ENANTIOSELECTIVE CROSS-COUPLING OF MONOSUBSTITUTED FERROCENES IN CHIRAL IONIC LIQUIDS

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BY

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ABSTRACT

ENANTIOSELECTIVE CROSS-COUPLING OF MONOSUBSTITUTED FERROCENES IN CHIRAL IONIC LIQUIDS

Planarly chiral ferrocenes have applications in pharmaceuticals, agrochemicals, and biomedical research for their use as ligands or catalysts in asymmetric synthesis. Previous methods of enantioselective synthesis of planar-chiral ferrocenes involve directed *ortho*-metalation with either a pre-installed centrally chiral group or chiral resolution. These methods use sensitive organometallic reagents, have low atom economy, and require additional steps to remove the chiral auxiliary or perform chiral resolution. Asymmetric cross-coupling is an enticing alternative, although enantioselective C-H bond activation poses a challenge. N-heterocyclic carbenes including imidazoliums can complex to palladium catalysts to act as a chiral ligand and strong σ donor and have previously been used to achieve C-H activation in arylations of benzaldehydes. This research aimed to achieve enantioselective arylation of ferrocenes, using a catalytic system comprising $Pd(OAc)_2$, imidazolium salts and Cs_2CO_3 to achieve enantioselective catalysis, enabling asymmetric cross-coupling of aryl halides to monosubstituted ferrocenes, which yielded trace amounts of product. The addition of p-benzoquinone and $Cu(OAc)_2$- acting as oxidants- expands the scope of the reaction to facilitate

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asymmetric cross-coupling of monosubstituted ferrocenes with aryl boronic acids. Additionally, a homocoupling reaction between aryl bromides with 65% yield was developed, which could also offer access to axially chiral biphenyl compounds. The enantiomerically pure compounds created using these techniques have applications in many areas of organic, bio and medicinal chemistry, including drug design, ligand synthesis for asymmetric catalysis and polymer chemistry used in research, medicine, and industry.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

CHAPTER ONE: REVIEW OF IONIC LIQUIDS AND CROSS-COUPLING

LIST OF TABLES

LIST OF FIGURES

LIST OF REACTION SCHEMES

SYMBOLS AND ABBREVIATIONS

CIL	chiral ionic liquid
BINOL	1,1’-bi-2-naphthol
BIPOL	1,1’-biphenyl-2,2’-diol
DCM	dichloromethane
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1’-bis(diphenylphosphino)ferrocene
%ee	enantiomeric excess
HPLC	high performance liquid chromatography
HRS	hours
IL	ionic liquid
min	minutes
MS	mass spectrometry
MW	microwave
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
TosMIC	p-toluenesulfonylmethyl isocyanide

CHAPTER ONE: REVIEW OF IONIC LIQUIDS AND CROSS-COUPLING

1.1 Ionic Liquids

1.1.1 General Background

Ionic liquids (ILs) are highly viscous salts with melting points typically below 100°C[1]. They consist of a positively charged ionic group and a paired organic or inorganic anion. The ions are weakly coordinated, resulting in a low melting point[2]. Usually, the cations are bulky, with long alkyl chains and the anions are small[2]. ILs have uses as solvents, reagents and catalysts. They generally display good chemical, thermal, air and moisture stability. As solvents, they have the ability to dissolve both organic and inorganic compounds, are miscible with many solvents including water and show good ion conductivity[1,3]. Moreover, the physical and chemical properties (including solubility, polarity, and chiral discrimination capabilities) can be adjusted depending on the structure of the ions used. By modifying the chemical and physical properties of the ions, as well as pairing different ions, ILs can be optimized for specific reactions[3,4]. ILs generally don't produce as harmful waste compared to traditional solvents, are not volatile and can be reused, making them a more environmentally friendly and potentially cheaper option than traditional organic solvents[3]. Figure 1 shows a few examples of ionic liquid cations and anions seen in the literature. IL research is still relatively new, so the potential of ionic liquids is still being uncovered[5-7]. New research is expanding the examples of ILs, as well as their scope and applications.

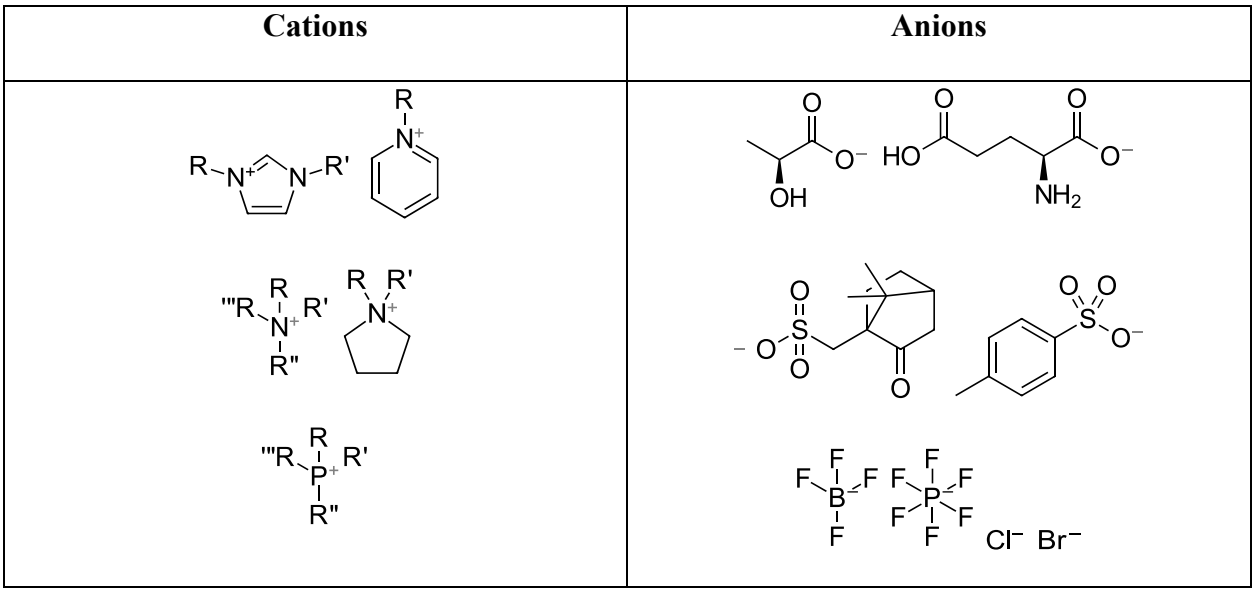


Figure 1. Common ions used in ILs[8].

1.1.2 Ionic Liquids as Solvents

ILs have become attractive replacements for conventional organic solvents because they offer high customizability to specific reactions and substrates, the ability to solvate compounds of varying polarity, high thermal stability and reusability make them potentially cheaper and more environmentally friendly[2,4]. The physical and chemical properties of ILs can be dramatically altered with slight adjustments to the structure of an ion or its counter ion, giving ILs the moniker of "designer solvents"[1,2]. ILs are considered polar compounds, due to their ionic nature; however, they possess the ability to dissolve a wide range of polar and non-polar compounds. Ion-ion interactions, van der Waal's forces, dipole interactions, π- π interactions, hydrogen bonding and hydrophobic interactions all contribute to an IL's solvation capabilities[2,9]. There are also several modifications that can be made to an IL to adjust its solvating capabilities. For example, basic ions (e.g., NO_3^-) and shorter alkyl chain length can be used to increase water solubility[1,2]. The high thermal stability and low vapour pressure, due to Columbic forces between

the ions, make ILs attractive solvents for high-temperature reactions including microwave reactions[2]. The heat capacity and melting point of an IL can also be adjusted. For example, increasing alkyl chain length will decrease the melting point, while increasing the symmetry will increase the melting point[2]. Increasing the alkyl chain length will also increase the viscosity, a limitation of ILs, because the high viscosity can interfere with their ability to effectively mix systems[1]. Notably, ILs have been shown to effectively absorb microwave energy and act as an assistant stabilizer, making ILs an enticing option for microwave-assisted synthesis[10]. ILs can also be synthesized from inexpensive organic starting materials such as imidazole and inorganic salts. They can also be recovered and reused several times, making them both a lower cost and environmentally friendly alternative to traditional organic solvents[2].

1.1.3 Chiral Ionic Liquids

Chiral ionic liquids (CILs) are a relatively new area of research, with the first CIL reported in 1997[11]. They contain at least one chiral center on either the cation or anion. For example, imidazole based CILs may contain chiral alkyl chains, often derived from natural molecules, including citronellol, menthol, sugars and amino acids. CILs have applications as catalysts or ligands in asymmetric catalysis, chromatographic separation and in spectroscopy[12]. Enantioselective capabilities can be tuned by adjusting the number of chiral centers and the location of the chiral centers[13]. For example, Zhang et al. used imidazolium spiroborate CILs as an additive to cyclodextrins to separate racemic drugs using capillary electrophoresis. They found that adjusting the size of alkyl group attached to the chiral center of the anion affected the resolution in the separations of racemic drugs[13]. In general, chiral groups proximal to the ionic portion of the molecule offer better enantioselective capabilities.

1.1.4 Imidazole-based Ionic Liquids

The use of imidazole-based cations in ILs (Figure 2) has become increasingly popular due to their tunability, thermal stability, electrochemical window and ionic conductivity[12]. Imidazole is amphoteric- meaning it can both accept and donate protons. Therefore, a range of reactions are possible to chemically modify the ring, including S_N2 reactions at the 3-position, nucleophilic reactions where the secondary amine at the 1-position acts as the nucleophile and deprotonation at the 2-position to generate a carbene[12]. Additionally, the associated counter-ion is fairly mobile, meaning that it can move freely throughout the medium and can be easily exchanged to further tune the IL. 1,3-Dialkylimidazolium ILs have emerged as an attractive area of research, with many new molecules being developed (Figure 3)[14]. Readily available and cheap reagents from the chiral pool can added at the 1 and/or 3 position to synthesize imidazolium CILs. Chiral anions can also be used.

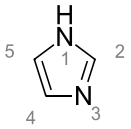


Figure 2. Imidazole numbering.

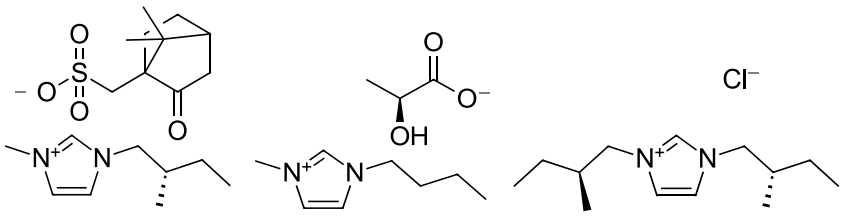


Figure 3. Common imidazolium CILs[14]. A chiral alkyl chain can be used to impart chirality on the cation. The anion can also be chiral, or both cation and anion.

1.1.5 N-heterocyclic Carbenes

When treated with base and/or heated, imidazole-based ILs can be converted to N-heterocyclic carbenes (NHCs) (Figure 4). Carbenes are molecules containing a neutrally charged carbon atom, with a lone pair of nonbonded electrons. Carbenes are capable of coordinating to transition metals, giving them wide applications as ligands in transition metal catalyzed reactions. In general, NHCs formed *in situ* from their corresponding imidazolium salt are more effective than pre-formed NHCs[15]. The sp^2 hybridized lone pair gives the NHC strong σ-donor ability[16]. NHCs also possess weak π-acceptor abilities, making them similar to the ever-popular phosphine ligands[15]. NHCs can be advantageous over phosphine ligands, because NHCs form shorter, stronger bonds with transition metals than phosphine ligands, and are easier to modify[16]. Diverse libraries of NHCs can then be created by using substituted imidazole based ILs. Both steric and electron donating abilities of a ligand (in this case an NHC) are important considerations when developing transition metal catalysts for organic synthesis. The alkyl groups (usually at the 1 and 3 positions), can be used to alter the steric properties (quantified with the "buried volume" parameter) and the electronic properties (described by the Tolman electronic parameter)[17, 18]. NHCs containing chiral alkyl chains can also be used to generate chiral catalysts.

Therefore, NHCs offer an avenue to tune the reactivity and enantioselectivity of transition metal catalysts for applications such as cross-coupling reactions.

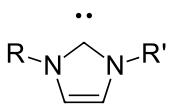
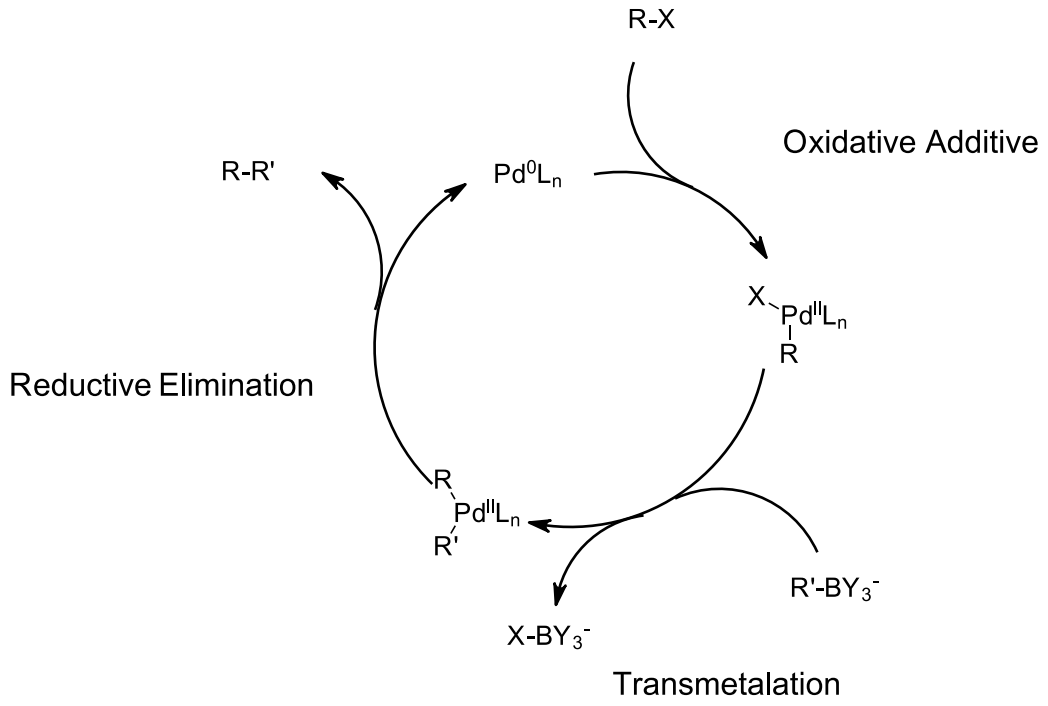


Figure 4. An imidazole based NHC. A lone pair of electrons sits on the 2-carbon, which is neutrally charged.

1.2 Cross-coupling

1.2.1 General overview

Cross-coupling reactions join two different fragments, normally forming a new carbon-carbon bond, although carbon-heteroatom bonds such as carbon-oxygen and carbon-nitrogen bonds are also possible[19]. These reactions have important applications in synthesis, particularly in the pharmaceutical industry, and the types, scope, scaling and applicability of cross-coupling reactions is an active area for researchers[19]. Most typically, an organohalide or triflate is reacted with an organometallic reagent (e.g., organoboranes and organotins), but other coupling partners are possible, including terminal alkenes and alkynes, in place of organometallics. A wide variety of cross-coupling reaction partners have been identified and studied, including Suzuki-Miyaura, Tsuji Trost, Heck, Sonogashira, and Stille reactions. In all cases, they are catalyzed by transition metals, such as palladium, ruthenium, nickel, iron and copper, with palladium being most commonly used[19,20]. Mechanistically, cross-coupling generally occurs in three steps: oxidative addition, transmetalation, and reductive elimination. Suzuki cross-coupling reactions between boronic acids and organohalides, in the presence of palladium(0) catalysts are among the most common cross-coupling reactions and are well understood mechanistically (Scheme 1).



Scheme 1. A generic Suzuki cross-coupling catalytic cycle, comprising three steps: oxidative addition, transmetalation and reductive elimination.

In the first step, oxidative addition, the organohalide will add to the palladium catalyst, across the carbon-halide bond, thus oxidizing the palladium catalyst to palladium(II). This step is usually the rate limiting step[21]. In the case of palladium and other d-block elements, the palladium complex will be most stable with 18 electrons in its outer shell, meaning that palladium complexes with fewer electron donating ligands (i.e., starting with the outer shell having 12, 14 or 16 electrons) will generate a more reactive catalyst, as the organohalide will more readily add to the unsaturated palladium catalyst and donate electrons to the deficient outer shell of palladium[21-23]. This is often accomplished by using bulky ligands (e.g., bulky phosphines and N-heterocyclic carbenes)[22,23]. A balance must be struck however, because excessively bulky ligands may sterically block the organohalide from adding to the catalyst[21,22]. Better leaving groups will also promote a faster oxidative addition.

In the second step, transmetalation, the halogen ligand on the palladium is exchanged for the R group attached to a boronic acid. Transmetalation is generally base promoted. The base is thought to play one of two roles. It could react with the boronic acid to form a trialkoxyboronate which can then react nucleophilically with the palladium complex, or it could complex to the palladium, forming a more reactive palladium oxo complex, that can react with the boronic acid [24,25]. This second possibility seems likely in certain cross-coupling mechanisms requiring C-H activation[20,26].

The final step, reductive elimination, occurs when the two original reagents couple together, and are eliminated from the palladium complex, to form the product, while reducing the palladium and regenerating the original catalyst.

ILs are an attractive solvent choice for cross-coupling reactions because the wide range of organic, inorganic and organometallic compounds used in cross-coupling reactions can be dissolved in a single IL[10], which isn't normally possible in conventional organic solvents, which rely on biphasic systems in the presence of a phase-transfer agent.

1.2.2 C-H Cross-coupling

Cross-coupling reactions are generally precipitated on the formation of highly reactive aryl or alkyl palladium(II) intermediates, which then form carbon-carbon and carbon-heteroatom bonds. The formation of these aryl or alkyl palladium intermediates is usually facilitated by "activated" carbons, attached to electron withdrawing groups (EWGs), such as halides or triflates; and electron donating groups, such as organoboronic acids and organotins. Given the prevalence of carbon-hydrogen bonds in organic compounds, the selective activation of C-H bonds for cross-coupling reactions is an extremely attractive area of research[27]. Cross-coupling

reactions employing one or two C-H bond cleavages by palladium(II) catalysts offer access to novel disconnections in retrosyntheic analysis, and access to new synthetic pathways[20,27]. Palladium(II) catalysts are typically used because there is usually no oxidation in the initial addition step[21]. Palladium(II) acetate is a popular catalyst choice for these types of reactions[20,26].

An adjacent, strongly-coordinating, nitrogen-containing group is generally needed for C-H activation reactions, in order to coordinate to and activate the catalyst in a nearby area to the C-H bond. That being said, other directing groups are currently a focus of research, and other directing groups have been successfully used, including aldehydes and methoxy imines[15, 28].

The mechanisms of cyclopalladation to form aryl/alkyl palladium(II) intermediates vary and are still being elucidated. A methylamino directing group, palladium(II) acetate catalyst and organometallic coupling partner are commonly used reagents to achieve these reactions[20]. Under these conditions, the lone pair on the nitrogen coordinates to the palladium, bringing the *ortho* C-H bond in closer proximity to the catalyst. The palladium can then coordinate to both the carbon and hydrogen atoms in the C-H bond[20]. The stereoselectivity is primarily governed by the directing group (in this case, methylamino groups direct *ortho*), but also the acidity and sterics of the hydrogen in the activated C-H bond. The hydrogen can then also complex with the carbonyl on one of the acetate groups, with the acetate group acting as an internal base (Figure 5)[20]. From there, transmetalation and reductive elimination occur in one step; when the product is formed the $Pd^{II}(OAc)_2$ catalyst is reduced to Pd^0 [20]. An oxidation system using benzoquinone and a source of acetate (e.g., $Cu(OAc)_2$) can be used to complete the catalytic cycle (Scheme 2)[20]. The mechanisms for C-H activation cross-coupling reactions vary; however, an understanding of these mechanisms is important to be able to adjust reaction conditions accordingly.

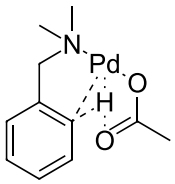
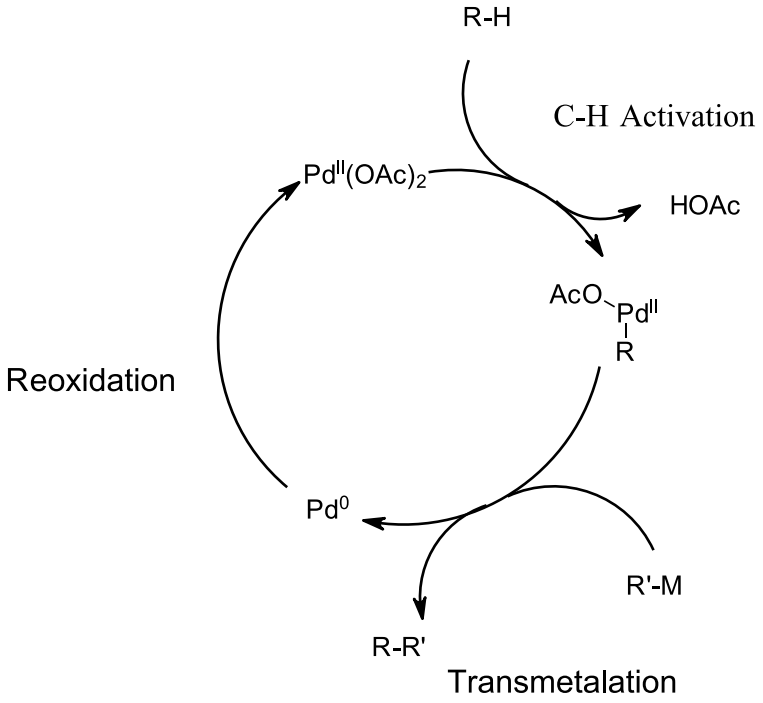


Figure 5. A proposed transition state of a C-H cross-coupling reaction after C-H activation[20]. A methylamino directing group complexes to the palladium and an acetate group acts as an internal base to assist in C-H activation.



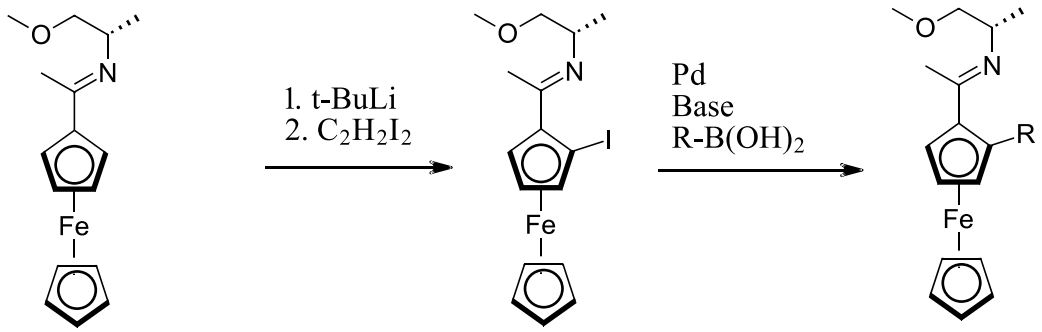
Scheme 2. A proposed mechanism for a C-H cross-coupling reaction with an aryl boronic acid[20].

1.2.3 Ferrocenes

Ferrocene and its derivatives have garnered significant interest for their applications in organometallic and materials chemistry. The ferrocene molecule consists of a central iron atom in the +2-oxidation state, with 2 negatively charged aromatic cyclopentadienyl rings, which are π coordinated to the iron atom, forming a sandwich-like structure. Ferrocene dissolves in organic solvents, is air and temperature stable, inexpensive, and, when suitably functionalized, reacts readily to ligate transition metals. Ferrocenylphosphines are especially commonly used and are synthesized either through lithioferrocene or Friedel-Crafts reactions. 1,1′-Bis(diphenylphosphino)ferrocene (dppf) is the most used ferrocenylphosphine and is used as a ligand for palladium complexes to form catalysts such as $PdCl_2$(dppf), an effective catalyst for cross-coupling reactions, including the Buchwald-Hartwig amination and for homo-coupling aryl halides[29-31]. Chiral ferrocenes are also possible, either from a substituted group containing a centrally chiral carbon, or through the planar chiral exhibited by disubstituted ferrocenes (if the two substituents are different)[29]. Chiral ferrocenes, and especially planarly chiral ferrocenes can be used as ligands in asymmetric catalysis and other enantioselective syntheses[29].

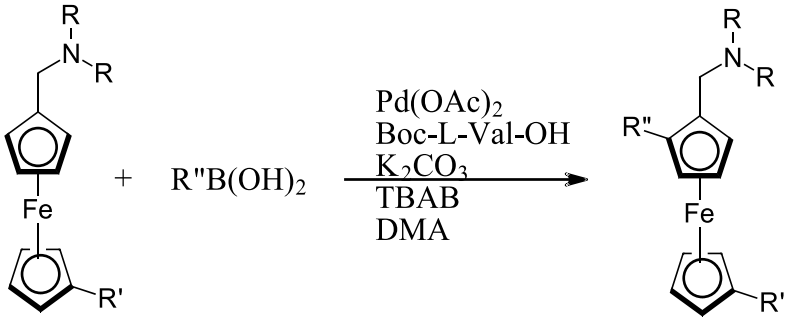
1.2.4 Synthesis of Planarly Chiral Ferrocenes

The synthesis of asymmetric ferrocenes is accomplished through one of two general approaches. The first is by pre-installing a centrally chiral group to an unsubstituted cyclopentadienyl ring and using that group to direct which side a new substituent is added. For example, an enantioselective *ortho*-lithiation can be achieved by including a centrally chiral carbon in the directing metal group (Scheme 3)[32-34].



Scheme 3. The typical method for synthesis of planarly chiral disubstituted ferrocenes[33]. An enantioselective lithiation is followed by lithium halogen exchange and finally a cross-coupling reaction.

The second approach is to selectively cross-couple achiral monosubstituted ferrocenes using chiral catalysts (Scheme 4). To accomplish this, at least one C-H activation (at the 2, 3, 4, or 5 position) must be achieved. The electronic effects of the directing group then become important. Gao and colleges have synthesized planarly chiral disubstituted ferrocenes by coupling aminomethyl ferrocenes and aryl boronic acids using Boc-L-Ile-OH and other amino acid ligands to control enantioselectivity with moderate yields (14-81%) and high enantioselectivity (>99%) (Scheme 4)[35]. Gao and colleagues have also accomplished double C-H activation- coupling ferrocenes with heteroarenes with moderate to high yields (36-86%) and high enantioselectivity (95-99% enantiomeric excess (ee))[36]. The σ donating characteristics of N-heterocyclic carbenes can promote oxidative addition (the step involving C-H activation), so are an attractive choice as ligands instead of monoprotected amino acids in ferrocene cross-coupling reactions.



R = Me, Et, -$(CH_2)_4$-
R' = H, Br

Scheme 4. Previous synthesis of planarly chiral distituted ferrocenes through C-H cross-coupling using Boc-protected amino acids as ligands.

1.2.5 C-H activation of benzaldehydes

NHCs have previously been used to arylate benzaldehydes with aryl chlorides and bromides[15]. This is an enticing reaction, because it uses an aldehyde directing group, instead of the typical nitrogen-containing directing groups. This can simplify potential synthetic schemes if an oxygen-containing group is desired in the final product. There is also potentially greater access to aryl chlorides and bromides, compared to traditional organometallic coupling partners, like organoboranes and organotins. The aryl halides also yielded product with both electron withdrawing and donating groups, furthering the scope of the reaction[15]. Catalytic amounts of electron-rich and bulky NHCs and palladium(II) acetate, in the presence of base (Cs_2CO_3), afforded a catalytic system that made this reaction possible[15]. Based on these results, it was hypothesized that similar conditions could be used to arylate ferrocenecarboxaldehyde, due to its aldehyde group and similar (although more electron rich) aromatic system.

1.3 Microwave Assisted Synthesis

1.3.1 General Review

The use of microwave energy to heat chemical reactions has become increasingly popular due to its potential to decrease reaction time, increase reactivity and increase solubility. Microwaving a chemical reaction produces heat by agitating polar molecules or ions in an oscillating electric or magnetic field. Polar molecules rapidly rotate to align with the oscillating field, generating heat. In the process of orienting themselves with the field, their movement is restricted by intermolecular forces. Through the resistance of these intermolecular forces, they move, and produce heat[37]. Microwaves also cause ions in solution to move back and forth, which produces heat as the ions collide with each other and other (e.g., solvent) molecules[37]. Microwave energy is a more efficient heating source than conventional conduction, increasing the rate of reactions by 10 to 1000 times[37]. In some cases, microwave synthesis can also improve yields[37]. Another advantage of microwave heating is the ability to heat reactions faster, more efficiently and more uniformly, meaning that microwave reactions require less energy to heat[37]. In microwave heating, the solvent and reagents are heated directly, so less solvent is required[37].

1.3.2 Microwave Assisted Synthesis Using Ionic Liquids

Ionic liquids are especially attractive solvents for use in microwave reactors due to the ion conduction effect, where the oscillating electric field induces the ions to move back and forth and collide with other molecules. This increases the efficiency of heating and allows for faster heating compared to conventional organic solvents. Even a small amount of IL added to a conventional solvent (e.g., toluene, hexane, dioxane, THF) can induce faster and more efficient heating and can permit the heating of solvents well above their boiling point[38]. Lastly,

microwave reactors can achieve higher temperatures than oil or sand baths, and ionic liquids are very thermally stable and have low vapour pressures, meaning that they can tolerate the high temperatures in the microwave without decomposition or pressure buildup[38].

1.4 Project Objectives

The main object of this project is to achieve an imidazolium-CIL promoted and enantioselective Suzuki cross-coupling reaction between aryl boronic acids and monosubstituted ferrocenes. This will be accomplished by determining and optimizing reaction conditions, including solvent, base, catalyst, microwave temperature and time and additives. Furthermore, the synthesis of a library of imidazolium CILs to use in the reaction will also help to explore the effects of imidazolium CILs in these types of C-H cross-coupling reactions. A secondary objective is to investigate imidazolium CIL promoted cross-coupling of monosubstituted ferrocenes (in particular, ferrocene carboxaldehyde), with aryl halides.

CHAPTER TWO: SYNTHESIS OF A LIBRARY OF CHIRAL IONIC LIQUIDS

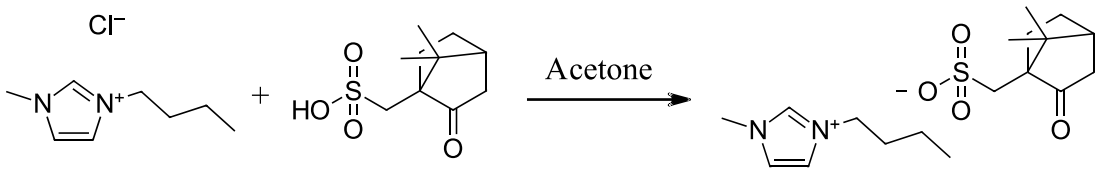
2.1 Introduction

In order to accomplish the primary objectives of achieving CIL-promoted, enantioselective cross-coupling reactions of monosubstituted ferrocenes, a variety of CILs to test in cross-coupling reactions were synthesized. Imidazolium CILs were prepared, because of their ability to act as NHCs that complex to palladium catalysts and increase the reactivity towards the C-H activation and/or oxidative addition steps of a C-H cross-coupling catalytic cycle, and for their ability to induce enantioselectivity when acting as NHCs. The two nitrogen atoms in the imidazole ring can act as nucleophiles, so substitution reactions were chosen as a main strategy for synthesizing 1,3-dialkyl imidazole CILs. The Van Leusen synthesis was also attempted as a way to generate *de novo* imidazole rings, with the option of having (potentially chiral) alkyl groups at the 4- and 5- positions as well. Different anions were also explored, including chiral anions.

2.2 Results and Discussion

2.2.1 Syntheses of CILs with Chiral Anions

ILs using achiral imidazolium cations and chiral anions were first synthesized. **1** (Scheme 5) was synthesized by mixing equimolar 1-(S)-10-camphor sulfonic acid and 1-butyl-3-methyl imidazolium chloride. The (R)- enantiomer was also synthesized.



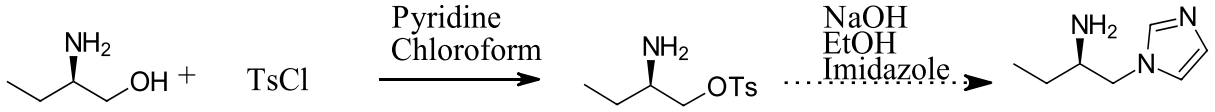
1

Scheme 5. Synthesis of 1-butyl-3-methylimidazolium camphorsulfonate.

2.2.2 Syntheses of CILs using S_N2 Reactions

The first attempts at synthesizing CILs with chiral imidazolium cations used an S_N2 strategy. Substitution reactions were attempted starting from primary and secondary alcohols, which were then either tosylated or halogenated and could be added at the 1- and 3-positions via an S_N2 reaction.

An initial approach was to tosylate 2-amino-1-butanol, before performing a substitution reaction with imidazole. 2-Amino-1-butanol was successfully tosylated; however, the subsequent substitution reaction with imidazole, in the presence of base, did not yield more than a trace amount of product (Scheme 6).



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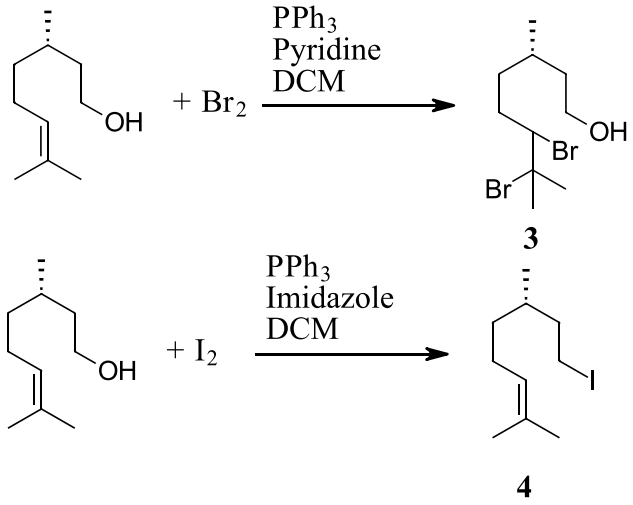
Scheme 6. Tosylation of (R)-2-amino-1-butanol to form **2**, followed by the substitution reaction with imidazole.

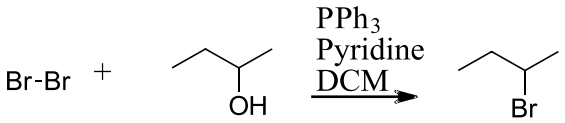
Another approach was to add citronellol- a naturally occurring chiral alcohol- to imidazole. To do this, the alcohol would first need to be converted to a halogen. A bromination was done according to the method developed by Sankaranarayana et al.[39]. After purification,

bromination was observed across the alkene as the main product, instead of the desired substitution (Scheme 7). It was hypothesized that this could be due to the use of dichloromethane, instead of the tetrachloromethane used by Sankaranarayana et al.[39]. It is possible that in the presence of tetrachloromethane, the triphenylphosphine nucleophilically attacks one of the chlorine atoms in tetrachloromethane to form a positively charged chlorotriphenyl phosphine species and a negatively charged trichloromethane species. The trichloromethane species could deprotonate the alcohol, which can in turn nucleophilically attack the chlorotriphenylphosphine species. This mechanism is analogous to that of the Appel reaction. The reaction was later conducted under anhydrous conditions, with similar results (bromination of the alkene). An attempt was made to iodinate the alcohol of citronellol (Scheme 7), due to the lower reactivity of iodide to alkenes compared to bromide. This proved to be successful, albeit with a yield of 22%.



Scheme 7. Halogenations of citronellol.

2-Butanol was also brominated under similar conditions (Scheme 8). The product turned black when exposed to light, which was attributed to a radical chain reaction, so in further attempts the reaction vessel was covered with aluminum foil. A butyl-substituted CIL was not synthesized because the experimenters only had access to racemic 2-butanol; however, the methodology could be used to brominate other primary and secondary alcohols.



5

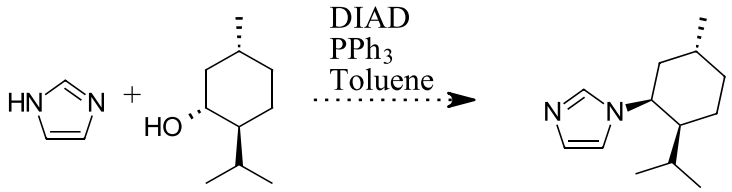
Scheme 8. Bromination of racemic 2-butanol **(5)**.

2.2.3 Synthesis of 1,3-(di)alkyl Imidazoles through the Mitsubobu Reaction

An alternative way to add an electrophile to either nitrogen in the imidazole ring is through the Mitsunobu reaction. There are advantages to using a Mitsunobu reaction over an S_N2 reaction in this case. First, they allow for alcohols to react as electrophiles, so there is no need to isolate a more reactive intermediate, such as an alkyl halide or alkyl triflate in the case of S_N2 reactions starting from alcohols. Second, Mitsunobu reactions proceed with predictable inversion of the stereochemistry of the alcohol. Third, there is no risk of a competing elimination reaction, or other side reactions, like the bromination of the alkene that was seen when attempting to brominate citronellol for use in an S_N2 reaction.

A Mitsunobu reaction to add menthol to imidazole based on the conditions developed by Kim *et al*.[39] was attempted (Scheme 9); however, did not yield product. Kim *et al*. mainly used primary alcohols, with a few unhindered secondary alcohols, like 2-hexanol[40], so it is possible

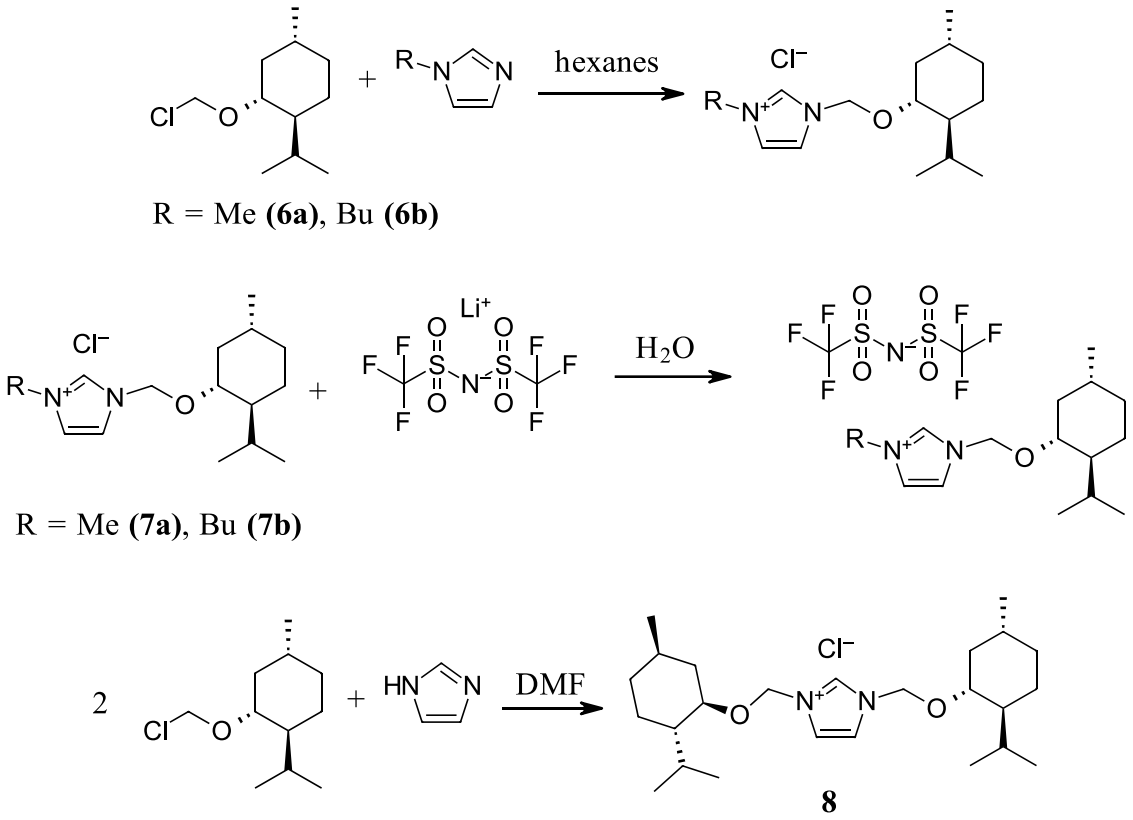
that the steric hindrance from the secondary alcohol and adjacent isopropyl group did not allow for the reaction to proceed.



Scheme 9. Attempted Mitsunobu reaction between imidazole and menthol. No product formation was seen.

2.2.4 Syntheses of Methyl Menthyl Ether Imidazolium CILs

Previous examples in the literature used chloromethyl menthyl ether to add the methyl menthyl ether to imidazole nitrogens[41,42]. As an added convenience, the chloride leaving group acts as an anion, generating a CIL in one step. 1-Butyl imidazole and 1-methyl imidazole were used to add a single methyl menthyl ether at the 3- position[41], generating two sterically different CILs (Scheme 10). The conditions developed by Feder-Kubis *et al*. were used to synthesize the symmetrical and bulky 1,3-bis[menthoxymethyl]imidazolium chloride enantiomers[42] (Scheme 10). Symmetric ILs have may more attractive physical properties, including lower volatility, higher temperature stability and lower viscosity, compared to asymmetrical ILs[42]. Finally, 1,3-dialkylimidazolium chlorides were reacted with lithium bis(trifluoromethylsulfonyl) imide to exchange the anion (Scheme 10).



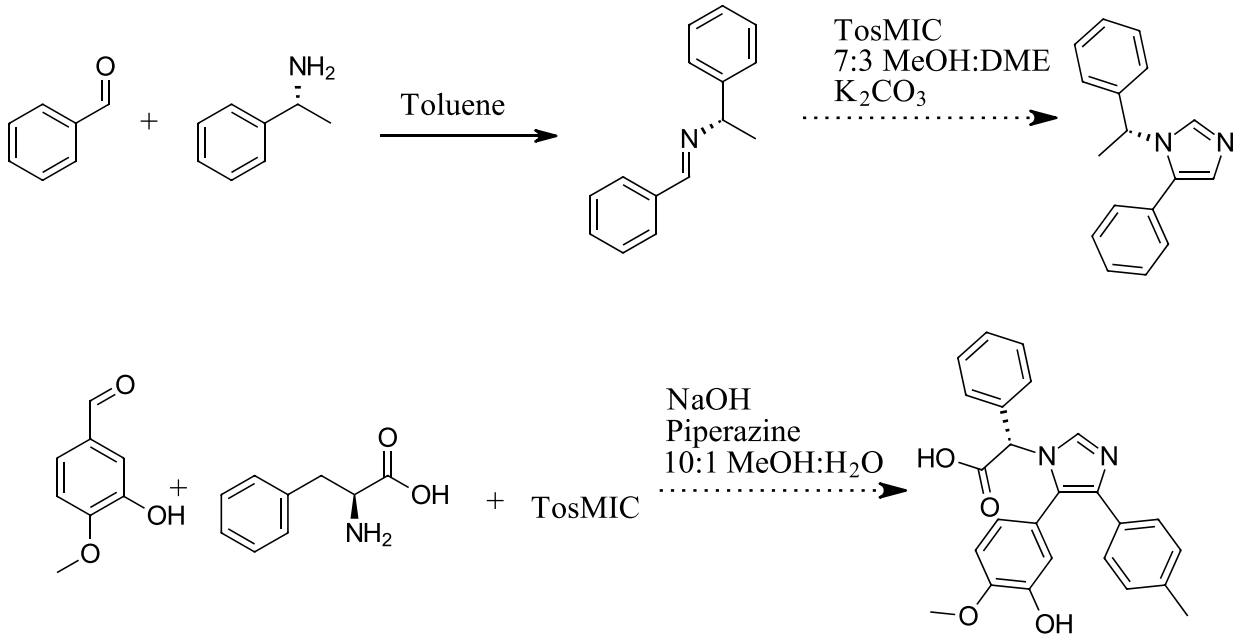
Scheme 10. Methyl menthyl ether substituted CIL syntheses.

2.2.5 Van Leusen Synthesis of CILs

As an alternative strategy to substitution reactions, Van Leusen synthesis of substituted imidazoles for CILs was attempted. The Van Leusen reaction reacts ketones or aldehydes and tosylmethylisocyanide in the presence of base to transfer the cyano group. When aldehydes are used, elimination of the tosyl group occurs to form oxazoles. If an imine is used instead of an aldehyde, then an imidazole is formed. In this strategy, the chirality is already set on the starting imine (or aldehyde), and stereochemistry is retained throughout the reaction. Van Leusen reactions can also be used to synthesize imidazoles alkylated at the 2, 4, and 5- positions, in addition to the 1- and 3- positions that are already available through substitution reactions.

In order to generate a chiral imine, a condensation between butanal and (R)-(+)-1-phenylethylamine in the presence of aluminum oxide was attempted, based on the conditions developed by Roefofsen et al.[43]. Unfortunately, this method did not yield product, so it was attempted to push the equilibrium of the reaction forward by reacting benzaldehyde with (R)-(+)-1-phenylethylamine in toluene with a Dean Stark trap to remove the water formed in the condensation, before using the imine for a Van Leusen reaction to form a 1,5-disubstituted imidazole ring[44] (Scheme 11). Significant side product formation was observed, including an imidazole ring substituted with the tosyl group at the 4-position (i.e., the tosyl group was not eliminated), but no significant amounts of product.

Finally, an attempt to form the imine *in situ* was conducted according to the method developed by Sisko *et al.*[45] (Scheme 11). It was determined that there was only starting material in the reaction mixture and product formation was not observed.



Scheme 11. Various Van Leusen reaction attempts.

2.3 Conclusions and Future Work

The strategy of substituting imidazole with chloromethyl menthyl ethers was selected as the main strategy to synthesize CILs for the cross-coupling reactions for two reasons. First, significant challenges were faced with the various substitution and Van Leusen reactions, and the menthyl methyl ether substituted imidazoles from chloromethyl menthyl ethers were able to be synthesized with relative ease. Second, methyl menthyl ether imidazolium chlorides are an attractive choice for C-H activation cross-coupling reactions due to the steric bulkiness of the menthyl group, and the chloride anion. Previous work on NHCs in C-H activation cross-coupling reactions suggests that a chlorine anion may be the most effective for that type of transformation[27]. Future work could expand on the experiments performed, including further attempts at Mitsunobu reactions between imidazole and sterically hindered secondary alcohols. Furthermore, most imidazolium CILs are substituted at the 1- and 3-positions, so if efficient Van Leusen syntheses can be developed, a wider range of imidazolium CILs- with substituents at the 2, 4, and 5 positions- will be available, which will have difference physical properties and enantioselective abilities.

CHAPTER THREE: INVESTIGATIONS INTO THE SYNTHESES OF AMINOMETHYL FERROCENES

3.1 Introduction

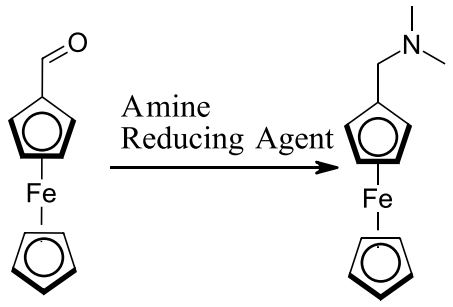
Aminomethyl ferrocenes are an enticing starting point to attempt a cross-coupling reaction because the methylamine functional group is a desirable and common directing group for C-H activation. Gao and colleagues have previously enantioselectively cross-coupled aminomethyl ferrocenes with boronic acids and heteroarenes[35]. Therefore, it was important to be able to efficiently synthesize aminomethyl ferrocenes.

3.2 Results and Discussion

3.2.1 Investigation into the Reductive Amination of Ferrocenecarboxaldehyde

Ferrocenecarboxaldehyde was chosen as the starting material to synthesize aminomethyl ferrocenes by way of reductive amination. Three different reductive amination reaction conditions were tested, two general methods[46], and a method developed specifically for the reductive amination of ferrocenecarboxaldehyde[47] (Table 1). The conditions for the reductive amination of ferrocenecarboxaldehyde developed by Khrushcheva and Sokolov[47] were the only successful method.

Table 1. Summary of reductive amination reaction conditions.



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Entry	Amine	Reducing Agent	Base	Solvent	Temperature	%Yield
1	$HN(Et)_2$	$NaBH(OAc)_3$	-	THF	RT	-
2	$HN(Et)_2$	$NaBH(OAc)_3$	-	1,2-dichloroethane	90°C	-
3	$HMe_2(HCl)$	$NaBH(OAc)_3$	Et_3N	DCM	32°C	55

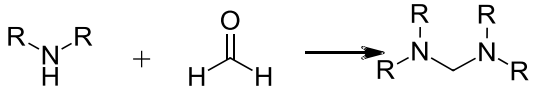
It was also found that increasing the reaction temperature from room temperature to 32°C (near the boiling point of DCM), pushed the reaction forward (monitored by thin layer chromatography). Conducting the reaction in dry and/or under an inert nitrogen atmosphere did not improve the yield. Repeated trials of the same reaction conditions generally led to significant side product formation and lower yields, so alternative methods of synthesizing aminomethylferrocenes were sought out.

3.2.2 Investigations into Methyl Diamine Synthesis

Lednicer and Hauser have previously aminomethylated ferrocene using N,N,N',N'-tetramethylmethylenediamine in the present of phosphoric and sulfuric acid[47]. N,N,N',N'-Tetramethylmethylenediamine has been preciously synthesized by reacting formaldehyde with dimethylamine in aqueous solution[49]. The preparation of N,N,N',N'-tetramethylmethylenediamine was attempted using formaldehyde in aqueous solution and

dimethylamine in ethanol solution (due to reagent availability), which yielded the imine intermediate, but not the desired product. Diethylamine was available, so the corresponding reaction was conducted in water. Upon successful synthesis of N,N,N',N'-tetraethylmethylenediamine, using aqueous formaldehyde and diethylamine, a range of secondary amines were used in the reaction (Table 2).

Table 2. Methylene Diamine synthesis using different secondary amines.

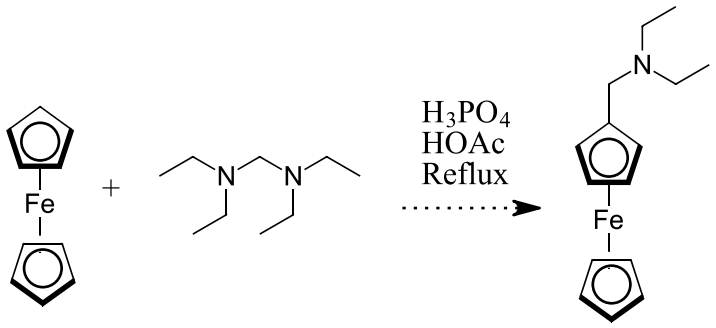


Entry	10	R	Solvent System	% Yield
1	a	Me	H_2O/ EtOH	-
2	b	Et	H_2O	45.6
3	c	Morpholine	H_2O	11.7
4	d	Imidazole	H_2O	-
5	e	i-Pr	H_2O	26.7
6	f	Cylclohexyl	H_2O	-

After the synthesis of N,N,N',N'-tetraethylmethylenediamine led to imine formation, the first step of the reaction, but no amination of the imine, attempts were made to promote the second amination by increasing the number of equivalents to 4, increasing the reaction time to 48 hours and by using dimethyl amine hydrochloride in order to conduct the reaction in just water, as opposed to a water/ ethanol mix. None of these methods were successful, and it was concluded that using water as the solvent is integral to the success of the reaction.

3.2.3 Investigations into Aminomethylations of Ferrocene

An aminomethylation of ferrocene was attempted using N,N,N',N'-tetraethylmethylenediamine (Scheme 12). Lednicer and Hauser have previously aminomethylated ferrocene using N,N,N',N'-tetramethylmethylenediamine[48], but the synthesis of N,N-diethylaminomethylferrocene has not yet been accomplished using this method. Initial attempts yielded ferrocenecarboxaldehyde. No plausible mechanistic explanation was proposed for this result; however, the experiment was repeated with similar results. The phosphoric acid was also substituted with sulfuric acid, which did not yield any product.



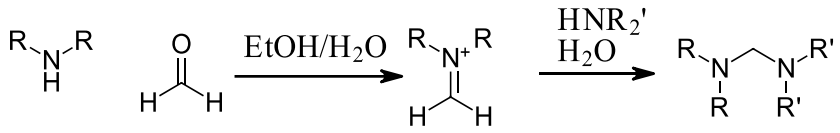
Scheme 12. Attempted aminomethylation of ferrocene. Instead of the shown desired product, ferrocenecarboxaldehyde was formed.

3.3 Conclusions and Future Work

The synthesis of pure N,N-dimethylaminomethylferrocene by way of reductive amination to give even moderate yields proved challenging. Additionally, the reaction did not give consistent yields. Further work is required to better understand why the reaction sometimes proceeds further than other times. Given the observation of side product formation and ferrocene decomposition, it is possible that atmospheric conditions need to be more tightly controlled.

The successful synthesis of three new methylenediamines offers access to bulkier methylene diamines, that can be used for aminomethylation reactions, including that of ferrocene. The bulkier secondary amines (imidazole, dicyclohexylamine) did not yield their corresponding methylene diamine, so ongoing research to synthesize bulkier methylenediamines is warranted. The reactions use water as a solvent, and water is an excellent microwave solvent, so microwave synthesis could be an avenue to explore in order to increase reactivity. The successful synthesis of **10d** could offer access to interesting new ILs, which could potentially be dicationic, and have extended conjugation from the second heterocyclic ring.

The finding that the reaction only proceeds to the intermediate imine when the reaction is conducted in a mix of ethanol and water, suggests that it may be possible to synthesize asymmetric methylenediamines by tuning reactivity through the solvent system. For example, the imine could be formed in a mix of ethanol and water, then the solvent and residual amine removed, before a second amine and water is added (Scheme 13).



Scheme 13. A proposed method to synthesize asymmetric methylenediamines.

While a variety of methylenediamines were synthesized, the corresponding methylamino ferrocenes have not yet been successfully synthesized. Further research into aminomethylation is required, because the present conditions to yield N,N-dimethylamionmethylferrocene do not yield the bulkier N,N-diethlyaminomethylferrocene. Moreover, a reasonable mechanistic explanation for the production of ferrocenecarboxaldehyde during the reaction has not yet been determined. Should the aminomethylation of ferrocene be successful, a more diverse range of

directing groups will be available to perform cross-coupling reactions on aminomethyl ferrocenes. This would allow access to bulkier directing groups, which could potentially help to stabilize transition metal intermediate complexes.

CHAPTER FOUR: DEVELOPMENT OF A METHOD OF CROSS-COUPLING ARYL BORONIC ACIDS TO MONOSUBSTITUTED FERROCENES

4.1 Introduction

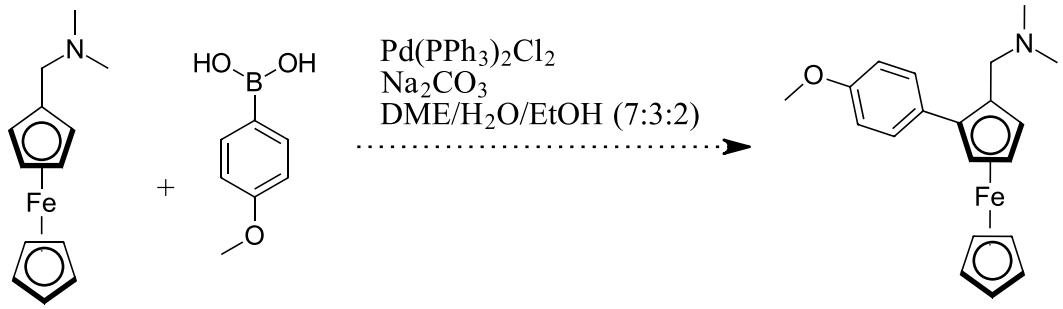
The selective C-H functionalization of monosubstituted ferrocene compounds at either the 2- or 5-positions will produce asymmetric molecules with planar chirality. The first objective was to enantioselectivity cross-couple monosubstituted ferrocenes with aryl boronic acids using CILs to promote C-H activation and to impart chirality. The aminomethyl directing group was chosen, because it has previously been used in cross-coupling reactions between ferrocenes and aryl boronic acids[35].

4.2 Results and discussion

4.2.1 Initial Attempts

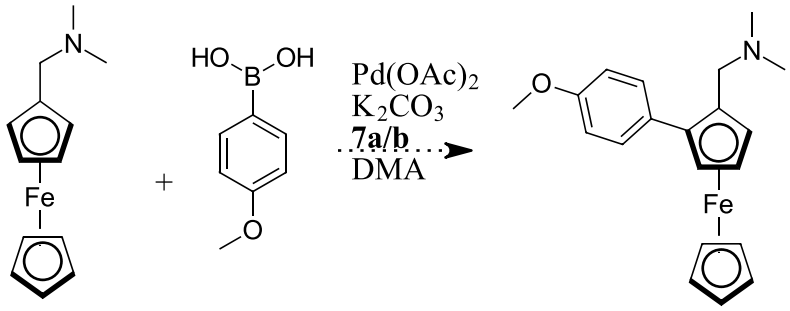
Initial microwave conditions for a cross-coupling reaction between 4-methoxyphenylboronic acid and N,N-dimethylaminomethylferrocene were based on suggested conditions for standard cross-coupling reactions in the microwave, using bis(triphenylphosphine)palladium dichloride, sodium carbonate and a 7:3:2 mixture of dimethoxy ethane, water and ethanol[50] (Scheme 14). This method was not successful, and no product formation was observed. The reaction was only able to reach 130 ℃ (with a target temperature of 160 ℃), and rapid oxidation and decomposition (blackening) of materials was observed. Lowering the temperature to 115 °C reduced the oxidation and decomposition; but did not yield any product. Based on these results, it was hypothesized that the addition of IL to the reaction mixture would create a more efficient and stable system to absorb microwave energy to

allow the reactions to get up to higher temperatures and reduce errant oxidation and breakdown of materials and would make the palladium catalyst more reactive in the C-H activation step.



Scheme 14. Initial, unsuccessful attempt at a cross-coupling reaction between 4-methoxyphenylboronic acid and N,N-dimethylaminomethylferrocene in the microwave reactor.

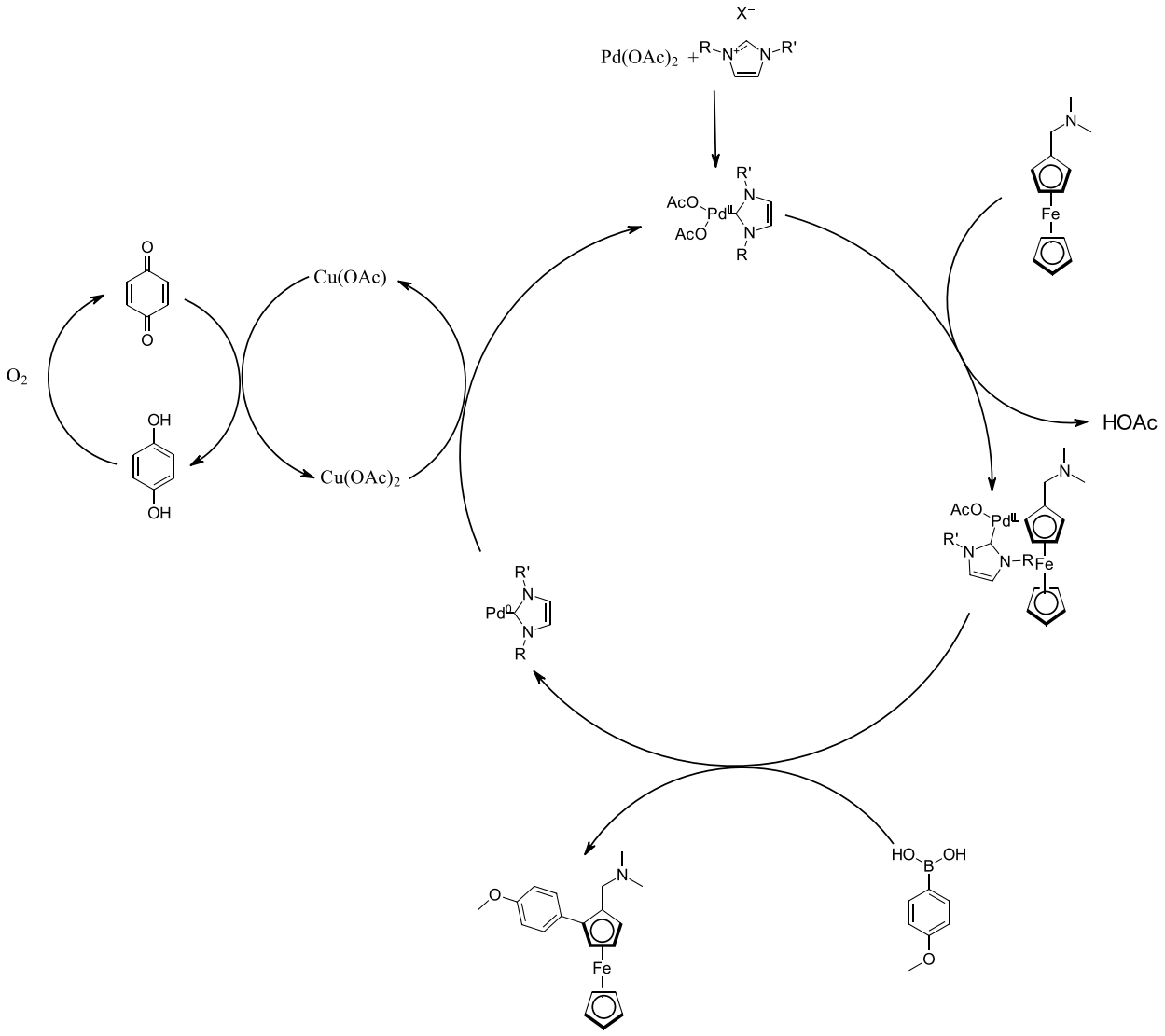
Similar conditions to the approach of Gao *et al.*[35] were attempted next (Scheme 15). Instead of using a Boc-protected amino acid like Gao et al., **7b** (Scheme 10) was selected to act as an NHC for the palladium(II) acetate catalyst. **7a** was mixed with the DMA solvent in 1:1 ratio (v/v). This reaction was heated in the microwave reaction. After the reaction was complete, starting material was recovered and no product formation was observed. **7b** (Scheme 10) was also used in the same approach, with the hope that the bulkier butyl group at the 1-position of the imidazole ring would help to stabilize the palladium complex intermediate after C-H activation. This method also returned starting material, with no product. Lastly, the CIL-DMA mixture was quite viscous, and it was hypothesized that that could be impeding efficient mixing of the reaction mixture, so the amount of CIL was reduced to 10% (v/v); however, this also did not yield product.



Scheme 15. Initial, unsuccessful attempt at a cross-coupling reaction between 4-methoxyphenylboronic acid and N,N-dimethylaminomethylferrocene in the microwave reactor using CILs.

4.2.2 Addition of an Oxidation System

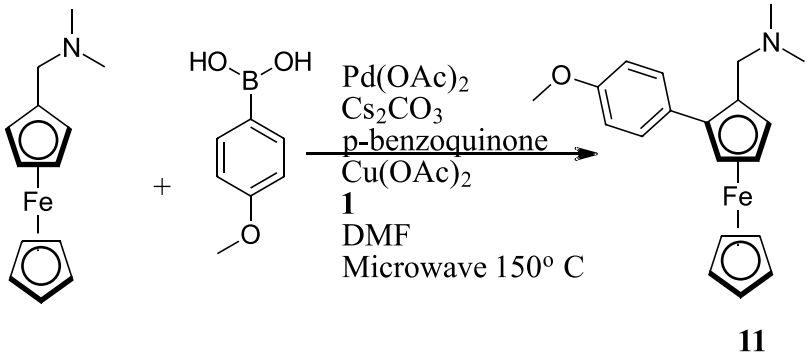
From there, a closer look at the catalytic cycle for this reaction led to improved reaction conditions. It was hypothesized, based on previous mechanistic work[20], that instead of the usual oxidative addition taking place in the first step, a C-H activation would occur, adding the N,N-dimethylaminomethylferrocene across the 2- or 5-position C-H bond, and expelling an acetate group as acetic acid (Scheme 16). Importantly, the palladium remains in the +2-oxidation state (i.e., it is not oxidized). It is worth noting that the CIL would play an important role in this step by increasing the electron density around the palladium atom, by acting as a bulky ligand to stabilize the palladium intermediate, and by imparting enantioselectivity, as this is the step where chirality is established. After the product is formed during following transmetalation/reductive amination step, the palladium catalyst is left in the 0-oxidation state, without ligands. In the absence of oxidants, this leads to a broken catalytic cycle, where the original palladium(II) acetate catalyst cannot be regenerated. There, it was hypothesized that the addition of an oxidant(s) would be necessary to complete the catalytic cycle and allow the reaction to proceed.



Scheme 16. Proposed catalytic cycle for the reaction between N,N-dimethylaminomethylferrocene and 4-bromoanisole.

A combination of p-benzoquinone and copper (II) acetate has previously been used as an oxidation system in C-H activation cross-coupling reactions[20] and was selected for this reaction (Scheme 17). Cesium carbonate was also used as the base, as it is a stronger base than potassium carbonate, with better solubility. Only a catalytic amount of CIL was used (5.6 mol%), because the primary function of the CIL at this stage was to act as an NHC and complex to the palladium,

and because it was observed that the reactions were able to achieve significantly higher microwave temperatures with the addition of only catalytic amounts of CIL, and the lower viscosity of low concentration CIL mixtures ensured effective mixing. These changes led to product formation (88% conversion, determined by ^{1}H NMR and seen on MS), so the reaction was further optimized.



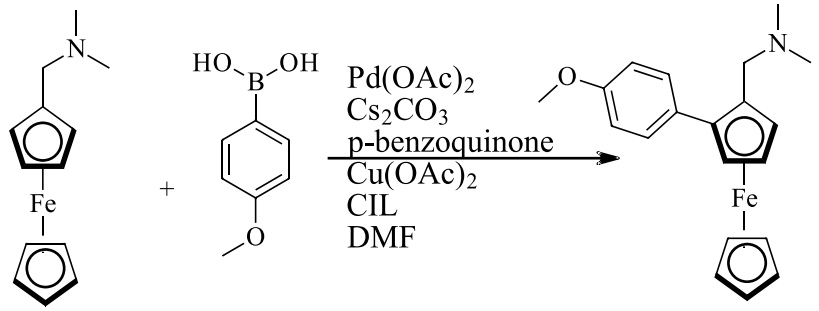
Scheme 17. Initial successful reaction conditions of a cross-coupling reaction between N,N-dimethylaminomethylferrocene and an aryl boronic acid.

4.2.3 Optimization of Reaction Conditions

Once the reaction had yielded product, the reaction conditions were optimized. It was decided to optimize yield first. Enantioselectivity was predicted to be primarily determined by the alkyl groups at the 1 and 3 positions on the imidazole of the CIL used, so generic CILs were chosen to optimize the yield. One challenge seen when performing microwave synthesis for this reaction was that numerous side products were formed (as seen by TLC), resulting in lengthy purification by silica column chromatography. To speed up the optimization process, ^{1}H NMR peak areas between the product and starting N,N-dimethylaminomethylferrocene were compared. First, two different CILs (**1** and **6a**; Schemes 5 and 10) were tested, under two different temperatures and reaction times (Table 3). Conventional heating (with a sand bath, to

reflux) was also tested. The primary purpose of this was to determine if the anion affected the reaction, and the effects of temperature on the reaction. Given the ability of ILs to absorb microwave energy, it seemed pertinent to examine the two different ILs at two different temperatures to see if one was more effective at higher temperatures.

Table 3. Cross-coupling reaction between N,N-diemethylaminomethylferrocene and 4-methoxyphenyl boronic acid, using different CILs and microwave settings.



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Entry	CIL	Time (min)	Temperature (°C)	%Conversion*
1	**1**	10	175 (MW)	63
2	**1**	30	150 (MW)	88
3	**6a**	10	175 (MW)	-
4	**6a**	30	150 (MW)	-
5**	**1**	48 hrs	153 (reflux)	7.6

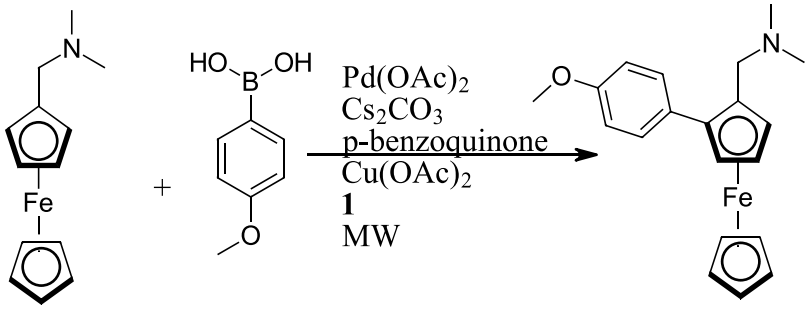
*%Conversion determinations explained in Experimental section.

**Heated with a sand bath to reflux.

These results indicated that microwave heating is superior to conventional heating in the context of this reaction. Further, increasing the temperature of the reaction did not have much effect when compared with increasing the time the reaction was heated. Furthermore, side

product formation was observed, but less so at the lower temperatures (based on thin layer chromatography and NMR analysis). Therefore, it is proposed that the lower temperatures (with longer reaction time) may lead to a more controlled reaction, with more product formation and less side product formation. From there, solvents were tested to further optimize the reaction (Table 4).

Table 4. Percent conversions for a cross-coupling reaction between N,N-diemethylaminomethylferrocene and 4-methoxyphenyl boronic acid in different solvents for 10 minutes at 175°C.



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Entry	Base	Solvent	Catalyst	CIL	%Conversion
1	Cs_2CO_3	DMF	$Pd(OAc)_2$	**1**	63
2	Cs_2CO_3	Acetonitrile	$Pd(OAc)_2$	**1**	63
3	Cs_2CO_3	DMSO	$Pd(OAc)_2$	**1**	-

4.3 Conclusions and Future Work

Further work is needed to optimize the reaction between N,N-dimethylaminoferrocene and aryl boronic acids. A wider scope of solvents that effectively absorb microwave energy and/ or have been shown to be effective in cross-coupling reactions should be tested, including water, 1,4-dioxane, DMA and isopropanol. A test of a variety of bases would also be beneficial. Cesium

carbonate was selected primarily because it is more soluble in organic solvents than sodium carbonate or potassium carbonate; however, it is worth attempting the reaction with these bases as they are less expensive. It could also be worthwhile to attempt the reaction with organic bases, such as triethylamine and pyridine. Additionally, testing a wider variety of imidazolium CILs would help to better understand the effects of factors like steric bulk, chiral carbon location and anion on the yield and enantioselectivity of the reaction. Palladium(II) acetate was chosen as it is commonly used in similar NHC-promoted C-H cross-coupling reactions, but other common palladium(II) catalysts could also be tested, like palladium(II) chloride, bis(triphenylphposphine) palladium(II) dichloride and [1,1'-bis(diphenylphposphino)ferrocene]dichloropalladium, and even palladium(0) catalysts like tetrakis(triphenylphosphine)palladium and palladium on carbon. An oxidation system of copper (II) acetate and benzoquinone was selected as the oxidation system, based on previous work[20,27]. It would be worthwhile to test different oxidants, such as gold (I) acetate, molecular oxygen, di-*tert*butyl peroxide and sodium periodate[20,27]. Finally, the conditions showing the highest percent conversions should be attempted, and fully purified (likely using silica column chromatography) in order to determine yields, as percent conversion is not always completely accurate due to the formation of side products.

The finding that the reaction proceeded with the imidazolium camphorsulfonate (**1)**, but not the imidazolium chloride (**6a**), is interesting. It should be noted that the cations of **1** and **6a** were not identical, although they were relatively similar. Imidazolium chlorides have been the most common NHC source for C-H functionalization[27]. Imidazolium alkyl sulfates have yet to be used as NHCs in transition metal catalyzed reactions. The effects of the counter ion on NHC effectiveness are not clear; however, these results provide a rationale for attempting other types of NHC-promoted cross-coupling reactions using imidazoliums with organic anions, including

alkylsulphates, alkylphosphates and acids. Furthermore, while the chiral discrimination abilities of the CIL are expected to be primarily determined by the imidazolium cation, because it complexes to the palladium catalyst, the anion also has the potential to contribute to the chiral discrimination capability of the CIL. Organic anions provide access to chiral anions which inorganic anions do not. For example, in addition to camphorsulfonate, a BINOL-phosphate anion could be derived from BINOL-phosphoric acid, or amino acid anions could be used to give chiral anions. From there, an investigation into the chiral discrimination abilities of different CILs could be conducted in order to optimize the enantioselectivity of the reaction. The number of chiral centers, the location of the chiral centers (especially the distance between the chiral centers and the 2-carbon of the imidazolium ring) and the presence or absence of a chiral anion could all be explored.

CHAPTER FIVE: DEVELOPMENT OF A METHOD OF CROSS-COUPLING FERROCENECARBOXALDEHYDE TO ARYL BROMIDES

5.1 Introduction

The second objective was to achieve enantioselective cross-coupling of aryl halides to monosubstituted ferrocenes. Like the cross-coupling reaction between aryl boronic acids and monosubstituted ferrocenes, enantioselective C-H functionalization at the 2- or 5-position is necessary to cross-couple aryl halides to monosubstituted ferrocenes and produce chiral ferrocene compounds. The ability to use aryl halides as substrates would expand the scope of enantioselective cross-coupling reactions with monosubstituted ferrocenes beyond aryl boronic acids, thereby increasing the utility of the reaction. Aryl boronic acids and aryl halides have opposite reactivities, so it was hypothesized that an electron-withdrawing directing group would be needed on the cyclopentadienyl ring. It was also hypothesized that oxidative addition would occur before C-H activation, so additional oxidants would not be necessary.

5.2 Results and discussion

5.2.1 Initial Attempts

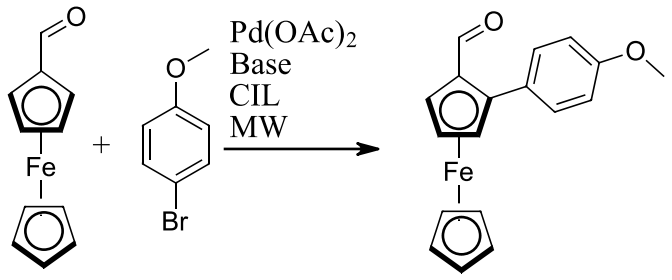
Initial attempts reacted N,N-dimethylaminomethylferrocene with p-bromoanisole using bis(triphenylphosphine)palladium chloride, sodium carbonate in a 7:3:1 mixture of dimethoxy ethane, water and ethanol[50]. This method was not successful, as no product was observed. The reaction mixture also did not achieve the desired temperature of 160℃, and there was rapid oxidation and decomposition.

Previous work done by Gurbuz *et al*.[15] cross-coupled aryl halides with benzaldehydes, using cesium carbonate, palladium(II) acetate, and NHCs. In this case, the aldehyde served as the directing group to achieve C-H activation at the adjacent carbon. Based on this work, a cross-coupling reaction between ferrocenecarboxaldehyde and *p*-bromoanisole, using CILs, cesium carbonate and palladium acetate in DMF was attempted. This method yielded detectable amounts of product by mass spectrometry.

5.2.2 Optimization of Cross-coupling Reaction between Aryl Halides and Ferrocenecarboxaldehyde

Once the cross-coupling reaction between aryl halides and ferrocenecarboxaldehyde had yielded product, the process was optimized for yield. One challenge seen when performing microwave synthesis for this reaction was that numerous side products were formed (as seen by TLC), requiring lengthy purification by silica column chromatography. To speed up the optimization process, ^{1}H NMR peak areas between the product and starting ferrocenecarboxaldehyde were compared. Base, solvent and microwave temperature/time were optimized (Table 5). Unfortunately, no more than trace amounts of product were synthesized across the different conditions. The cross-coupling reaction was also conducted using *m*-bromoanisole and *p*-bromonitrobenzene, as well as with conventional heating, to no avail. Throughout the attempts to achieve the cross-coupling of ferrocenecarboxaldehyde with aryl bromides, it was noticed that in certain reaction conditions, the 4-methoxypehnyl boronic acid was homocoupling. Percent conversions of the homocoupling side product for each of the initial conditions were calculated.

Table 5. Summary of optimization efforts of a cross-coupling reaction between ferrocenecarboxaldehyde and *p*-bromoanisole conducted using microwave heating. The yields of the homocoupling product are also shown.

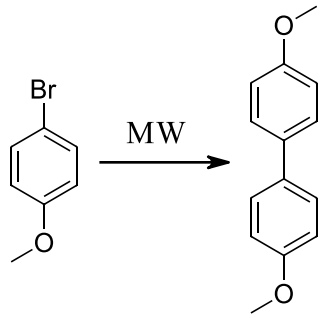


Entry	Base	Solvent	Catalyst	CIL	%Conversion	%Conversion of Homocoupling Product
1	Cs_2CO_3	DMF	$Pd(OAc)_2$	**6a**	N/A	3.4
2	Cs_2CO_3	1,4-dioxane	$Pd(OAc)_2$	**6a**	N/A	13
3	Cs_2CO_3	Isopropanol	$Pd(OAc)_2$	**6a**	N/A	0
4	Cs_2CO_3	Acetonitrile	$Pd(OAc)_2$	**6a**	N/A	80
5	Cs_2CO_3	Water	$Pd(OAc)_2$	**6a**	N/A	13
6	Na_2CO_3	DMF	$Pd(OAc)_2$	**6a**	N/A	8.8
7	K_2CO_3	DMF	$Pd(OAc)_2$	**6a**	N/A	13
8	Pyridine	DMF	$Pd(OAc)_2$	**6a**	N/A	0
9	Triethylamine	DMF	$Pd(OAc)_2$	**6a**	N/A	0

5.2.3 Investigations into Homocoupling of Aryl Bromides

The discovery of the formation of side product first led to an investigation into which reagents were required for homocoupling to occur (Table 6). The reaction was also conducted in dry conditions, with no improvement found in %conversion to give the desired cross-coupled product.

Table 6. Homocoupling of aryl bromides in the absence of certain reagents. All reactions, except for entry #5 were done in dried flasks. The reactions were performed in DMF and microwaved for 30 minutes at 150℃.



Entry	Base	CIL	Catalyst	%Conversion
1	Cs_2CO_3	408	$Pd(OAc)_2$	5.9
2	None	None	$Pd(OAc)_2$	0
3	None	408	$Pd(OAc)_2$	0
4	Cs_2CO_3	None	$Pd(OAc)_2$	8.5
5	Cs_2CO_3	408	$Pd(OAc)_2$	7.3*
6	Cs_2CO_3	None	None	0

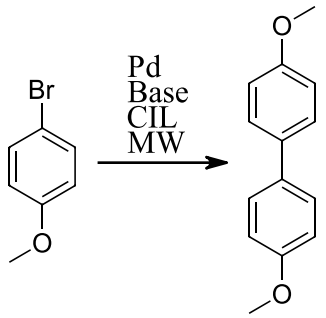
*Not conducted in dried flask

These results suggested that the palladium catalyst and carbonate base were essential for homocoupling to occur, but not the imidazolium salt. From there, the microwave settings, solvent, and catalyst were optimized.

5.2.4 Optimization of the Homocoupling of Aryl Bromides

A variety of different temperatures and reaction times were attempted in the microwave reactor. A clear pattern emerged that the reaction would not proceed without high temperatures. This meant using solvents that can reach high temperatures (e.g., DMF, DMSO), and/ or the addition of CILs to allow the reactions to reach higher temperatures. In one example, acetonitrile with 0.5% (w/v) CIL reached a maximum temperature of 130 °C, while acetonitrile with 1.7% (w/v) CIL facilely reached 170 °C (Table 7, entries 3 and 4).

Table 7. Microwave temperature and reaction times, in different solvents. All reactions used Cs_2CO_3 as the base, $Pd(OAc)_2$ as the catalyst, and CIL-528 and were performed in the microwave reaction (except for entry 1). Entries 3-6 were performed in pressure-sealing vials.



Entry	Solvent	Temperature (°C)	Time	%Conversion
1*	DMF	100	16 hours	-
2	Acetonitrile	75	45 min	-
3**	Acetonitrile	130	30 min	-
4***	Acetonitrile	170	7 min	1.4
5	DMSO	235	5 min	13
6	DMSO	170	7 min	2.8

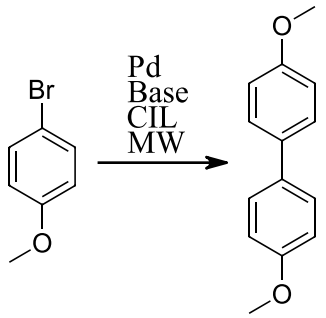
*Heated using a conventional sand bath.

**The reaction temperature was set to 170 ℃; however, the reaction was only able to reach a maximum temperature of 130 ℃.

***Additional CIL was added to allow the reaction to reach 170 ℃.

Solvents, base and catalyst were next tested, with DMF, K_2CO_3, and $Pd(PPh_3)_2Cl_2$, respectively, emerging as the most effective (Table 8).

Table 8. Summary of optimization of the homocoupling of *p*-bromoanisole. All reactions were microwaved for 10 minutes at 175 ℃, except for entry 4, which was microwaved at 170 ℃ for 7 minutes.

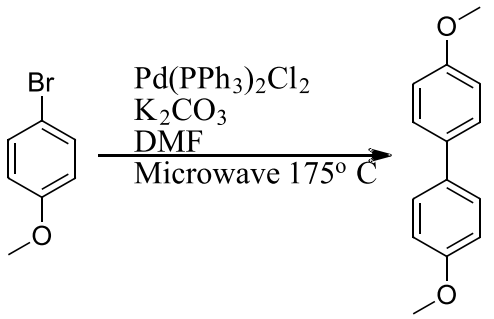


Entry	Base	Solvent	Catalyst	CIL	%Conversion
1	Cs_2CO_3	DMF	$Pd(OAc)_2$	**6a**	8.5
2	Cs_2CO_3	1,4-dioxane	$Pd(OAc)_2$	**6a**	1.7
3	Cs_2CO_3	Water	$Pd(OAc)_2$	**6a**	5.6
4*	Cs_2CO_3	DMSO	$Pd(OAc)_2$	**6a**	2.8
5	Cs_2CO_3	Acetonitrile	$Pd(OAc)_2$	**6a**	1.4
6	K_2CO_3	DMF	$Pd(OAc)_2$	**6a**	11
7	Cs_2CO_3	DMF	$Pd(PPh_3)_2Cl_2$	**6a**	28
8	Cs_2CO_3	DMF	Pd/C	**6a**	11
9	Cs_2CO_3	DMF	$Pd(OAc)_2$	**1**	1.7
10**	Cs_2CO_3	DMF	$Pd(OAc)_2$	**6a**	5.7

*Microwaved at 170 ℃ for 7 minutes

**One equivalent of copper (II) acetate was added for entry 10.

The final conditions used DMF as the solvent, bis(triphenylphosphine)palladium chloride as the catalyst and potassium carbonate as the base (Scheme 18). No CILs were added, as they did not improve yields. The reaction yielded the product in a 65% yield.



Scheme 18. Final homocoupling reaction conditions.

5.3 Conclusions and Future Work

While product was seen, the cross-coupling of aryl halides to ferrocenecarboxaldehyde was ultimately not successful, as no significant amounts of product were synthesized. Exploring different reagents, including different directing groups on the ferrocene cyclopentadienyl ring, different catalysts and different imidazolium CILs could potentially improve the reaction. Gao et al. had success cross-coupling aryl boronic acids to aminomethylferrocenes using amino acid ligands[35,36]. N-protected amino acids have been used as ligands in conjunction with $Pd(OAc)_2$ to achieve a range of C-H activation cross-coupling reactions[15,36,51]. The amide nitrogen of N-protected amino acids can complex to palladium, while the carbonyl oxygen can hydrogen bond to the hydrogen of the C-H bond to-be-activated[51]. It is possible that this coordination of N-protected amino acids could work synergistically with an imidazolium NHC, when the N-protected amino acid is substituted on the imidazole ring to stabilize palladium intermediates (Figure). Amino acid-substituted imidazoliums would also be chiral, having the potential to impart chirality on an asymmetric cross-coupling reaction.

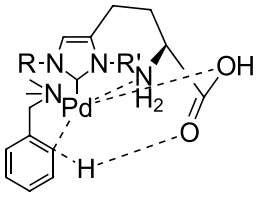


Figure 6. A possible transition state of a C-H activation cross-coupling reaction using an imidazole NHC substituted at the 4-position with an amino acid and palladium(II) acetate.

The homocoupling of aryl bromides provided moderate yields, so the next step would be to attempt the reaction using a wider variety of substrates, including aryl bromides with either electron-withdrawing or electron-donating groups at the *para*- and *meta*-positions to determine substituent effects, as well as to attempt the reaction using aryl chlorides, aryl iodides and aryl triflates. Expanding the scope of available starting materials would make the reaction more versatile for synthesis. Further, it would be valuable to attempt the reaction with sterically bulky aryl halides, including 1-halonaphthalenes and aryl halides with bulky substituents at the *ortho*-position. The product of these reactions would display axial chirality, which has the potential to be enantiomerically controlled by chiral NHCs complexed to palladium. This would offer access to axially chiral biphenyls and binaphthyls like BIPOL and BINOL through an aryl halide homocoupling route. Additionally, DMF emerged as the most effective solvent at 175 ℃; however, DMF was not tested at higher temperatures. Given the increase in yield seen from increasing the temperature from 170 ℃ to 235 ℃ seen with DMSO, it would be worthwhile to examine the effects of temperature more carefully on the reaction progress. It is also possible that DMF would not reach those higher temperatures, or may decompose; however, the addition of CILs to the reaction mixture may allow for higher temperatures to be reached with greater stability.

CHAPTER SIX: EXPERIMENTAL

6.1 General Information

Reagents and solvents were obtained from a variety of suppliers, but were all of commercial grade, with purities of >99% and were used without further purification, with the exception of the following:

- Cesium carbonate was oven dried prior to use.

Organic layers collected from separatory funnels were dried using $MgSO_4$ and gravity filtered. Column chromatography was conducted using SiliaFlash P60 40-63 μm (230-400 mesh) silica gel.

NMR spectra were obtained with a 500 MHz Bruker Advance Neo spectrometer and analyzed with Bruker TopSpin 4 software. ^{1}H NMR was performed using 16 scans, while ^{13}C NMR was performed using 1024 scans with power gated decoupling. ^{1}H NMR chemical shifts are reported in parts per million (ppm) based on an internal standard of tetramethylsilane (TMS) set to δ 0.00 ppm. ^{13}C NMR chemical shifts are reported in parts per million (ppm) based on the $CDCl_3$ solvent residual peak as an internal standard set to δ 77.16.

Mass spectra were acquired with an Advion Expression CMS spectrometer in atmospheric chemical pressure ionization (APCI) mode and introduced using the atmospheric solid analysis probe (ASAP) or an HPLC-MS system consisting of a Waters 1525 Binary HPLC pump with an Xselect CSH C18 5um column attached to a Waters Acuity QDa mass detector.

Microwave reactions were performed on a CEM Discover 2.0 Synthesizer. All microwave reactions at or below 150 ℃ were performed in round bottom flasks, equipped with condensers. All microwave reactions above 150 ℃ were performed in 35 mL pressure vials.

Percent conversion was determined using ^{1}H NMR results. The peak area of a selected product peak was divided by the sum of the peak area of the same product peak and the peak area of a selected starting material peak (accounting for the relative number of protons corresponding to the starting material peak and the product peak, if necessary). Selected product and starting material peaks were consistent in the analysis of each reaction. In general, the chosen product and area peaks were selected because they had very different chemical shifts than any other starting material, product, side product or solvent peaks.

6.2 Synthesis of Chiral Ionic Liquids

(1) *(1R)-(-)-1-butyl-3-methylimidazolium camphorsulfonate*

(1R)-(-)-10-Camphorsulfonic acid (2.3289 g, 10 mmol) and 1-butyl-3-methylimidazolium chloride (1.7477g, 10 mmol) were added to a round bottom flask containing acetone (4 mL) and a stir bar. The flask was flushed with nitrogen, heated to 50℃ and stirred for 16 hours. The contents of the flask were concentrated with a rotavapor to yield a yellow-orange oil (4.121 g, >100% of theoretical yield). The larger-than-possible yield was attributed to a small amount of residual acetone, that could be not removed with a rotavapor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 4.31 (t, J = 7.4 Hz, 2H), 4.09 (s, 3H), 3.21 (q, J = 78.7 Hz, 2H), 2.09 (t, J = 4.5 Hz, 2H), 2.04 (m, 1H), 1.86 (m, 4H), 1.39 (m, 4H), 1.09 (s, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.71, 122.91, 121.33, 58.58,

49.98, 48.43, 48.19, 42.99, 42.72, 36.80, 32.13, 26.99, 25.42, 19.87, 19.75, 19.52, 13.45. $[M+H]^+$ calculated for $C_8H_{15}N_2$: 139.1, found 139.1.

(2) *2-amino-1-(*p-*tolylsulfonyloxy)-butane*

(R)-(-)-2-Amino-1-butanol (0.188 mL, mg, 2 mmol) was added to chloroform (2 mL) and cooled over ice. Pyridine (0.322 mL, 4 mmol), and tosylchloride (0.572 g, 3 mmol) were added while stirring. The reaction mixture was stirred at room temperature for 12 hours. The contents of the flask were taken up in diethylether, washed with 10% HCl, a saturated solution of aqueous sodium bicarbonate, and water. The organic layer was dried, filtered and concentrated. Flash column chromatography (1:1 hexanes to ethyl acetate) yields the a crude product as a clear oil (0.204g, 42%yield). ^{1}H NMR :(500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 3.90 (m, 2H), 3.29 (m, 1H), 2.44 (s, 3H), 1.46 (m, 2H), 0.69 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.19, 138.20, 129.56, 127.08, 60.40, 54.91, 25.37, 21.05, 14.20. $[M+H]^+$ calculated for $C_{11}H_{17}N_3S$: 244.1, found: 244.2

*Addition of 2-amino-1-(*p-*Tolylsulfonyloxy)-butane to imidazole*

Imidazole (57.1 mg, 0.8 mmol) was added and stirred until dissolved in a solution of 0.5 M NaOH in ethanol (3 mL). **2** (0.204 g, 0.8 mmol) was added, and the reaction mixture was refluxed for 72 hours. The contents of the flask were concentrated with a rotavapor and diluted with ethyl acetate, washed with 10% HCl, then 10% NaOH, then water twice, then brine. The organic layer was dried, filtered and concentrated. Silica column chromatography (2:1 hexanes to ethyl acetate; followed by ethyl acetate) recovered the starting material.

(3) *6,7-dibromo-3,7-dimethyloctanol*

Dichloromethane (8 mL) was cooled over ice. Triphenylphosphine (1.574 g, 6 mmol) was added, followed by bromine (1 mL, 19.4 mmol) in dichloromethane (2 mL) and the mixture was stirred on ice for 30 minutes. A mixture of (S)-(-)-citronellol (0.911 mL, 5 mmol) and pyridine (0.445 mL, 5.5 mmol) in dichloromethane (2 mL) was added and the mixture was stirred at room temperature for 12 hours. The contents of the flask were concentrated with a rotavapor and purified with silica column chromatography (hexanes) to give **3** as a clear orange oil (93 mg, 6% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (t, J = 8.9 Hz, 1H), 3.50 (m, 1H), 2.46 (m, 1H), 1.99 (d, J = 0.8 Hz, 3H), 1.91 (m, 2H), 1.82 (s, 3H), 1.74 (q, J = 9.2 Hz, 2H), 1.57 (s, 2H), 1.28 (m, 2H), 0.95 (t, J = 6.7 Hz, 3H).

(4) *8-Iodo-2,6-dimethyl-2-octene*

Triphenylphosphine (1.260 g, 4.8 mmol), imidazole (0.327 g, 4.8 mmol) and iodine (1.240 g, 4.8 mmol) were added to a round bottom flask containing dichloromethane (17 mL) and molecular sieves. (S)-(-)-citronellol (0.732 mL, g, 4.8 mmol) in dichloromethane (4 mL) was added. The flask was flushed with nitrogen and stirred at room temperature for 12 hours. The contents of the flask were concentrated with a rotavapor and purified with silica column chromatography (8:1 hexanes: ethyl acetate) to yield **4** as a clear oil (0.284 g, 22% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (t, J = 5.7 Hz, 1H), 3.20 (m, 2H), 1.98 (m, 2H), 1.89 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.34 (m, 2H), 1.17 (m, 1H), 0.89 (d, J = 5.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.28, 124.70, 39.91, 29.15, 25.73, 25.46, 21.06, 19.57, 17.65, 14.20. $[M+H]^+$ calculated for $C_{10}H_{19}I$: 267.1, found: 267.2.

(5) *2-bromobutane*

Dichloromethane (8 mL) was added to a dried flask, which was subsequently cooled on ice and flushed with nitrogen. Triphenylphosphine (1.574 g, 6 mmol) was added, followed by a mixture of 2-butnaol (0.445 mL, 4.9 mmol) and pyridine (0.445 mL, 5.5 mmol) in dichloromethane (2 mL). Bromine (1 mL, 19.4 mmol) in dichloromethane (2 mL) was added dropwise and the mixture was stirred at room temperature for 5 days, while flushed with nitrogen. The contents of the flask were concentrated with a rotavapor, diluted with hexanes and washed three times with water. The organic layer was dried, filtered and concentrated with a rotavapor to give the product as a yellow oil (0.636g, 93%yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 1H), 1.81 (m, 2H), 1.70 (d, J = 6.6 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 58.54, 31.25, 18.44, 9.65. $[M+H]^+$ calculated for C_4H_9Br: 137.0, found: 137.2, 139.2

Mitsunobu Reaction between Menthol and Imidazole

Triphenylphosphine (1.312 g, 5 mmol) and imidazole (0.681 g, 10 mmol) were added to a dried flask with toluene (15 mL). Menthol (78 mg, 0.5mmol) was added and the flask was cooled over ice. Diisopropylazodicarboxylate (0.99 mL, 5 mmol) was added, and the reaction mixture was flushed with nitrogen, and stirred over ice for 10 minutes, then heated to 60°C for 24 hours. The contents of the flask were concentrated with a rotavapor and diluted with hexanes and extracted with 5% HCl. The combined aqueous phases were washed twice with ethyl acetate, then basified to pH 13 with 10% NaOH, then extracted three times with chloroform. The organic layer was dried, filtered and concentrated; however, no product was observed by ^{1}H NMR.

General Procedure 1

1-Alkylimidazole (4 mmol) and chloromethylmenthylether (0.833 ml, 4 mmol) were added dropwise to hexanes (6 mL) and molecular sieves in a round bottom flask. The solution was stirred at room temperature for 1 hour, then concentrated with a rotavapor.

(6a) *1-(+)-[menthoxymethyl]-3-methyl-imidazolium chloride*

General procedure 1 was followed to yield **6a** as a white powder (1.0853 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.39 (s, 1H), 7.23 (s, 1H), 5.80 (q, *J* = 50.4 Hz, 2H), 4.12 (s, 3H), 3.40 (q, *J* = 7.5 Hz, 1H), 2.13 (d, *J* = 11.6 Hz, 1H), 1.95 (m, 1H), 1.80 (q, *J* = 16.4 Hz, 2H), 1.64 (t, 2H), 1.46 (m, 2H), 1.26 (m, 1H), 0.92 (d, *J* = 4.9 Hz, 3H), 0.87 (d, *J* = 5.9 Hz, 3H), 0.52 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.17, 122.94, 120.79, 79.99, 47.79, 40.32, 36.75, 34.04, 31.15, 25.52, 22.82, 22.12, 20.97, 15.64. $[M+H]^+$ calculated for $C_{15}H_{27}N_2OCl$: 286.2, found: 251.3 $[M-Cl]^+$.

(6b) *1-(+)-menthoxymethyl]-3-butyl-imidazolium chloride*

General procedure 1 was followed to yield **6b** as a white powder (0.731 g, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.39 (s, 1H), 7.21 (s, 1H), 5.85 (q, *J* = 58.0 Hz, 2H), 4.35 (t, *J* = 7.0 Hz, 2H), 3.44 (m, 1H), 2.14 (d, *J* = 11.1 Hz, 1H), 1.91 (m, 4H), 1.61 (m, 2H), 1.49 (m, 1H), 1.41 (m, 2H), 1.25 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.80 (m, 3H), 0.51 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.77, 121.44, 120.78, 80.02, 50.04, 47.73, 40.42, 34.03, 32.15, 31.08, 25.53, 22.78, 22.12, 20.95, 19.51, 15.59, 13.42. $[M+H]^+$ calculated for $C_{18}H_{33}N_2OCl$: 328.2, found: 293.3 $[M-Cl]^+$.

General Procedure 2

Alkylimidazole (4 mmol) and chloromethylmenthylether (0.833 ml, 4 mmol) were added dropwise to hexanes (6 mL) and molecular sieves in a round bottom flask. The solution was stirred at room temperature for 1 hour, then concentrated with a rotavapor. Water (16 mL) was added to the flask, along with Li[(FC_3SO_2)N] (1.148 g, 4 mmol). The reaction mixture was stirred for 1 hour at room temperature, decanted and washed three times with water, before excess water was removed with a rotavapor.

(7a) *1-(+)–menthoxymethyl]-3-methyl-imidazolium bis(trifluoromethanesulfonyl)imide*

General procedure 2 was followed to yield **6a** as a clear oil. The round bottom flask containing the reaction mixture was dropped before an accurate yield could be determined. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 5.58 (d, *J* = 10.5 Hz, 1H), 5.51 (d, *J* = 10.5 Hz, 1H), 3.97 (s, 3H), 3.28 (m, 1H), 1.96 (m, 2H), 1.63 (m, 2H), 1.39 (m, *J* = 4.2 Hz, 1H), 1.25 (m, 1H), 0.95 (q, *J* = 6.9 Hz, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.51 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.90, 124.30, 121.69, 79.96, 77.09, 47.74, 40.06, 36.40, 34.04, 31.12, 25.39, 22.79, 21.95, 20.87, 15.30. $[M+H]^+$ calculated for $C_{15}H_{27}N_2OCl$: 286.2, found: 251.3 $[M-C_2S_2O_4F_6N]^+$.

(7b) *1-(+)–menthoxymethyl]-3-butyl-imidazolium bis(trifluoromethanesulfonyl)imide*

General procedure 2 was followed to yield **7b** as a clear oil (1.599 g, 70% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.49 (br s, 2H), 5.60 (d, *J* = 10.6 Hz, 1H), 5.53 (d, *J* = 10.6 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 2H), 3.29 (m, 1H), 1.95 (m, 2H), 1.85 (m, 2H), 1.63 (t, *J* = 13.1 Hz, 2H), 1.38 (q, *J* = 7.5 Hz, 2H), 1.33 (d, *J* = 7.4 Hz, 1H), 1.25 (t, *J* = 11.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 3.5 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.79 (q, *J* = 8.8

Hz, 1H), 0.49 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.30, 123.12, 121.91, 80.10, 79.15, 50.07, 47.67, 40.16, 34.05, 32.08, 31.12, 25.43, 22.82, 21.95, 20.85, 19.29, 15.32, 13.20). $[M+H]^+$ calculated for $C_{20}H_{33}N_3O_5S_2F_6$: 573.2, found: 293.1 $[M-C_2S_2O_4F_6N]^+$.

(8) *1,3-Bis[-(+)-menthoxymethyl]imidazolium chloride*

Imidazole (0.102 g, 0.75 mmol) was added to a dried flask with molecular sieves and DMF (3.5 mL). (+)-chloromethylmenthyl ether (0.617 mL, 1.5 mmol) was added dropwise. The reaction was stirred at 35º C for 12 hours. The reaction mixture was concentrated with a rotavapor and washed three times with hexanes to yield **7** as a brown oil (1.010 g, >100 %yield). The larger-than-possible yield was attributed to residual DMF that couldn't be removed with a rotavapor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 5.81 (d, *J* = 106.9 Hz, 4H), 3.42 (t, *J* = 9.5 Hz, 2H), 2.15 (m, *J* = 10.8 Hz, 2H), 2.00 (m, *J* = 9.8 Hz, 2H), 1.65 (m, *J* = 7.7 Hz, 4H), 1.43 (m, 2H), 1.28 (m, *J* = 5.9 Hz, 2H), 0.88 (d, *J* = 4.9 Hz, 12H), 0.82 (q, *J* = 2.8 Hz, 6H), 0.56 (d, *J* = 5.8 Hz, 6H). $[M+H]^+$ calculated for $C_{25}H_{45}N_2O_2Cl$: 442.32, found: 441.9. 405.5 $[M-Cl]^+$.

Van Leusen Reaction from Preformed Imine

Benzaldehyde (0.408 mL, 4 mmol) was added to a round bottom flask with a stir bar and toluene (1 mL). (S)-(-)-1-phenylethylamine (0.052 mL, 4 mmol) was added. A Dean Stark trap was filled with toluene and equipped onto the round bottom flask, along with a condenser. The system was covered with aluminum foil and refluxed until no new water was adding to the trap (5 hours). The reaction mixture was concentrated with a rotavapor, then taken up in a 7:3 mix of methanol (28 mL) and dimethoxyethane (12 mL). TosMIC (1.292 g, 6 mmol) and potassium carbonate (1.219 g, 8 mmol) were added and the reaction was refluxed for 72 hours. The reaction mixture

was concentrated with a rotavapor, taken up in DCM and washed with water. The organic layer was dried, filtered and concentrated with a rotavapor. Silica column chromatography (hexanes) yielded a mixture of side-products.

In Situ Van Leusen Reaction

3-Hydroxy-4-methoxybenzaldehyde (0.304 g, 2 mmol), L-phenylalanine (0.330 g, 2 mmol) and NaOH (0.08 g, 2 mmol) were added to a solution of methanol (6 mL) and water (0.6 mL). The mixture was sonicated until everything was dissolved, then stirred at room temperature for 5.5 hours. Tosylmethylisocyanide (0.293 g, 1.5 mmol) and piperazine (0.172 g, 2 mmol) were added to the reaction mixture, which was sonicated until everything was dissolved. The mixture was stirred at room temperature for 48 hours. The contents of the flask were concentrated with a rotavapor, diluted with ethyl acetate and basified to pH 10.5 with 10% NaOH. The mixture was extracted with water. The aqueous layer was acidified with concentrated HCl to pH 3 and extracted three times with ethyl acetate. The organic layer was dried, filtered and concentrated with a rotavapor to give left over starting material.

6.3 Reductive Amination of Ferrocenecarboxaldehyde

(9) *N,N-dimethylaminomethylferrocene*

To a round bottom flask with DCM (20 mL) and a stir bar was added ferrocenecarboxaldehyde (0.107 g, 0.5 mmol), dimethylamine hydrochloride (0.0448 g, 0.55 mmol), triethylamine (0.077 mL, 1.25 mmol) and sodium triacetoxyborohydride (0.264 g, 1.25 mmol), portion wise. The reaction mixture was stirred at room temperature for 48 hours, then heated to 32°C for an additional 24 hours. The reaction was quenched with sodium bicarbonate, extracted three times with DCM, then the combined organic layers were washed twice with water. The organic layer

was collected, dried, and concentrated with a rotavapor to yield a red oil (67 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (t, J = 1.7 Hz, 2H), 4.11 (s, 7H), 3.29 (s, 2H), 2.17 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 72.16, 70.66, 69.11, 68.79, 58.09, 42.86. $[M-H]^-$ calculated for $C_{13}H_{17}FeN$: 242.1, found: 242.0.

6.4 Synthesis of Methylenediamines

General Procedure 3. 37% wt. % formaldehyde in water (6.07 g, 7.5 mmol, 1.0 equiv) was added to a round bottom flask and cooled over ice. Diamine (15 mmol, 2 equiv) was added dropwise while stirring. The solution was warmed to room temperature and stirred overnight. Potassium hydroxide pellets were added until the two layers separate and the top layer was collected.

(10b) *N,N,N',N'-tetraethylmethylenediamine*

General procedure 3 was followed to yield **10b** as a clear oil (5.419 g, 45.6%) yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 2H), 2.57 (q, J = 7.1 Hz, 8H), 0.99 (t, J = 7.1 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.14, 45.07, 11.83. $[M+H]^+$ calculated for $C_9H_{22}N_2$: 158.2, found 159.0.

(10c) *N-(Morpholinomethyl)morpholine*

General procedure 3 was followed to yield **10c** as a clear oil (1.630 g, 11.7% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (t, J = 4.5 Hz, 8H), 2.91 (s, 2H), 2.50 (t, J = 4.2 Hz, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 60.41, 21.06, 14.21. $[M+H]^+$ calculated for $C_9H_{18}N_2O_2$: 187.1, found: 187.1.

(10e) *N,N,N',N'-tetraisopropylmethylenediamine*

General procedure 3 was followed on a 1.5mmol scale to yield **10e** as a clear oil (86 mg, 26.7% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 (s, 2H), 2.92 (m, 4H), 1.05 (d, J = 3.3 Hz, 12H), 1.03 (d, J = 3.5 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.32, 50.91, 18.88. $[M-H]^-$ calculated for $C_{13}H_{30}N_2$: 215.2, found: 215.3.

6.5 Homocoupling of p-bromoanisole

(12) *1-methoxy-4-(4-methoxyphenyl)benzene*

DMF (3 mL), 4-bromoanisole (0.125 mL, 1.0 mmol), $Pd(PPh_2)_2Cl_2$ (35 mg), and K_2CO_3 (0.276 g, 2.0 mmol) were added to a 35 mL pressure vial equipped with a stir bar. The reaction mixture was microwaved at 175°C for 120 min. The reaction was taken up in water and extracted three times with ether, then dried with $MgSO_4$. The solvent was evaporated off and the crude product was purified using silica column chromatography (8:1 hexanes: ethyl acetate). The product was collected as a white powder (70 mg, 65.4% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.6 Hz, 4H), 6.96 (d, J = 8.4 Hz, 4H), 3.84 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.70, 132.35, 127.74 , 114.16, 55.44. $[M+H]^+$ calculated for $C_{14}H_{14}O_2$: 215.1, found 215.0.

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