Exploring Iron-NHC Complexes as Catalysts for Organic Reactions

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# Abstract

Although iron-NHC complexes have been explored as homogenous catalysts for a wide range of organic transformations, they have yet to be screened for their ability to catalyze Michael and aza-Michael additions; they are considered to be essential reactions in the synthetic tool box of organic chemists. Two iron-NHC complexes, (2,6-bis(imidazolylidene)pyridine)FeBr<sub>2</sub> (catalyst 1), and an in-situ Fe(acac)<sub>3</sub>/IPr complex (catalyst 2), that exhibited interesting electronic properties and whose reaction scope were considered underexplored were selected to be screened for catalytic ability on the chosen reactions. Unexpected challenges rose in the synthesis of catalyst 1 and during the control experiments for catalyst 2 postponing their screening on the selected reactions. Catalyst 2 is still in the process of being synthesized. The control experiments for catalyst 2 lead to the question of whether an *in-situ* Fe(acac)/IPr complex was actually forming as reported. To date, no isolable Fe(acac)/IPr complex has been reported. After repeating the reported *in-situ* formation reaction, and performing stoichiometric ratio and decomposition control experiments, the results were inconclusive. Characterization of the reaction mixtures suggested the degradation of the IPr in the solvent used rather than coordination with  $Fe(acac)_3$ . Theoretically, the formation of the *in*situ complex seems implausible as it was difficult to create structures that met the 18 electron-rule and exhibited iron's preferred geometry. Future work should focus on finishing synthesizing catalyst 1 and determine what was responsible for the catalyzing the reaction catalyst 2 was reported to catalyze.

# Introduction

#### **Green Chemistry**

Throughout the 1900s, humans began to realize the harmful effects the industrial revolution and their lifestyle had on the environment and to themselves. In 1952, London experienced a disastrous smog caused by factory air pollution that killed approximately 4,000 people over the course of a few days. A similar, but less deadly, smog occurred in Pennsylvania in 1948 that killed 20 people and caused 7,000 infections. Water was also under attack: in 1969, Ohio's Cuyahoga River caught on fire due to dumping of untreated chemical waste. These events and countless others inspired US congress to pass the Clean Air Act in 1963 and Clean Water Act in 1972 aimed at reducing air and water pollution.<sup>1</sup> In the 1970s, researchers Molina and Rowland discovered that chlorofluorocarbons (CFCs), released by everyday household aerosol items, were not broken down in the lower atmosphere like many chemicals, but instead reacted with ozone. Other researchers found that this reaction between ozone and CFCs caused a hole in the ozone layer which protects earth from harmful UV radiation. The discovery inspired the beginning of legislature that focused on preventing pollution by curtailing waste production instead of only aiming to reduce the pollution. In 1987, the Montreal Protocol, a global agreement, was enacted which banned the production of ozone-depleting chemicals.<sup>2</sup> To further the preventative measures, congress passed the Pollution Prevention Act of 1990 which focused on source reduction. The act applied to a variety of disciplines, including chemists who utilize a range of resources.<sup>3</sup> In 1994, the U.S. chemical industry was responsible for 20% of the total U.S. energy consumption and greenhouse gas emissions.<sup>4</sup> The most energy intensive chemical sector was the synthetic chemical sector, consuming 33% of the chemical industrial energy consumed in 1994 (**Figure 1**). The main culprit in this sector is the production of ethylene by petrochemical companies and its wide use in feedstocks for plastics and resins.<sup>4</sup>



**Figure 1.** Energy breakdown of the U.S. chemical industry in 1994. Image from Berkeley National Laboratory report.<sup>4</sup>

Inspired by the Pollution Prevention Act, chemists in America launched "green" chemistry programs and designed a set of guidelines, known as the 12 principles of green chemistry, to make chemical processes more sustainable (**Figure 2**). Almost thirty years later, this initiative has led to progressive research in developing bio-based polymers, catalysts, benign solvents, and reducing use of hazardous chemicals. Out of all of the green chemistry initiatives, catalysis has been referred to as the "foundational pillar of green chemistry" due to its applicability to the other principles.<sup>3</sup>



**Figure 2.** The 12 Principles of Green Chemistry. The green boxes represent which other principles catalysis is applicable.<sup>3</sup>

### **Overview of Catalysis**

# Types of Catalysts

Catalysts are widely used throughout industries due to their selectivity and efficiency; approximately, "90% of all US chemical manufacturing processes involve catalysis". Selectivity refers to the ability of the catalyst to only react with the desired reagent and form the desired product. The main processes that utilize catalysts are chemical and petroleum processing and modern-energy efficient environmental technologies.<sup>5</sup> By definition, a catalyst is a substance that accelerates a chemical reaction and is regenerated, which is how it is applicable to the waste prevention principle (**Figure 2**).<sup>6</sup> Ideally, the catalyst would be able to be isolated from the reaction and reused. The main types of catalysts are acid/base, enzymes, and metals. Acids/bases catalyze a reaction by protonating/deprotonating a target molecule causing it to become more reactive and either attack or be attacked (depending on the reaction conditions) by the other target. Enzymes are nature's catalysts: they are proteins that catalyze individual steps in metabolic pathways in organisms. The six classes of enzymes are oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. The reaction occurs at the active site which selectively binds to the substrate and forms the desired product.<sup>7</sup> Transition metal mechanisms will be discussed in detail later.

An aldol reaction can be catalyzed by all three types of catalysts (**Figure 3**). An aldol reaction is the 1,2-addition of an enol to an aldehyde or ketone. In an acid catalyzed process, the carbonyl oxygen on **1** is protonated by the acid which then undergoes tautomerization.



**Figure 3.** Types of Catalysts. Aldol reactions being catalyst by (A) an acid (B) an enzyme, fructose 1,6-diphosphate aldolase, and (C) a metal complex. COD is 1,5-Cyclooctadiene and *R*-binap is (R)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine).<sup>7-9</sup>

The newly formed enol attacks the carbonyl carbon on **2**, forming a carbon-carbon bond. This step is facilitated by the protonation of **2** by the acid which draws the electron density away from the carbonyl carbon (**Figure 3A**).<sup>8</sup> The enzyme fructose 1,6-diphosphate aldolase catalyzes the aldol reaction step in glycolysis. Its active site contains the amino acid residues of lysine, cysteine, and histidine, which are responsible for the binding to the substrate and stabilization of the intermediates to form the two desired products (**Figure 3B**). Lastly, the reaction can also be catalyzed by a rhodium complex in conjunction with (R)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine), diethylmethylsilane, and an acid (**Figure 3C**).<sup>9</sup>

The two broad classifications of organometallic catalysts are homogenous and heterogenous. A heterogenous catalyst is present in a different phase than the reagents, such as a fluid with the dissolved reagents passing over a bed of solid catalyst. A homogenous catalyst is present in the same phase as the reagents (dissolved in the solvent with the reagents). Heterogenous catalysts are more frequently used than homogenous in manufacturing industries due to easy recovery and recyclability after each processing batch. Although homogenous catalysts far surpass heterogenous catalysts in activity and selectivity, most industries believe the disadvantage of isolating the homogenous catalyst outweighs those benefits.<sup>5</sup> An example of how this issue can be addressed is with biphasic catalysis. In biphasic catalysis, the catalyst is soluble in water and the solvent used in the reaction is immiscible with water. This enables the reagents to interact with the catalyst and for the catalyst layer to be separated by decantation.<sup>10</sup> A few industrial processes that utilize homogenous catalysts are Monsanto's acetic acid production, DuPont's adiponitrile production, Celanese's butanal production, and the Wacker process for acetylaldehyde.<sup>5</sup> Another advantage of homogenous catalysts is the ability to study reaction mechanisms with accessible techniques such as nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and mass spectrometry (MS). However, studies on heterogenous systems are increasing as surface spectroscopy capabilities increase, such as atomic force microscopy, tunneling electron microscopy, and scanning electron microscopy. Studying the reaction mechanism of a catalyst is essential to improving its selectivity and reaction yield.

#### Organometallic Catalytic Reaction Mechanisms

Catalysis applies to the green chemistry principle of atom economy by increasing the efficiency of a reaction at the molecular level (**Figure 2**). Atom economy refers to the conversion of the atoms in the reactants to the desired product. A catalyst guides the reagents to form the desired product thereby increasing the amount of reagent that forms the final product and reducing the formation of by-products that are unwanted and potentially hazardous, applicable to principle 11 (**Figure 2**). Without a catalyst offering a reaction site to assist reagents in bond formation, the rate of the process would depend on the probability of the reagents colliding in solution and the probability that they collide in the orientation that enables the desired bond formation; interactions in undesired manners would lead to the formation of undesired products.

An organometallic catalyst controls this process using a series of possible mechanistic steps: oxidative addition and reduction elimination, migratory insertion and  $\beta$ -elimination,

coordination and dissociation. Oxidative addition of X-Y involves the cleavage of the X-Y bond and the subsequent addition of X and Y to the metal center. This addition increases the oxidation state of the metal center by two. If oxidative addition is involved, then reductive elimination occurs later in the catalytic cycle. The step involves the dissociation of two groups coordinated to the metal center which reduces oxidation state of the metal center by two. Migratory insertion involves the insertion of one ligand into another ligand on the metal center. If the metal does not coordinate to another substrate, then its oxidation state decreases by one. This mechanism is reversed by  $\beta$ elimination which involves the cleavage of the bond  $\beta$  to a nucleophile and the formation of a  $\pi$ bond. If the metal center has a vacant coordination site *cis* to the leaving group, the leaving group could fill that spot. The most common  $\beta$ -elimination is  $\beta$ -hydrogen elimination Coordination similar to oxidative addition, in that after a ligand attaches to the metal center a  $\sigma$ -bond is formed. Dissociation is the breaking of one  $\sigma$ -bond.<sup>10</sup>

The catalytic cycle of the Wacker process demonstrates how an organometallic complex utilizes those mechanisms to bind to the substrate and form the desired product. The Wacker process was developed in the 1950s and catalyzes the conversion of ethylene to acetaldehyde using a palladium (II) chloride catalyst (**Figure 4**).

The cycle is initiated when a chloride ligand disassociates, and an alkene is associated (**a**). Then water performs a nucleophilic attack on the alkene, breaking the double bond and forming an alcohol (**b**). Next,  $\beta$ -hydrogen elimination occurs, resulting in formation of a double bond and the hydrogen replaces a chloride ligand (**c**). An attack by a chloride initiates a migratory insertion of the hydrogen to produce a  $\sigma$ -bonded CH(OH)CH<sub>3</sub> group (**d**). Dissociation of the product, acetaldehyde, and formation of by-products, HCl and chloride ions, occurs via a reductive elimination. The palladium is reduced to an oxidation state of zero (**e**). The catalyst is then regenerated with an oxidation agent and ready to begin the cycle again (**f**). It is important to note that the Wacker process is not a perfect catalytic cycle since the palladium requires the use of an oxidation reagent to be regenerated.<sup>10</sup>



**Figure 4.** Catalytic cycle for the Wacker process. Image adapted from Housecroft, C. E.; Sharpe, A. G. *Inorganic Chemistry*, 4th ed.; Pearson Education Limited: Harlow, England, 2012.<sup>10</sup>

A catalyst drives a reaction by making the steps more energetically favorable by destabilizing the reactants and/or stabilizing the transition states. The destabilization of the reactants and stabilization of transition states decreases the energy gap required to achieve the transition states (**Figure 5**). For instance, in the Wacker process, the reactants are destabilized upon coordination with Pd due to the stretching of the pi cloud (**Figure 4a**). That destabilization enables the ethylene to be more susceptible to nucleophilic attack than uncoordinated ethylene, thereby lowering the energy required to achieve the transition state and subsequent intermediate (**Figure 5**). By lowering the activation energy, a process could then proceed at a lower temperature and pressure without reducing the yield.<sup>11</sup>



**Reaction Coordinate** 

Figure 5. General Energy Diagram.

#### **Designing an Organometallic Catalyst**

When designing an organometallic catalyst for a specific process, the two components to determine are the metal center and the surrounding ligands. The principles of green chemistry can be utilized in the design process. The complex could have a relatively short mild synthesis that utilizes reagents with renewable feedstocks (i.e. use non-precious metals or reagents derived from plant sources) and are soluble in polar or ionic solvents to follow the green chemistry principles six, seven, eight, and eleven. By avoiding hazardous chemicals when possible, green chemistry principles three, four, five, and twelve are incorporated into the synthesis. And finally, if the catalyst degrades naturally and is eco-friendly, it can incorporate the last principle of green chemistry to be mentioned, principle ten (**Figure 2**).

# Selecting the Metal Center

When selecting a metal, the important characteristics to consider are the metal's previously reported reactivity, its commercial availability, possible oxidation states, preferred geometry, and general toxicity. Knowing the types of reactions a metal can catalyze provides notable insight on what other reactions it could possibly catalyze. The metal's achievable oxidation states and type

of geometry also influences the types of reactions it could potentially catalyze. The geometry influences how many substrates can be coordinated at once. The commercial availability and toxicity play a factor in the ease of synthesis of the complex.

Most commercial processes utilize catalysts that contain platinum group metals, which are also precious metals, such as palladium (as shown in the Wacker process), rhodium, iridium, and ruthenium. The platinum group metals are widely used as catalysts due to their resistance to chemical attack, ability to easily be oxidized, and their thermal and conductive properties.<sup>12</sup> The petrochemical industry uses platinum catalysts to refine crude oil and for other processes in the production of high-octane gasoline. The automotive industry is the largest consumer of platinum group metals; platinum, rhodium, and palladium, are used as the oxidative catalysts in catalytic converters that filter exhaust emissions from automobiles. Other uses of these metals include making fine jewelry, circuits and computer hard drives, and medical uses such as dental materials and anticancer drugs (i.e. cisplatin).<sup>12,13</sup> While these metals have proven themselves to be efficient and applicable to a wide scope of reactions, they are expensive, not abundant compared to other metals, and can form toxic waste.<sup>14</sup> South Africa is the world's largest producer of platinum group metals, producing 120,000 kilograms of platinum alone in 2016, and contains the largest reserves. However, the mining industry in South Africa faces labor unrest and safety failures. One of South Africa's largest mining companies had a five-month long worker's strike in 2014 that drastically reduced production. The other countries that produce precious metals are Zimbabwe, Russia, Canada, and United States. The world reserves of these metals are estimated to be over 100 million kilograms (approximately 11,000 tons).<sup>12</sup>

The green chemistry initiatives, and cost of precious metals, have sparked research in developing catalysts that utilize environmentally-sustainable metals, such as copper, zinc, and iron, as the central metal. Out of those, iron could be considered the most sustainable and cost-efficient choice due to its high abundance in the earth's crust and non-toxicity.<sup>14</sup> Iron is obtained by heating iron ore in the presence of a reductant, a process known as smelting. Iron ore is over 8,000 times cheaper than ruthenium, the least expensive platinum group metal (**Table 1**).<sup>15</sup> Countless iron complexes and salts are already commercially accessible or easily synthesized.<sup>14</sup> The majority (98%) of iron ore is used in steel production and it is mined in 50 countries. The largest producers are Australia and Brazil and the world reserves of iron ore is estimated to be 800 billion tons which would contain over 230 billion tons of iron, approximately 21 million times the reserves of all the

precious metals.<sup>16</sup> Not only is iron the sustainable choice for a metal center, but has already demonstrated catalytic ability for various reactions.

Prices of Metals (USD/ kg)					
Rhodium	48,226.12				
Palladium	32,697.31				
Iridium	31,186.22				
Platinum	30,253.85				
Ruthenium	4,822.61				
Copper	6.91				
Zinc	3.26				
Iron Ore	0.06				

**Table 1.** Prices of Selected Metals.<sup>15</sup>

Iron catalysts offer a broad range of synthetic transformations, such as additions, reductions, and coupling reactions, due to iron's Lewis acid character and ability to easily change oxidation states. However, the scope of iron catalysts remained limited for decades while palladium and nickel reactions were more frequently developed.<sup>17</sup> There has been a recent expansion of iron catalysts used for the reduction, oxidation, and coupling chemistry reactions widely used in industries.<sup>14</sup> The reduction reactions include hydrogenation of nitro-aromatics, aryl azides, and C=C and C=O bonds, catalytic transfer hydrogenations, and hydrosilylations.<sup>18</sup>

The common oxidation states for iron are +2 and +3, with +3 being more stable. Iron (II) complexes typically have a coordination number of six with octahedral geometry while iron (III) generally coordinates to three or eight ligands while also preferring octahedral geometry. Iron (III) is a harder Lewis acid than (II). For catalysis, the oxidation states of 0, -1, and -2 are more important due to being able to form more reactive complexes than iron (II) or (III).<sup>19</sup> According to crystal field theory, the magnetism of an octahedral iron (II) complex depends on whether the complex is low or high- spin; low spin complex is diamagnetic while the high-spin is paramagnetic As for an iron (III) octahedral complex, both the low and high-spin complexes are paramagnetic

(Figure 6). The type of ligands surrounding the iron also dictate whether the complex is low or high spin.<sup>10</sup>



**Figure 6.** (Right) High-spin and (Left) Low- spin octahedral complexes for Fe(III).

#### Selecting the Ligands

When selecting ligands, it is essential to keep in mind properties such as electronics, sterics, electronics, and hydrophobicity or hydrophilicity. When classifying electronic properties of ligands with crystal field theory, the ligands can be separated into two categories: weak field and strong field. Weak field ligands can cause the complex to be high- spin while strong field ligands can cause the complex to be low- spin. To continue with the octahedral example, the energy separation between the d orbitals ( $\Delta_{oct}$ ) increases as the strength of the field ligands increases. The strength of the field ligand depends on the donor atom, in which the strength of the field ligand tends to increase as the electron donating ability of the donor atom decreases. To illustrate, ligands that contain nitrogen or carbon as the donor atom would be more likely to form a low-spin complex with iron than a halogen or oxygen-donor atom ligand. Another electronic property to keep in mind are the donating and withdrawing abilities of the ligands to the metal center. Hydrogen, terminal halogens, and alkyl groups are examples of ligands that donate 1-electron. Two-electron donor groups include carbenes, and trivalent-phosphines. If the non-bonding orbitals of the metal center overlap symmetrically with the ligand orbitals,  $\pi$ - electron interactions can occur between the center and ligand. A  $\pi$ -donating ligand donates electrons from its filled *p*-orbitals to vacant metal orbital while  $\pi$ -accepting ligand accepts electrons from a filled *p*-orbital on the metal to one of its empty antibonding orbitals (also known as back-bonding). Examples of  $\pi$ -donating and  $\pi$ accepting ligands include halogens and carbenes respectively.  $\pi$ -acceptor ligands can help stabilize low oxidation state metals.<sup>10</sup>

Varying the steric hindrance of a ligand significantly impacts the complex's catalytic ability. Bulkier ligands can possibly stabilize the active catalytic species and decrease its potential to decompose during the reaction. However, there is a limit to this effect. A complex reaches a point in which if the ligand is too bulky, it can be unfavorable for the substrate to approach and bind to the metal center which consequently reduces the complex's catalytic ability.<sup>20</sup> There is a wide range of molecules that can act as ligands, from organic compounds like trivalent phosphines to carbonyls, to inorganic compounds like ammonia, each having their advantages and disadvantages. For instance, phosphines generally form cone-shaped spatial arrangements which enable it to be less sterically demanding than other ligands; however, it is somewhat difficult to synthesize structural variations of phosphine ligands.<sup>21,22</sup>

#### **N-Heterocyclic Carbene Ligands**

#### History and Electronic Properties of NHCs

*N*-Heterocyclic carbenes (NHCs) ligands have increased in popularity due to their relatively simple synthesis and ability to stabilize compounds. Carbenes alone are unstable because they contain a divalent carbon atom that has an incomplete octet and are coordinately unsaturated; they were considered to only exist as highly reactive intermediates in certain organic processes, like cyclopropanation.<sup>21</sup> In the 1990's, the Arduengo group stabilized a carbene by incorporating it into a nitrogen heterocycle. The simple synthesis involved deprotonating 1,3-di-I-adamantylimidazolium chloride with sodium hydride in THF in the presence of catalytic dimsyl anion at room temperature to yield 1,3-di-I-adamantylimidazol-2-ylidene (**Figure 7A**).



Figure 7. Overview of N-heterocyclic carbenes. Image from Hopkinson et al.<sup>21</sup>

The carbene formed was easily isolated and determined to be stabilized by the  $\pi$ -donation into the out-of-plane carbene *p*-orbital by the N-C=C-N  $\pi$  -system (**Figure 7B**).<sup>23</sup> This relatively simple synthesis sparked numerous studies and libraries of NHCs. An NHC is defined as a "heterocyclic species containing a carbene carbon and at least one nitrogen atom within ring structure" thus various molecules with differing ring sizes, substitution patterns, and degrees of heteroatom stabilization fall under this class of molecule (**Figure 7C**). Stable NHCs have been formed that are not aromatic (has saturated backbone), have various *N*-substituents, are stabilized by nitrogen and one other electronegative atom (O or S), are stabilized by only one nitrogen, and are four, five, or six- membered rings (**Figure 7C**). All those features greatly impact the stability, sterics, and electronics of an NHC. Increasing the ring size leads to greater steric shielding due to the greater N-C-N angle pushing the *N*-substituents closer to the carbene carbon.<sup>21</sup> Although NHCs could be stable with an unsaturated backbone, a saturated backbone adds aromaticity which provides greater electronic stabilization to the system and increases the ligand's ability to act as a  $\pi$ -acid. Substituents could be added to the backbone which could increase or decrease the  $\pi$ -donor ability of the nitrogen atoms to the carbene center.<sup>21,24</sup>

Five-membered rings with two nitrogen heteroatoms and an unsaturated backbone make up the largest class of NHCs thus this review will mainly focus on imidazolylidenes (**Figure 7**). The insertion of two nitrogen atoms adjacent to the carbene center causes the carbene to exhibit a singlet ground electronic configuration with the highest occupied molecular orbital to be the  $sp^2$ hybridized lone pair on the carbene center and the lowest unoccupied molecular orbital to be the unoccupied *p*-orbital. As stated earlier, the nitrogen heteroatoms stabilize the carbene center by being  $\sigma$ -electron withdrawers from and  $\pi$ -electron donors to the carbene center. This arrangement stabilizes the carbene center inductively by lowering the energy of the occupied  $\sigma$ -orbital and mesomerically by donating electrons into the unoccupied *p*-orbital. A less important, but still noteworthy, stabilization factor than the nitrogen heteroatoms is the *N*-substituents. NHCs typically feature bulky *N*-substituents which stabilizes the species by making it sterically unfavorable for the carbenes to dimerize as predicted by the Wanzlick equilibrium. This cyclic arrangement also contributes to the singlet ground electronic state configuration.<sup>21</sup>

#### Coordination and Applications of NHCs

Carbenes are considered electrophilic, but the electronic arrangement of NHCs render them nucleophilic and excellent  $\sigma$ -donors with the carbene center lone pair being the electron donor.<sup>21</sup>

NHCs are able to bind to a variety of metallic and non-metallic species. They form stable complexes with non- and semi-metallic species due to the NHC donating  $\sigma$ -electrons into the unoccupied  $\sigma$ -orbital of *p*-block elements. This strong coordination can stabilize *p*-block elements in the zero-oxidation state. A popular group of NHC *p*-block complexes are NHC-borane complexes which exhibit greater stability and less likely to uncoordinate with the borane than the previously used ether- or amine-borane complexes. NHC-borane complexes can act as nucleophiles or bases and only undergo hydroboration of ketones in presence of Lewis acid. The major applications of NHC *p*-block complexes include activation of small molecules, creating frustrated Lewis pairs, stabilization of reactive species, and reagents in organic synthesis.<sup>21</sup>

The majority of NHC applications involve NHC-transition metal complexes. Broadly, the main applications of these complexes are in metallopharmaceuticals as antibacterial and anticancer agents, as important components of organometallic materials (i.e. coordination polymers, photoactive materials, liquid crystals), in coordination to metal surfaces (i.e. gold nanoparticles), and most importantly, their use in homogeneous catalysis. NHCs form strong bonds with transition metals due to their excellent  $\sigma$ -donating ability into the empty  $\sigma$ -orbital of the transition metal. Another noteworthy component of their coordination is the  $\pi$ -back bonding from the metal into the empty carbene orbital and the  $\pi$ -donation from the carbene orbital to the metal. However, the  $\pi$ -donating abilities are weak thus NHC coordination to a metal is considered to be limited to a single instead of a double bond. This strong coordination provides NHC-transition metal complexes with high thermal stability and lessens decomposition of the complex which is why they are widely used in organometallic materials and as homogenous catalysts for organic reactions. NHCs have been successfully complexed with all transition metals in varying oxidation states, alkali and alkaline earth metals, and f-block metals.<sup>21</sup> NHC-transition metal complexes have successfully been applied to a wide range of organic transformations such as Pd catalyzed Mizoroki-Heck reaction, Ru- and Ir- catalyzed hydrogenation and hydrogen transfer, oxidation of primary amines to primary alcohols, Rh- and Pt- catalyzed hydrosilyation, ethylene oxide polymerization, gold-catalyzed insertion of and much more.<sup>21,24</sup> The most important classes of reactions that have been extensively studied with these complexes are cross-coupling (when coordinated to palladium) and olefin metathesis (when coordinated to ruthenium).

### Advantages of NHCs Compared to Popular Ligands

As stated earlier, a ligand greatly impacts the sterics and electronic properties of a complex thus impacting a complex's catalytic ability. The advantages of selecting an NHC ligand over other types, specifically the widely compared phosphine and cyclopentadienyl ligands, are the abilities of the NHC ligand to form a stronger metal-ligand bond and form a complex that can be easily tweaked to give various steric and electronic properties. NHCs form a stronger bond with the metal centers than other ligands, such as ones with a P- donor atom, due to their inherent electron donating abilities. The stronger a bond, the higher the dissociation energy and shorter the bond length. NHC-metal bonds are typically shorter and have higher dissociation energies over the tricyclohexylphosphine (PCy<sub>3</sub>) counterparts making the formed complexes more thermally and oxidatively stable. This increase in bond strength leads to an increase in catalytic stability stemming from a decrease in rate of catalyst decomposition. As for sterics, phosphine ligands form a cone-shaped arrangement whereas NHCs form a usually less sterically demanding "umbrella" or "fan" arrangement around the metal. The synthesis for NHCs with various substituents are relatively simple, especially when compared to varying phosphine substituents. On NHCs, the substituents on each nitrogen can be individually modified providing more parameters to test. The starter compound for synthesizing NHCs are typically azolium salts which are bench stable solids and a variety are commercially available. NHC active catalysts may be easily formed in situ with an azolium salt and metal precursor.<sup>21</sup>

Lastly, NHC catalysts have shown reactivity pathways unobserved with other classes of complexes. An excellent example that demonstrates all these advantages of an NHC ligand over widely utilized PCy<sub>3</sub> is the comparison of Grubbs second and first-generation catalysts for olefin metathesis. The first-generation Grubbs catalyst features two PCy<sub>3</sub> ligands coordination to ruthenium while the second features one PCy<sub>3</sub> and one SIMes (SIMes= 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene) (**Figure 8**). Consequently, the second-generation Grubbs catalyst exhibits greater thermal stability and has a higher turnover rate at a lower catalyst loading amount than the first generation. The second generation expanded the substrate scope for the metathesis reactions. Kinetic studies determined that the second generation more favorably forms the active catalyst (disassociation of a PCy<sub>3</sub>) than the first generation which increases its affinity for the substrate and subsequently its efficiency. For cross coupling, NHCs have shown improvements over other ligands in the catalytic cycle. A widely used NHC for cross

coupling is the Pd-PEPPSI-NHC pre-catalyst which is easily varied to widen the substrate scope (PEPPSI= Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation). In the cycle, the NHC effectively stabilizes the zero-oxidative state palladium center and enhances the reactivity of the complex to oxidatively add the substrate. The complex is more reactive towards the oxidative addition due to the electron donating ability of the NHC to the metal center. The bulkiness of the ligand then makes the reductive elimination step more favorable and regenerates the catalyst.<sup>21</sup>



Figure 8. Comparison of iterations of Grubbs catalyst. <sup>21</sup>

## Iron-NHC Complexes

While most studies focus on palladium-NHC cross-coupling, iron-NHC complexes have also showed promise and efficiency.<sup>21</sup> Iron-NHC complexes did not receive much attention until 2000 when Grubbs reported an iron-NHC complex [(MeI*i*Pr)<sub>2</sub>FeX<sub>2</sub> (X=Cl, Br)] that excelled at catalyzing atom-transfer radical polymerization reactions (ATRP). The complex was easily synthesized and could even be formed *in situ*, however *in situ* formation caused a slight decrease in the rate of reaction. Grubbs concluded that the high catalytic activity of the complex in ATRP reactions was due to high electron donor ability of the NHC ligand to the iron center.<sup>25</sup> Since then, there has been a growing interest in iron-NHC complexes as homogenous catalysts for a wide range of reactions due to the versatility and ease of synthesis of NHC ligands and the affordability of both the NHC ligand and iron precursors. Iron-NHC complexes have successfully catalyzed polymerization, hydrosilylation, C-H activation, aziridine synthesis, Kochi cross-coupling, carbometallation of alkynes reactions and others.<sup>26,27</sup> Due to the extensive reaction scope of iron-NHC complexes being analyzed for catalytic activity in this thesis will be discussed in detail.

### **Catalysts in Question**

Two iron-NHC complexes were selected that exhibited interesting electronic properties and whose reaction scope were considered underexplored (**Figure 9**).



Figure 9. Iron-NHC complexes whose reactivity will be explored in this study.

## Catalyst 1 [(2,6-bis(imidazolylidene)pyridine)FeBr<sub>2</sub>]

The first complex in question, catalyst **1**, was reported by the Danopoulos group (Fig 9). In 2002, the group synthesized the CNC pincer ligand and easily complexed it with ruthenium; the complexed showed catalytic activity. This was the first report of a chelating carbene ligand. By diffraction methods, they determined that the ligand exhibited a planar conformation and the lone pairs on the carbene and pyridine were *anti* to each other.<sup>28</sup> Due to the initial success, the group further tested the ligand by later complexing it with palladium<sup>29</sup> and finally, iron.<sup>30</sup> Danopoulos suggested that **1** shows catalytic potential for oligomerization, polymerization, oxidation, and C-C bond formation reactions based on its structural similarity to complexes that have demonstrated reactivity for those reactions.<sup>30</sup> Danopoulus tested **1** for the ability to catalyze a challenging coupling reaction that even Ni and Pd based complexes struggle with: the coupling of primary and secondary alkyl halides that have  $\beta$ -hydrogens. This class of reactions is virtually impossible without the presence of a catalyst and even when a catalyst is present, a  $\beta$ -elimination occurs that forms undesired alkenes (**Figure 10**).



**Figure 10.** The undesired  $\beta$ -elimination that occurs when cross-coupling primary and secondary alkyl halides that have  $\beta$ -hydrogens. Scheme adapted from Bedford et al. *J. Org. Chem.* **2006**, 71 (3), 1104–1110.<sup>31</sup>

Out of the phosphine, phosphite, arsine, and fellow carbene ligands screened on a secondary aryl bromide and secondary Grignard reaction, 1 had the second highest conversion to the desired coupling product (94%) and was determined to be significantly more active than the other systems. This was accomplished with only 5 mol % loading of 1 (Figure 11).<sup>31</sup>

A

Α	——————————————————————————————————————	[cat] Et <sub>2</sub> O		+	2 +	$\bigcirc$
В			4	+		- <u>5</u>

$\mathbf{Ligands}^{a}$		conversion to given compound (%) <sup>b</sup>					
		2	3	4	5		
Monodentate phosphines, phosphites, and arsines (13 entries)	27-87	0-10	0-1	0-8	6-26		
Bidentate phosphine and Arsine (10 entries)		0-7	0	0-7	0-17		
Carbene Ligands (5 entries)		1-4	0	1-6	5-15		
Catalyst 1	94	0	0	1	10		

<sup>a</sup> Conditions: FeCl<sub>3</sub> (0.05 mmol) (not added for Cat. 1); ligand (0.2 mmol); CyBr (1.0 mmol); MeC<sub>6</sub>H<sub>4</sub>MgBr (2.0 mmol); Et<sub>2</sub>O; reflux, 30 min. <sup>b</sup> Conversion to products 1-5 determined by GC (mesitylene internal standard).

Figure 11. Coupling of 4-Tolylmagnesium bromide with cyclohexyl bromide catalyzed by various ligands and catalyst 1. (A) scheme of reaction (B) results of ligands screened. Scheme and data adapted from J. Org. Chem., Vol. 71, No.3, **2006**.<sup>31</sup>

Notably, Danopoulos reported the first  $N_2$  stabilized iron-NHC complex by reducing 1 with Na(Hg) under a nitrogen atmosphere, affording an iron (0) complex.<sup>32</sup> Notably, a separate group, the Gibson group, complexed the CNC ligand with iron simultaneously.<sup>33</sup> The Gibson group placed the CNC ligand on first row transition metals (Ti to Co) and tested their ability to catalyze ethylene oligomerization and polymerization. The iron-CNC was deemed completely inactive for that reaction. The complex was instead methylated by methylaluminoxane (MAO) which was used as the co-catalyst.<sup>33</sup> After that study, the reports of **1** are scarce. Given how catalyst **1** has only been tested for ethylene oligomerization and polymerization and the Grignard coupling of primary and secondary alkyl halides, the complex is considered to be underexplored in terms of its catalytic potential.

# Catalyst 2 (in-situ Fe(acac)<sub>3</sub> and IPr)

Catalyst 2, an *in situ* complex of iron(acac)<sub>3</sub> and IPr, was reported by Hayashi (Figure 9).<sup>34</sup> While the reaction scope of iron $(acac)_3$  and IPr individually are extensive, no other reports of 2

were found. IPr is one of the most widely used NHC ligands, frequently complexed with nickel, palladium, copper, silver, gold, ruthenium, and platinum in catalytic complexes. IPr-transition metal complexes have been reported to catalyze C-S cross couplings, coupling of organoboron reagents with CO<sub>2</sub>, Buchwald-Hartwig aminations, aryl aminations, C-C cross coupling, Sarvlation, olefin metathesis, alcohol racemization, and more.<sup>20</sup> Iron(acac)<sub>3</sub> has been found to have catalytic abilities by itself and when used as a precursor or co-catalyst. Alone, it had a wide substrate scope when used as a catalyst for cross-coupling reactions of alkyl Grignard reagents with heteroaryl and aryl triflates, tosylates, and chlorides. It outperformed the iron salt and iron salen complex tested.<sup>35</sup> Bolm and co-workers used iron(acac)<sub>3</sub> along with chiral Schiff base ligands to form an *in situ* catalyst that demonstrated high enantioselectivity during the oxidation of sulfides.<sup>14</sup> Hayashi screened the addition of arylmagnesium bromides to aryl(alkyl)acetylenes in the presence of iron(acac)<sub>3</sub> and an added ligand. Adding IPr compared to adding various phosphine ligands and iron(acac)<sub>3</sub> alone resulted in the highest yield (91%) and showed regioselectivity for the *E*-isomer (*E*: Z 88:11). The system was determined to have a wide substrate scope, affording 69-93% yields when R, Ar<sup>1</sup>, and Ar<sup>2</sup> were replaced with a variety of groups (Figure 12).<sup>34,36</sup> Therefore, the reaction scopes of 1 and 2 have been underexplored and they have shown catalytic potential.



**Figure 12.** Scope of Fe(acac)3- IPr (cat. 2) catalyzed arylmagnesiation of internal alkenes. Scheme from *Adv. Synth. Catal.* **2013**, 355 (1), 19–33.<sup>36</sup>

#### **Organic Transformations in Question**

#### Michael Addition Reaction

The Michael reaction, named after Arthur Michael, is the 1,4-addition of a nucleophile to an  $\alpha$ ,  $\beta$ -unsaturated carbonyl compound. This reaction faces competition with the possible 1,2-addition of the nucleophile due to the electrophilic nature of the carbonyl carbon. In general, soft nucleophiles add 1,4 while hard nucleophiles tend to add 1,2 (**Figure 13A**).<sup>37</sup>



**Figure 13.** (A) Competition between the 1,2- and 1,4- addition of a nucleophile to an  $\alpha$ ,  $\beta$  unsaturated carbonyl compound. (B) Types of enolates. (left) Kinetic and (right) Thermodynamic.

The main type of Michael addition uses a carbanion, typically an enolate, as the nucleophile which results in the formation of a carbon-carbon bond. This reaction can also occur intramolecularly and multiple times, called a "double" Michael addition.<sup>38</sup> The initial step of the carboanion addition is enolization. Depending on the reaction conditions and the symmetry of the starting ketone, two regioisomeric enolates can form: one that leads to the thermodynamic product and one that leads to the kinetic product. The kinetic product has a lower activation energy, thus is more easily formed than the thermodynamic one. However, the thermodynamic product is more stable due to having a lower energy level. Thus, on an unsymmetrical ketone, the thermodynamic product would have the negative charge on the more substituted  $\beta$ -carbon while the kinetic would have the negative charge on the more substituted  $\beta$ . The formation of the kinetic enolate requires the use of strong and bulky base, like LDA (lithium diisopropylamide), at low temperatures in aprotic solvents. Meanwhile, the thermodynamic product forms at room temperature or above, using slim bases in polar protic solvents.<sup>39</sup>

Michael additions have been found to occur in nature, like in the synthesis of Calichaemicin, an antibiotic molecule synthesized by the bacterium *Micromonospora echinospora*, and is widely used in medicinal chemistry.<sup>37,38</sup> The Michael addition is used in the synthesis of antibiotics, such as Fredericamycin and Forskolin, synthesis of quinone compounds, and others. Quinone compounds have attracted the attention of pharmaceutical scientists due to being very biologically active; these compounds have been found to have insecticidal, anti-malaria, anti-oxidant, and antibacterial affects.<sup>38</sup> However, the most well-known application of the Michael addition is its use in the Robinson annulation, a widely-used steroid synthesis process. The Michael addition is the first step of the process, which is then followed by an intramolecular aldol condensation to form a bicyclic enone.<sup>39</sup> The Michael addition step in the Robinson annulation has been catalyzed by

organocatalysts, mainly L-proline, Bronsted bases, Wichterle phase transfer catalyst, biocatalysts, and various organometallic compounds. Organometallic complexes containing scandium, cobalt, copper, zinc, palladium, silver, and lanthanum have been used and achieved good yields. It is important to note that none of the complexes had NHC ligands.<sup>39</sup> For Michael additions not in the Robinson annulation, thermomorphic fluorous phosphines and even genomic salmon testes DNA have been able to catalyze the reaction.<sup>40,41</sup>

Based on a preliminary literature search, no iron-NHC complexes have been reported that catalyze Michael additions. However, iron-based compounds have been found to catalyze this reaction. In the 1980s, a polymer anchored iron (III) acetylacetonate was used in the addition of  $\beta$ -diketones to  $\beta$ -nitrostyrenes with low catalyst loading but only afforded moderate yields. Iron (III) acetylacetonate alone could only catalyze the addition of ethyl acetoacetate to cyclohexanone in the presence of an equimolar amount of a Lewis acid, and still only afforded moderate yields (**Figure 14**).<sup>42</sup>



Figure 14. Fe(acac)<sub>3</sub> as a catalyst for Michael addition. Scheme from *Chem. Rev.* 2004, 104 (12), 6217-6254.<sup>42</sup>

Then in 1997, FeCl<sub>3</sub>·6H<sub>2</sub>O was able to catalyze the addition of various cyclic and acyclic  $\beta$ -dicarbonyls to many acceptors with low catalyst loadings and mild reaction conditions, affording high yields of up to 97% (**Figure 15**).<sup>43</sup> It is regarded as the best catalyst for Michael reactions. FeCl<sub>3</sub>·6H<sub>2</sub>O can also catalyze intramolecular Michael addition, only if used to produce medium sized rings and is regioselective, producing only the trans-fused bicyclic product. For instance, a five-membered ring forms in high yield while a fifteen membered ring achieves low yield even after more intense reaction conditions (**Figure 15**).Notably, FeCl<sub>3</sub>·6H<sub>2</sub>O was able to catalyze the addition of acetylacetone to methylvinyl ketone in dehalogenated ionic liquids as solvents, having turnover frequencies of up to 63 h<sup>-1</sup>. This system was recently improved by replacing the anionic spectator ligands (chloride) with perchlorate. This switch to Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O was able to catalyze addition of 2-methoxy carbonyl cyclopentanone to methylvinyl ketone with a catalyze loading of

0.35 mol % and afforded 100% yield. An area in which iron complexes, and other metals, fail is in the ability to catalyze asymmetric Michael additions.<sup>42</sup>



n=1 conditions= 5 mol% FeCl<sub>3</sub> $\bullet$ 6H<sub>2</sub>O, rt, 12 h yield= 80% n=11 conditions= 10 mol% FeCl<sub>3</sub> $\bullet$ 6H<sub>2</sub>O, sonication, rt, 2 h then rt, 6 h yield= 8%

**Figure 15.** Michael additions using iron salt as catalyst. (A) addition of various cyclic  $\beta$ -dicarbonyls to acceptors (B) intramolecular additions of various rings. Scheme adapted from *Chem. Rev.* **2004**, *104* (12), 6217–6254.<sup>42</sup>

#### aza-Michael Addition Reaction

The aza-Michael reaction is the 1,4-addition of a nitrogen-containing nucleophile to an  $\alpha$ ,  $\beta$ -unsaturated carbonyl compound that results in the formation of a C-N bond.<sup>44</sup> It is considered one of the most essential reactions in modern organic synthesis since it is by far the best method to use for C-N bond formation. The aza-Michael addition easily forms  $\beta$ -amino carbonyl derivatives which are the building blocks for the synthesis of various nitrogen-containing compounds that are biologically active, such as 1,3-amino alcohols,  $\beta$ -lactams,  $\beta$ -amino acids, and  $\beta$ -ketones.<sup>45</sup> The most important class of compounds that utilize the aza-Michael addition are quinolones. Quinolones constitute essential broad-spectrum antibacterial drugs and act as anticancer and antimalarial agents. An intramolecular aza-Michael addition is utilized in the synthesis of chiral substituted 2,3-dihydro-4-quinolones which inhibit tumor growth by halting mitosis.<sup>46</sup>

For reactive nucleophiles, such as amines and lithium amides, catalysts are not required. However, for reactions involving less reactive nucleophiles, such as aliphatic, aromatic, and

substituted amines, Lewis acidic metal catalysts are typically required for the reaction to progress. Nitrogen tends to act as a base instead of a nucleophile. A Lewis acid "activates" the amine by coordinating with the nitrogen which results in the nitrogen having a positive charge since the Lewis acid draws electron density away from the nitrogen. The positive nitrogen is then more likely to act as a nucleophile instead of a base and attacks the alkene to form the N-C bond. Various transition metal salts and complexes have been found to catalyze aza-Michael additions. Catalytic amounts of FeCl<sub>3</sub>, LiCl, HgCl<sub>2</sub>, InCl<sub>3</sub>, and lanthanide triflates have led to the addition of aliphatic amines to  $\alpha$ ,  $\beta$ -unsaturated carbonyls in aqueous and non-aqueous solvents. Platinum-group based complexes have effectively catalyzed the addition of amines to acrylic acid derivatives. Metal salts were also useful for the reaction of enones with benzyl carbamate as the nitrogen nucleophile. Out of a variety of transition metal salts tested, some of the most effective were ZrCl<sub>4</sub>, ReCl<sub>5</sub>, Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O, and PdCl<sub>2</sub>(MeCN)<sub>2</sub> (Figure 16).<sup>47</sup> The Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O was mentioned previously; it afforded an excellent yield for carbanion Michael additions. Other iron-based complexes that have successfully catalyzed the aza-Michael addition include FeCl<sub>3</sub>, FeCl<sub>3</sub>·6H<sub>2</sub>O, and FeCl<sub>3</sub> with a stoichiometric quantity of Me<sub>3</sub>SiCl (Figure 16).<sup>42,48</sup> Those iron salts have mainly only been tested for the ability to catalyze the conjugate addition of ethyl carbamate to chalcone. It is important to note that carbamates are already a reactive species due to the carbonyl group drawing electron density away from the nitrogen, promoting its desire to act as a nucleophile instead of a base. Thus iron-based complexes have not had their aza-Michael reaction scope explored.42



**Figure 16.** aza-Michael additions catalyzed by transition metals. (A) addition of enones to benzyl carbamates. Scheme adapted from *Org. Lett.* **2002**, *4* (8), 1319–1322.<sup>47</sup> (B) aza-Michael addition catalyzed by an iron salt. Scheme from Christoffers et al.<sup>48</sup>

#### Why Catalysts 1 and 2 have Potential in Catalyzing the Selected Reactions

After evaluating the current scope of Michael and aza-Michael additions, there is reason to believe that the iron-NHC complexes selected could potentially be able to catalyze these reactions (**Figure 9**). Iron-based compounds, specifically iron (III) based, have demonstrated the ability to catalyze these reactions. Currently, one of the best catalysts for both reactions is FeCl<sub>3</sub>·6H<sub>2</sub>O, and it has a substantially limited substrate scope. For the Michael addition, only (*E*)- substituted enones can be used as substrates and the diastereoselectivity could be improved. With both aza Michael and Michael additions, the FeCl<sub>3</sub>·6H<sub>2</sub>O has only been tested using activated substrates. The FeCl<sub>3</sub>·6H<sub>2</sub>O has only demonstrated catalytic ability for Michael additions using β-dicarbonyls, which easily guide the formation of the enolate. The two carbonyls draw electron density away from the β-hydrogen, causing it to be more acidic. As for the aza-Michael, the reaction scope is limited to using carbamates as the nucleophile which is an active species due to the carbonyl group drawing electron density away from the nitrogen, causing it to act more nucleophilic than basic.

Since the reaction depicted in **Figure 15** was improved by replacing the FeCl<sub>3</sub>·6H<sub>2</sub>O with Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O, that demonstrated the positive effect electron density around the iron and decreased ligand dissociation has on the efficiency of the Michael addition. As described earlier,

NHC ligands are excellent at back-donating electron density to the metals they are complexed with which results in strong bond formation and decreases the chance of ligand dissociation. For both reactions, an iron (II) based compound has not been tested for catalytic ability thus catalyst **1** would change that and determine if iron (II) can have the same catalytic abilities. Although according to hard acid soft base theory, iron (II) is not as strong of a Lewis acid as iron (III), it generally still acts as a Lewis acid. Furthermore, the issue with using salts as catalysts is the lack of tuneability. As previously mentioned, NHC ligands are well known for their ease of synthesis and tuning their electronic properties. Therefore, the selected complexes could be tweaked to widen their potential reactivity scope. The reactions depicted in **Figure 15** and **Figure 16** will be used to screen the selected complexes to accurately compare the catalytic abilities of the complexes to what has already been accomplished (**Figure 17**).



**Figure 17.** Reactions that the selected iron-NHC complexes will be screened on to test for catalytic ability.

This study aims to broaden the reactivity scope of iron-NHC complexes on industrially relevant reactions that currently utilize unsustainable platinum-group metal-base complexes as catalysts or that simply need optimization.

# **Results and Discussion**

The original project design was to synthesize catalyst 1 while performing control experiments with catalyst 2 since catalyst 2 has a relatively simpler synthesis than catalyst 1. However, as experimental work progressed both parts of the project morphed for differing reasons. Simultaneous challenges for synthesizing catalyst 2 and unexpected results with control

experiments for catalyst **1** necessitated a change of direction from the initial research plan. The control experiments were halted to explore a newly developed question, and the complexes were unable to be screened for catalytic ability on the reactions in question due to time constraints. The newly developed research question was prioritized over the synthesis of catalyst **1**, therefore the bulk of the discussion focuses on the former and the synthesis of catalyst **1**.

#### Catalyst 1 [(2,6-bis(imidazolylidene)pyridine)FeBr<sub>2</sub>]

The synthesis for catalyst **1** was adapted from previously reported syntheses and has two components: construction of the ligand (**3**) and the iron species (**4**). Construction of the ligand is a two-step process, beginning with the reaction of 2,6-diisopropylaniline (**1**) to form **2**. From there, **2** is reacted with 2,6-dibromopyridine to form the ligand. The iron species **4** can be synthesized simultaneously with the ligand, formed by reaction of FeCl<sub>2</sub> with Li[N(SiMe<sub>3</sub>)<sub>2</sub>]. Once **3** and **4** have been made, the final step is to complex them to form catalyst **1**.

Scheme 1. Synthesis of Catalyst 1



# Synthesis of 2 (1-(2,6-Diisopropylphenyl)-1H-imidazole)

Multiple attempts were made to synthesize **2**; the difficulty specifically lies in its isolation and purification. For the first attempt, the protocol by the Szadkowska group was followed without any changes besides longer reflux time and yielded a questionable orangey-brown sticky sludge as the crude product.<sup>49</sup> After purification via column chromatography, the resulting sandy-brown products obtained after removing the volatiles of the fractions were characterized by <sup>1</sup>H NMR. Based on the drastic difference in color (Szadkowska reported a dark-brown solid) and the

inconsistencies between the <sup>1</sup>H NMR spectra, it was determined that **2** was not synthesized (**A1**).<sup>49</sup> The aromatic region of the synthesized was consistent with the reported in the  $\delta$ 7.45-7.23 range except for the appearance of a peak at  $\delta$  6.93 with an extra proton; other discrepancies included the lack of a peak at  $\delta$ 3.44 and the isopropyl peaks integrated for eight protons instead of the expected fourteen (**A1**).

Other syntheses of **2** were compared to the synthesis used in the first attempt. Overall the protocols were similar as they were generally based on the Liu group's well-known protocol for the synthesis of 1-arylimidazoles.<sup>49–51</sup> However, an important discrepancy was noticed. Even though the Szadkowska group specifically cited the Liu paper and stated that their spectroscopic data was consistent, their <sup>1</sup>H and <sup>13</sup>C NMR reported peaks were not consistent. <sup>49,51</sup> The Liu paper's <sup>1</sup>H and <sup>13</sup>C NMR data was consistent with others in their shifts and integration.<sup>52</sup> The Szadkowska group reported an extra peak in their <sup>1</sup>H NMR at  $\delta$ 3.44 and were missing a peak at  $\delta$ 6.97 and a proton in the aromatic region. In addition, their <sup>13</sup>C NMR was missing two peaks believed to represent the imidazole at  $\delta$ 138.77 and  $\delta$ 133.12. Their spectroscopic data is more consistent with the starting reagent **1** than product **2.** Also, the Szadkowska group reported a dark brown solid whereas other groups obtained a white product after purification suggesting the group still had a large amount of starting reagent in their "purified" product. It is doubtful the Swadkowska group successfully synthesized **2**.

In my second attempt the following changes were made based on the other reported syntheses. The solvent was doubled in the first stage of reacting the glyoxal and 2,6-diisopropylaniline because it was noticed that the reagents immediately formed a yellow clump that did not enable adequate stirring for the full 24 hours; the additional solvent did enable more stirring to occur. Since it is not clear what went wrong and when in the first synthesis, the extra characterization method, <sup>1</sup>H NMR, was used in conjunction with TLC ensure the reagents were reacting at critical steps (before and after the addition of H<sub>3</sub>PO<sub>4</sub>). For the purification by column chromatography the polarity of the eluent was decreased from 1:1 to 3:1 hexane-ethyl acetate as suggested by another synthesis of **2**.<sup>50</sup> A white product was obtained from one of the column fractions and was determined to be **2** upon characterization with <sup>1</sup>H NMR and matching reported spectra (**Figure 18**).<sup>51,52</sup> Unfortunately, the fractions were combined based on TLC and were not all checked with <sup>1</sup>H NMR before combining. This resulted in a final yellow product whose <sup>1</sup>H NMR and melting point of 110-118°C were inconsistent with the reported spectra and melting

point (121-125°C) (A2).<sup>51,52</sup> There is an impure substance that elutes after 2 that is theorized to be compounds with an uncyclized imidazole ring based on the extra peaks in the  $\delta$ 3-5 region (A2 peaks D-F).



Figure 18. <sup>1</sup>H NMR characterization of the second attempt to synthesize 2. Acquired in chloroform- $d_3$ .

The product was combined with the impure fractions and re-run through the column in a third attempt to isolate 2; smaller fractions were collected for better analysis. The fractions containing a pure product, according to TLC analysis, were characterized with <sup>1</sup>H NMR. The analysis of the isolated product showed inconsistencies with the expected integration of 2 but has the consistent peaks (A3). Other fractions containing the isolated product will be characterized to determine if they are consistent with 2. The cause of the inconsistent integration is unknown since the desired product was able to be isolated in the second attempt.

Detailed TLC of the fractions collected showed the "stickiness" of 2 to the silica gel column. Out of the 40 fractions collected, what is believed to be 2 is visible throughout all the fractions tested (24) but is only isolated in 5 and more fractions still must be collected. Basic compounds in general can be difficult to separate on a silica gel column due to the acidic character of the silica gel. Nitrogen is a strong base and therefore amines are especially attracted to the silica making them difficult to separate out; this attraction can increase with increasing amount of nitrogen in the molecule. Even though a 3:1 hexane: ethyl acetate eluent was used, which is relatively nonpolar, unreacted **1** elutes first from the column instead of **2** even though **2** is a more non-polar compound. If not enough of **2** is collected, the other fractions containing **2** will be combined and re-run through the column except a deactivator will be used to pretreat the column. Triethylamine is a common reagent used that is added to the eluent in the initial wetting of the column. Triethylamine is basic and helps coat and neutralize the silica enabling the molecules in the sample to better separate and not stick to the column.<sup>53</sup>

### Synthesis of 4 (bis[bis(trimethylsilyl)amido]iron(II)

The synthesis of **4** was adapted from Holland, P. L. et al. and required much caution since **4** is pyrophoric (Scheme 1).<sup>54</sup> Li[N(SiMe<sub>3</sub>)<sub>2</sub>] dissolved in diethyl ether was added to a cooled FeCl<sub>2</sub> diethyl ether solution and stirred at room temperature for 48 hours. The crude product was extracted and washed with anhydrous pentane. The synthesis was halted before the final distillation step due to <sup>1</sup>H NMR analysis suggesting the reaction did not go to completion as it did not match the previously reported value of a broad shift at 64.9 ppm (A4).<sup>54</sup> Although a shift in the methyl peak can be observed upon comparision of Li[N(SiMe<sub>3</sub>)<sub>2</sub>] and the product synthesized, it is not a large enough shift to suggest formation of the desired product. In addition, impurities possibly caused by undesired side reactions can be observed (A5).

### Catalyst 2 (in-situ Fe(acac)<sub>3</sub> and IPr)

IPr (1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene) was purchased since it is widely commercially available. Fe(acac)<sub>3</sub> was easily synthesized by reacting FeCl<sub>3</sub>·6H<sub>2</sub>O, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>·3H<sub>2</sub>O, and 2,4-pentanedione in methanol and purified via recrystallization with methanol and water to yield red crystals (82%). The product was characterized with FT-IR and <sup>1</sup>H-NMR and confirmed to be Fe(acac)<sub>3</sub> upon agreement with predicted and previously reported spectra.<sup>55,56</sup> Comparison <sup>1</sup>H-NMR of 2,4-pentanedione and the product demonstrates a noticeable shift in peaks and peak broadening associated with coordination with Fe(III) due to the paramagnetism (**Figure 19**).<sup>57</sup> For instance, the 2,4-pentadione carbonyl peak shifted from  $\delta$ 5.03 to  $\delta$ 7.09 upon coordination with iron (III).



**Figure 19.** Characterization of  $Fe(acac)_3$ .<sup>1</sup>H NMR analysis of  $Fe(acac)_3$  (1) compared with 2,4-pentadione (2) obtained in benzene-d<sub>6</sub>. 3) FT-IR of  $Fe(acac)_3$  synthesized.

#### **Decomposition Studies**

Control experiments were performed to select the optimal solvent and temperature for each reaction (Michael and aza-Michael) to ensure the catalyst and reagents react rather than decompose. Solvents typically utilized in organic and organometallic synthesis were screened: benzene and acetonitrile. Fe(acac)<sub>3</sub> and IPr (1:4 molar ratio) were dissolved in each deuterated solvent, heated at a range of temperatures, and periodically monitored with <sup>1</sup>H NMR spectroscopy. Trials were performed in duplicate. In the acetonitrile-d<sub>3</sub> trials, interaction between the solvent and species was observed by 50°C after 4 hours. The isopropyl peaks ( $\delta$ 1.15-2.00) of the IPr became defined after heating in both trials suggesting that the acetonitrile was interfering with any interaction between the IPr and Fe(acac)<sub>3</sub> (**A6A7**). Acetonitrile is known to be a coordinating ligand with the nitrogen performing the electron donating; nitrogen is a hard base while iron (III) is a hard acid therefore they theoretically prefer to interact.<sup>10</sup>

Catalyst **2** was stable in benzene-d<sub>6</sub> until it was subjected to 100°C for 24 hours, as depicted by the decomposition of the isopropyl peaks at  $\sim \delta 1.20$  (**A8A9**). Since catalyst **2** was more stable in

benzene than acetonitrile, the next series of control experiments would have been to repeat the conditions but with only the reagents for the Michael and aza-Michael additions to determine their thermal stability and extent of interaction without the catalysts, and then with the reagents and catalyst **2**. However, the decomposition study of catalyst **2** prompted an important question that was explored instead of continuing with the control experiments: is the IPr binding to the Fe(acac)<sub>3</sub> and forming an *in-situ* complex like Hayashi reported?<sup>34</sup>

This question was prompted upon comparison of the <sup>1</sup>H NMR spectra of catalyst **2** in acetonitrile and benzene with IPr (**Figure 20**). Upon reaction with Fe (III), which is paramagnetic, the IPr peaks were expected to be broader and more shifted than observed, similar to the noticeable shift upon coordination of 2,4-pentanedione to Fe(III) (**Figure 19**).



**Figure 20.** <sup>1</sup>H NMR comparison of  $Fe(acac)_3$  and IPr (1:4 molar ratio) at room temperature in **1**) benzene-d<sub>6</sub> **2**) acetonitrile-d<sub>3</sub> and **3**) IPr in benzene-d<sub>6</sub>.

#### Do Fe(acac)<sub>3</sub> and IPr form an in-situ complex?

Although the Hayashi group proposed a mechanism for the Fe(III)/IPr system involving the formation of an Fe-IPr complex, the group made no attempt to confirm the formation of an *in-situ* complex utilizing standard experimental methods including isolation followed by characterization, GC-MS of the reaction mixture during catalysis, or computational modeling and analysis of the proposed reaction intermediates (**Figure 21**).<sup>34</sup>



**Figure 21.** The Hayashi group's proposed mechanism for iron-catalyzed arylmagnesiation. Image from Hayashi et al.<sup>34</sup>

The literature was examined to determine if the proposed structure had been previously synthesized and characterized; there have been no reports of an Fe-acac-IPr complex, or even any Fe-acac-NHC complex. The search had to be broadened to any oxygen donor ligand to the Fe center with any five membered NHC in order to find remotely similar structures. The most similar structure featured coordination with two NHC ligands via double bonds and with two acetates. It is worthy to note that a similar palladium complex has been reported (**Figure 22**).<sup>58,59</sup>



**Figure 22.** Reported structures that are similar to the possible  $Fe(acac)_3/IPr$  *in-situ* complex. **1**) Iron, bis(acetato- $\kappa$ O)bis(1,3-dihydro-1-methyl-3-octyl-2H-imidazol-2-ylidene)-, (T-4)- reported by Abrams M. B.<sup>58</sup> **2**) palladium/acetate/IPr/Cl complex reported by Marion, N.<sup>59</sup>

The compound was reported in a patent regarding potential metallocarbene compounds that could comprise a bleaching system along with a peroxy compound and act as an activator for the peroxy compound to make the bleaching system a more effective. Unfortunately, since the compound was

reported in a patent limited information regarding the synthesis and characterization was available. Only the synthesis of a similar compound (one with two trifluoromethanesulfonate ligands instead of acetate) was available but did not supply any characterization information. Although the patent describes experiments performed with a few of the patented complexes, it is difficult to believe they truly synthesized the structures without providing the characterization data.<sup>58</sup>

The structure search also led to an article with similar experiments to the one catalyst **2** is from. As a reminder, the Hayashi group screened various catalyst systems comprised of Fe(acac)<sub>3</sub> as iron source with additive ligands (IPr, PPh<sub>3</sub>, etc) for their ability to catalyze the arylmagnesiation of aryl(alkyl)acetylenes.<sup>34</sup> The Wu group screened various catalyst systems comprised of FeF<sub>3</sub> or Fe(OTf)<sub>2</sub> as iron source and SIPr or IPr as the added ligand for their ability to catalyze the crosscoupling of aryl chlorides and tosylates with aryl Grignard reagents.<sup>60</sup> The Wu group found the Fe(OTf)<sub>2</sub>/ IPr system to be efficient at catalyzing the arylmagnesiation reaction, and, did not appear to attempt to isolate any of the active complexes in their catalyst systems.<sup>60</sup>

Therefore Fe-OR-IPr complexes have been found to catalyze various arylmagnesiation reactions and isolating the active complex could be lucrative and interesting to determine the structure. Experiments for determining the structure were conducting while attempting to determine the structure theoretically. The decomposition studies raised the question of whether the *in-situ* Fe(acac)<sub>3</sub>/IPr complex only forms and is stable in certain solvents. The conditions reported by Hayashi were repeated to test the formation of the complex in THF. The formation was tested by reacting IPr and Fe(acac)<sub>3</sub> in THF separately overnight and for 30 minutes. Similar to the decomposition trials in benzene and acetonitrile, the Fe(acac)<sub>3</sub>/IPr system did not have any noticeable shift in proton peaks and drastic increase in peak broadness suggesting the formation of an *in-situ* complex. Since the benzene solvent peak itself is broad, it is unlikely the minimal broadness of the peaks is due to coordination (**Figure 23**). The compound in the overnight system was precipitated with pentane and characterized again but did not provide any more information on the compound (**A10**).



**Figure 23**. <sup>1</sup>H NMR comparison of  $Fe(acac)_3$  and IPr stirred in THF for 1) 30 minutes 2) overnight and 3) IPr. All spectra obtained in benzene-d<sub>6</sub>.

The Hayashi group used a 1:4 molar ratio in their catalytic system. However, it is predicted the IPr would coordinate in either a 1:1 or 1:2 ratio with the  $Fe(acac)_3$  and possibly replace an acac ligand. To test this hypothesis,  $Fe(acac)_3$  and IPr were reacted in a 1:1.1 and 1:2.1 ratio in THF and then characterized after crashing the solid out of solution with pentane. From both, a red solid was obtained. The lack of difference between the two stoichiometric ratios suggest that the excess IPr does not affect the coordination, therefore it is likely that the  $Fe(acac)_3$  and IPr coordinates in a 1:1 ratio. However, there is still no drastic shift in the spectra compared to IPr or any visible free 2,4-pentadione ligand (**Figure 24**).



**Figure 24.** <sup>1</sup>H NMR comparison of *in-situ* complex formed from  $Fe(acac)_3$  and IPr in **1**) 1: 1.1 molar ratio **2**) 1: 2.1 molar ratio in THF and precipitated out with pentane over course of a few days **3**) IPr. Spectra obtained in benzene-d<sub>6</sub>.

Control experiments determining the stability of Fe(acac)<sub>3</sub> and IPr separately in the THF/pentane system were conducted alongside the previously mentioned experiments along with experiments determining stability of IPr overnight in THF and determining if 2,4-pentadione and IPr interact. The Fe(acac)<sub>3</sub> remained relatively stable and precipitated out of solution along same time line as the other experiments (A11). IPr and 2,4-pentadione were determined to not immediately interact or cause degradation of each other (A12). However, IPr was found to degrade in THF overnight and consequently in the THF/pentane system over course of few days. The IPr THF/pentane solution visibly changed from clear to reddish-brown within three days (**Figure 25**).



Figure 25. <sup>1</sup>H NMR characterization of experiments regarding stability of IPr in 1) THF overnight 2) in 1:1 THF: pentane and 3) IPr alone. Spectra obtained in benzene- $d_6$ .

The peaks are broadened and the doublet-of-doublets isopropyl peak appears like a triplet due to the degradation. Therefore, IPr is not stable in the solutions for the length of time the stoichiometric ratio and overnight isolation of the *in-situ* complex in THF experiments were conducted. The slight broadening observed in the stoichiometric ratio and determining formation of the complex in THF could be due to the degradation of the IPr (**Figure 23Figure 24**). The triplet-like isopropyl peak was first interpreted as suggesting coordination in such a way to disturb the isopropyl peaks but it is more likely due to degradation in the THF. IPr could have been degraded by any residual water in the THF as it is more likely that water irresponsible for the degradation than the THF.

Ultimately, the formation of an *in-situ* complex was unable to be confirmed but remains doubtful under the conditions specified by the Hayashi group (*in-situ* complex supposedly formed in five minutes at room temperature and then reaction was held at 60°C for 16 hours).<sup>34</sup> Further

experimentation is necessary and the possibility of reporting the first Fe(acac)/IPr complex is an intriguing prospect but seems unlikely as it is even difficult to theorize the structure of the complex.

# What would the Fe(acac)/IPr complex look like?

Structures were theorized and determined plausible if they followed the 18 electron-rule and had the preferred coordination geometry of iron. While main group elements follow the octet rule, transition metals follow the 18-electron rule; it is used to predict and rationalize structures for stable transition metal-organometallic complexes. Iron (II) complexes typically have a coordination number of six with octahedral geometry. Iron (III) complexes may coordinate to three or eight ligands, typically preferring octahedral geometry.<sup>10</sup> **Figure 26** depicts the most stable structures theorized for the *in-situ* Fe(acac)/IPr complex.



**Figure 26.** Theoretical structures of an Fe/IPr/Acac complex. (A) Possible structure when in benzene (B) structure of 1:1 ratio of Fe to IPr (C) structure of 1:2 ratio of Fe to IPr when Fe is 2+ or 3+.

Although structure A seems impractical as it involves a coordinating benzene in replace of an acac ligand along with the IPr and formation of an Fe-Fe dimer, each Fe has octahedral geometry and an electron count of 18. Also, the Fe-Fe bond could be easily broken, opening a coordination site for a substrate during a catalytic cycle. However, this structure is only possible if the reaction occurs in benzene and THF is the solvent being used. Structures B and C depict the theoretical structures of what was experimentally attempted. Experimentally, it was determined that excess IPr (more than 1:1 ratio) had no effect on any possible coordination between the Fe(acac)<sub>3</sub> and IPr. Theoretically, while both fail to meet the 18 electron-rule with an Fe(III) center, structure C is more plausible since it has octahedral geometry and B only has a coordination number of five. However, structure C does not offer a possible coordination site during a catalytic cycle as it is unlikely the metal-carbon bond of IPr or both metal-oxygen bonds of acac would disassociate. Structure B has two possible geometries with a coordination number of 5: trigonal bipyramidal

and square planar. Iron trigonal pyramidal complexes have been reported, but not with an iron (III) center; some iron (III) trigonal pyramidal complexes have been determined by DFT calculations to be feasible experimentally but yet to be synthesized and structurally confirmed.<sup>61</sup> Several square pyramidal iron (III) complexes have been reported so that configuration is more plausible than trigonal bipyramidal.<sup>62</sup> In addition, since iron (III) prefers a coordination number of six, structure B already has an open coordination site for a substrate. It is interesting to note that with an Fe(II) center, structure C meets the 18 electron-rule and therefore achieves the conditions desired for a stable complex.

# **Future Directions**

Due to limited time, not all of the experiments desired were able to be performed. Since the control experiments of IPr in THF demonstrated the instability of IPr for the length of time the experiments were conducted, they should be repeated under shorter time conditions. The protocol will be adapted from Przyojski, J; the  $Fe(acac)_3$  and IPr will stir for a few hours before precipitating out any solids and isolating them for characterization.<sup>63</sup> The length of time for the reaction will be determined based on the time IPr remains stable in THF. The solubility of Fe(acac)<sub>3</sub> and IPr could be tested in other solvents that have more affordable deuterated versions for easier NMR analysis, but THF appears to be the solvent favored for reactions involving iron complexes and NHC ligands.<sup>58,60,63</sup> The reactants had limited solubility for the deuterated benzene and acetonitrile control experiments but it could be worth determining their solubility separately in benzene since decomposition of them together was not observed until they were subjected to 100°C overnight (A8-A9). Instead of IPr, IPr<sup>Cl</sup> could be used along with a base to determine if forming the NHC ligand *in-situ* influences the formation of the desired complex. Similar procedures have been used successfully.<sup>58,59</sup> Also, since IPr coordinates through the carbanion, the lack of that imidazolium salt proton peak would be able to be interpreted as the base working and possibly coordination occurring. However, these conditions would not be able to be used in the catalysis reactions as most bases would interact with the Grignards or other substrates.

The characterization methods used to confirm the formation of the desired complex will be expanded from <sup>1</sup>H NMR to also include Evans <sup>1</sup>H NMR, UV-Vis, and mass spectrometry. Electrospray ionization (ESI) would be used as the mass spec method. This would aid in determining the structural composition of the complex (e.g. how many acac ligands, IPr). This

would be determined by analyzing the fragmentation pattern and searching for masses that correlate to those ligands (e.g. acac:~100 g, IPr: 390.604 g). Ideally, in order to determine the geometry of the complex a crystal structure would be obtained, however that may be challenging therefore the Evans method could be utilized. The Evans NMR method estimates the magnetic moment of the paramagnetic sample and aids in determining the electronic structure of the complex (e.g. whether metal center is high or low spin and the geometry). The method works by comparing the shift in peaks of the sample to an inert reference. The complex is determined to be high or low spin by comparing the magnetic moment with the theoretical one; theoretical magnetic moments for an Fe(III) octahedral complex is 5.92  $\mu_B$  for high spin and 1.73  $\mu_B$  for low spin.  $^{10,57}$  The magnetic moment is related to the magnetic susceptibility of the complex and can also be related to the spin and orbital contributions. For a first-row transition metal, like Fe, the orbital contribution is small and can be omitted from consideration, leaving only the spin quantum contribution. The spin-only magnetic moment can provide a direct way to compare the magnetic moment calculated with the number of unpaired electrons in the complex. For a d<sup>5</sup> complex like Fe(III), there are two distinct electron configurations for high and low spin but there is no difference in configuration for a high or low spin square pyramidal or trigonal bipyramidal d<sup>5</sup> structure as both of them, and the low spin octahedral, only have one unpaired electron (Figure 6).<sup>64</sup> Unfortunately, Evans NMR method would not be able to determine between a square pyramidal and trigonal bipyramidal structure. Fe(acac)<sub>3</sub> has been reported to have an observable magnetic moment of 5.23  $\mu_B$ , meaning it is a high spin octahedral complex. Comparing the magnetic moment of Fe(acac)<sub>3</sub> to the *in-situ* complex formed would indicate whether the IPr coordinated to the Fe center; a change in magnetic moment infers coordination while no change infers no coordination occurred. UV-Vis could be useful in the characterization since both reagents are UV-Vis active and therefore so is the product, thus the absorption of the reagents can be compared to the complex formed to determine if the reagents coordinated. If coordinated, there should be a change in absorption. Since iron (II) has a small but positive redox potential, it is difficult to determine if that change in absorption would be positive or negative shift. If the iron is difficult to reduce, a positive shift would be expected. One way to predict how drastic the shift in absorbance would be is by comparing the colors of Fe(acac)<sub>3</sub> to an Fe-NHC complex.<sup>10</sup> Fe(acac)<sub>3</sub> is red while FeCl<sub>3</sub>IPr is orange, therefore a very noticeable shift is predicted.<sup>63</sup> A solvent would be used that does not absorb in the same region as the reagents and that the reagents are the most soluble in. Common UV-Vis solvents include 1-butanol, hexane, cyclohexane, and toluene.

Since the Hayashi group did report high yields in their arylmagnesiation reaction with the addition of IPr to the  $Fe(acac)_3$ , it would be interesting to repeat their experiment and compare results. Although different amounts of IPr was screened to determine effect on yield, IPr alone was not tested for ability to catalyze the reaction. Halving the amount of IPr, from 20 mol % to 10 mol %, did decrease the reaction yield suggesting IPr plays a large role in the catalytic cycle.<sup>34</sup> NHCs have been reported to act as organocatalysts, with the majority of catalyzed reactions involving substrates that are able to be nucleophillically attacked by the carbene, such as aldehydes, Michael acceptors, and esters. They have been found to catalyze various Umpolung reactions and polymerization reactions.<sup>21</sup> The reaction could be halted at various points in an attempt to isolate their active catalytic complex. Also, the substrates alone were never screened for their reactivity. Fe(acac)<sub>3</sub> without any additives only afforded a 23% yield, so it would be interesting to determine if the substrates without a catalyst are able to achieve that yield. If they are able to, then that would suggest the Fe(acac)<sub>3</sub> does not play either a role or only a small role in the catalytic mechanism. It is important to note that the other additives screened ( $P(n-Bu)_3$ ,  $P(t-Bu)_3$ , PPh<sub>3</sub>) achieved low yields (16-33%) and they are known to not have catalytic abilities by themselves. The only other additive besides IPr that achieved a decent yield was  $P(n-Bu)_3) + CuBr$ , but it is possible the copper itself could have catalyzed the system.<sup>34</sup>

# Conclusion

Two iron-NHC complexes were selected based on their previous reported catalytic reactivity to be screened on the Michael and aza-Michael addition reactions. Those reactions are essential in the pharmaceutical industry and no iron-NHC complexes have been reported to catalyze them. Unexpected difficulties rose in the synthesis of catalyst 1 and therefore was unable to be completed in the time frame; **2** is still in the process of being isolated and characterized. The decomposition experiments performed for catalyst 2 raised the question of whether the  $Fe(acac)_3$  and IPr coordinate to form an *in-situ* complex as reported by the Hayashi group. Experiments were performed to repeat the original reaction conditions and to determine if  $Fe(acac)_3$  and IPr coordinate in a 1:1 or 1:2 ratio. Overall, the results do not suggest the formation of an in-situ complex and instead show that the instability of IPr in THF is the culprit of the questionable peaks

from the <sup>1</sup>H NMR characterizations. This project will be continued with priority given to repeating the Hayashi screening conditions in selecting the catalyst system for the arylmagnesiation reaction and performing control experiments to determine if the Fe(acac)<sub>3</sub> plays an active role or if IPr itself is responsible for the high reaction yields.<sup>34</sup>

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# **Experimental Methods**

# **General Considerations**

All reactions unless specified were performed under a nitrogen atmosphere either in a Schlenkline or an Inert Lab 2GB Glovebox System from Innovative Technology. The solvents were distilled using the following drying agents and stored over activated molecular sieves: THF and benzene-d<sub>6</sub> (Na/benzophenone), diethyl ether, dichloromethane, and dichloromethane-d<sub>2</sub> (CaH<sub>2</sub>). NMR: Spectra were obtained on a JEOL 300 MHz and solvents were referenced to the following chemical shifts: CDCl<sub>3</sub> ( $\delta$ 7.26), C<sub>6</sub>D<sub>6</sub> ( $\delta$ 7.16), and CD<sub>3</sub>CN ( $\delta$ 1.94). Analysis of NMR spectra was performed using Mnova 10.0.2. IR: Nicolet 380 Fourier Transform-Infrared Spectroscopy (FT-IR) with Attenuated Total Reflectance (ATR) accessory was used. The LiN(SiMe<sub>3</sub>)<sub>2</sub>, 2,6diisopropylaniline, glyoxal 40% w/w aq solution, 37% formaldehyde in water, FeCl<sub>2</sub> anhydrous powder, and anhydrous pentane were purchased from Alfa-Aesar. FeCl<sub>3</sub>·6H<sub>2</sub>O, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>·3H<sub>2</sub>O, 2,4-pentanedione, hexane, ethyl acetate, and methanol purchased from Sigma Aldrich. IPr purchased from Strem. Mass measurements recorded in the glovebox are approximate due to vibrational issues with the scale.

# **Synthesis of Catalysts**

*Synthesis of 1-(2,6-diisopropylphenyl)imidazole*. Adapted from Szadkowska, A et. al and Wang, Z et al.<sup>49,50</sup> Under normal atmospheric conditions, 2,6-diisopropylaniline (9.6 mL, 54 mmol) and 40% glyoxal (6.4 mL) were stirred in methanol (100 mL) for 4 days at room temperature. Ammonium chloride (5.42 g, 0.10 mol), formaldehyde (37% solution in H<sub>2</sub>O, 8 mL), and more

methanol (200 mL) were added to the solution and refluxed for 4 hours. Then H<sub>3</sub>PO<sub>4</sub> (85%, 7.2 mL) was added and the reaction was refluxed for approximately 8 hours until completion as determined by TLC (1:1 hexane: ethyl acetate v/v). The solvent was evaporated, and the resulting brown sticky solid was mixed with crushed ice. KOH solution (8 M) was added to the ice until the pH was 9. The desired product was extracted with diethyl ether (5 x 75 mL). The organic layers were dried with anhydrous MgSO<sub>4</sub> and then the volatiles were removed leaving a sandy brown solid. The crude product was carefully purified by silica gel column chromatography (3:1 hexane: ethyl acetate v/v). Still in process of being isolated and characterized. <sup>1</sup>H NMR (CD<sub>3</sub>Cl): A1-A3, Figure 18.

*Synthesis of Fe*[ $N(SiMe_3)_2$ ]<sub>2</sub>. Adapted from Broere, D. L. J. et al.<sup>54</sup> In a glovebox, anhydrous FeCl<sub>2</sub> powder (0.574 g , 4.5 mmol) was dissolved in Et<sub>2</sub>O (18 mL) while Li[ $N(SiMe_3)_2$ ] (1.5 g, 9 mmol) was separately dissolved in Et<sub>2</sub>O (27 mL). The Li solution was added to a cooled FeCl<sub>2</sub> solution (8°C) and then the mixture was stirred for 48 hours at room temperature. The volatiles were removed, and product was extracted and washed with anhydrous pentane (25 mL) and concentrated under vacuum. The dark green oil was distilled under reduced pressure at 80-90°C. The synthesis stopped before the distillation. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) before distillation: **A4**.

Synthesis of  $Fe(acac)_3$ . Adapted from Glidewell, C.<sup>65</sup> Under atmospheric conditions, FeCl<sub>3</sub>·6H<sub>2</sub>O (2.7 g, 10 mmol) was dissolved in water (6 mL) while separately NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>·3H<sub>2</sub>O (5.0 g, 37 mmol) was dissolved in water (10 mL). The NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>·3H<sub>2</sub>O solution was slowly added to the iron solution. 2,4-pentanedione (4 mL, 39 mmol) was dissolved in methanol (10 mL). The Fe/Na solution was slowly added to the methanol. After stirring for 5 minutes, red solid was collected via vacuum filtration and washed with water. The solid was recrystallized by being dissolved in boiling methanol (60 mL) and then slowly adding water. Solution was left in fridge until red crystals were visible. Solution was filtered, and crystals washed with cold water (2.89 g, 82%). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  7.09, 3.15, 1.46, 1.01, 0.15. IR (cm<sup>-1</sup>): 1566, 1517, 1349, 1271, and peaks in 1006-548 range. Spectra is consistent with previously reported data.<sup>56,55</sup> (**Figure 19**).

#### **Control Experiments**

*Decomposition of Catalyst 2 in C*<sub>6</sub> $D_6$ . A J-Young tube was loaded with Fe(acac)<sub>3</sub> (5 mg, 0.0142 mmol), IPr (22 mg, 0.0566 mmol) and approximately 1 mL of a C<sub>6</sub> $D_6$ . The tube was heated at certain temperatures (22, 50, 75, and 100°C) and checked by <sup>1</sup>H NMR for decomposition every

three hours. The procedure was repeated in duplicate. Decomposition was not observed until 24 hours at 100°C. <sup>1</sup>H NMR in appendix: **A8-A9**.

*Decomposition of Catalyst 2 in CD*<sub>3</sub>*CN*. The procedure utilizing  $C_6D_6$  as the solvent was repeated with the following changes: Fe(acac)<sub>3</sub> and IPr dissolved in 1 mL of CD<sub>3</sub>CN. Decomposition was not observed in either tube until 4 hours at 50°C. <sup>1</sup>H NMR in appendix: A6-A7.

# Determining extent of interaction between Fe(acac)<sub>3</sub> and IPr

*Repeating conditions of Hayashi et al overnight*.<sup>34</sup> Fe(acac)<sub>3</sub> (~10 mg, 0.0283 mmol) and IPr (~20 mg, 0.0512 mmol) were stirred overnight at room temperature in enough THF to dissolve them both (~4 mL). The volatiles were removed, characterization was performed, and then pentane was added dropwise to the sample. Five days later, red solid was fully precipitated out. <sup>1</sup>H NMR ( $C_6D_6$ ) before and after precipitation: **A10**, **Figure 23**.

*Repeating conditions of Hayashi et al.*<sup>34</sup> Fe(acac)<sub>3</sub> (~3 mg) and IPr (~15 mg) (1:4 molar ratio) were stirred for 30 minutes in enough THF to dissolve them both (~3 mL). <sup>1</sup>H NMR ( $C_6D_6$ ): **Figure 23**.

*Do*  $Fe(acac)_3$  and *IPr interact in 1:1 ratio.* Fe(acac)3 (34 mg, 0.100 mmol) and IPr (43 mg, 0.110 mmol) were stirred in THF (~4.5 mL) for 30 minutes and then pentane was added in a 1:1 ratio. <sup>1</sup>H NMR was acquired when solid (dark red powder) finished precipitating a few days later. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): **Figure 24**.

*Do*  $Fe(acac)_3$  and *IPr interact in 1:2 ratio.* Reaction conditions for determining if Fe(acac)\_3 and IPr interact in 1:1 ratio were repeated with following changes: Fe(acac)\_3 (30 mg, 0.089 mmol) and IPr (73 mg, 0.187 mmol) and yielded red solid with a sludge texture. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): **Figure 24**.

Stability of IPr in THF. IPr (~ 20 mg, 0.051 mmol) was dissolved in THF (~4 mL)and left overnight. <sup>1</sup>H NMR ( $C_6D_6$ ): Figure 25.

*Stability of IPr in THF and Pentane*. IPr (18 mg, 0.046 mmol) was dissolved in THF (2.5 mL) and solution was layered with 1:1 ratio of pentane. Before NMR was performed few days later, color change from clear to reddish-brown was observed. <sup>1</sup>H NMR ( $C_6D_6$ ): **Figure 25**.

*Stability of Fe*(*acac*)<sup>3</sup> *in THF and Pentane*. Repeated reaction conditions of determining stability of IPr in THF and pentane with following changes: Fe(acac)<sup>3</sup> (19 mg, 0.054 mmol) dissolved in 4 mL THF. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): **A11**.

Stability of IPr and 2,4-pentadione in THF. Dissolved IPr (0.08 g, 0.2 mmol) and 2,4-pentadione (0.02 mL, 0.2 mmol) in THF (4 mL) and stirred for 6 minutes before characterization. <sup>1</sup>H NMR ( $C_6D_6$ ): A12.

# Appendix





A2. <sup>1</sup>H NMR characterization of combined column chromatography fractions after second attempt to isolate 2. Obtained in chloroform- $d_3$ .



A3. <sup>1</sup>H NMR characterization of isolated product in third attempt to isolate 2. Obtained in chloroform- $d_3$ .





# A4. <sup>1</sup>H NMR of attempt to synthesize 4. Obtained in benzene-d<sub>6</sub>.

**A5.** <sup>1</sup>H NMR comparison of starting reagent LiN(SiMe<sub>3</sub>)<sub>2</sub> (red) and of product formed in attempt to synthesize **4** (blue) (**A4**). Both obtained in benzene-d<sub>6</sub>.





A6.Decomposition studies of catalyst 2 (Fe(acac)<sub>3</sub>: IPr 1:4 molar ratio) in acetonitrile-d<sub>3</sub>. Trial 1.

**A7.** Decomposition studies of catalyst 2 (Fe(acac)<sub>3</sub>: IPr 1:4 molar ratio) in acetonitrile-d<sub>3</sub>. Trial 2.





# **A8.** Decomposition studies of catalyst 2 (Fe(acac)<sub>3</sub>: IPr 1:4 molar ratio) in benzene-d<sub>6</sub>. Trial 1.

# A9. Decomposition studies of catalyst 2 (Fe(acac)<sub>3</sub>: IPr 1:4 molar ratio) in benzene-d<sub>6</sub>. Trial 2.



A10. <sup>1</sup>H NMR characterization of solid precipitated out from  $Fe(acac)_3$  and IPr being stirred overnight in THF. Obtained in benzene-d<sub>6</sub>.



A11. <sup>1</sup>H NMR characterization of stability of  $Fe(acac)_3$  in THF and pentane over course of six days. Obtained in benzene-d<sub>6</sub>.



A12. <sup>1</sup>H NMR of control experiment determining stability of IPr in presence of 2,4-pentadione (1:1 molar ratio). Obtained in benzene- $d_6$ .



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