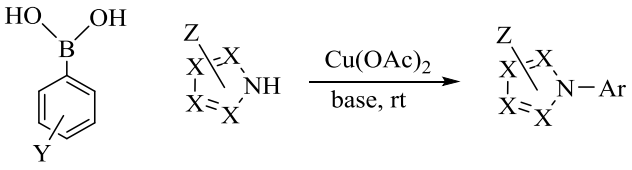


X = Cl, Br, I, OTf
Y = substituents
base: NaOt-Bu, LHMDS, K2CO3, CsCO3

An alternative to the Buchwald-Hartwig reaction was developed by Chan and Lam as an umpolung modification of the Ullmann condensation (Scheme 1.1-3).[7] This modern Ullmann coupling reaction utilizes aryl boronic acids, arylamines, weak base, and Cu(II) salts. The

reaction is carried out at room temperature and in an aerobic atmosphere. The use of inexpensive copper(II) salts, mild reaction conditions, and functional-group tolerance have made the Chan-Lam cross-coupling reaction a powerful tool for synthetic chemists.

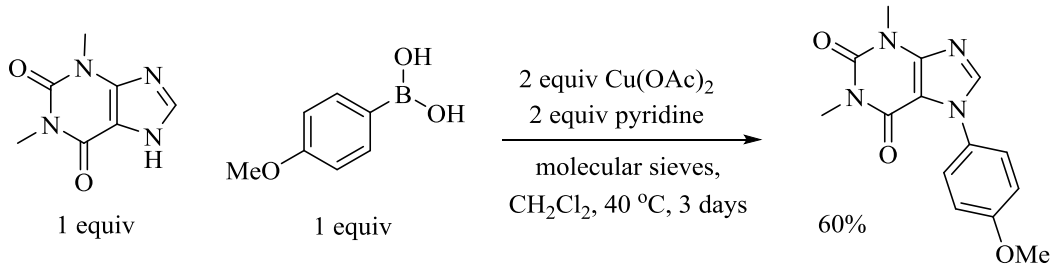
Scheme 1.1-3: Chan-Lam Cross-Coupling



X = N, CH
Y, Z = substituents or benzofused
base: Et_3N or pyridine

Many biologically active compounds have been synthesized using Chan-Lam conditions.[8] Xanthines are known kinase inhibitors and fluorophores. Hong and coworkers developed derivatives of theophylline (a xanthine) that can be used as fluorescent xanthine-based kinase inhibitors. They functionalized theophylline using the Chan-Lam reaction (Scheme 1.1-4) by coupling theophylline and *p*-methoxyphenylboronic acid and obtained the product in 60% yield.

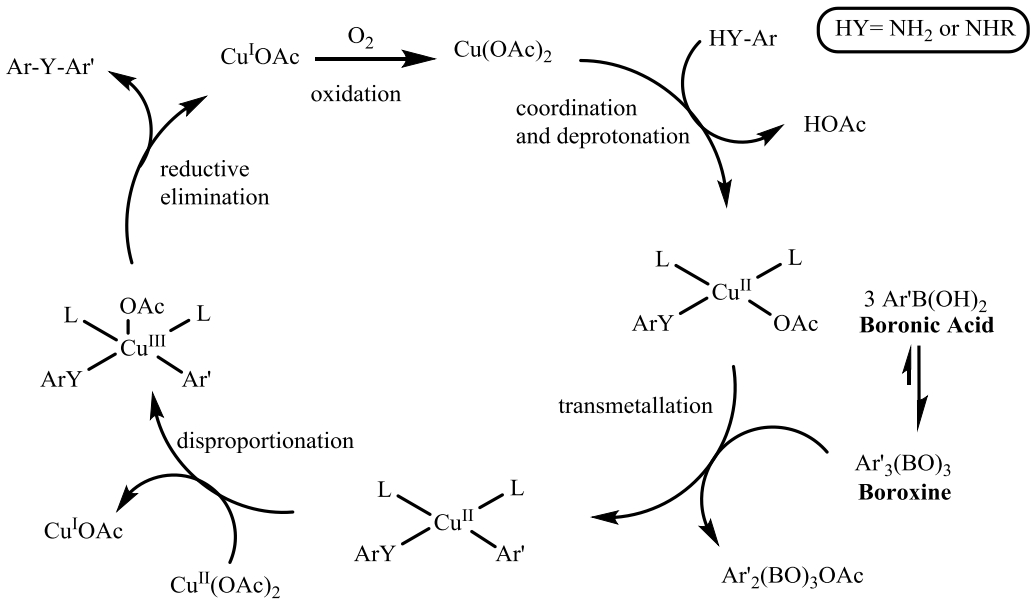
Scheme 1.1-4: Theophylline Functionalization Through Chan-Lam Reaction



1.2 Proposed Mechanism for the Chan-Lam Oxidative Coupling

The Chan-Lam reaction is a net oxidative coupling of two nucleophiles, boronic acid and an amine. Although the mechanism is still being investigated, Lam has postulated (Figure 1.2) that it involves coordination then deprotonation of the amine to the copper(II) species, followed by transmetalation with boronic acid.[9] Disproportionation of copper(II) to copper(III) allows for reductive elimination to afford the product. The copper(III) complex has also been proposed in the Ullmann condensation mechanism, and is thought to be the rate-determing step. Recently, Stahl also demonstrated the presence of the copper(III) intermediate in the copper(II)-catalyzed methoxylation of aryl boronic esters.[10]

Figure 1.2: Proposed Mechanism for Chan-Lam Cross Coupling



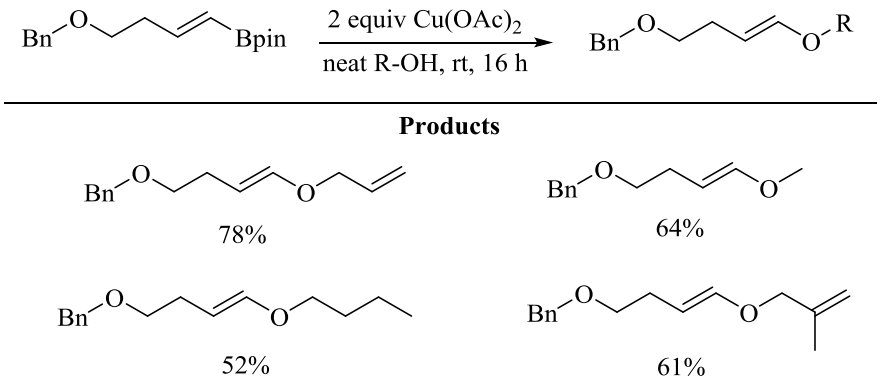
Boronic acids exist in equilibrium with the corresponding boroxines; this equilibrium can be shifted towards the anhydride form by use of dehydrating agents such as molecular sieves.[1] The boroxine species has not been shown to affect catalysis. Excess boronic acid is typically used since two major side reactions occur with the boronic acid, protodeboronation and coupling

with water to convert it into phenol.[11] A study was performed by Lam and coworkers using $^{18}O_2$ and $H_2{}^{18}O$ to identify whether the phenol side-product was being formed through an oxocopper(III) intermediate or from adventitious water from the boroxine formation.[12] No ^{18}O incorporation was observed when the experiment was done in an $^{18}O_2$ atmosphere. However, when the experiment was performed with $H_2{}^{18}O$, ^{18}O incorporation was observed in the phenol side-product. These results explain the improved yields when molecular sieves are used in the reaction.

1.3 Ligand Investigation in Copper Mediated Oxidative Couplings

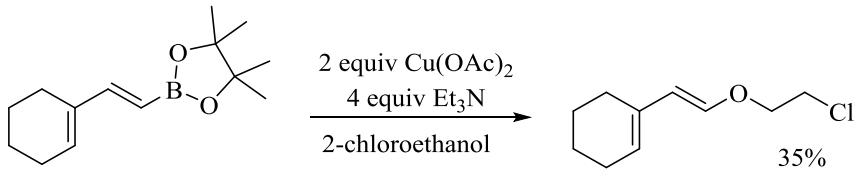
Olefins and alkynes are known to serve as ligands in transition-metal-catalyzed reactions by tuning the selectivity or reactivity of the metal.[13] Previous work in the Merlic lab investigated C-O oxidative couplings of boronate esters and alcohols using modern Ullmann conditions to prepare allyl vinyl ethers, which are substrates for the Claisen rearrangement.[14] During the screening of alcohol substrates for the C-O coupling reaction, an interesting result was observed (Table 1.3-1). Yields decreased as the alkyl chain length of the alcohol coupling partner increased. However, much higher yields were obtained when allyl alcohol was used when compared to butyl alcohol or even methanol. Substituted ethyl alcohols did not benefit the reaction which suggested the improved yield observed for allyl alcohol is not an inductive electronic effect. Merlic and coworkers hypothesized that the olefin of allyl alcohol might be acting as a π Lewis base to copper.

Table 1.3-1: Effect of Alcohol Length on Yield



While synthesizing deprotectable alkoxydiene substrates for Diels-Alder reactions, the yields obtained for the coupling of cyclohexenylethenylboronate and chloroethanol were dissapointing (Scheme 1.3).[15]

Scheme 1.3: Coupling of Chloro-Alcohols Using Chan-Lam Conditions

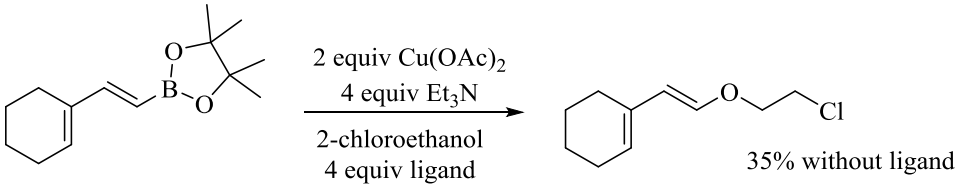


However, dramatic effects were observed when alkenes were added as ligands. In an effort to improve the yields for this reaction, a number of ligands were screened.[16] Electron deficient phosphine ligands, such as triphenylphosphite, were tested and caused the yield to decrease to 14%. Triphenylphosphine and tri(ortho-tolyl)phosphine did not affect the yield. More electron rich tri-(2-furyl)phosphine improved the yield to 60%.

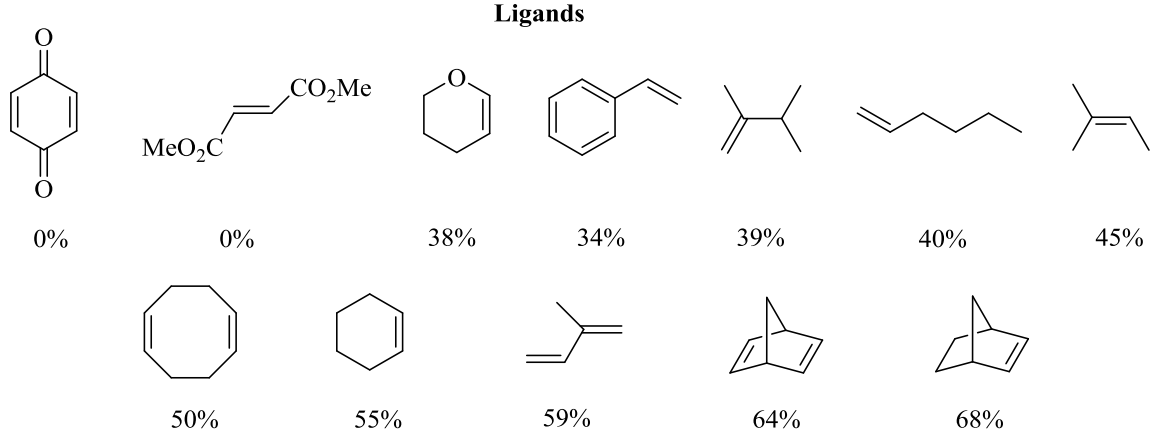
Electron deficient alkenes such as para-benzoquinone and dimethyl fumarate failed to give any product (Table 1.3-2), even when the starting material had been completely consumed. Instead, only protodeboronated alkene side product was observed by TLC. Mono- and di-

substituted alkenes did not increase the yields substantially, and tri-substituted alkene (2-methyl-2-butene) only increased the yield slightly to 45%. However, cyclic and conjugated alkenes were beneficial to the reaction. Cyclohexene provided the desired product in 55% yield and 2-methyl-1,3-butadiene in 59% yield. Bicyclic alkenes norbornadiene and norbornene proved to be the most beneficial with yields of 64% and 68%, respectively. It has been reported in the literature that ring strain increases the Lewis basicity of cycloalkenes due to favorable rehybridization of the alkene carbon atoms.[17] These results corroborated the hypothesis that a π Lewis base ligand is affecting the oxidative coupling reaction.

Table 1.3-2: Screening of Alkene Ligands



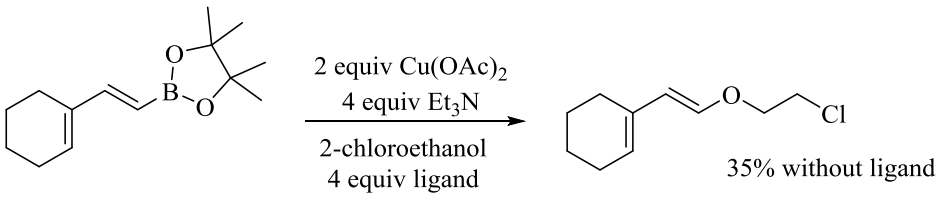
Ligands



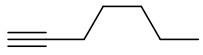
Given that alkynes have two π bonds and a linear geometry, due to the sp-hybridized carbons, they should be better Lewis bases than alkenes and less sterically demanding upon coordinating to copper. With this knowledge, Winternheimer tested a series of alkynes similarly to the alkenes previously discussed (Table 1.3-3). Terminal alkynes decreased the yield of the

reaction, possibly by reacting with copper to produce a copper acetylide complex which is a well-documented reaction.[13] The electron deficient dimethyl acetylenedicarboxylate did not improve the control reaction yield of 35%. These results are consistent with those observed for benzoquinone in the alkene screening. However, unlike benzoquinone where all starting material was converted to the side-product protodeboronation, this electron deficient alkyne succesfully produced some of the desired coupling product. Electron rich alkynes such as 2-methylhex-1-ene-3-yne, diphenylacetylene, and bis(trimethylsilyl)acetylene all managed to double the yield of the reaction to above 60%. The use of silanes was discontinued due to a black coloration, which may be caused by copper reacting with the alkynyl silanes. However, using 3-hexyne as an additive in the coupling of 2-(trimethylsilyl)ethanol prevented the dark coloration. 3-Hexyne gave the highest yield (80%) and was identified as the ligand of choice for all future studies. 3-Hexyne has a low molecular weight (82.14 g/mol) which would only require small amounts when used as a ligand, is commercially available, and has a low enough boiling point (81 ^{o}C) that it can be removed *in vacuo* during workup.

Table 1.3-3: Screening of Alkyne Ligands



Ligands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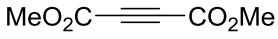
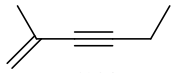
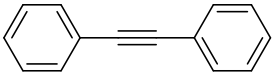


35%


60%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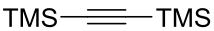
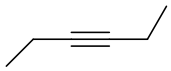


70%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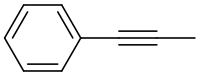
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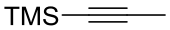

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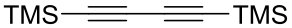
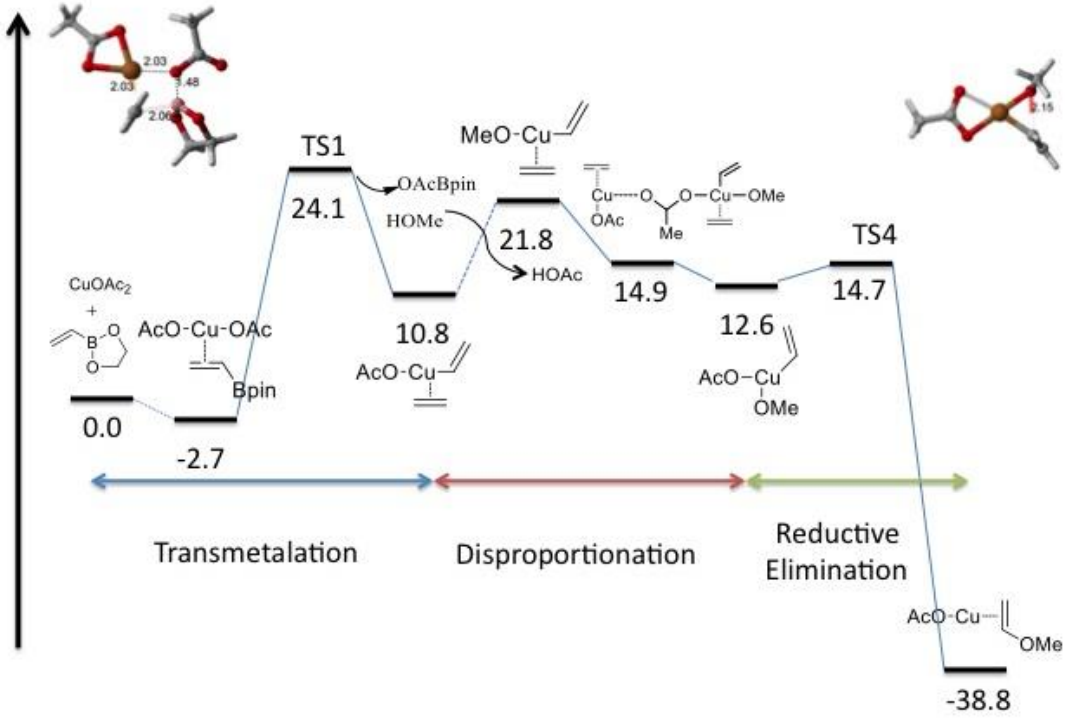


15%

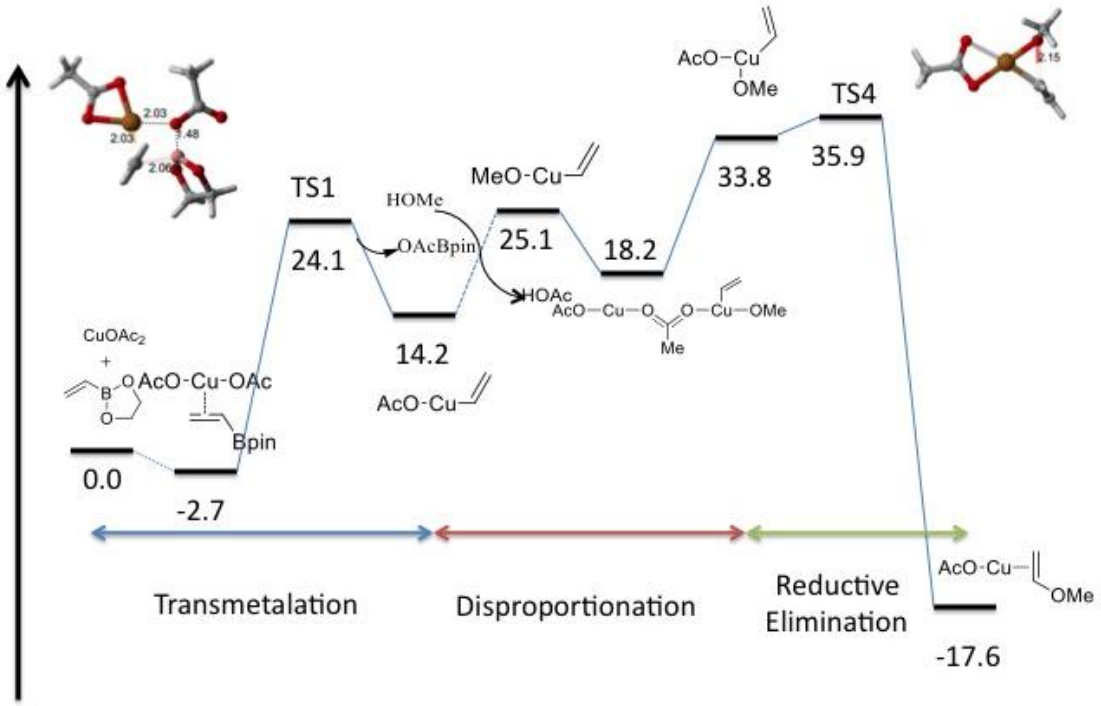
Density Functional Theory (DFT) calculations performed in the Merlic lab have shown that addition of the π ligand in the cross coupling reaction affected the ligand exchange and disproportionation steps (Figure 1.2).[18] The π ligand lowered the free energy of the disproportionation step by binding strongly to the copper(I) byproduct and is exothermic by 9.2 kcal/mol to generate the copper(III) intermediate that is critical to release of product (Figure 1.3-1).

Figure 1.3-1: Energy Profile for Copper Promoted Vinyl Ether Synthesis with π Ligand



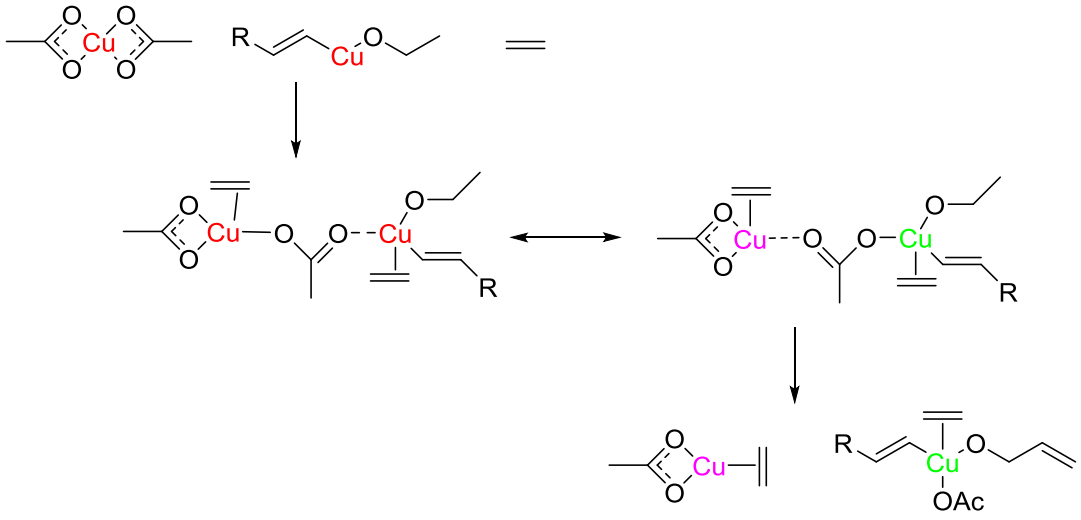
Without the use of a π ligand, the rate determining step is the reductive elimination (Figure 1.3-2); however, when a π ligand is present, transmetalation is the rate determining step. It was also found that the ligand binds more strongly with copper(I) than copper(III). These findings agree with those reported by Stahl and coworkers where they also identified transmetalation to be the rate determining step.[19]

Figure 1.3-2: Energy Profile for Copper Promoted Vinyl Ether Synthesis without π Ligand



Complexation of the π ligand to copper(I) byproduct, from the disproportionation step, might also prevent it from undergoing other unproductive side-reactions (Figure 1.3-3).

Figure 1.3-3: Interaction of π Ligand with Copper(I) byproduct



Copper Oxidation States: Cu(I) Cu(II) Cu(III)

Adducts of Cu(I) with acetylene were isolated and structurally elucidated two decades ago.[20] More recently, Cu(I), Ag(I), and Au(I) complexes with 3-hexyne, [N{(C_3F_7)C(Dipp)N}$_2$]Cu(EtC≡CEt), have been reported in the literature.[21] X-ray diffraction showed 3-hexyne coordinating in a η^2-type structure to copper. Significant deviation from linearity for the C≡C-C angle of 3-hexyne was observed (156.5^o). DFT calculations and X-ray analysis revealed a slight elongation of the C≡C bond in the adduct (1.233 Å experimental and 1.246 Å calculated) in comparison to the C≡C bond distance calculated for 3-hexyne of 1.215 Å. The C≡C bond elongation and deviation from the linear C≡C-C angle is due to the alkyne→metal σ-donation and metal→alkyne π-back-donation which weakens the bond. The copper(I) adducts of 3-hexyne characterized in this study support the results obtained in the Merlic lab from DFT calculations, which also showed copper(I) binding more strongly with the π ligand than copper(III).

1.4 Aim of the Study

The evidence presented in this section shows a strong π ligand effect on copper in the C-O oxidative coupling reaction. Specifically, the copper(II) mediated oxidative coupling of boronate esters with aryl and alkyl alcohol nucleophiles. The ligand lowers the free energy of the reaction and changes the rate-determining step from the reductive elimination to the transmetalation of the boron species with copper(II). This occurred by facilitating the key Cu(II)/Cu(II) to Cu(III)/Cu(I) disproportionation step through coordination of the Cu(I) byproduct. We hypothesized that using a strained π ligand should increase its Lewis basicity, which, in turn, would increase the stabilization of the disproportionation step, therefore benefiting the reaction. We also hypothesized that the observed π ligand effect was not limited to

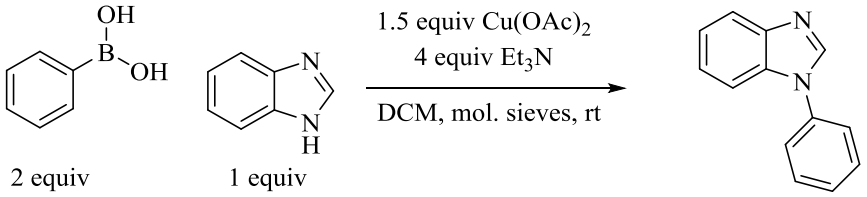
our alcohol plus vinylboronate oxidative cross coupling, but could be more general for copper-based coupling reactions. With these findings in hand, we set out to apply this methodology, and investigate the effect of π ligands, on copper(II)-mediated carbon-nitrogen oxidative couplings. Herein, we report an expanded study of the effect of 3-hexyne and the use of a novel ligand, 1,2-cyclononadiene, in a series of N-arylations.

II. RESULTS AND DISCUSSION

2.1 Preceding Results

The Merlic group has previously shown that 3-hexyne had a beneficial impact on the yield of C-N couplings.[15] Complexation of copper(I) with 3-hexyne might prevent it from undergoing side-reactions that would decrease the yield of the desired product. It was proposed that a pure oxygen atmosphere would benefit this reaction by allowing Cu(I) intermediate to be re-oxidized to the active Cu(II) species. Using 1.5 equivalents of copper(II) acetate and triethylamine under an inert atmosphere or open to air roughly doubled the yields when 3-hexyne was added (Table 2.1). However, the ligand did not have a significant impact when the reaction was performed under a pure oxygen atmosphere. In the case where the reaction was performed with 3-hexyne as the ligand under an ambient atmosphere caused the yield to double. This could be due to the enhanced stabilization of the Cu(I) intermediate provided by the π ligand.[16]

Table 2.1: Previously Reported Yields Using 3-Hexyne



	yield (%)	
	without 3-hexyne	with 4 equiv of 3-hexyne
argon	17	35
ambient	28	42
oxygen	90	87

2.2 1,2-cyclononadiene: A Novel Ligand for Cu(II) Mediated Oxidative Coupling

In an effort further investigate the effect of π-ligands on this reaction, the allene 1,2-cyclononadiene (Cy9) was investigated (Figure 2.1).

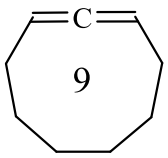
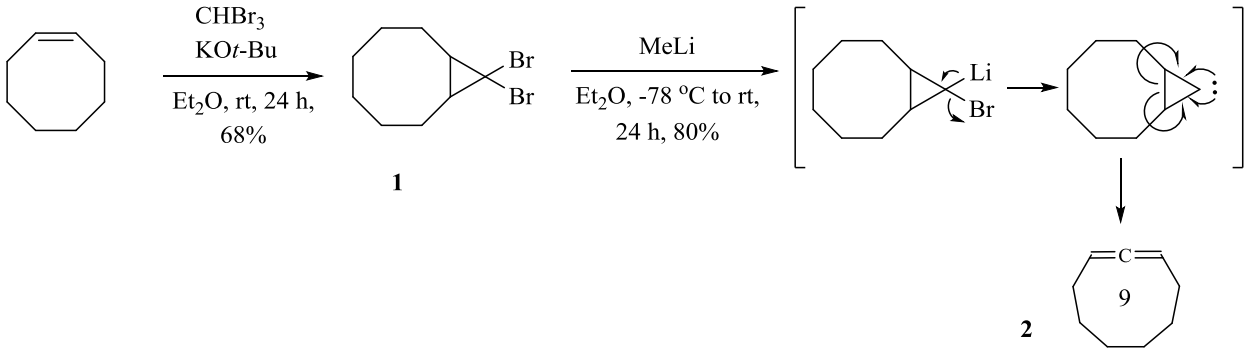


Figure 2.2: 1,2-cyclononadiene (Cy9)

Allenes contain a central carbon that is sp hybridized with two σ bonds and two π bonds. The two terminal carbons are sp^2 hybridized and the three carbons form a linear geometry.[22] A cyclic allene such as Cy9 should be more strained than an acyclic allene, which would increase its Lewis basicity as has been observed with cyclic alkenes.[13] All these properties are postulated to make 1,2-cyclononadiene a more active π ligand than 3-hexyne in copper(II) mediated cross-couplings. Cy9 is readily synthesized by a two-step procedure. First, addition of dibromocarbene to cyclooctene generates a dibromocyclopropane product (Scheme 2.2). Dehalogenation with methyllithium gives 1,2-cyclononadiene through a Skattebøl rearrangement. Cy9 is synthesized in multi-gram scale from readily available starting materials and reaction times can be reduced in order to synthesize Cy9 in one day. Owing to its hydrocarbon nature, it is non-polar and elutes first in standard silica column chromatography allowing it to be recovered and reused.

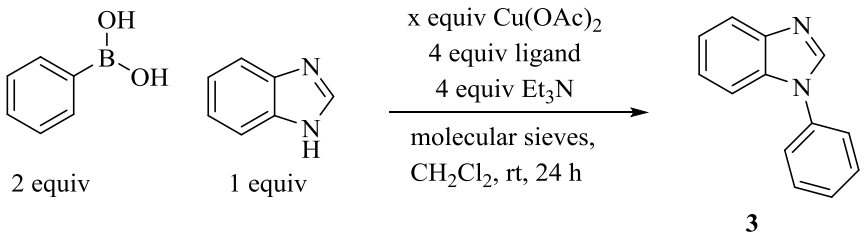
Scheme 2.2: Synthesis of 1,2-cyclononadiene (Cy9)



2.3 Reaction Atmosphere Study

Phenylboronic acid and benzimidazole were chosen as model substrates for the copper promoted coupling reactions. Nitrogen, air, and oxygen atmospheres with and without ligands were examined (Table 2.3). The yields for reactions performed under an inert atmosphere and open to air were modest, at best, with only a slight improvement seen when 1,2-cyclononadiene was the ligand. The postulated mechanism for this reaction involves a copper(III) intermediate that undergoes reductive elimination to furnish the product and copper(I) that is then re-oxidized to copper(II) by oxygen. Super-stoichiometric amounts of copper (4 equiv) were investigated to determine whether the yields could be improved by bypassing the catalytic cycle without the need to re-oxidize copper. This attempt did not prove fruitful as the yields failed to improve. Excess copper in the reaction most likely protodeboronated the aryl boronic acid or coupled with water to make phenol instead of performing the desired transmetalation. Lam and coworkers found that when copper(II) acetate and boronic acid were stirred together in the absence of other substrates the half-life of the boronic acid was about 30 minutes. Protodeboronation was the only product observed.[23]

Table 2.3: **Optimization of Reaction Atmospheres**



Equiv of $Cu(OAc)_2$	Atmosphere	4 equiv ligand	yield (%)
2	nitrogen	Cy9	29
4	nitrogen	3-hexyne	19
4	nitrogen	none	17
2	air	Cy9	39
2	air	none	20
2	oxygen	Cy9	75
2	oxygen	none	89

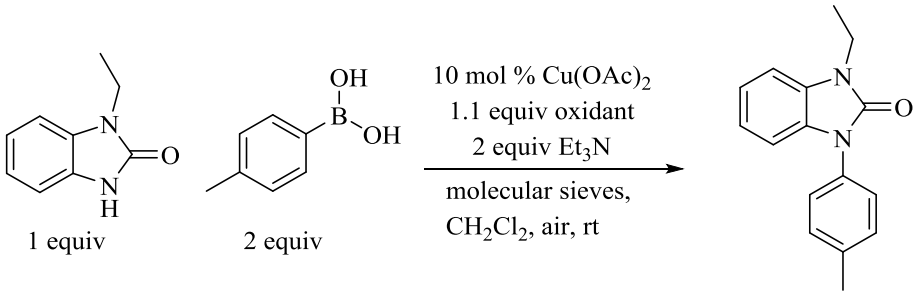
Studying different reaction atmospheres and ligands found that an oxygen atmosphere gave the best results; however, the purification was very difficult due to the formation of a red insoluble solid believed to be copper(I) oxide. Furthermore, no significant difference was observed when the reaction was performed with or without ligands. It is also worth noting that the yields obtained in all cases are comparable to those previously reported by the Merlic group (Table 2.1). Initially, the procedure used to set-up reactions in an air atmosphere involved capping the reaction vessel after adding all the reagents in order to prevent evaporation of the solvent and allowed it to stir for the required amount of time. While screening reaction conditions, we postulated that not enough oxygen was present in the flask to re-oxidize copper(I) to copper(II) due to the small size of the reaction vessels being used. A drying tube filled with

calcium chloride was used in subsequent screenings with the hope that more oxygen could come in contact with the solution.

2.4 Catalytic Study

Lam and coworkers explored a series of catalytic systems for the cross-coupling of N-H and O-H nucleophiles with boronic acids using copper(II) and different oxidants (Figure 2.4).[24] It appears that oxygen alone is not enough to re-oxidize copper in this reaction in order to be catalytic and a co-oxidant is required. The oxidants screened had to be strong enough to oxidize Cu(I) back to Cu(II), but mild enough to prevent oxidation of boronic acid to phenol. The phenol side product competes with the substrate to form bis-*p*-toluyl ether. Of all the oxidants tested, pyridine N-oxide gave the highest yields, although this was not the case for all the substrates studied.

Figure 2.4: Oxidants Screened by Lam and coworkers



pyridine N-oxide > TEMPO > N-methylmorpholine N-oxide > di-t-butylnitroxide > $K_3Fe(CN)_6$ > mCPBA

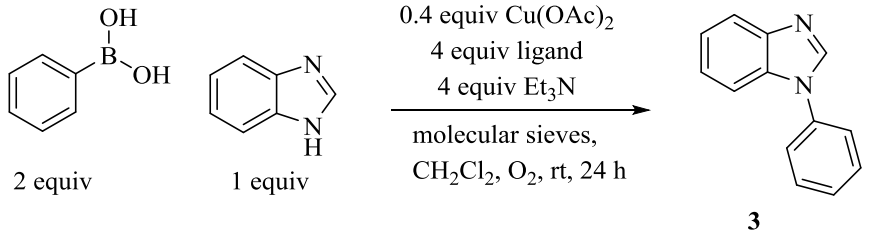
69% 64% 62% 55% 11% 6%

Several catalytic combinations were investigated based on their preliminary results: (a) cat. $Cu(OAc)_2/O_2$, (b) cat. $Cu(OAc)_2$/TEMPO in air, (c) cat. $Cu(OAc)_2$/PNO in air, (d) cat. $[Cu(OH)•TMEDA]_2Cl_2/O_2$ (catalyst developed by Collman).[25] Different substrates required

different catalytic combinations and a wide range of temperatures from room temperature to 50 ^{o}C in order to obtain good to moderate yields. For some substrates, yields ranging from 30-50% were the highest that could be obtained. It appears that not one catalytic system worked for all substrates. This catalytic protocol would not be a very general synthetic method.

We wanted to examine whether the stabilization provided by the π ligand to the copper(I) intermediate could help increase the yields when catalytic amounts of copper(II) acetate are used. In order to test this hypothesis, 0.4 equivalents of copper (II) acetate, 4 equivalents of our π ligands, and an oxygen balloon were used (Table 2.4).

Table 2.4: **Catalytic Study**



ligand	yield (%)
none	<9
3-hexyne	36
Cy9	17

The yields obtained using a catalytic amount of copper were lower than those obtained when using two equivalents of copper. Using a π ligand did increase the yield compared to the control reaction without added ligand. The yield obtained with 3-hexyne was double in comparison to when Cy9 was used. It is possible that the pure oxygen atmosphere decomposed Cy9 into an inactive ligand. Since the yields obtained in this catalytic screening were not synthetically useful,

and much lower than those obtained when stoichiometric amounts of copper(II) acetate were used, further exploration of a catalytic system was not pursued further.

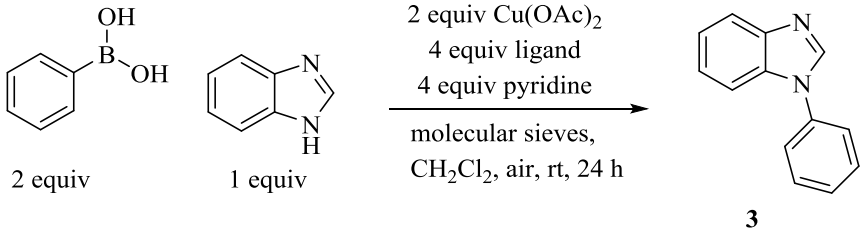
2.5 Base Study

The choice of base can have a significant impact on the Chan-Lam coupling. Most examples of this reaction use non-nucleophilic amine bases such as triethylamine or pyridine. The Merlic group investigated a series of amine and inorganic bases and found that the amine additive is acting as a base and a ligand.[16] The amine donates electron density to copper(II) and allows it to oxidize to the intermediate copper(III) species. During the transmetalation step a molecule of acetic acid is produced which is captured by the amine base. The presence of acid in the reaction would lead to the major side product, protodeboronation. Copper(II) acetate is insoluble in dichloromethane, the most popular solvent used in this reaction, and forms a suspension in this solvent. Addition of a nitrogen base solubilizes the catalyst which can be observed by the formation of a deep blue-green solution following the addition of amine.

Initial studies using Cu(II) acetate (2 equiv), phenyl boronic acid (2 equiv), triethylamine (4 equiv), and no additive in an air atmosphere only gave the desired product in 20% yield (Table 2.3). Chan and Lam found pyridine to be an effective base in their original N-arylation reaction.[7] In an effort to improve the yields of our cross-coupling reactions, pyridine was screened as the base. We were pleased to find that our yields increased significantly up to 60% when no additive was used (Table 2.5). This is three times higher than when the reaction was done using triethylamine. When 3-hexyne or 1,2-cyclononadiene were used the yields were superior to the reaction where no ligand was used. In the case of Cy9 the yield was excellent in 95%, which is an improvement from the previously published yield of 90% by our lab using a pure oxygen

atmosphere (Table 2.1). It is worth mentioning that for an unknown reason using 1 equivalent of copper(II) acetate under a pure oxygen atmosphere and same reaction conditions as Table 3.1 failed to give the desired product **3**.

Table 2.5: Ligand Screening Using Pyridine



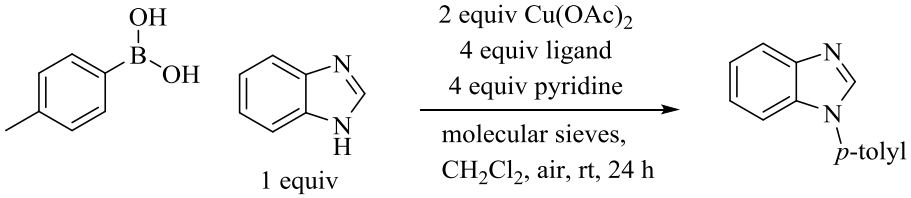
Ligand	Yield (%)
none	60
3-hexyne	88
Cy9	95

2.6 Substrate Scope

Having identified optimal reaction conditions that provide high yields of product and demonstrate a strong π ligand effect, we decided to expand the scope of this methodology to other boronic acids and aryl amine coupling partners that would benefit from this π ligand effect. Coupling of *p*-tolylboronic acid and benzimidazole produced excellent yields of the coupled product **4** in the presence of the π ligands (Table 2.6-1). Again, a dramatic increase of yields was observed with added π ligand when compared to the reaction without any additive. These results are almost identical to the ones obtained by Collman and coworkers who used a much more

expensive catalyst $[Cu(OH)\bullet TMEDA]_2Cl_2$ than Cu(II) acetate.[25] It was also a great improvement from the 67% yield reported by Chan and Lam in their original publication in 1998.[7]

Table 2.6-1: Screening of *p*-tolylboronic acid

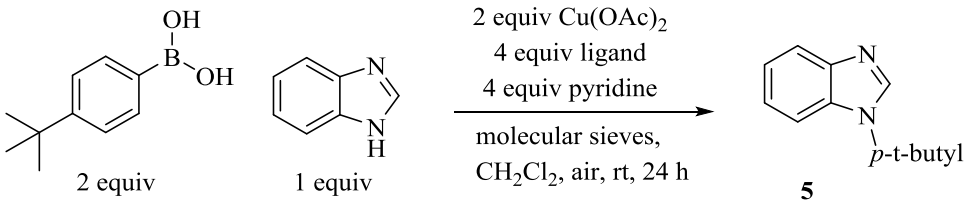


4

Ligand	Yield (%)
none	58
3-hexyne	81
Cy9	99

para-tert-butylboronic acid was tested in the same way as *p*-tolylboronic acid and also gave excellent yields when a π ligand was added (Table 2.6-2). The synthesis of this product was recently reported in 63% yield using a copper(II) species with a salen type ligand developed by Bora and coworkers.[26] Our method would be a more efficient route to prepare the coupled product **5**. Winternheimer performed this coupling using similar conditions but with 1 equivalent of copper(II) acetate and 5 equivalents of triethylamine, and was only able to obtain compound **5** in 22% yield.[16]

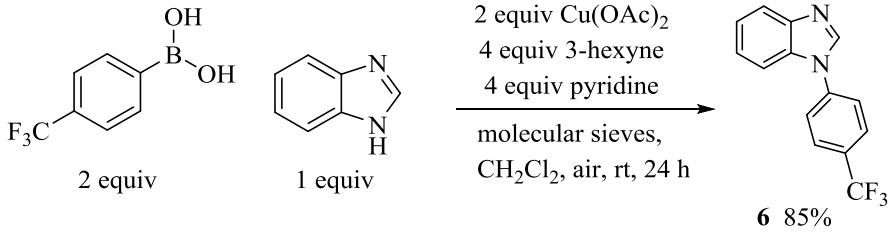
Table 2.6-2: Screening of *p*-tert-butylboronic acid



Ligand	Yield (%)
none	79
3-hexyne	94
Cy9	96

Electron deficient *para*-(trifluoromethyl)phenyl boronic acid was also coupled with benzimidazole using 3-hexyne as the additive using the methodology that we developed (Scheme 2.6-1). The coupled product **6** was obtained in 85% yield. Screening of this reaction with 1,2-cyclononadiene and without any additive is ongoing.

Scheme 2.6-1: Coupling of *p*-(trifluoromethyl)phenyl boronic acid Using 3-hexyne

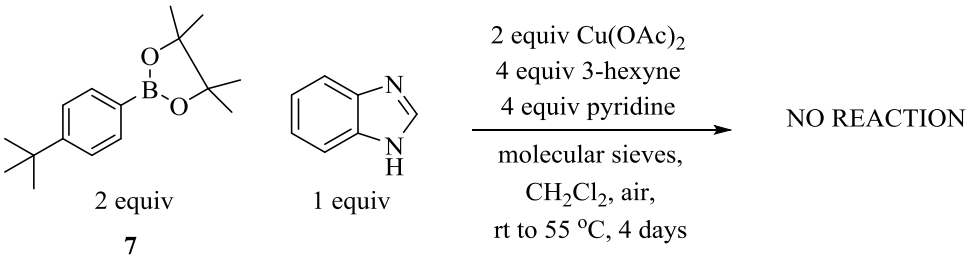


Slightly better yields were obtained when electron rich boronic acids were used in comparison to electron deficient boronic acids. This observation has also been reported in the literature, however, only a small difference is occasionally observed.[27] Attempts at trying to rationalize the reactivity of electronically diverse boronic acids in the coupling with nitrogen nucleophiles has not shown a clear trend.[28] It appears that steric effects play a bigger role in the

reactivity of boronic acids since the yields of *ortho*-substituted boronic acids were lower than *para*-substituted.

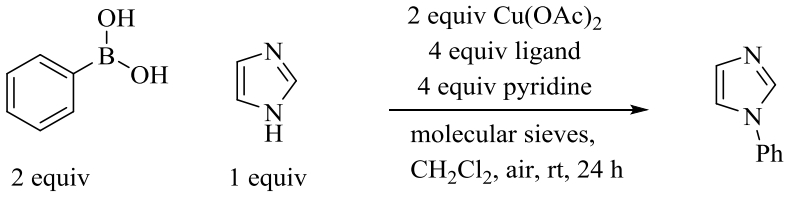
Steric effects are thought to be the reason why the reaction of *para*-tert-butylboronic acid pinacol ester **7** and benzimidazole failed to react at room temperature for 2 days and even when heated at 55 ^{o}C for an additional 2 days. Only starting material was recovered (Scheme 2.6-2). We have observed decomposition of boronate esters to the protodeboronated side-product when heating above 55 ^{o}C in the presence of copper(II) and further heating above those temperatures is discouraged. Cyclic amines might already be too sterically demanding around copper and would prevent another bulky substrate, such as arylboronic pinacol esters, from undergoing transmetalation. Cross couplings between boronate esters and nitrogen nucleophiles are well known using ethylene glycol arylboronic esters, isopropyl arylboronic esters, and propylene glycol arylboronic esters.[29] Reactions using arylboronic pinacol ester and catechol esters tend to give very low yields. In contrast, C-O couplings between alcohols and pinacol boronic esters are well known in the literature and have been extensively studied by the Merlic lab (Scheme 1.2-1).[14]

Scheme 2.6-2: Coupling of *para*-tert-butyl pinacol boronic ester



Other nitrogen containing heterocycles were studied in order to explore the scope of the effect of our π ligands. Couplings of phenyl boronic acid with imidazole gave modest yields with only a slight increase observed when 3-hexyne and 1,2-cyclononadiene were used (Table 2.6-3).

Table 2.6-3: Screening of Ligands with Imidazole

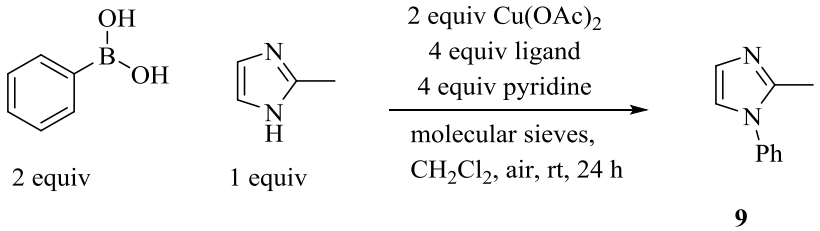


2 equiv 1 equiv **8**

Ligand	Yield (%)
none	52
3-hexyne	63
Cy9	72

Using 2-methylimidazole gave low yields with no advantage observed when using the π-ligands (Table 2.6-4). The low yields could result from steric hindrance around the nitrogen due to the adjacent methyl substituent. Another factor that could be influencing the success of these imidazole coupling reactions is their basicity. The conjugate acid of benzimidazole has been reported to have a pKa of 5.55, imidazole at 7.05, and 2-methylimidazole at 8.15.[30, 31] A clear trend of increasing basicity can be observed when going from benzimidazole, imidazole, and 2-methylimidazole. Therefore, 2-methylimidazole is over two orders of magnitude stronger base than benzimidazole which is likely the reason why couplings with this substrate gave lower yields. This evidence suggests that halogenated or ester-substituted imidazoles should be explored as substrates.

Table 2.6-4: Screening of Ligands with 2-methylimidazole



2 equiv 1 equiv **9**

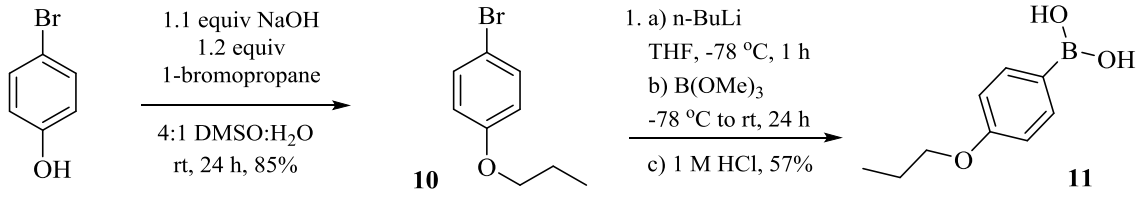
Ligand	Yield (%)
none	46
3-hexyne	45
Cy9	47

Imidazole and 2-methylimidazole are presumably coordinating to copper more strongly than benzimidazole and, thus, blocking the free coordination site at the copper center from the π ligand. They might also be competing with pyridine (pKa 5.23) as the base. Competition with pyridine would prevent the initial step of deprotonation/coordination to copper(II) and hinder the reaction. Some of the more basic nitrogen containing substrates might not need an additional base additive in order to obtain better yields. Xie and coworkers reported N-arylation using Chan-Lam conditions without the use of base.[32] The yields for several examples were moderate and ranged from 39-78%. From these results, it can be inferred that a lower amount of base additive, less than 4 equivalents, could benefit imidazole couplings. Investigation of the stoichiometry of pyridine or use of a more basic amine, like triethylamine, for these imidazole substrates is currently underway.

2.7 Self-Ligation Study

Inspired by the results obtained previously in our lab in the C-O oxidative coupling investigation where the presence of allyl alcohol provided a significant boost in yields compared to those using methanol we decided to explore substrates containing nonaromatic π bonds to determine whether they would perform auto-ligation with copper. To test whether this hypothesis of auto-ligation was viable, we decided to look into *para*-alkoxyphenylboronic acids. (*p*-propoxyphenyl)boronic acid **11** was synthesized by etherification of *p*-bromophenol with 1-bromopropane to give alkylated product **10**.[33] Lithium-halogen exchange and trapping with trimethylborate followed by acidic work up furnished boronic acid **11**.[34]

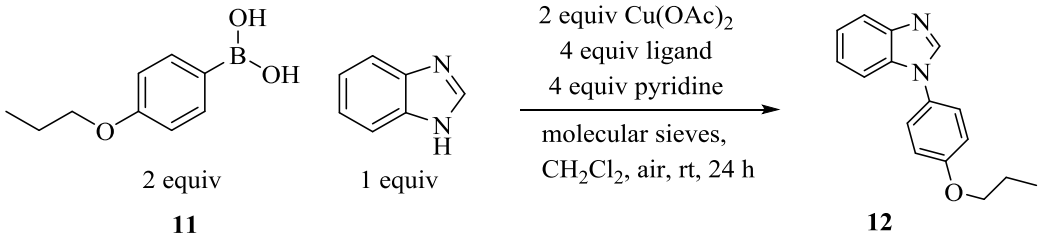
Scheme 2.7-1: Synthesis of (*p*-propoxyphenyl)boronic acid



(*p*-propoxyphenyl)boronic acid was coupled with benzimidazole using the reaction conditions that we developed in the presence and absence of π ligands (Table 2.7-1). To the best of our knowledge, compound **12** has not yet been reported in the literature. Using 1,2-cyclononadiene gave excellent yields (97%) as well as when 3-hexyne was used (95%). In the absence of any ligand additive, somewhat lower yields were obtained (88%). The coupling reaction to obtain **12** without ligand gave higher yields than those using phenyl boronic acid (Table 2.5) in accordance with the observation that electron rich boronic acids couple more efficiently. The reaction using the *p*-propoxy substituted boronic acid without any additive will

constitute the control reaction for future studies involving unsaturated alkyl substituted boronic acids (Table 2.7-2).

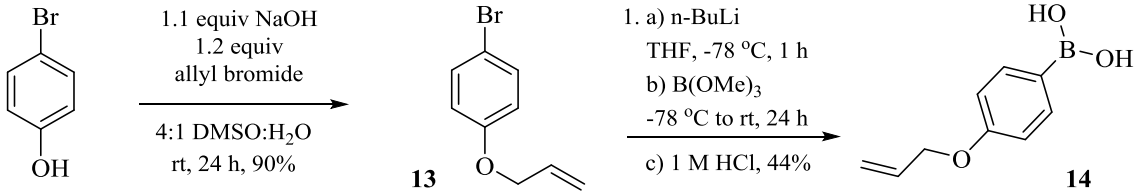
Table 2.7-1: Ligand Screening in the Synthesis of N-(4-propoxy-1-phenyl)benzimidazole



Ligand	Yield (%)
none	83
3-hexyne	95
Cy9	97

(4-(allyloxy)phenyl)boronic acid **14** was synthesized using the same procedure used to obtain boronic acid **11**.

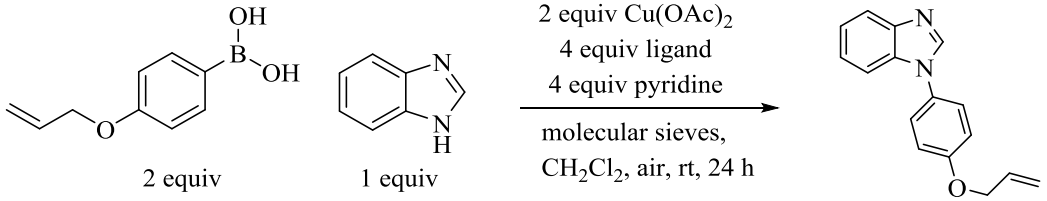
Scheme 2.7-2: Synthesis of (*p*-allyloxyphenyl)boronic acid



We postulated that this unsaturated boronic acid containing a π bond should provide a self-ligand effect to copper similar to what has already been observed for added 3-hexyne and Cy9. The

oxidative coupling of **14** with benzimidazole gave the novel coupled product **15** in outstanding yields. A small increase in the yield between the control reaction using the saturated alkoxy boronic acid **12** vs. the allyloxy boronic acid **15** was observed. The reactions using our π ligands gave virtually identical yields in both systems. Although the increase in yield in the absence of 3-hexyne and Cy9 ligands for **12** and **15** was small, it shows that there is, in fact, an auto-ligation effect from the allyl substituted boronic acid, albeit small.

Table 2.7-2: Ligand Screening in the Synthesis of N-(4-allyloxy-1-phenyl)benzimidazole



Ligand	Yield (%)
none	88
3-hexyne	94
Cy9	96

An aryl boronic acid substrate containing an alkyne moiety at the *para* position, analogous to structure **15**, is postulated to show a stronger self-ligating effect. We have previously mentioned that alkynes having an additional π bond and a linear geometry, compared to alkenes, are more Lewis basic. Attempts at synthesizing (4-(but-2-yn-1-yloxy)phenyl)boronic acid via the same procedure (Scheme 2.7-1) used for previous boronic acids has proven problematic. A plethora of side products in the reaction mixture has made purification quite

difficult; although formation of the desired boronic acid has been observed by ^{1}H NMR in the crude mixture. Other protocols are currently being explored to synthesize this alkyne-substituted boronic acid and identify whether a self-ligating effect is observed.

III. CONCLUSIONS

A set of reaction conditions to test the π ligand effect on copper mediated carbon-nitrogen oxidative coupling reactions was developed. Six reactions that showcase this ligand effect were identified. The reaction of phenyl boronic acid with 2-methylimidazole did not show a strong ligand effect which could be due to steric hindrance from the methyl substituent affecting the coordination to copper but the increased basicity of this imidazole is also likely an issue. Pyridine base was found to give higher yields than triethylamine in the oxidative coupling of heterocyclic amines and boronic acids. Two equivalents of copper(II) acetate were required in order to obtain synthetically useful yields. 1,2-cyclononadiene proved to be a more efficient ligand than 3-hexyne for the reactions investigated. Further studies using these π ligands and different combinations of boronic acids and heterocyclic amines will be conducted. The copper-1,2-cyclononadiene complex will be analyzed by NMR, UV-Vis, and IR spectroscopy. Ideally, an X-ray quality crystal of the complex will be obtained in order to understand its geometry and role in the mechanism of the Chan-Lam C-N cross-couplings. We would like to identify other copper based oxidative coupling examples that are impacted by the π-ligand whether positively or negatively, in order to understand their role in the Chan-Lam coupling. Furthermore, identifying if the π ligand is interacting with a specific oxidation state of copper or all oxidation states in the catalytic cycle, in addition to how it is binding to copper will be important questions to answer. Kinetic studies will provide an insight on whether the increased yield observed in the reactions using the π ligands is due to the reaction being completed faster or by inhibiting the distribution of side products (such as protodeboronation and phenol formation).

IV. EXPERIMENTAL

Reagents were used as received from commercial sources. DCM, triethylamine, and pyridine were distilled fresh from CaH_2. THF was distilled fresh from Na/benzophenone.

Representative Procedure for N-arylation

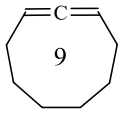
A round-bottom flask was charged with 0.8 mmol of boronic acid (2.0 equiv), 0.4 mmol heterocyclic amine (1.0 equiv), 200 mg of 4 Å molecular sieves, and was stirred with 5 mL of DCM for 15 minutes. Sequentially, 0.16 mmol ligand (4.0 equiv), 0.8 mmol $Cu(OAc)_2$ (2.0 equiv), and 0.16 mmol pyridine (4.0 equiv) were added to the reaction mixture. The reaction flask was equipped with a drying tube containing $CaCl_2$ and allowed to stir overnight. Silica gel was added to the reaction mixture and the solvent was evaporated. The solid was directly loaded onto a column of silica gel. The product was eluted using standard solvent mixtures with 1-2% triethylamine.

Representative Procedure for Etherification of *p*-bromophenol

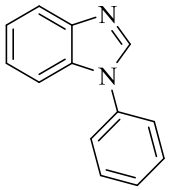
In a round-bottom flask 38 mmol of NaOH (1.25 equiv) were dissolved in 25 mL DMSO : H_2O (4 : 1). 30 mmol *p*-bromophenol (1.0 equiv) were then added and stirred at room temperature for 30 minutes. To this solution, 33 mmol alkyl halide (1.1 equiv) were added and reaction mixture was allowed to stir overnight at room temperature. Reaction was diluted with 200 mL of H_2O and extracted with hexanes. The organic layer was washed with water, dried with $MgSO_4$ and, evaporated to give the product as a colorless oil. Product was used without further purification.

Representative Procedure for Boronic Acid Synthesis

In a dry round-bottom flask purged with N_2, 13 mmol of aryl halide (1.0 equiv) were dissolved in 20 mL of THF and cooled to -78 ^oC. Dropwise, 18 mmol *n*-BuLi (1.2 equiv) were added and allowed to stir for 1 hour. 23 mmol of trimethylborate (1.5 equiv) were added dropwise and the reaction mixture was allowed to slowly warm up to room temperature overnight. Carefully, 5 mL of water were added dropwise followed by acidification with 1 M HCl and stirred for 1 hour. The mixture was extracted with diethyl ether and the organic layer was dried with $MgSO_4$ and evaporated. The crude product was purified by silica column chromatography eluted with a mixture of hexanes : ethyl acetate (3 : 2).



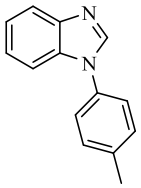
1,2-cyclononadiene (2) was synthesized according to literature procedure, see: Shea, K. J.; Kim, J-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044.



N-phenylbenzimidazole (3)

Using the general procedure for N-arylation, 98 mg of benzimidazole was reacted with phenyl boronic acid to give 97 mg (60% yield) without ligand, and 142 mg (88% yield) with 3-hexyne of compound **3**. For screening with Cy9, 47 mg of benzimidazole was reacted with phenyl boronic acid to give 74 mg (95% yield) of **3**.

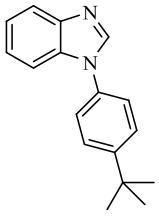
For characterization, see: Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2010**, *12*, 2508.



N-(4-methyl-1-phenyl)benzimidazole (4)

Using the general procedure for N-arylation, 98 mg of benzimidazole was reacted with p-methylphenyl boronic acid to give 100 mg (58% yield) without ligand, and 140 mg (81% yield) with 3-hexyne of compound **4**. For screening with Cy9, 47 mg of benzimidazole was reacted with p-methylphenyl boronic acid to give 82 mg (99% yield) of **4**.

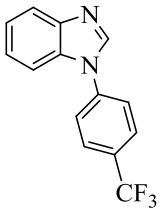
For characterization, see: Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294.



N-(*p*-(*tert*-butyl)-1-phenyl)benzimidazole (5)

Using the general procedure for N-arylation, 47 mg of benzimidazole was reacted with *p*-(*tert*-butyl)phenyl boronic acid to give 79 mg (79% yield) without ligand, and 94 mg (94% yield) with 3-hexyne of compound **5**. For screening with Cy9, 43 mg of benzimidazole was reacted with *p*-(*tert*-butyl)phenyl boronic acid to give 89 mg (96% yield) of **5**.

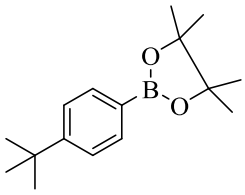
For characterization, see: Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007,** *72*, 6190.



N-(4-trifluoromethyl-1-phenyl)benzimidazole (6)

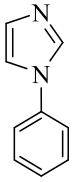
Using the general procedure for N-arylation, 47 mg of benzimidazole was reacted with (4-(trifluoromethyl)phenyl)boronic acid to give 89 mg (85% yield) with 3-hexyne of compound **6**.

For characterization, see: Liu, B.; Liu, B.; Zhou, Y.; Chen, W. *Organometallics.* **2010,** *29*, 1457.



2-(4-(tert-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)

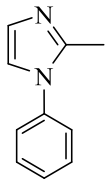
For synthesis and characterization, see: Gerbino, S. D.; Mandolesi, H. G.; Schmalz, J. C.; Podestá, J.C. *Eur. J. Org. Chem.* **2009**, (29), 3964.



1-phenylimidazole (8)

Using the general procedure for N-arylation, 52 mg of imidazole was reacted with phenyl boronic acid to give 62 mg (52% yield) without ligand, and 76 mg (63% yield) with 3-hexyne of compound **8**. For screening with Cy9, 32 mg of imidazole was reacted with phenyl boronic acid to give 52 mg (72% yield) of **8**.

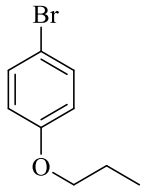
For characterization, see: Suresh, P.; Pitchumani, K. *J. Org. Chem.* **2008**, *73*, 9121.



1-phenyl-2-methylimidazole (9)

Using the general procedure for N-arylation, 68 mg of 2-methylimidazole was reacted with phenyl boronic acid to give 60 mg (46% yield) without ligand, and 59 mg (45% yield) with 3-hexyne of compound **9**. For screening with Cy9, 41 mg of imidazole was reacted with phenyl boronic acid to give 37 mg (47% yield) of **9**.

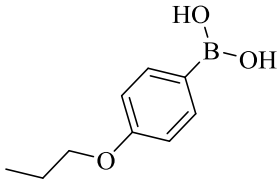
For characterization, see: Suresh, P.; Pitchumani, K. *J. Org. Chem.* **2008**, *73*, 9121.



1-bromo-4-propoxybenzene (10)

Using the general procedure for etherification of *p*-bromophenol, 5.19 g of *p*-bromophenol was reacted with 1-bromopropane to give 5.5 g of **10** in 85% yield.

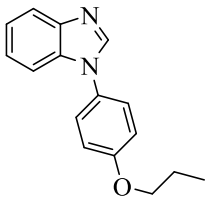
For characterization, see: Belloni, M.; Manickam, M.; Wang, Z.; Preece, J.A. *Mol. Cryst. Liq. Cryst.* **2003**, *399*, 93.



***p*-propoxyphenyl boronic acid (11)**

Using the general procedure for the synthesis of boronic acids, 2.6 g of 1-bromo-4-propoxybenzene **10** was reacted to give 1.25 g of **11** in 57% yield**.**

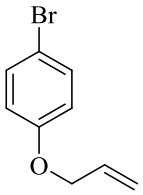
For characterization, see: Yu, Z. N.; Tu, H. L.; Wan, X. H.; Chen X. F.; Zhou, Q. F. *Mol. Cryst. Liq. Cryst.* **2003**, *391*, 41.



N-(4-propoxy-1-phenyl)benzimidazole (12)

Using the general procedure for N-arylation, 47 mg of benzimidazole was reacted with *p*-propoxyphenylboronic acid **11** to give 84 mg (83% yield) without ligand, 96 mg (95% yield) with 3-hexyne, and 98 mg (97% yield) with Cy9 of compound **12**. Product was chromatographed using silica gel eluted with ethyl acetate : hexanes (3 : 2) and 2% triethylamine.

IR (ATR): 3054, 1614, 1516, 1489, 1250, 1229, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.05 (1 H, s), 7.87 (1 H, d, *J* = 8.0 Hz), 7.25-7.46 (5 H, m), 7.03 (2 H, m), 3.97 (2 H, t, *J* = 8.0 Hz), 1.85 (2 H, m, *J* = 7.2 Hz), 1.07 (3 H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.8, 143.9, 142.6, 134.4, 128.9, 125.6, 123.4, 122.4, 120.4, 115.5, 110.3, 69.9, 22.5, 10.4; HRMS (ESI-TOF) *m/z* calculated for $C_{16}H_{16}N_2O$ $[M+H]^+$ 253.1341, found 253.1330

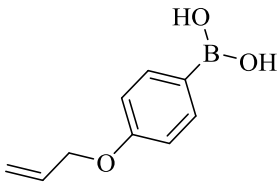


1-bromo-4-allyloxybenzene (13)

Using the general procedure for etherification of *p*-bromophenol, 5.19 g of *p*-bromophenol was reacted with allyl bromide to give 5.76 g of **17** in 90% yield.

For characterization, see:

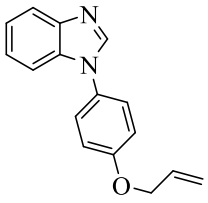
Bujok, R.; Bieniek, M.; Masnyk, M.; Michrowska, A.; Sarosiek, A.; Stępowska, H.; Arlt, D.; Grela, K. *J. Org. Chem.* **2004,** *69*, 6894.



***p*-allyloxyphenyl boronic acid (14)**

Using the general procedure for the synthesis of boronic acids, 2.56 g of 1-bromo-4-allyloxybenzene **17** was reacted to give **15** in 44% yield**.**

For characterization, see: Sidall, T. L. *et al.* (Dow Agrosciences LLC, US). Preparation of 1-alkyl-4-benzoyl-5-hydroxypyrazole derivatives as herbicides, US Patent WO 1998-US10154, May 18, 1998.



N-(4-allyloxy-1-phenyl)benzimidazole (15)

Using the general procedure for N-arylation, 47 mg of benzimidazole was reacted with *p*-allyloxyphenyl boronic acid **14** to give 88 mg (88% yield) without ligand, 94 mg (94% yield) with 3-hexyne, and 96 mg (96% yield) with Cy9 of compound **15**. Product was chromatographed using silica gel chromatography eluted with ethyl acetate : hexanes (3 : 2) and 2% triethylamine.

IR (ATR): 3078, 1614, 1512, 1489, 1456, 1226, 832, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.03 (1 H, s), 7.85 (1 H, dt, *J* = 8.8, 3.7 Hz), 7.25-7.45 (5 H, m), 7.05 (2 H, dt, *J* = 8.0, 3.0 Hz), 6.06 (1 H, ddt, 17.6, 10.8, 5.2 Hz), 5.44 (1 H, dq, 17.4, 1.6 Hz), 5.32 (1H, dq, 10.6, 1.6 Hz), 4.58 (2 H, dt, *J* = 5.2, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.2, 143.7, 142.4, 134.1, 132.7, 129.2, 125.5, 123.4, 122.5, 120.4, 118.0, 115.8, 110.3, 69.1; HRMS (ESI-TOF) *m/z* calculated for $C_{16}H_{14}N_2O$ $[M+H]^+$ 251.1184, found 251.1191

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