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THE FORMATION OF BIARYL BONDS VIA CROSS-DEHYDROGENATIVE COUPLING

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THE FORMATION OF BIARYL BONDS VIA CROSS-
DEHYDROGENATIVE COUPLING

BY

ASHLEY L. PORTER

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
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MASTER OF CHEMISTRY THESIS
OF
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2013

ABSTRACT

Biaryl bonds are a common motif found in biologically active compounds and the majority of marketed pharmaceuticals. The contemporary methods used to synthesize these biaryl bonds, albeit high yielding, are not economical because they require several prefunctionalization steps that create a high volume of waste and byproducts. Cross-dehydrogenative coupling (CDC) is the future of green coupling techniques, since it requires no prefunctionalization of substrates and can obtain high yields with a relatively low catalyst loading. Herein, we report on advances being made in the field of CDC, and our own efforts to achieve cross coupling utilizing benzimidazole moieties.

The first manuscript, “Aryl-Aryl Bond Formation via CDC Reactions” is a comprehensive review of the latest and most notable achievements being made in the area of biaryl CDC reactions. The manuscript focuses on cross-dehydrogenative coupling as a green method that can be used to create aryl-aryl bonds on a vast array of substrates. Several different classes of CDC reaction conditions were examined including Pd, Rh, Ru, Cu, and Fe-based catalytic systems.

The second manuscript, “Intramolecular Arylation of Benzimidazoles via Pd(II)/Cu(I) catalyzed Cross-Dehydrogenative Coupling” describes research done on the intramolecular biaryl CDC reaction between simple arenes and benzimidazoles. This novel reaction is carried out on N-benzylbenzimidazoles that upon cyclization forms a fused polycyclic system. The reaction conditions were optimized and tested on a large library of substrates, and the mechanism was probed using kinetic isotope studies and varied reaction conditions to suggest a unique Pd(II)/Cu(I) catalytic cycle.

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I want to thank my first chemistry teacher, **Jack Hayes**, for instilling me with a love of chemistry. He inspired me throughout my whole time in college, and I hope that someday I can be that same inspiration for my students.

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PREFACE

The following work is presented in manuscript format according to the guidelines presented by the University of Rhode Island Graduate School. The thesis will consist of two manuscripts that are currently in the process of publication.

Manuscript 1 entitled, “Aryl-Aryl Coupling via CDC Reactions” is being published in 2014 as a chapter in the book “Carbon-carbon Bond Formations via Cross-Dehydrogenative Coupling of C-H Bonds” by the Royal Society of Chemistry and edited by C. J. Li.

Manuscript 2 entitled, “Intramolecular Arylation of Benzimidazoles via Pd(II)/Cu(I) catalyzed Cross-Dehydrogenative Coupling” has been presented as a poster at the 252nd ACS National Meeting and Exposition in Philadelphia (August 2012) and will be submitted to Tetrahedron Letters for publication in October 2013.

TABLE OF CONTENTS

ABSTRACT	ii
ACKNOWLEDGMENTS	iii
PREFACE	iv
TABLE OF CONTENTS	v
LIST OF TABLES	vii
LIST OF SCHEMES	viii
LIST OF SPECTRA	x
INTRODUCTION	1
References	6
MANUSCRIPT 1	
Aryl-Aryl Bond Formation via CDC Reactions	7
Abstract	8
General Introduction	8
Pd Catalyzed CDC Systems	10
Molecular Oxygen as an Oxidant and Ligand Controlled Regioselectivity	11
Oxidant Controlled Regioselectivity	13
Catalytic Oxidants with O ₂ Terminal Oxidant	15
Organic Peroxide and F ⁺ Oxidants	16
Stoichiometric Metal Oxidants	18
Rhodium and Ruthenium Catalyzed CDC Systems	22

Copper Mediated CDC Systems.....	24
Other CDC Systems.....	27
References	30

MANUSCRIPT 2

Intramolecular Arylation of Benzimidazoles via Pd(II)/Cu(I) catalyzed Cross-Dehydrogenative Coupling	37
Abstract.....	38
Introduction	38
Results and Discussion	40
Conclusions	47
Methods	47
Acknowledgements	49
Experimental Section.....	50
References	84

LIST OF TABLES

TABLE	PAGE
Manuscript 2	
Table 1. Optimization of the Reaction Conditions	41
Table 2. Scope of the Cyclization of N-benzylbenzimidazoles	43

LIST OF SCHEMES

SCHEME	PAGE
Introduction	
Scheme 1. Conventional Biaryl Coupling Techniques	2
Scheme 2. Catalytic Mechanism for Conventional Coupling Techniques	3
Scheme 3. Catalytic Mechanism for CDC	4
Manuscript 1	
Scheme 1. Biaryl Synthesis via CDC and Traditional Suzuki Coupling Techniques...	9
Scheme 2. Pd-catalyzed Aerobic Intramolecular CDC Reactions.	12
Scheme 3. Arylation of Indoles via CDC with Ligand Controlled Regioselectivity ..	13
Scheme 4. Scope of Oxidant Controlled Regioselectivity	14
Scheme 5. Redox Cycle for a Pd-catalyzed CDC with a Catalytic Metal Oxidant and O ₂ Terminal Oxidant	15
Scheme 6. Aerobic Arylation of Benzofuran via Pd-catalyzed CDC and Catalytic HPMV Oxidant	16
Scheme 7. Pd-catalyzed CDC Reactions Utilizing Organic Peroxide and F ⁺ Oxidants	17
Scheme 8. Pd-catalyzed CDC of Thiophenes and Fluorinated Arenes with a Ag(I) Oxidant	19
Scheme 9. Pd-catalyzed CDC of Benzoquinoline and Arenes with a Ag(I) Oxidant.	19
Scheme 10. Medium Ring Synthesis via Intramolecular Pd-catalyzed CDC with a Cu(II) Oxidant	20

SCHEME	PAGE
Scheme 11. Pd-catalyzed Cross Coupling of Heterocycles with a Cu(II) Oxidant	21
Scheme 12. Rh-catalyzed Biaryl CDC with a Tertiary Benzamide Directing Group.	23
Scheme 13. Ru-catalyzed CDC of Methylthiophenes with Benzoquinolines and Quinoxalines	24
Scheme 14. CDC of Naphthyl Derivatives by a N-heterocyclic Carbene-Cu(II) Complex.....	25
Scheme 15. Daugulis Conditions for Iodination and Direct Arylation Using CuI/I ₂ .	25
Scheme 16. Cu-catalyzed CDC of Pyridyl Arenes and Azoles	26
Scheme 17. Hypervalent Iodine Mediated CDC of Thiophenes with Arenes and Heterocycles	28
Scheme 18. Aerobic Fe-catalyzed CDC of Naphthols.....	29
Manuscript 2	
Scheme 1. The Conventional Suzuki-Miyaura Cross Coupling Method vs. CDC	39
Scheme 2. KIE Study on Aryl-Benzimidazole Cyclization	44
Scheme 3. Control Reactions Using AgOAc as an Oxidant	45
Scheme 4. Proposed Mechanism for the Pd(II)/Cu(I) Catalyzed Cyclization of N-benzylbenzimidazoles.....	46

LIST OF SPECTRA

SPECTRUM	PAGE
Manuscript 3	
Spectrum 1. ^1H NMR of Compound 2	52
Spectrum 2. ^{13}C NMR of Compound 2	53
Spectrum 3. ^1H NMR of Compound 3	55
Spectrum 4. ^{13}C NMR of Compound 3	56
Spectrum 5. ^1H NMR of Compound 7	58
Spectrum 6. ^{13}C NMR of Compound 7	59
Spectrum 7. ^1H NMR of Compound 9	61
Spectrum 8. ^{13}C NMR of Compound 9	62
Spectrum 9. ^1H NMR of Compound 11	64
Spectrum 10. ^{13}C NMR of Compound 11	65
Spectrum 11. ^1H NMR of Compound 15	67
Spectrum 12. ^{13}C NMR of Compound 15	68
Spectrum 13. ^1H NMR of Compound 16	70
Spectrum 14. ^{13}C NMR of Compound 16	71
Spectrum 15. ^1H NMR of Compound 17	73
Spectrum 16. ^{13}C NMR of Compound 17	74
Spectrum 17. ^1H NMR of <i>N</i> -benzylbenzimidazole.....	76
Spectrum 18. ^{13}C NMR of <i>N</i> -benzylbenzimidazole.....	77
Spectrum 19. ^1H NMR of 1-((furan-2-yl)methyl)-5,6-dimethyl-1H-benzimidazole ..	80

SPECTRUM	PAGE
Spectrum 20. ^{13}C NMR of 1-((furan-2-yl)methyl)-5,6-dimethyl-1H-benzimidazole.	81
Spectrum 21. ^1H NMR of 1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzimidazole	83
Spectrum 22. ^{13}C NMR of 1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzimidazole	84

INTRODUCTION

The formation of aryl-aryl bonds is one of the most fundamental reactions in organic synthesis. Biaryls are contained in many bioactive therapeutic agents including, anti-inflammatory, antifungal, antiviral, and anticancer agents,¹ making it a highly desirable motif to the pharmaceutical industry.² Also, many useful synthetic materials contain biaryls, including dyes, semiconductors, agrochemicals, and many types of ligands.³ With such a vast scope of uses, the ability to easily synthesize these aryl-aryl functionalities on nearly any compound is a demand that researchers have been trying to improve on over the past century.

One of first published examples of aryl-aryl bond formation was the Ullmann reaction originally published in 1901.⁴ The Ullmann reaction was able to synthesize symmetric biaryls by heating two equivalents of an aryl-halide and one equivalent of copper at very high temperatures. This reaction was a great success; however, it utilized a stoichiometric amount of copper metal and had limited success with non-symmetric coupling. Despite these shortcomings, aryl-aryl bonds continued to be made mainly using copper Ullmann type conditions until the 1970s.³

Only in the past few decades has the use of other transition metals like Pd, Pt, Rh, and Ru taken a prominent role in aryl-aryl bond formation. These metals can be used in catalytic amounts and can catalyze cross coupling as well as homocoupling of arenes. The use of Pd especially has become common since the Kumada cross coupling conditions on olefins were shown to work with a Pd catalyst in 1975 by Murahashi.⁵ Palladium has since been found to work very well in aryl-aryl bond

formation because of its ability to tolerate a wide variety of organometallic nucleophiles including tin, silica, boron, lead, and magnesium species.³ Today, most of the contemporary biaryl coupling techniques utilize catalytic amounts of Pd to form aryl-aryl bonds. Some of the more common ones are highlighted in (Scheme 1).

Scheme 1- Conventional Biaryl Coupling Techniques

All of the Pd catalyzed aryl coupling techniques above are theorized to operate under a similar mechanistic scheme. (Scheme 2) There are three main steps to the catalytic cycle, the first of which is oxidative addition of the Pd(0) catalyst into the C-halogen bond of an aryl-halide. As the Pd is inserting it forms two new covalent bonds and is oxidized to a Pd(II) complex with one aryl group and a halide. This oxidative addition step is often the rate-limiting step of the catalytic cycle.⁶ Next,

transmetalation occurs, and a second aryl group is swapped for the halide on the Pd(II) complex from another aryl-metal species, such as B, Sn, or Zn. This step loads both aryl groups on the Pd without changing the oxidation state of either metal during transmetalation.

Scheme 2- Catalytic Mechanism for Conventional Coupling Techniques

The final step is reductive elimination of the two aryl groups from the Pd(II) complex, which simultaneously forms a new biaryl bond and reduces Pd back to its original state. The Pd is then poised to undergo the cycle again.

Although most of these coupling methods are extremely robust, they still have short-comings. All of these methods have one main problem: the aryl groups must be prefunctionalized with halogens and metals. This is costly in terms of the time required to make the prefunctionalized aryl-metals and aryl-halides, and in terms of the waste generated from the additional reactions and purification steps.⁷ Therefore, “greener” methods to synthesize these biaryl bonds are being sought.

A method that would cut out costly prefunctionalization steps and couple simple hydrocarbons, would be ideal. Therefore, much research has lately been focused on cross-dehydrogenative coupling (CDC) as a means to synthesize biaryls. CDC is desirable due to the fact that two simple C-H bonds can be coupled, throwing out the need to prefunctionalize and giving a higher overall step economy.

Mechanistically, palladium-catalyzed CDC differs from traditional coupling techniques because it undergoes a Pd(II)/Pd(0) catalytic cycle instead of a Pd(0)/Pd(II) catalytic cycle. Because Pd(0) is not able to oxidatively insert into a C-H bond, a Pd(II) source is used to facilitate two separate C-H activations through means such as concerted metalation deprotonation or electrophilic aromatic metalation.⁸⁻⁹ (**Scheme 3**) Once the aryl groups are loaded onto the Pd, reductive elimination then occurs generating the product and leaving Pd in its reduced state. The final step is to oxidize Pd(0) back up to Pd(II) for the cycle to start again.

Scheme 3- Catalytic Mechanism for CDC

When comparing traditional coupling techniques to CDC, it is clear that CDC is the greener method. For economical and environmental reasons, it appears that the future of biaryl coupling should be in CDC. Much research is now being devoted to developing new aryl-aryl CDC reactions and making them as green as possible by eliminating superfluous reagents from the reaction. The research described herein will provide an in depth look into cross-dehydrogenative coupling, by examining its advantages and shortcomings, and how it can be utilized in the formation of aryl-aryl bonds.

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MANUSCRIPT 1

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Aryl-Aryl Bond Formation via CDC Reactions

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MANUSCRIPT 1

Aryl-Aryl Bond Formation via CDC Reactions

Abstract

The formation of biaryl motifs via oxidative coupling of hydrocarbons is a challenging and highly sought after process in both academia and industry. Contemporary biaryl coupling techniques include prefunctionalization steps that lower the overall step economy of the reaction and increase expenses and waste. The cross coupling of C-H bonds is a green technique that requires no prefunctionalization and can significantly lower wasteful byproducts. This chapter highlights advances in the field of oxidative coupling of hydrocarbons through biaryl cross-dehydrogenative coupling (CDC). It includes insight into a variety of CDC methods including aerobic coupling and metal catalyzed CDC using metals such as: Pd, Rh, Ru, and Cu.

General Introduction

Currently there is a need for environmentally friendly ways to incorporate carbon-carbon bonds into organic molecules. Specifically, biaryl C-C bonds are of high priority, since aryl or heterocyclic groups are contained in 75% of marketed pharmaceuticals.¹ The traditional methods for making biaryl C-C bonds include Suzuki, Negishi, Stille, and Kumada coupling,² all of which involve the coupling of an aryl-halide and an aryl-metal species. These methods might appear green since they use small quantities of metal catalysts and require no external oxidant. However, they suffer from wasteful and costly prefunctionalization steps and poor atom economy.³

The ideal scenario would be to oxidatively couple two aryl C-H bonds and produce a new biaryl C-C bond. This coupling method, herein known as cross-dehydrogenative coupling (CDC), would require no prefunctionalization steps and generate fewer byproducts as waste (**Scheme 1**).

Scheme 1- Biaryl Synthesis via CDC and Traditional Suzuki Coupling Techniques

Compared to traditional coupling techniques, CDC would provide a greener synthetic route by improving the overall step economy of the reaction, since functionalization is not a prerequisite in CDC. The number of additional steps required to install functional groups prior to coupling is often time consuming, expensive, and wasteful.

In 1912, the first oxidative biaryl coupling was reported by Scholl, in which simple arenes were coupled using a stoichiometric amount of AlCl_3 .⁴⁻⁵ Since the introduction of the Scholl reaction, publications of biaryl CDC reactions have continued to grow, attracting much interest in both academic and industrial settings. However, these reactions come with many challenges that must be overcome before they can be implemented in industry.

One of the main challenges with CDC methodology is finding ways to readily activate C-H bonds, since they are short, strong, and hard to activate via oxidative addition with organometallic complexes. Traditional coupling methods, such as the Suzuki reaction, are successful because prefunctionalization with a halogen or boronic acid creates species that are amenable to metalation via oxidative addition or transmetallation. Another challenge is using inexpensive and readily available oxidants. Coupling between two C-H bonds could ideally produce hydrogen gas as a byproduct; however, that is often thermodynamically unfavorable; thus, requiring an external oxidant to drive the reaction forward.⁶ Finally, controlling the selectivity of C-H activation has proved difficult. Unwanted dimer byproducts often plague CDC reactions, and finding conditions that minimize homocoupling is difficult. Regioselectivity is the other selectivity problem due to the omnipresence of C-H bonds. Many times this is resolved by the use of a preinstalled directing group that can coordinate with a metal catalyst to facilitate insertion into a nearby C-H bond.

Despite the difficulty of biaryl synthesis via CDC, much progress has been made on the subject over the past century, with most of the advances being realized in the past decade. This chapter will focus on some of the exciting highlights and recent advancements of these green reactions.

Pd Catalyzed CDC Systems

Although many different metal catalysts have been used in oxidative coupling reactions, the most common ones are late transition metals, including Pd, Rh, Ru, and Cu.² Undoubtedly, Pd is used in the majority of examples, probably due to its high versatility and activity.⁷ The first biaryl dehydrogenative coupling reaction catalyzed

by Pd was reported by Van Heldon and Verberg, in which biphenyl was formed in high yields.⁸ This initiated a wave of studies using Pd catalysts in CDC reactions. Because Pd(0) has the potential to easily form a colloid and fall out of solution, a ligand or solvent system that can coordinate Pd(0) can be used to ameliorate this problem.⁹ However, the phosphine ligands that are commonly employed in traditional cross coupling chemistry are not stable in the oxidizing environments required for most CDC reactions, so simple palladium salts are often used, such as Pd(OAc)₂ or PdCl₂.⁷ Hartwig and co-workers observed that ligandless anionic palladium species more readily cleave C-H bonds compared to hindered phosphine ligated palladium catalysts.¹⁰ Thus providing evidence as to why most Pd catalyzed CDC reactions work efficiently without ligands. Pd catalyzed CDC reactions typically run in an acidic medium for up to several days¹¹ at a temperature over 100 °C. An external oxidant is needed in these reactions. The greenest option is to use O₂; though, other less green alternatives including peroxysulfates and metal salts of Cu(II) or Ag(I) are more common.

Molecular Oxygen as an Oxidant and Ligand Controlled Regioselectivity.

Several groups have successfully utilized molecular oxygen as the sole oxidant in aerobic Pd catalyzed biaryl CDC reactions. These reactions are probably the greenest CDC reactions that exist right now due to the fact that using O₂ or air as the oxidant is inexpensive and makes water as a final biproduct. Most of these O₂ oxidized reactions take place in an acidic environment and at temperatures ranging anywhere from 55-120 °C.

In 1973, Yoshimoto and Itatani successfully carried out a biaryl Pd catalyzed dehydrogenative coupling reaction with pressurized O₂ as the oxidant.¹² They coupled biphenylethers intramolecularly, but also got an equal amount of intermolecular dimers as side products. The experimental conditions were harsh (50kg/cm² of 1:1 oxygen and nitrogen and heated to 150 °C) and were not regioselective. In 1999, Akermarck and co-workers published a Pd catalyzed CDC reaction that intramolecularly coupled arylaminoquinones.¹³ This reaction worked in only 1 atm. of O₂; however, when coupling biphenylethers or biphenylamines, the reaction required additional tin(II) acetate additives to prevent bulk Pd from falling out of solution.

Later, the groups of Fagnou, Ohno, and Kandekar developed improved intramolecular aerobic CDC examples in which all experimental conditions included a Pd(OAc)₂ catalyst, a base, pivalic or acetic acid, and oxygen (**Scheme 2**). These reactions were successful on biphenylethers¹⁴ and biphenylamines¹⁴⁻¹⁵ up to 99% yield and N-benzoylindoles^{14,16} and N-benzoylpyrroles¹⁷ up to 92% yield.

Scheme 2- Pd-catalyzed Aerobic Intramolecular CDC reactions

Several examples of aerobic intermolecular coupling via CDC of aryls were also published, using similar conditions.¹⁸⁻¹⁹ Perhaps the most interesting example to date was by Stahl and co-workers in 2011. They aerobically coupled indoles and arenes via intermolecular CDC using Pd catalysts and diazafluorene ligands.²⁰ While optimizing the reaction, they found that both the anionic ligands in the Pd(II) salts and the neutral diazafluorene ligands could control regioselectivity (**Scheme 3**).

Scheme 3- Arylation of Indoles via CDC with Ligand Controlled Regioselectivity

The combination of the pivalate anion with a diazafluorenone ligand was selective for C2 coupling, whereas the combination of the trifluoroacetate anion with a dimethyldiazafluorene ligand was selective for C3 coupling. In both catalyst systems the presence of electron donating groups deteriorated the regioselectivity; however the presence of electron withdrawing groups improved selectivity with the C2 selective catalyst system.

Oxidant Controlled Regioselectivity. Another aspect that has been shown to readily influence site selectivity in CDC reactions is the choice of oxidant (**Scheme 4**).

Scheme 4- Scope of Oxidant Controlled Regioselectivity

In 2007, DeBoef and co-workers showed that regioselectivity could be manipulated in the arylation of benzofurans with different oxidants.²¹⁻²² They found upon examining the reaction in acidic conditions, that CDC reactions employing the heteropoly acid H₄PMo₁₁VO₄₀ (HPMV) gave almost exclusive C2 site selectivity. The use of Cu(OAc)₂ also gave moderate C2 selectivity, and the use of AgOAc gave no selectivity. That same year Fagnou and co-workers showed that, when arylating indoles, regioselectivity could be controlled by using different oxidants.²³⁻²⁴ They found that using Cu(OAc)₂ gave C3 selectivity and using AgOAc gave C2 selectivity.

Further studies have come from the DeBoef group on oxidant controlled regioselectivity, in which both benzofuran and indole arylations were examined in different solvent parameters.²⁵⁻²⁷ They summarized that solvent had little overall effect

on regioselectivity compared to oxidant choice,²⁷ and both DeBoef and Fagnou reasoned that site selectivity is most likely due to the formation of polymetallic clusters during catalysis.^{23-24,25}

Catalytic Oxidants with O₂ Terminal Oxidant. Using O₂ as the only oxidant is, to date, the greenest condition for the synthesis of biaryls via CDC; however, several studies have shown that catalytic amounts of a metal oxidant can be used along with O₂ as a terminal oxidant (**Scheme 5**).^{12,22,28-30}

Scheme 5- Redox Cycle for a Pd catalyzed CDC with a catalytic metal oxidant and O₂ terminal oxidant

These “cocatalyst” oxidants are sometimes needed to help prevent bulk Pd from falling out of solution, they are often strong oxidants that can readily reoxidize Pd(0) back to Pd(II) before it falls out of solution.¹³ Transition metal salts, such as Sn(OAc)₂,¹³ Ag₂O,²⁹ Cu(OTf)₂³⁰ and Mn(OAc)₃·H₂O,³¹ have been used, but perhaps one of the most unique examples was by DeBoef and co-workers in which they used the heteropoly acid HPMV as a cocatalyst oxidant to afford high yields in the arylation of benzofurans via CDC reactions (**Scheme 6**).²²

Scheme 6- Aerobic arylation of benzofuran via Pd catalyzed CDC and catalytic HPMV oxidant

Heteropoly acids have been shown to be quite efficient as catalytic oxidants due to their highly reversible oxidizability.³¹ The study utilized these efficient oxidants, and found that they contributed to high yields, and would tolerate substrates containing the presence of electron donating groups on the aryl moiety, which increased the reaction rate. Alternatively, the presence of electron withdrawing groups shut down the reaction. Subsequent mechanistic studies have shown that the HPMV/ O_2 -oxidized reactions proceed via a Pd(II)/Pd(IV) mechanism.²⁷

Organic Peroxide and F^+ Oxidants. Another green oxidant option for Pd catalyzed biaryl CDC reactions is to use organic peroxides or F^+ oxidants such as sodium persulfate ($\text{Na}_2\text{S}_2\text{O}_8$) or N-fluorobenzenesulfonamide (NFSI) (**Scheme 7**).

Scheme 7- Pd Catalyzed CDC reactions utilizing organic peroxide and F⁺ oxidants

All of these are strong oxidants and are simultaneously inexpensive and environmentally friendly, since they do not contain transition metals.³² Given that these peroxides and F⁺ reagents are even stronger oxidants than most metal salts, it has been proposed that they are capable of causing the CDC to go through a Pd(II)/Pd(IV) catalytic cycle rather than the usual Pd(0)/Pd(II).³⁴⁻³⁶ A directing group is used in most of the Pd catalyzed biaryl CDC reactions with organic oxidants, most likely to help control site selectivity.

The oxidant, sodium persulfate, has been used in several Pd catalyzed biaryl CDC reactions by such groups as Dong, Cheng, Lu, and Knochel, all of which also used a strong acid, such as TFA.^{32-34,37-39} Strong acids are proposed to aid metallation of the C-H bond by increasing the electrophilicity of the Pd catalyst.³² These biaryl CDC reactions oxidized by sodium or potassium persulfate couple simple arenes (several with directing groups), and can even be used to make phenanthridinone derivatives (*e.g.* **1**, **Scheme 7**).³³ The Dong group has also shown that using sodium persulfate is an effective oxidant in the CDC of arenes with O-phenylcarbamates.³²

Their coupling reaction achieved up to 98% yield and worked on a large library of substrates (*e.g.* **2**, **Scheme 7**). Finally, exciting new work has come out of the labs of Yu and Seayad that utilize F^+ oxidants.³⁵⁻³⁶ These F^+ oxidants were used along with Pd catalysts and ligand sources to couple simple arenes³⁵ or arylate furans³⁶ in yields up to 85% (*e.g.* **3**, **Scheme 7**).

Stoichiometric Metal Oxidants. The most widely used conditions for biaryl CDC reactions require stoichiometric amounts of metal oxidants. Although stoichiometric metal oxidants make them the least green of all the Pd catalyzed CDC reactions, they are still attractive due to the fact that the starting materials do not need prefunctionalization. The most frequently used metal oxidants are Ag(I) and Cu(II) salts. Both have been shown to work readily in the inter- and intramolecular coupling of simple arenes and heterocycles, and as seen in the section **Molecular Oxygen as an Oxidant and Ligand Controlled Regioselectivity**, DeBoef and Fagnou have even shown that metal oxidants influence regioselectivity.²¹⁻²⁷

Silver (I) salts have been used extensively as oxidants in many different types of biaryl CDC reactions, such as the arylation of indoles,^{23-24,40-42} azoles,⁴³ thiophenes,⁴⁴ chromones,⁴⁵⁻⁴⁶ xanthines,⁴⁷ uracils,⁴⁸ and pyridine N-oxides.^{41-42,49} They are also used in inter- and intramolecular coupling of simple arenes.⁵⁰⁻⁵⁵ Recently, Zhang and co-workers oxidatively coupled thiophene derivatives and fluorinated arenes, using only 2.5 mol percent of $Pd(OAc)_2$ as a catalyst and $AgCO_3$ as an oxidant (**Scheme 8**).⁴⁴

Scheme 8- Pd Catalyzed CDC of Thiophenes and Fluorinated Arenes with a Ag(I) Oxidant

Their reaction worked on a large library of thiophene substrates, and was even shown to arylate benzofurans and indoles in the same conditions. The reaction also tolerated a vast array of functionalities including, amides, esters, aldehydes, and olefins. These perfluoroarene-thiophene compounds are being used in various electronic materials including diodes and transistors,⁴⁴ making Zhang's reaction a superior way to produce these materials.

Another interesting Pd catalyzed CDC reaction with a Ag oxidant was reported by the Sanford group in which they intermolecularly coupled arenes in high yields and high regioselectivity (**Scheme 9**).⁵⁵

Scheme 9- Pd catalyzed CDC of benzoquinoline and arenes with a Ag(I) oxidant

Intermolecular coupling between two arenes is less common due to the fact that heterocycles are easier to regioselectively functionalize due to the intrinsic electronic differences of the C-H bonds.⁵⁵ The Sanford group solved this problem by using benzoquinoline as one of their coupling partners. The substrate's basic nitrogen served as a directing group that coordinated Pd and, thus, controlled site selectivity. They were able to achieve moderate to high yields, even in the presence of electron withdrawing and electron donating functionalities on the arenes.

Copper(II) salts are commonly used oxidants. They are relatively inexpensive, and have been shown to work in a wide array of Pd catalyzed CDC reactions such as the arylation of heterocycles,^{22-25,27,56-57} and intermolecular coupling of arenes.⁵⁸ However in biaryl synthesis, they are chiefly utilized in intramolecular couplings^{22,59-64} and the cross coupling of heterocycles.⁶⁴⁻⁶⁷

In 2011, Greaney and co-workers used a $\text{Cu}(\text{OAc})_2$ oxidant with a $\text{Pd}(\text{OAc})_2$ catalyst for an intramolecular CDC reaction that created medium-sized, biaryl-containing rings (**Scheme 10**).⁶²

Scheme 10- Medium ring synthesis via intramolecular Pd catalyzed CDC with a Cu(II) oxidant

This reaction was unique in that it formed seven- and eight-membered rings, instead of the usual aromatic five member rings, as in the formation of carbozoles.^{15,30,51,60} Medium-size rings occur naturally in many biologically active compounds, and are generally more difficult to synthesize than small rings and large macrocycles, making methods for their synthesis highly desirable.⁶² Greaney's group was able to achieve the synthesis of these rings and incorporate indole into their products, since indole is a common biologically active moiety. The reaction gave high yields, and worked with several other heterocycle coupling partners, like azoles. It also had an exceptional tolerance for amine and ether functionalities within the newly formed rings.

Another interesting Pd mediated reaction with a Cu(II) oxidant comes from a study by the You group in 2011, in which they were able to cross couple heterocycles in high yields with good regioselectivity (**Scheme 11**).⁶⁷

Scheme 11- Pd catalyzed cross coupling of heterocycles with a Cu(II) oxidant

You used a $[\text{Pd(dppf)Cl}_2]$ catalyst and a $\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ oxidant system. They also added a catalytic amount of X-Phos ligand, to prevent decomposition of indole

derivatives, and a CuCl additive, that further helped control regioselectivity. The reaction conditions were found to couple a wide array of heterocycles including, xanthines, pyridine N-oxides, azoles, indoles, and pyrroles in good to excellent yields.

Rhodium and Ruthenium Catalyzed CDC Systems

Catalysts based on rhodium and ruthenium are becoming increasingly popular for the synthesis of biaryls via CDC reactions. Palladium catalysts, although they exhibit good functional group tolerance and require mild reaction conditions, often need 10-20 mol % catalyst loading and a gross excess of one of the coupling substrates for a reaction to reach completion.⁶⁸ Rhodium and ruthenium, on the other hand, have many of the same catalytic properties as Pd,⁶⁸ but usually require less catalyst loading (1-5 mol %) and have potentially novel selectivity properties.⁶⁹ Newfound interest in these metals as catalysts for biaryl CDC has been growing since a study on Ru catalyzed dehydrogenative coupling of 4-pyridines by Suzuki and co-workers in 2007.⁷⁰

Rhodium catalyzed oxidative biaryl coupling is still in its infancy, given that it first started appearing in independent studies by Glorius, Miura, and You in 2012. All of these studies used either Rh(I) or Rh(III) catalysts and Cu(II) oxidants to carry out arylations of heterocycles,⁶⁸ intramolecular couplings⁷¹ or dual heterocycle couplings.^{69,72}

One example by Glorius and co-workers showed that a Rh(III) catalyst in the presence of a AgSbF₆ cocatalyst, could successfully couple two arenes with the use of a tertiary benzamide directing group (**Scheme 12**).⁶⁸

Scheme 12- Rh catalyzed biaryl CDC with a tertiary benzamide directing group

It was suggested that the AgSbF_6 was involved in generating an electrophillic Rh(III) species as the active catalyst. This reaction was remarkable in that it took only 5 mol% catalyst loading and achieved high yields and regioselectivity. Both electron withdrawing and electron donating groups were tried in different positions on the arenes resulting in moderate to high yields with close to a 3:1 meta/para regioselectivity in most cases. It is also interesting to note that the reaction did not couple to the ortho position of bromobenzene; making it possible to exclusively synthesize meta-substituted biaryls using 1,3-haloarenes.

Ruthenium has been used in several oxidative homocoupling reactions;^{70,73-74} however, its use in oxidative cross coupling is brand new. The You group recently published the initial findings of a novel Ru catalyzed biaryl CDC, wherein 2-methylthiophene was successfully coupled to both benzoquinoline and quinoxaline motifs (**Scheme 13**).⁷²

Scheme 13- Ru catalyzed CDC of methylthiophenes with benzoquinolines and quinoxalines

This reaction, although not extensively studied yet, exhibited moderate yields with high regioselectivity.

Copper Mediated CDC Systems

Palladium is used in the majority of biaryl CDC reactions; however copper would be an ideal economical alternative since it is abundant and relatively inexpensive.⁷⁵ It has seen historical use in oxidative naphthyl homo-couplings to synthesize chiral ligands like BINOL.⁷⁶⁻⁷⁸ Although, due to the radical nature of the reaction, the hetero-coupling of naphthyls has proved to be a difficult task since radical-radical recombination produces a majority of homo-coupled products.⁷⁹ Several groups have found solutions to this,⁷⁹⁻⁸³ including Collins and co-workers, who used NHC (N-heterocyclic carbene) ligands in a bis-NHC-Cu(II) complex to catalyze the cross coupling of naphthyl derivatives via CDC (**Scheme 14**).⁷⁹

Scheme 14- CDC of naphthyl derivatives by a N-heterocyclic carbene-Cu(II) complex

The presence of the NHCs greatly effects the electronic properties of the Cu(II) making it possible to cross couple naphthyls. The CDC was believed to proceed via a radical-addition mechanism.

All other Cu mediated CDC reactions fall under two groups: Daugulis iodination conditions,⁸⁴⁻⁸⁵ and Miura's CDC arylation of heterocycles.⁷⁵ Daugulis's conditions include the presence of a Cu(I) salt and I₂ (**Scheme 15**).⁸⁵

Scheme 15- Daugulis conditions for iodination and direct arylation using CuI/I₂

It is known to proceed through a one-pot iodination and then Cu mediated direct arylation. The fact that the reaction is prefunctionalizing one of the C-H bonds

perhaps makes it not a true CDC; however, the reaction requires no initial functionalization steps beforehand giving it the outward appearance of a CDC. Daugulis and co-workers have used their CuI/I₂ conditions on the coupling of a vast array of heterocycles as well as both electron rich and electron poor substrates, making this a highly versatile reaction.

The final category of Cu mediated biaryl CDC is the work by Miura and co-workers in 2011. Miura was able to cross couple arenes with a variety of azoles using excess Cu(OAc)₂ (**Scheme 16**).⁷⁵

Scheme 16- Cu catalyzed CDC of pyridyl arenes and azoles

The reaction gave moderate yields, and the use of a directing group on the arenes provided high regioselectivity. Even though this reaction used excess Cu(OAc)₂, it is still desirable because copper is more economical than other catalytic metals like Pd. Daugulis⁸⁶ and Mori⁸⁷ have successfully shown that catalytic Cu can be used in aryl oxidative dimerizations. Therefore, the goal of using Cu in catalytic

amounts for biaryl CDC, aside from radical naphthyl or iodination coupling, seems promising.

Other CDC Systems

To date there are only a few other examples of CDC systems used for biaryl coupling. The majority of them fall under single electron transfer (SET) oxidants like hypervalent iodine reagents. Kita and co-workers have monopolized the field of using hypervalent iodine in biaryl CDC reactions.⁸⁸⁻⁹²

Hypervalent iodine oxidants are known to be safe,⁸⁸ mild oxidants⁸⁹ that can readily form aromatic cation radicals with electron rich arenes through SET.⁹⁰ They usually require low temperatures and short reaction times. Unwanted dimerization can often plague these aryl CDC reactions, so Kita typically uses one coupling partner like naphthalene, which is electron rich and prone to forming an aromatic cation radical with a hypervalent iodine oxidant, and a second coupling partner that is more nucleophilic so as to cause a nucleophilic attack on the radical and subsequent cross coupling.⁹⁰ Kita and co-workers have also shown that using hypervalent iodine reagents to couple thiophenes can form intermediate thienyl iodonium(III) salts (**Scheme 17**).⁸⁹ The formation of these intermediate salts effectively eliminates dimerization and gives excellent regioselectivity. The reaction tolerated a large library of functionized arenes and heterocycles and gave moderate to high yields.

Scheme 17- Hypervalent iodine mediated CDC of thiophenes with arenes and heterocycles

A few remaining CDC systems include V(V) catalytic systems,⁹³ and Tl(III) catalytic systems;⁹⁴⁻⁹⁵ both of which have been used in intramolecular aryl coupling via free radicals, although in low yields and harsh reaction conditions. Autoxidizing CDC conditions developed by Bergman are also of interest, in which one of the coupling partners, quinoline, serves as the sole oxidant as it is coupled to indole or pyrrole moieties.⁹⁶ Finally, the use of iron in biaryl CDCs is also being developed.⁹⁷⁻⁹⁹ Katsuki and co-workers published a study in 2011 on an aerobic Fe catalyzed cross coupling of naphthol derivatives to make unique BINOL ligands (**Scheme 18**).⁹⁷

Scheme 18- Aerobic Fe catalyzed CDC of naphthols

This reaction was quite green since it used an iron catalyst, which is non-toxic and inexpensive, and only a 4 mol % catalyst loading. Also, the oxidant was molecular oxygen from the air, giving off water as a byproduct. The reaction was suggested to go through a radical-addition, and produced moderate yields and high enantioselectivity on a wide range of substrates. This makes it a desirable new method for synthesizing enantiomeric BINOL ligands.

Future efforts in the CDC of arenes will perhaps include enzyme mediated reactions, since enzymes have low toxicity, high catalytic turnovers, and are able to run in very mild conditions. In 2006,¹⁰⁰ d'Ischia and co-workers used peroxidase enzymes to catalyze the oxidative dimerization of indole derivatives. This technology, albeit low yielding, appears to be an excellent lead to optimize for cross-dehydrogenative coupling.

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Intramolecular Arylation of Benzimidazoles via Pd(II)/Cu(I) catalyzed Cross-
Dehydrogenative Coupling

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Intramolecular Arylation of Benzimidazoles via Pd(II)/Cu(I) catalyzed Cross-Dehydrogenative Coupling

Abstract

Electron poor benzimidazole substrates were arylated via an intramolecular cross-dehydrogenative coupling (CDC) reaction. These CDC reactions were catalyzed by a Pd(II)/Cu(I) catalyst system, capable of producing moderate yields on a large library of substrates. The substrate scope consisted of tethered arene-benzimidazoles that upon coupling, produced a fused polycyclic motif.

Introduction

The biaryl motif is a prominent structure in many biologically active compounds, and green methods to synthesize these biaryl bonds are highly desired.¹ Conventional aryl coupling methods (i.e. Suzuki² or Stille³ coupling) contain prefunctionalization steps to form activated C-metal or C-halogen bonds, which can readily undergo catalytic coupling. However, this prefunctionalization decreases the overall step economy of the synthesis and produces large amounts of waste. A far more advantageous coupling method would be cross-dehydrogenative coupling (CDC). It can be used to inter- and intramolecularly couple two aryl hydrocarbon bonds, requiring no prefunctionalization of substrates and affording high yields with minimal byproducts and waste (**Scheme 1**).

Scheme 1- The Conventional Suzuki-Miyaura Cross Coupling Method vs. CDC

Much attention has been given to incorporating heterocycles into biaryl CDC reactions, since heterocyclic components are often found in nature and play a prominent role in pharmaceutical candidates.¹ The benzimidazole moiety alone has been shown to have many important uses including an antiviral for HIV-1,⁴ antibacterials,⁵⁻⁶ and possible anticancer agents.⁷ However, imidazoles are rarely found as coupling substrates in CDC reactions. Mori and coworkers have shown an efficient homocoupling reaction for imidazoles,⁸ and the You group has found successful coupling of imidazoles to electron-rich substrates like thiofurans.⁹⁻¹⁰ However, oxidative coupling between imidazoles and benzenes has proved to be a challenging task. Dominguez and Dubois have arylated imidazoles using aryl iodides,¹¹⁻¹² but, to our knowledge, the only example of coupling imidazoles with simple arenes via CDC is the coupling of N-styryl-imidazoles by Bao and coworkers.¹³

With this in mind, we decided to try palladium-catalyzed CDC reactions between benzimidazoles and arenes. To help overcome coupling difficulties, the arene was tethered to the benzimidazole prior to coupling by installing an N-benzyl

substituent. The tether would help in the metallation of both coupling partners by keeping them in close proximity to each other, and at the same time reducing unwanted dimerization. CDC should cause this tethered substrate to cyclize into a fused polycyclic system.

Results and Discussion

The optimization studies for this reaction were performed on *N*-benzyl benzimidazole, substrate **1**, which was synthesized through a substitution reaction using deprotonated benzimidazole and benzyl chloride. Substrate **1** was then purified by column chromatography and afforded a 70% yield. Initially, we thought that a Cu(I) halide source would be a beneficial catalyst since it has been shown that CuI can arylate the C2 position on azoles via intramolecular coupling with aryl iodides.¹¹ Since **1** did not contain a halogen, it was also theorized that a catalyst such as Pd(OAc)₂ would be needed to activate the aryl C-H bond. However both Pd(OAc)₂/CuI and Pd(OAc)₂/CuCl catalyst systems proved to be ineffective, since they both gave low conversion of starting materials and a mixture of byproducts. Next, a rhodium based catalyst, [RhCl(coe)₂]₂, was tried, but it suffered from low yields and dimerization. Simply using Pd(OAc)₂ as the catalyst with a Cu(OAc)₂·H₂O oxidant provided a superior system, therefore further optimization reactions were run with this catalyst system (**Table 1**).

Entry ^a	Pd(OAc) ₂ mol %	Cu(OAc) ₂ ·H ₂ O (equiv)	CsOPiv (equiv)	CuOAc (equiv)	Time, Temp.	Yield ^b		
						2	3	4
1	10	4	0	0	1h, 160°C	--	21%	minor
2	10	2	0	0	1h, 120°C	19%	--	minor
3	10	2	0	0	8h, 120°C	31%	--	minor
4	10	2	0	0	4h, 120°C	23%	12%	minor
5	10	2	2.5	0	4h, 120°C	28%	--	--
6	20	2	2.5	0	4h, 120°C	47%	--	--
7	20	1.5	2	0	6h, 120°C	41%	--	minor
8	20	2	2	0	3h, 150°C	56%	--	--
9	20	2	2	0	4h, 150°C	46%	--	--
10	20	1.5	2	0.5	3h, 150°C	58%	--	--

^a All reactions subjected to microwave heating

^b Isolated yield

Table 1- Optimization of the Reaction Conditions

At the outset, undesired byproducts including the dimer **4** and the acetoxylation compound **3** plagued the reaction. It was found that lowering the amount of Cu(OAc)₂·H₂O oxidant helped reduce the amount of acetoxylation products since the amount of acetate anion was reduced. Also simply lowering the temperature and time of the reaction helped lower byproduct formation. Interestingly, the addition of CsOPiv (**Table 1**, entry 5) eliminated compound **3**, most likely due to the steric nature of the pivalate anion. It has been suggested by Fagnou that the addition of pivalate helps facilitate C-H bond cleavage by forming Pd(OPiv)₂ prior to palladation.¹⁴⁻¹⁶ Fagnou and coworkers also showed that reactions performed in pivalic acid instead of acetic acid greatly reduced unwanted oxidative byproducts including dimers.¹⁴

Upon doubling the amount of Pd(OAc)₂, compound **2** was recovered in a nearly twofold yield (**Table 1**, entry 6), suggesting that catalyst turnover was a problem in the reaction. After many trials, the optimal time and temperature for the coupling reaction was found to be 3 hours at 150 °C under microwave heating (**Table**

1, entry 8). The longer reaction times led to a decrease in product, perhaps due to decomposition (**Table 1**, entry 9). Finally, we were excited to discover that the addition of 0.5 equivalents of CuOAc, improved the yield, giving the best isolated yield of 58% (**Table 1**, entry 10).

Another interesting observation during the optimization of this reaction was the copper coloration present in the organic layer while extracting the product. Cu(II) has been known to coordinate to pyrazole ligands in isolatable complexes;¹⁷ thus we speculated that copper was forming a complex with our benzimidazole products, and therefore lowering the isolated yield. A stronger ligand was perhaps needed to remove the copper and free the final product. Immediately following the coupling reaction, we added Na₂S·9H₂O to the reaction and stirred at room temperature for an hour. This removed all copper coloration from the organic extract, and simultaneously increased the yields of the coupled product.

Next, an array of substrates was screened with the optimized conditions to determine the scope of the reaction (**Table 2**). Comparing compounds **2**, **5**, **16**, and **17** gave evidence that the presence of an electron donating group on the benzimidazole moiety increased the coupling yield; however, electron withdrawing functionalities on the benzimidazole, compound **9**, seemed to hinder coupling. When comparing electron rich and electron poor arene coupling partners, there didn't appear to be a significant trend in reactivity. The starting materials for products **8**, **9**, and **13** were synthesized in inseparable mixtures, thus the cyclization reactions produced mixtures of isomers. The cyclization was successful in forming a new six-membered ring, compound **21**, but failed to couple compounds **19** and **20**, which would have produced new seven

membered rings. This indicated that the length of the tether highly influenced the success of the reaction.

Table 2- Scope of the Cyclization of *N*-benzylbenzimidazoles^a

^aReaction conditions: 0.384 mmol substrate, 20 mol% Pd(OAc)₂, Cu(OAc)₂·H₂O (0.768 mmol), CuOAc (0.192 mmol), CsOPiv (0.960 mmol) in 5 mL of 1,4-dioxane at 150 °C for 3 hr under microwave heating. Isolated yields throughout.

Intramolecular coupling reactions between benzimidazole and other heterocycles, such as furan, imidazole, and the caffeine derivative, benzyl theophylline, were also tried under our optimized conditions; however, the attempts were unsuccessful. (e.g. **12**, **14**, **22**, Table 2).

Kinetic isotope effects of the reaction were evaluated by carrying out competition studies. The first competition study utilized equimolar amounts of *N*-benzylbenzimidazole and deuterated *N*-benzyl-*d*₇ benzimidazole, and subjected both substrates to the optimized coupling conditions. Relative amounts of the products were obtained from GC-MS analysis and a KIE of 1.03 was obtained (**Scheme 2**). This indicated that the metalation of the arene coupling partner was not rate limiting, but more of a facile step in the reaction.¹⁸ A second competition study was carried out with equimolar amounts of *N*-benzylbenzimidazole and *N*-benzyl-3-deuterobenzimidazole, but the KIE results of this test proved to be inconclusive due to H/D scrambling.

Scheme 2- KIE Study on Aryl-Benzimidazole Cyclization

With the KIE studies in hand, we sought to propose a plausible mechanism for this unique intramolecular CDC reaction. Based on all data, it seemed that the coupling was taking place through a Pd^{II}/Cu^I catalyzed system. Our reasoning behind the dual metal catalysis was supported by several factors. It was known from previous studies that Cu(I) was capable of enhancing azole coupling,⁸⁻¹¹ so we speculated that Cu(I) was needed to activate the C2 position of the benzimidazole. Because the

addition of Cu(I) only raised the percent yield slightly (**Table 1, entry 10**), we needed to be sure that the addition of Cu(I) was in fact essential in the formation of the product. Since the $\text{Cu}(\text{OAc})_2$ oxidant could disproportionate into Cu(I), we theorized that there was perhaps some Cu(I) present to catalyze the reaction. This would explain why we did not see a significant raise in yield upon the addition of a Cu(I) source.

To test whether Cu(I) was utilized in the mechanism, we had to eliminate the use of $\text{Cu}(\text{OAc})_2$ as an oxidant. (**Scheme 3**) A control was carried out using AgOAc as an oxidant and $\text{Pd}(\text{OAc})_2$ as the only catalyst. The GC-MS results showed that there was low conversion of the starting material into a small amount of the acetoxyated product **2** and dimer **4**. None of the desired arylation product **2** was formed, suggesting that Cu is needed in the reaction.

Scheme 3- Control Reactions Using AgOAc as an Oxidant

We next ran a second control using only a Cu(I) catalyst and AgOAc as the oxidant. The GC-MS results showed there was a low conversion of the starting material into the dimer **4**. (**Scheme 3**) Consequently, we concluded that Cu(I) could

activate the benzimidazole moiety and form the benzimidazole dimer. This control also supported that Pd played a pivotal role in the activation of the arene for coupling.

Our proposed mechanism (**Scheme 4**) utilizes two independent metalation steps. First, Cu(I) inserts in the 2 position of benzimidazole, forming acetic acid and a Cu(I)-benzimidazole complex. Next, the arene is palladated, again producing acetic acid as a byproduct. At this point, a transmetalation could occur in which CuOAc is released and a biaryl Pd(II) complex is formed. The final step of the reaction would include a simple reductive elimination to form the coupled aryl-benzimidazole product and Pd(0). Subsequent oxidation of the Pd by the Cu(OAc)₂ oxidant would regenerate both the Pd(II) and Cu(I) catalysts. To our knowledge, two independent C-H activations by different metals followed by a single transmetalation, is a novel mechanism, and would warrant future investigations.

Scheme 4-Proposed Mechanism for the Pd(II)/Cu(I) Catalyzed Cyclization of N-benzylbenzimidazoles

Based on the KIE studies, it was concluded that the palladation of the arene is not rate limiting and does not go through a concerted metalation deprotonation (CMD)

mechanism. Instead it more likely proceeds through some kind of electrophilic aromatic metalation. For a CMD mechanism a much higher KIE value of 3-4 would have been expected, since the rate limiting step consists of simultaneous C-H bond cleavage and palladation. Electrophilic metalation on the other hand, would have a lower KIE value, since palladation occurs before deprotonation. Electrophilic palladation of the arene causes a loss of aromaticity, which provides for easy subsequent deprotonation of arene in order to restore aromaticity.

Conclusions

In conclusion, we have developed an intramolecular coupling reaction between the 2-position of benzimidazole and a tethered arene to form fused polycyclic heterocycles. The use of cross-dehydrogenative coupling in this reaction makes it highly atom economical and cost efficient, since no prefunctionalization is required. Mechanistic investigations led us to propose that the reaction proceeds via a dual $\text{Pd}^{\text{II}}/\text{Cu}^{\text{I}}$ catalyst system with a $\text{Cu}(\text{OAc})_2$ oxidant. A large library of electron poor and electron rich arene-benzimidazoles were coupled in moderate yields, suggesting that this reaction could be a valuable tool in the synthesis of biologically useful heterocyclic compounds.

Methods

Representative Procedure for CDC Coupling. A magnetically stirred solution of *N*-benzylbenzimidazole (82 mg, 0.395 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg,

0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **2** (82 mg, 53% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Representative Procedure for Synthesizing N-Tethered Starting Materials. Under an inert nitrogen atmosphere, benzimidazole (4.0 g, 33.8 mmol) was added to a solution of potassium tert-butoxide (5.7 g, 50.8 mmol) in 40 mL of DMF at 0 °C and magnetically stirred for 15 minutes. To the mixture was added a solution of benzyl chloride (4.7 g, 37.3 mmol) in an additional 15 mL of DMF. The mixture was then left to warm to room temperature and stirred for 2 hours. After the reaction was complete, it was quenched with 90 mL of water and extracted three times with 90 mL portions of ethyl acetate. The organic extracts were washed with three 90 mL portions of water followed by three 90 mL portions of brine. The organic extracts were dried with magnesium sulfate and condensed at reduced pressure. The crude product was then purified via column chromatography to give pure *N*-benzylbenzimidazole (4.10 g, 58% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

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Experimental Section

The novel compounds synthesized are reported below.

Reagents

All reagents, including benzimidazoles, benzyl chlorides, sodium sulfide nonahydrate, potassium *tert*-butoxide, ethyl acetate, hexanes, 1-4-dioxane, copper(II) acetate monohydrate, copper(I) acetate, and cesium pivalate were purchased from Fisher Scientific and Sigma Aldrich and used without purification. Column chromatography was performed on Silicycle silica gel (60 Å, 40-63 µm). Palladium (II) acetate was purchased from Precious Metals Online (<http://www.precmet.com/au/>). It was then dried at 100 °C for approximately 6 hours under vacuum. All reagents were stored in an inert nitrogen atmosphere.

Instrumentation

Reactions were carried out with a CEM Discover Microwave. A Bruker Avance 300 MHz spectrometer and a JEOL GSX 400 MHz spectrometer were used for NMR analysis. GC/MS analysis was carried out with an Agilent Technologies 6890 GC fixed with a 5973 Mass Selective Detector.

Synthesis of 11-*H*-Isoindolo[2,1-*a*]benzimidazole (**2**)

A magnetically stirred solution of *N*-benzylbenzimidazole (80 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **2** (45 mg, 58% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexanes/Ethyl acetate (70:30 v/v) = 0.4

¹H NMR (300 MHz, CDCl₃) δ= 8.02 (dd, J= 6.5 Hz, 1.39 Hz, 1H), 7.83-7.81 (m, 1H), 7.53-7.44 (m, 3H), 7.39-7.36 (m, 1H), 7.26-7.23 (m, 2H), 4.95 (s, 2H)

¹³C NMR (75 MHz, CDCl₃) δ= 158.46, 148.34, 143.48, 132.63, 129.47, 129.32, 128.70, 123.83, 122.64, 122.14, 121.98, 120.48, 109.32, 47.17

LRMS EI (m/z): [M⁺] calc'd for C₁₄H₁₀N₂ 206.1, observed 206.2

Spectrum 1- ^1H NMR of Compound 2

Spectrum 2- ^{13}C NMR of Compound 2

Synthesis of **3**

A magnetically stirred solution of *N*-benzylbenzimidazole (125 mg, 0.6 mmol), palladium acetate (14 mg, 0.06 mmol), copper(II) acetate (479 mg, 2.4 mmol), and 4.5 mL dioxane was microwave heated 160 °C for 1 hours. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **3** (33 mg, 21% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexanes/Ethyl acetate (70:30 v/v) = 0.30

¹H NMR (300 MHz, CDCl₃) δ= 7.97 (d, J= 7.4 Hz , 1H), 7.82-7.79 (m, 1H), 7.60-7.57 (m, 2H), 7.55 (s, 1H), 7.52-7.47 (m, 2H), 7.30-7.27 (m, 2H), 2.24 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ=170.98, 157.28, 148.60, 143.47, 131.89, 130.92, 130.41, 129.44, 126.73, 125.03, 123.98, 122.94, 122.16, 120.76, 110.78, 20.93

LRMS EI (m/z): [M⁺] calc'd for C₁₆H₁₂N₂O₂ 264.1, observed 264.1

Spectrum 4- ¹³C NMR of Compound 3

Synthesis of **7**

A magnetically stirred solution of N-(3-chlorobenzyl)-benzimidazole (0.093 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **7** (13 mg, 15% yield). The product was analyzed by GC-MS, and ^1H NMR and ^{13}C NMR spectroscopy.

^1H NMR (300 MHz, CDCl_3) δ = 7.97 (d, J = 8.2 Hz, 1H) , 7.83 (dd, J = 6.0 Hz, 3.2 Hz, 1H) , 7.56 (sd, J = 1.8 Hz, 1H) , 7.51 (dd, J = 8.2 Hz, 1.8 Hz, 1H) , 7.44 (dd, J = 6.0, 3.2 Hz, 1H) , 7.30 (d, J =3.2 Hz, 1H) 7.29 (d, J =3.2 Hz, 1H), 5.04 (s, 2H)

^{13}C NMR (75 MHz, CDCl_3) δ = 145.92, 139.03, 136.52, 130.22, 128.93, 125.31, 123.91, 123.87, 123.75, 123.37, 123.03, 121.61, 110.30, 47.95

LRMS EI (m/z): $[\text{M}^+]$ calc'd for $\text{C}_{14}\text{H}_9\text{ClN}_2$ 240.0, observed 240.0

Spectrum 5- ^1H NMR of Compound 7

Spectrum 6- ¹³C NMR of Compound 7

Synthesis of **9**

A magnetically stirred solution of a mixture of N-benzyl- (5-nitro and 6-nitro)benzimidazole (97 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **9** (26 mg, 29% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

¹H NMR (300 MHz, CDCl₃) δ= 8.69 (d, J= 1.7 Hz, 1H, isomer A), 8.40 (d, J= 1.7 Hz, 1H, isomer B), 8.24-8.20 (m, 1H, isomer A and B) 8.09 (s, J= 3.84 Hz, 1H, isomer A and B) 7.85 (d, J= 9.0 Hz, 1H, isomer B), 7.64-7.56 (m, 3H, isomer A and B), 7.49 (d, J= 8.6 Hz, 1H, isomer A), 5.17 (s, 2H, isomer B), 5.13 (s, 2H, isomer A)

¹³C NMR (75 MHz, CDCl₃) (isomer A) δ= 143.50, 138.73, 133.12, 130.83, 129.24, 124.16, 122.83, 120.21, 119.39, 118.77, 116.95, 109.04, 106.16, 47.63

LRMS EI (m/z): [M⁺] calc'd for C₁₄H₉N₃O₂ 251.1, observed 251.1

Spectrum 7- ¹H NMR of Compound 9

Spectrum 8- ^{13}C NMR of Compound 9

Synthesis of **11**

A magnetically stirred solution of N-(3-(trifluoromethyl)benzyl)-5,6-dimethylbenzimidazole (117 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **11** (57 mg, 50% yield). The product was analyzed by GC-MS, and ^1H NMR and ^{13}C NMR spectroscopy.

^1H NMR (300 MHz, CDCl_3) δ = 8.08 (d, J = 8.0 Hz, 1H) , 7.79 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.23 (s, 1H), 5.02 (s, 2H), 2.39 (s, 3H), 2.38 (s, 3H)

^{13}C NMR (75 MHz, CDCl_3), ^{19}F not decoupled δ = 143.67, 132.95, 132.86, 126.14, 126.09, 125.72, 121.96, 121.00, 120.93, 120.88, 120.82, 120.79, 109.91, 47.22, 29.71, 20.57, 20.40

LRMS EI (m/z): $[\text{M}^+]$ calc'd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2$ 302.1, observed 302.1

Spectrum 9- ^1H NMR of Compound 11

Spectrum 10- ^{13}C NMR of Compound 11

Synthesis of **15**

A magnetically stirred solution of N-(2-methoxybenzyl)-benzimidazole (80 mg, 0.33 mmol), palladium acetate (15 mg, 0.067 mmol), copper(II) acetate monohydrate (101 mg, 0.504 mmol), copper(I) acetate (21 mg, 0.17 mmol), cesium pivalate (157 mg, 0.672 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **15** (34 mg, 43% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexane/Ethyl acetate (50:50 v/v) = 0.30

¹H NMR (300 MHz, CDCl₃) δ= 7.83-7.80 (m, 1H), 7.63 (d, J= 7.6 Hz, 1H), 7.47-7.40 (m, 2H), 7.27-7.24 (m, 2H), 6.92 (d, J=8.2 Hz, 1H), 4.90 (s, 2H), 3.90 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ= 158.64, 155.05, 148.33, 132.70, 130.98, 130.68, 130.46, 122.62, 122.04, 120.51, 114.35, 111.29, 109.33, 55.43, 45.39

LRMS EI (m/z): [M⁺] calc'd for C₁₅H₁₂N₂O 236.1, observed 236.1

Spectrum 11- ¹H NMR of Compound 15

Spectrum 12- ^{13}C NMR of Compound 15

Synthesis of **16**

A magnetically stirred solution of N-(4-methoxybenzyl)-(5,6-dimethyl)benzimidazole (102 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **16** (64 mg, 63% yield). The product was analyzed by GC-MS, and ^1H NMR and ^{13}C NMR spectroscopy.

^1H NMR (300 MHz, CDCl_3) δ = 7.49 (s, 1H), 7.44 (sd, J =2.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.98 (s, 1H), 6.89 (dd, J =8.3 Hz, 2.3 Hz, 1H), 4.61 (s, 2H), 3.83 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H)

^{13}C NMR (75 MHz, CDCl_3) δ = 20.03, 20.40, 46.50, 55.53, 105.41, 109.54, 116.26, 120.27, 124.34, 130.62, 130.74, 131.08, 131.70, 135.34, 146.61, 157.50, 160.04

LRMS EI (m/z): $[\text{M}^+]$ calc'd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$ 264.1, observed 264.1

Spectrum 13- ^1H NMR of Compound 16

Spectrum 14- ¹³C NMR of Compound 16

Synthesis of **17**

A magnetically stirred solution of N-(4-methoxybenzyl)-benzimidazole (91 mg, 0.384 mmol), palladium acetate (18 mg, 0.076 mmol), copper(II) acetate monohydrate (115 mg, 0.576 mmol), copper(I) acetate (24 mg, 0.192 mmol), cesium pivalate (180 mg, 0.768 mmol), and 5 mL dioxane was microwave heated 150 °C for 3 hours. After the reaction was complete, sodium sulfide nonahydrate (0.6 g, 2.5 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The mixture was then filtered, using 3 mL ethyl acetate to rinse the reaction vial, and the filtrate was condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **17** (49 mg, 54% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

¹H NMR (400 MHz, CDCl₃) δ= 7.80 (d, J= 7.0 Hz, 1H), 7.52 (s, 1H), 7.38-7.34 (m, 2H), 7.25-7.22 (m, 2H), 6.98 (d, J= 8.4 Hz, 1H), 4.85 (s, 2H), 3.86 (s, 3H)

¹³C NMR (101 MHz, CDCl₃) δ= 160.23, 148.19, 138.10, 135.37, 132.72, 130.46, 124.52, 122.62, 122.08, 120.43, 116.89, 109.31, 105.76, 55.61, 46.78

LRMS EI (m/z): [M⁺] calc'd for C₁₅H₁₂N₂O 236.1, observed 236.1

Spectrum 15- ^1H NMR of Compound 17

Spectrum 16- ¹³C NMR of Compound 17

Synthesis of *N*-benzylbenzimidazole

Under an inert nitrogen atmosphere, benzimidazole (4.0 g, 33.8 mmol) was added to a solution of potassium *tert*-butoxide (5.7 g, 50.8 mmol) in 40 mL of DMF at 0 °C and magnetically stirred for 15 minutes. To the mixture was added a solution of benzyl chloride (4.7 g, 37.3 mmol) in an additional 15 mL of DMF. The mixture was then left to warm to room temperature and stirred for 2 hours. After the reaction was complete, it was quenched with 90 mL of water and extracted three times with 90 mL portions of ethyl acetate. The organic extracts were washed with three 90 mL portions of water followed by three 90 mL portions of brine. The organic extracts were dried with magnesium sulfate and condensed at reduced pressure. The crude product was then purified via column chromatography to give pure *N*-benzylbenzimidazole (4.10 g, 58% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexanes/Ethyl acetate (30:70 v/v) = 0.40

¹H NMR (300 MHz, CDCl₃) δ= 7.94 (s, 1H), 7.83 (dd, J= 8.1 Hz, 1.9 Hz, 1H), 7.33-7.25 (m, 6H) 7.18-7.15 (m, 2H), 5.33 (s, 2H)

¹³C NMR (75 MHz, CDCl₃) δ= 143.96, 143.21, 135.45, 133.88, 129.00, 128.23, 127.04, 123.04, 122.23, 120.41, 110.01, 48.77

LRMS EI (m/z): [M⁺] calc'd for C₁₄H₁₂N₂ 208.1, observed 208.1

Spectrum 17- ^1H NMR of N-benzylbenzimidazole

Spectrum 18- ^{13}C NMR of *N*-benzylbenzimidazole

Synthesis of 1-((furan-2-yl)methyl)-5,6-dimethyl-1H-benzo[d]imidazole

Under an inert nitrogen atmosphere, tosyl chloride (2.33 g, 12.1 mmol) was added to a solution of furfuryl alcohol (1.08 g, 11.0 mmol) and triethylamine (2.0mL, 14 mmol) in 10 mL of methylene chloride at 0 °C. The reaction was magnetically stirred and allowed to warm to room temperature. It was monitored by TLC until the reaction was complete. A second reaction mixture of 5,6-dimethylbenzimidazole (3.38 g, 23.1 mmol) and potassium tert-butoxide (3.87 g, 34.4 mmol) in 30 mL of methylene chloride was magnetically stirred for 30 minutes at room temperature. It was then cooled to 0 °C, and the first reaction mixture was added directly. The whole mixture was then left to warm to room temperature and stirred for 4-6 hours. After the reaction was complete, it was quenched with 50 mL of water and extracted three times with 10 mL portions of methylene chloride. The organic extracts were washed with two 30 mL portions of brine followed by two 10 mL portions of saturated sodium bicarbonate solution. The organic extracts were dried with magnesium sulfate and condensed at reduced pressure. The crude product was then purified via column chromatography to give pure 1-((furan-2-yl)methyl)-5,6-dimethyl-1H-benzo[d]imidazole (0.52g , 21% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexane/Ethyl acetate (30:70 v/v) = 0.33

¹H NMR (300 MHz, CDCl₃) δ= 7.82 (s, 1H), 7.55 (s, 1H), 7.37 (s, 1H), 7.19 (s, 1H), 6.34-6.30 (m, 2H), 5.24 (s, 2H), 2.38 (s, 3H), 2.36 (s, 3H)

^{13}C NMR (75 MHz, CDCl_3) δ = 148.80, 143.04, 142.39, 142.08, 132.27, 132.22, 131.16, 120.35, 110.59, 109.84, 108.84, 41.67, 20.63, 20.25

LRMS EI (m/z): $[\text{M}^+]$ calc'd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ 226.1, observed 226.1

Spectrum 19- ¹H NMR of 1-((furan-3-yl)methyl)-5,6-dimethyl-1H-benzimidazole

Spectrum 20- ¹³C NMR of 1-((furan-2-yl)methyl)-5,6-dimethyl-1H-benzimidazole

Synthesis of 1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzo[d]imidazole

Under an inert nitrogen atmosphere, 5,6-dimethylbenzimidazole (1.0 g, 6.8 mmol) was added to a solution of potassium hydroxide (0.58 g, 10.3 mmol) in 20 mL of DMF and magnetically stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and 3-trifluoromethyl benzyl chloride (1.16 mL, 7.52 mmol) was added. The mixture was then left to warm to room temperature and monitored by TLC. After the reaction was complete, it was quenched with 30 mL of water and extracted three times with 20 mL portions of ethyl acetate. The organic extracts were washed with 20 mL of DI water followed by two 20 mL portions of brine. The organic extracts were dried with magnesium sulfate and condensed at reduced pressure. The crude product was then purified via column chromatography to give pure **1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzo[d]imidazole** (1.52 g, 73% yield). The product was analyzed by GC-MS, and ¹H NMR and ¹³C NMR spectroscopy.

Rf-Value: Hexane/Ethyl acetate (10:90 v/v) = 0.33

¹H NMR (300 MHz, CDCl₃) δ= 7.84 (s, 1H), 7.60 (s, 1H), 7.56 (d, J= 7.7 Hz), 7.49 (s, 1H), 7.42 (t, J= 7.7, 1H), 7.24 (d, J=7.7 Hz, 1H), 7.00 (s, 1H), 5.34 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H)

¹³C NMR (75 MHz, CDCl₃), ¹⁹F not decoupled δ= 142.60, 142.35, 136.97, 132.64, 132.26, 131.49, 130.07, 129.66, 126.98, 125.60, 125.07 (q, J_{C-F}= 3.9 Hz), 123.67 (q, J_{C-F}= 3.9 Hz), 121.99, 120.55, 109.86, 48.13, 20.59

LRMS EI (m/z): [M⁺] calc'd for C₁₇H₁₅F₃N₂ 304.1, observed 304.1

Spectrum 21- ^1H NMR of 1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzimidazole

Spectrum 22- ¹³C NMR of 1-(3-(trifluoromethyl)benzyl)-5,6-dimethyl-1H-benzimidazole

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