INVESTIGATION OF IRON MEDIATED MOLECULAR TRANSFORMATIONS AND SYNTHESIS OF 2-AMINO-α-CARBOLINE AND ITS ANALOGUES RELEVANT FOR DNA ADDUCT FORMATION

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INVESTIGATION OF IRON MEDIATED MOLECULAR TRANSFORMATIONS AND SYNTHESIS OF 2-AMINO-α-CARBOLINE AND ITS ANALOGUES RELEVANT FOR DNA ADDUCT FORMATION

BY

ANITA ADJOA OPPONG

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OF

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ABSTRACT

The discovery of new synthetic methods and routes for making new bonds is one of the highest incentives to an organic chemist. Innovative, efficient, effective, economical and exceptionally environmentally friendly synthetic methods are being continuously discovered. Transition metal catalyzed C-H activation has been unearthed as one of these methods, especially iron catalyzed direct C-H activation. Fundamental to making more discoveries is understanding the mechanism behind a specific reaction. To this end, the mechanism behind iron catalyzed C-H activation was investigated. Results indicate the intermediary transition state for the iron species involves an Fe(I) species but the attempt to synthesize this Fe(I) species failed. We also confirmed that Fe(II) is definitely not the active species for this reaction. The nitrogen-based ligand might not have afforded us the Fe(I) complexes but there was evidence to show the reduction of the Fe(acac)$_3$ due to the formation of the biphenyl product.

In the same vein of discovery, we identified a mild, one-pot, FeCl$_2$ mediated procedure to produce 3-substituted allylic alcohols from $\alpha,\beta$-unsaturated ketones. The addition of an organolithium nucleophile produced tertiary allylic alcohol as an intermediate, which underwent a 1,3-OH migration assisted by FeCl$_2$. The proposed mechanism indicates that a syn-facial migration occurs for the significant product and we obtained yield as high as 98% from this one-pot reaction.

New synthetic methods are also very beneficial to the world outside chemistry. The study of the carcinogen 2-amino-$\alpha$-carboline (A$\alpha$C) and its interaction with DNA involved the synthesis of the A$\alpha$C-DNA adduct. We report the synthesis of A$\alpha$C and 2-nitro-$\alpha$-carboline (A$\alpha$C-NO$_2$) which also facilitate the synthesis of DNA adducts for biophysical studies. An attempt was made to synthesize the fluorinated 2-nitro-$\alpha$-carboline which will enable the use of $^{19}$F-NMR for monitoring of these studies. Cyclization of the coupled product for the fluorinated analogue could not be achieved.
due to the electron deficiency in the ring systems. $\alpha\ensuremath{\alpha}C$ was obtained in good yields of 88%, and the $\alpha\ensuremath{\alpha}C$-NO$_2$ was obtained in 60% yield.
ACKNOWLEDGEMENTS

‘Success is a journey, not a destination.’ -Arthur Ashe

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Roe Brooks, Evelyn, Irine, Spirit Central International, Rev Bryan, Beatrice, GAU and many more I will probably take more pages if I am to mention each and every one. I am blessed and humbled to have wonderful people in my life. God bless you all.
DEDICATION

This thesis is dedicated to my chief cheerleader, my loving husband.

The best to lean on, my parents, my mum and my dad.

You are my inspiration.
PREFACE

This dissertation is presented in a manuscript format according to the guidelines presented by the University of Rhode Island Graduate School. The dissertation consists of three manuscripts.

The first manuscript entitled “Efforts towards investigative mechanistic studies of iron catalyzed C-H activation reaction.” describes the mechanistic insight into iron catalyzed reactions. Findings suggests a pathway involving an Fe\textsuperscript{i}/Fe\textsuperscript{iii} intermediate.

The second manuscript entitled “FeCl\textsubscript{2} mediated allylic alcohol rearrangement” talks about a one pot procedure to produce 3-substituted allylic alcohols using FeCl\textsubscript{2}. The manuscript detailing this work has been published in ACS Omega.

The third manuscript entitled “Synthesis of 2-Amino-α-carboline and Analogues relevant for DNA Adduct Biophysical Studies” deviates from C-H bond transformation, but it explores the synthesis of 2-amino-α-carboline and its the analogues to be used for DNA adduct formation.
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1 GENERAL INTRODUCTION

In the field of organic and medicinal chemistry, synthetic routes to synthesize fine chemicals and materials are always being explored. The goal for these disciplines is to find synthetic routes which are effective, efficient and economical. With the rise in environmental concerns about syntheses and processes, many of these synthetic routes incorporate either environmentally friendly methods or chemicals.\(^1\) Fundamental to developing these synthetic routes, is understanding the mechanisms by which the active catalyst catalyzes the reaction of interest. Iron catalyzed C-H activation reactions have been identified as an economical, environmentally friendly and efficient method for synthesizing fine chemicals and materials.\(^2\) Though this method is well known and established, the mechanism through which these reactions happen under various conditions is not well understood, hence the need to investigate how iron catalyzes direct C-H activation in the presence of a Grignard.

Understanding how iron works is important because it has been established as a very versatile metal, able to be used in various chemical processes. A chemical process of interest is tertiary allylic alcohol rearrangement, which is an applied method where certain molecules, especially drugs, have been synthesized.\(^3\) Iron, an inexpensive first row transition metal has not been used for tertiary allylic alcohol rearrangement, though other rare and first row transitions metals like chromium \(^4\) and rhenium \(^5\) have been used. This prompted the investigation in using iron for this important rearrangement.

Finding new synthetic routes is also beneficial to the biological world. The effect of carcinogens on human cells have been studied extensively and these studies have focused on the interactions of the carcinogen with DNA. To facilitate these studies, there is the need for the synthesis of DNA adducts of these carcinogen -- a research frontier identified through previous studies.\(^6\) It was
found to be cost effective to synthesize the carcinogen of interest to be used for synthesis of the DNA adducts used for these biophysical studies hence the need to find quick, efficient and effective methods to synthesize these carcinogens.

1.1 WHY C-H ACTIVATION?

Synthetically the direct functionalization of a C-H bond into either a C-C or C-heteroatom will be of great advantage to the synthesis world, especially the pharmaceutical and fine chemical industry. Over a long period of time, organic chemists have explored ways to make molecular transformations. The use of nucleophiles, such as Grignard reagents, organocuprates, organolithium reagent, organozinc and arylborates for cross coupling reactions are some examples of conventional means of forming C-C and C-heteroatom bonds.

Organic chemists have developed and are still developing ways through which the C-H bond can be transformed into C-X bonds where X can be C, N or O. Examples of these methods includes but not limited to Kumada, Suzuki-Miyaura, Heck, Negishi and Sonogashira. Often at times, these transformations reactions are catalyzed by mostly transition metals coupling an electrophile to a nucleophile. (scheme 1.1)

In recent times, the innovative methods being explored involving direct functionalization of the C-H bond. The need for direct C-H activation arises primarily to eliminate the need for pre-functionalization of the C-H bond into halides or other leaving groups. By exploring the direct C-H functionalization, the organic chemist increases the sturdy and reliable methods already available. In the discussion of green and sustainable chemistry, direct C-H activation also eliminates a number of problems related to waste. Direct C-H activation also saves time, money and efforts and this is a key advantageous component for industries.
Iron Catalyzed C-H Activation

Until recently the most widely used transition metals for direct C-H activation had been limited to the 4d transition metals like palladium\textsuperscript{47,48}, rhodium\textsuperscript{49}, iridium\textsuperscript{50} and ruthenium.\textsuperscript{51} Most recent interest has been in iron\textsuperscript{52}, cobalt\textsuperscript{1} and nickel\textsuperscript{53} mainly due to availability and relatively low cost of these metals as compared to the other precious metals. Iron compared to nickel and cobalt is also very inexpensive and non-toxic. The advantages in the use of iron spearheaded off an intense investigation into its versatility. It is interesting to note that these iron catalyzed reactions are sometimes of better yields than their palladium counterparts\textsuperscript{54} as shown in scheme 1.2.

Scheme 1.1: Nucleophilic molecular transformation methods

1. Kumada Coupling
\[
\text{R} - \text{X} + \text{Y-Mg} \rightarrow \text{[Pd]/[Ni]} \rightarrow \text{R} - \text{Y-Mg} - \text{X}
\]

2. Suzuki-Miyaura
\[
\text{R} - \text{X} + \text{HO-B} \rightarrow \text{[Pd]} \rightarrow \text{R} - \text{HO-B} - \text{X}
\]

3. Heck
\[
\text{R} - \text{X} + \text{HO-B} \rightarrow \text{[Pd]} \rightarrow \text{R} - \text{HO-B} - \text{X}
\]

4. Negishi
\[
\text{R} - \text{X} + \text{Y-Zn} \rightarrow \text{[Pd]} \rightarrow \text{R} - \text{Y-Zn} - \text{X}
\]

5. Sonogashira
\[
\text{R} - \text{X} + \text{HO-B} \rightarrow \text{[Pd]/[Cu]} \rightarrow \text{R} - \text{HO-B} - \text{X}
\]
Mechanism for Iron Catalyzed C-H Activation

The mechanism for iron cross-coupled reactions has been studied extensively compared to direct C-H activation.\textsuperscript{11,55–58} The multifaceted nature of the electronic structure of iron makes the study of its intermediate in reaction cycles quite an exasperating task to achieve. Even though, there has been a number of physical methods that can be used to study or monitor these iron catalyzed C-H bonds transformation, the intrinsic mechanism of the iron species in the cycle has not been identified yet. There has been a couple of theories in working now but without a direct probing of the iron species generated in situ, there are restrictions on how these theories can be applied.

So far, two general mechanisms of how the iron activates the substrate have been proposed,

1. a low valent iron complex undergoes an oxidative addition into a C-H bond of the substrate to form the organoiron complex;
2. The iron complex deprotonates the substrates before the formation of the Fe-C bond, also known as direct deprotonation metalation.\textsuperscript{59}

The pioneering works done by Nakamura et al\textsuperscript{54,60–62} which demonstrated the use of iron for C-H activation (scheme 1.3), proposed an Fe(II)/Fe(III) system in the presence of organozinc or organoborons\textsuperscript{63} which utilizes general mechanism one. Other groups have confirmed this Fe(II)/Fe(III)\textsuperscript{64,65} though the mechanism involves a single electron transfer. Many of the proposed mechanism either goes through an Fe(I)/Fe(III) system\textsuperscript{11} and other lower oxidation states of iron\textsuperscript{66,67}. Till date, there has still not been a definite overall arching mechanism for iron catalyzed C-H activation.

Scheme 1.3: Iron catalyzed ortho-directed arylation of C-H activation
In the study to extend the scope of their reaction conditions to form biaryl heterocycles since these heterocycles form the basis for most of biological and pharmaceutical molecules, the iron catalyzed ortho directed arylation of the heterocycles such as pyridines, furans and thiophenes was investigated with good yields as shown in scheme 1.4. The reaction gave a complete conversion of starting material in 15 minutes and yields as high as 88%. Investigations led to findings that questioned the mechanism proposed by Nakamura.

We observed that the Fe(II) species proposed by Nakamura et al was not present because the use of Fe(acac)$_2$ did not yield any product. A reduced imine as a byproduct was detected, this implied a hydride was being formed during the reaction which can be only be introduced into the reaction if there were an Fe(II)H being formed. This led an investigation into finding the intermediary species for this reaction. This will be discussed further in manuscript one.

Scheme 1.4: Iron catalyzed direct arylation of heterocycles $^{54}$
1.2 1,3-TERTIARY ALLYLIC ALCOHOL REARRANGEMENT

Iron as a metal is very versatile. It has been shown to be comparable to palladium and in some cases, a better metal catalyst. Iron complexes have been found to be better Lewis acids in the Mukaiyama aldol condensation reaction of silyl ketene acetals and aldehydes. The iron complexes had better turnovers and stability to moisture and air and they were able to give good enantioselective aldol additions. Iron catalyzed Negishi reactions were also found to be robust, highly reproducible and made studies for reaction mechanism manageable. In view of these trends can iron outperform other known systems?

Allylic rearrangements involve the movement of a double bond in an allylic system usually facilitated by the addition of a nucleophile or an oxidant. The most practically known ones are the Cope and Claisen rearrangements, which are shown in scheme 1.5. 3',3-disubstituted allylic alcohol is often times a difficult system to synthesize though these systems are crucial in the synthesis of a lot of natural products.

Scheme 1.5: Cope and Claisen rearrangement

The most common methods of synthesizing these disubstituted molecules involve nucleophilic additions using organometallic reagents to propargyl alcohols and conjugated addition of
nucleophiles to yonones\textsuperscript{74–78}. Findings have shown that migration of the hydroxy group in tertiary allylic alcohol can help synthesize some of these complex and difficult systems but, until recent, not much attention had been given to this use of the tertiary alcohol 1,3-rearrangement.

Uses of Tertiary Allylic Alcohol

These 1,3-rearrangements are important as they help place functional groups in key positions during multistep synthetic pathways without changing the skeletal backbone of the molecule.\textsuperscript{79} This form of rearrangement has been used in many areas from medicinal chemistry to the fragrance industry. Examples include the use of chromium based reagents\textsuperscript{4} in synthesizing $\beta$ substituted and $\alpha,\beta$-disubstituted cyclic enones which are very important in the fragrance industry.\textsuperscript{79} 1,3-Rearrangement of allylic alcohols has been used in the synthesis of anti-malarial target molecules\textsuperscript{80}, valerenic acid\textsuperscript{81} (used for the treatment of dysfunction in the nervous system) (scheme 1.6) and two quinolone natural products isolated from \textit{Pseudonocardia sp.}\textsuperscript{82}

Scheme 1.6: Uses of 1,3-allylic alcohol rearrangement

![Scheme 1.6: Uses of 1,3-allylic alcohol rearrangement](image-url)
**Synthetic Method used for 1,3-Allylic Alcohol Rearrangement**

Reagents such as transition metal complexes\textsuperscript{4,83–86} and transition metal oxo complexes \textsuperscript{5,87,88} are generally known for mediating 1,3-rearrangement. Other reagents were explored due to the toxicity involved in using these transition metal based oxidants. Lewis acids like trifluoroacetic acid (TFA)\textsuperscript{3,81,89,90}, methanesulfonic acid\textsuperscript{91} iodoxybenzoic acid\textsuperscript{92,93}, Brensted acids like boronic acid\textsuperscript{94,95} and radical based reagents like TEMPO\textsuperscript{83,96} have been explored, as shown in scheme 1.7. Recent methods involve the use of mild reagents such as water\textsuperscript{97} and enzymes.\textsuperscript{98}

**Scheme 1.7: Types of methods used for 1,3-allylic alcohol rearrangement**

- **Transition metal oxo species**

  
  
  \[
  \text{HO} \quad \text{HOSiPh}_3 \quad \text{Ether, -50 °C, 0.5h} \quad \text{M} = \text{O}_3\text{ReOSiPh}_3
  \]

- **Radical based**

  
  
  \[
  R \quad \text{TEMPO}, \text{CuCl}_2 \quad \text{MeCN, O}_2, 7hrs, r.t
  \]

- **Lewis acid**

  
  
  \[
  \text{Et}_2\text{O, 0 °C} \quad \text{TFA/H}_2\text{O}
  \]

- **Transition metal complex**

  
  
  \[
  \text{THF, 0°C} \quad \text{Pd(TFA)}_2 \quad \text{CH}_3\text{CN/H}_2\text{O (5:1)} \quad \text{N}_2, 4h
  \]
Iron has been involved in a few substitution reactions via \( \pi \)-allylic system\(^{99-102} \) but the use of iron for 1,3-rearrangement has not been explored yet. We explored iron for this allylic rearrangement considering the fact that transition metals have been used for over long periods of time for this same type of rearrangement. It was interesting to discover that iron can break and functionalize strong C-O bonds, a unique synthetic characteristic that most conventional transition metals cannot do.

We reported a one pot iron mediated 1,3-rearrangement of tertiary allylic alcohols. This involved the addition of organolithium reagents to \( \alpha,\beta \)-unsaturated ketones, which then undergo a 1,3-rearrangement in the presence of \( \text{FeCl}_2 \) (scheme 1.8). This mechanism we believe for this novel reaction involves a cleavage of the C-O bond of the tertiary allylic alcohol and the intermediacy of an allylic cation. This is discussed further in manuscript 2.

Scheme 1.8: One pot iron mediated 1,3-rearrangement of tertiary allylic alcohols

1.3 SYNTHESIS OF 2-AMINO-\( \alpha \)-CARBOLINE AND ANALOGUES RELEVANT FOR DNA ADDUCT BIOPHYSICAL STUDIES

**Heterocyclic Aromatic Amines (HAAs)**

Heterocyclic Aromatic Amines (HAAs) consist of at least a ring containing heteroatoms mostly nitrogen and bears at least an indole ring. HAAs are compounds formed when foods, especially protein, are subjected to prolonged cooking at high temperatures\(^{103-107} \). Many of these HAAs have been found to be human carcinogens, examples include 2-amino-3,8-dimethylimidazo [4,5-
f]quinoxaline (MeIQx), 2-amino-3,4-dimethylimidazo[4,5-f] quinoline (MeIQ) and 2-amino-3,4-dimethylimidazo [4,5-f]quinoxaline (4-MeIQx) while some have been identified as potential carcinogens which include 1-methyl-9H-pyrido[4,3-b]indole (Harman).\textsuperscript{105} Their structures and mutagenicity ($x10^3$rev/µg) are shown in Figure 1.1.

A greater number of HAAs have been found to be more carcinogenic, higher mutagenicity than the usual carcinogens like nitrosamines, aflatoxins B\textsubscript{1} and benzo[α]pyrene.\textsuperscript{108} Studies have also shown that these HAAs are principal causes of most cancers like lung, breast, colon, stomach and prostate.\textsuperscript{109–112} Alpha carboline, a subgroup of HAAs has been found in the core structure for some natural products\textsuperscript{113,114} as shown in figure 1.2. They have a similar structure, relative to indoles and carbazoles and have served as a platform as a building block structure in medicinal chemistry\textsuperscript{115} and optoelectronic materials.\textsuperscript{116} They were isolated and identified several years ago and were found to be mutagenic against \textit{Salmonella typhimurium} TA 98 (TA 98). They were different from its isomers, β-carboline and γ-carboline\textsuperscript{117} in structure and activity. The latter carbolines had been identified to exhibit anticancer, antimalarial and antidopamine\textsuperscript{118} effects, thus interest to find the therapeutic or mutagenicity of α-carboline intensified.

\textbf{Figure 1.1:} Examples of known and potential carcinogenic HAAs
**Figure 1.2:** \( \alpha C \) as a core structure in some natural products

Characteristics of 2-Amino-\( \alpha \)-carboline (\( \alpha C \))

2-Amino-\( \alpha \)-carboline (\( \alpha C \)) and 2-amino-3-methyl-\( \alpha \)-carboline (Me\( \alpha C \)) have been studied especially for their mutagenicity. \( \alpha C \) has been reported as the second most consumed HAA in the United State.\(^{119}\) \( \alpha C \) has also been found having a higher concentration than the known carcinogen 4-aminobiphenyl (4-BP) in the urine of smokers.\(^{120,121}\) Studies, especially in animals, show a direct correlation between cancerous cells developed and the consumption of cooked meat.\(^{105}\) \( \alpha C \) has also shown antitumor activity towards Glioblastoma multiforme but unfortunately, the understanding of exactly how the HAA interacts with DNA leading to mutations is understudied.

It has already been reported on how HAAs are metabolized *in vivo*.\(^{104}\) The reactive intermediate is the N-acetoxyamine, which is easily transferred to DNA by the N-acetyltransferases found *in vivo*. Synthetically the best way is to convert an amine to N-acetoxyamine is by first converting the amine to nitro group, then partially reduce the nitro group to hydroxylamine, before acetylation the hydroxylamine. There has been a report though, of the use of a polyaniline nanofiber supported FeCl\(_3\) to acetylate an alcohol or amine to an acetoxy group.\(^{122}\) To study the biophysical interaction between \( \alpha C \) and DNA and how this leads to mutation, we looked into the synthesis of \( \alpha C \) and then 2-nitro-\( \alpha \)-carboline (\( \alpha C \)-NO\(_2\)).
Synthesis of Alpha-carboline

There have been various methods report for the synthesis of AαC (scheme 1.9). These include a modified Graebe-Ullmann reaction, intramolecular Diels Alder, annulation of substituted benzene and pyridines, photocyclization and transition metal catalyzed cross coupling.

a. Graebe-Ullmann reaction

This coupling reaction was discovered in the early 1900s but it was modified to aid the synthesis 2 decades after, when phenylenediamine and 2-chloropyridine were coupled together, followed by formation of a triazole then with the use of heat and polyphosphoric acid, the alpha carboline was obtained with the release of N$_2$ gas. This modified method has been used over the years to synthesis α-carbolines$^{123,124}$ and indoloquinoines for DNA Topoisomerase II Inhibitors.$^{125}$ The most recent use of this method involved the use of a microwave.$^{126}$

b. Intramolecular Diels-Alder reaction

Diels Alder reactions, a reaction that has helped incorporate rings into molecules in the synthesis of aromatic and heterocyclic compounds by forming C-C bonds. Molina et al.$^{127}$ did an intramolecular [4+2] addition of conjugated carbodiimides to form α-carboline, with the carbodiimide serving as both a diene and dienophile. Microwave has also been used for a Diels Alder reaction of an indole diene to maleimide to afford the adduct before dehydrogenation with Pd/C to give the α-carboline.$^{118}$ Wang et al. also did a [2+2+2] cycloaddition of functionalized alkyne-nitriles with ynamides to give substituted α-carbolines.$^{128}$

c. Annulation of substituted benzenes and pyridines

The use of suitable substituents on an indole or benzene ring can help achieve the synthesis of α-carboline. In these types of reactions, substitution is key. There are so many examples
including N-methyl tosylindole being reacted with a cyano-enolate in the presence of acid, formed an acetal which upon elimination of a formyl group closes the ring to form the α-carboline.\textsuperscript{129,130} Another method involves the use of iodo-indole and an azole stannane and Curtis rearrangement using diphenylphosphoryl azide (DPPA). Heating of the isocyanate product results in the α-carboline.\textsuperscript{131} Another form of this annulation involves radical cyclization of b-(3-indolyl)ketone o-2,4-dinitrophenyloxime in the presence of a strong base.\textsuperscript{132}

d. Photocyclization
In the photocyclization synthesis of carbazoles using anilino-pyridines, it was observed that the irradiation of the 2-anilinepyridine resulted in oxidative cyclization to give α-carboline. This began an investigation into the synthesis of α-carboline using photocyclization\textsuperscript{133,134} with the most recent method involving unimolecular radical substitution of 3-halo-N-phenylpyridin-2-amine.\textsuperscript{135}

Scheme 1.9: Methods for synthesis of alpha carboline
e. Transition metal cross coupling

Cross coupling is one of the versatile methods of forming C-C and C-N bonds. This makes it utility in synthesis ideal. In the synthesis of a-carboline, there have been reports of the use of Stille coupling\textsuperscript{136}, Suzuki coupling\textsuperscript{137} and Heck reaction\textsuperscript{138}. Other reports involve one pot synthesis utilizing Buchwald-Hartwig\textsuperscript{139} chemistry and the use of S\textsubscript{n}Z’ monoalkylation of nitroarylacetonitriles with Baylis-Hillman-acetates to form \(\alpha\)-carbolines.\textsuperscript{140}

**DNA Adduct Synthesis**

An important factor in determining the carcinogenic potential of a compound is its ability to form DNA adduct and A\(\alpha\)C has been shown to react with DNA at C-8 of guanine to form the DNA adduct. DNA adducts when formed are quickly repaired by glycosylases or AP endonucleases\textsuperscript{141} but sometimes traces are left behind. Theses stable HAA-DNA adduct accumulate over time, hence the need to understand how these are formed, repaired and/or how they cause mutations on the DNA.\textsuperscript{120,142} There are two main synthetic routes for the synthesis of DNA adduct, the biomimetic and total synthesis.\textsuperscript{143}

**Total synthesis**

Total synthesis involves reacting the most reactive form of the A\(\alpha\)C with guanine, one of the nucleic acid base, before it is reacted with a sugar, before the addition of a phosphate group. This resultant nucleotide then undergoes an automated oligopeptide synthesis. The advantage with this route is the selectivity in terms of building a specific nucleotide sequence. It eliminates the worry of having to find exactly where the A\(\alpha\)C bounded to the DNA. The disadvantage with this method is that it is expensive, time-consuming and involves a lot of steps.

**Biomimetic**

Biomimetic involves the reaction of the reactive form of the A\(\alpha\)C with a nucleotide sequence. The advantage with this route that it is quick, fewer resources needed and fewer steps needed. The
disadvantage however is knowing the exact location of the adduct. Should there be more than one guanine in the sequence the AαC will react with all of them making detection and monitoring quite cumbersome and difficult.

The best method to suit our aim was the Graebe-Ullmann modified method since it has fewer steps and the starting materials are readily available and this is discussed further in manuscript three.

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EFFORTS TOWARDS INVESTIGATIVE MECHANISTIC STUDIES OF
IRON CATALYZED C-H ACTIVATION REACTION

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ABSTRACT

Iron-catalyzed C-H activation reactions have been identified as an economical, environmentally friendly and efficient method for synthesizing fine chemicals and materials. Though this method is well known and established, the mechanism through which these reactions happen under various conditions is not well understood, hence the need to investigate how iron catalyzes C-H activation in the presence of Grignard reagents. Results indicate the intermediary transition state for the iron species involves an Fe(I) species but the attempt to synthesize this Fe(I) species failed. We also confirmed that Fe(II) is definitely not the active species for this reaction. The nitrogen-based ligand might not have afforded us the Fe(I) complexes but there was evidence to show the reduction of the Fe(acac)$_3$ due to the formation of the biphenyl product.

INTRODUCTION

Development of new innovative green methods for synthesis has been an intense driving force in recent times. Old traditional methods like Suzuki-Miyaura, Sonogashira and Kumada, though each has some “green” aspect to it, the use of expensive precious metals and the toxicity associated with them makes looking into other ways of transforming C-H bonds a necessity. Recent findings indicate the increasing use of 3d non-precious transition metals particularly iron, cobalt and nickel for these same reactions.

The use of iron for catalysis dates as far back as 1940 and 1970 and these iron-catalyzed reaction are ideal because iron is economically sustainable due to its abundance, biologically nontoxic nature and its inexpensiveness. The reactions have also been proven to be efficient and easily scalable. Iron catalyzed reactions have also been found to be robust, highly reproducible and are known to be ‘green’ considering that it is easily processed and its environmentally benign waste is appealing to the pharmaceutical and fine chemical industries.
Even though this discovery of iron’s reactivity and its use for the cross-coupled reactions was made before the use of palladium\textsuperscript{7–9} and nickel-based catalysis,\textsuperscript{10–13} the mechanistic catalytic cycle behavior of iron is still not clearly established. Iron’s electron configuration causes variable electron spin resulting in a very chemically reactive species compared with other first row transition metals. The variable electron spin of iron results in unreliable prediction of the reactivity of iron species making the study of the catalytic cycle difficult.\textsuperscript{14} Attempts have been made by various groups to establish this very useful but elusive phenomenon. The earliest reported catalytic cycle suggested for cross coupling reactions involved an Fe(I) species that oxidatively adds to a halide, forming Fe(III) species, then undergoing a transmetallation with a Grignard reagent before it reductively eliminates the product to give back the Fe(I) species.\textsuperscript{15} (scheme 2.1)

Scheme 2.1: Catalytic cycle for iron catalyzed cross coupling

Nakamura and co-workers were the first to report a direct C-H bond functionalization at low temperature (0 °C) which they discovered during a cross coupling reaction between diphenylzinc and 2-bromopyridine.\textsuperscript{16} Optimization of this reaction conditions resulted in arylation of the ortho
hydrogen on phenylpyridines, phenylpyrazoles, phenylpyrimidines and benzoquinoline. These ortho hydrogens were susceptible to the transformation regardless of the electronic effect of the substituents.\textsuperscript{17} Other groups then researched into the mechanism for iron catalyzed C-H activation.\textsuperscript{18–20} It should also be noted that iron has been found to activate not just C(sp\textsuperscript{2})-H, but also C(sp)-H and C(sp\textsuperscript{3})-H bonds using Fe complexes to form Fe-C bonds in the presence or absence of directing groups.\textsuperscript{21,22} The proposed mechanism for this iron catalyzed ortho directed arylation as shown in scheme 2.2

Scheme 2.2: Nakamura’s proposed mechanism for iron catalyzed ortho directed arylation
As the interest in iron catalyzed direct C-H activation increased, the inquiry into the mechanism also began. In respect of this, two general mechanisms of how the iron activates the activation have been proposed, a low valent iron complex undergoing an oxidative addition into a C-H bond to form the organoiron complex, or, the iron complex deprotonates the substrates before forming the Fe-C bond, also known as direct deprotonation metalation. These proposed mechanisms involves either a double electron transfer or a single electron transfer between the substrate and the iron. Unfortunately, the active Fe species involved in these reactions is dependent on many conditions, such as ligand, type of Grignard (nucleophile) used and but not limited to the presence or absence of a β hydride on the nucleophile.

The key step of interest was the reduction of Fe(acac)₃ by a Grignard reagent. The active Fe species is dependent on the type of Grignard reagent used. Nakamura used an aryl Grignard reagent which has been shown to form clusters of anionic Ph₃Fe(II) or Ph₄Fe(III) in THF. This implies the presence of both Fe(II) and Fe(III) species in solution. Computational studies also confirmed the Fe(II)/Fe(III) system but added the additional information of the presence of an Fe(I) species after the C-C bond formation through reductive elimination. Nakamura also proposed that the main intermediary species to be Fe(II)/Fe(III) system for a similar C-H activation using organoborons. Though the Fe(II)/Fe(III) system seems to explain a lot of these iron reactions, the fast rates of reactions and side products had led others to propose other mechanisms which include an Fe(I)/Fe(III) system, Fe oxo species and Fe⁻¹ species for other Fe-catalyzed processes.

Our group’s previous work expanded Nakamura’s ortho directed arylation of arenes containing directing groups to include the azoles and thiophenes heterocyclic substrates (scheme 2.3). The investigation led to the conclusion that Fe (III) catalysts, preferably Fe(acac)₃, were required for the reaction. Importantly, The Fe(II) catalyst precursor, Fe(acac)₂, did not catalyze the reaction. The by-product obtained was the reduced imine (7) implying a hydride was being produced in the
catalytic cycle. The use of radical scavenger, TEMPO, did not affect the reaction implying the catalysis did not proceed through radicals, eliminating the single electron transfer method of activation. High amounts of Grignard reagents had to be used to account for the high amounts of biphenyl produced even though the additive KF was added to reduce the homo-coupling as shown in scheme 2.3.

Scheme 2.3: Iron catalyzed direct ortho arylation of arylamine.

RESULT AND DISCUSSION
This led us to propose a mechanism that involves an Fe(III)/Fe(I) system (scheme 2.4a) or an Fe(III)/Fe(I) mechanism (scheme 2.4b). The FeX$_3$ (1) reacts with 2 equivalents of Grignard reagent to give an Fe(I)Cl (2) species in the presence of bidentate N–ligands as shown in scheme 2.4a. The Fe(I)Cl species then react with another equivalence of Grignard to give an Fe(I) aryl species (3). Then the aryl imine (4) coordinates to the Fe(I)aryl species before an oxidative addition to the
Fe(I)aryl species occurs to form an Fe(III) species. This Fe(III) species (5) then undergoes reductive elimination to give the product (6) and an FeH (8) species. The oxidant (9) converts the Fe(I)H species back to the Fe(I)Cl species for the cycle to continue.

Scheme 2.4a: DeBoef’s proposed Fe(I)/Fe(III) mechanism for iron catalyzed direct ortho arylation.
The Fe(III)/Fe(I) mechanism as shown in scheme 2.4b involves FeX₃ (1) reacting with 1 equivalent of the Grignard reagents to give Fe(III) species (11) which coordinates with the substrate and undergoes concerted metalation deprotonation to release (12).

**Scheme 2.4b:** DeBoef’s proposed Fe(III)/Fe(I) mechanism for iron catalyzed direct ortho arylation
The deprotonation of hydrogen happens as the Fe binds to the C to form species (13), which then undergoes reductive elimination to give product (14). The ligand dtbpy is added to maintain the Fe(I) species (15) formed from the reductive elimination of the product. The 1,2-dichloroisobutane (16) then converts the Fe(I) species into Fe(III) species (17) with 1 equivalent of Grignard reagent, to start the cycle again.

The effect of ligands, solvents, the effect and amounts of Grignard were investigated to help identify the intermediate of our observed reaction and whether these results fit our proposed mechanism. The ligand 1,2-bis(diphenylphosphino)benzene (dppbz) was used to ascertain which iron species gives the Fe(I) species. The ligand dppbz was selected because Fe(I) species with phosphino ligand have been reported by Bedford et al. Fe(acac)₃/ligand/Grignard was found to give the iron(I) intermediate for the reaction compared to other Fe catalysts. ³¹P NMR was used. Fe(I) cannot be detected in an NMR, so the disappearance of the peak for the ligand implies the Fe(I) species being formed was having an effect on the spectrum being taken. Only Fe(acac)₃ gave that effect in the presence of a Grignard.

The effect of three nitrogen bidentate ligands were investigated, 2,2′-bipyridyl (bpy), 1,10-phenanthroline (phen) and 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbpy) using UV/Vis spectrometry. The ligand bpy and phen only decreased the intensity of the Fe(acac)₃ shown in figure 2.1 and 2.2 respectively because bpy and phen were better ligands replacing the acac ligand. The dtbpy ligand was the only ligand that had an effect on the Fe(acac)₃ as shown in figure 2.3. This implied the ligand stabilized the Fe in the complex formed between dtbpy and Fe(acac)₃.
It was established that there was no reaction observed when the Fe(acac)₃ was mixed with the ligand, but changes start to occur when Grignard was added. The effect of Grignard on the reaction was then investigated as shown in figure 2.4. An increase in the amplitude of the absorption spectrum was initially observed the instant the Grignard was added to a solution of Fe(acac)₃ but within minutes a reaction occurred.
The initial peak is converted into another peak for a different species as the Grignard reacts with the Fe(acac)$_3$, confirming the hypothesis that the Fe(acac)$_3$ thus reacts with the Grignard as proposed in our proposed mechanism. The effect of Grignard on Fe(acac)$_3$ in the presence of ligand was also investigated. Grignard reacts with Fe(acac)$_3$, but in the presence of bpy ligand, the reaction between Fe and the Grignard reagent is not observed as shown in figure 2.5. This implies bpy ligand is able to stabilizes the Fe complex, preventing the reaction between Fe(acac)$_3$ and the Grignard.

Following works done by Bedford et al.\textsuperscript{34,35} we synthesized our iron (I) intermediate. Bedford used a bidentate phosphorus ligand in the presence of Grignard to synthesize and characterize an iron (I) species. (Scheme 2.5) We synthetized an “Fe(I)” and Fe(II) species using a bidentate nitrogen ligand, dtbpy. (scheme 2.6). Analysis by UV/VIS and IR spectroscopies revealed that we were able to obtain the iron (II) chloride species but we unable to obtain the Fe(I) species after characterization. Analysis of EPR spectroscopic data also confirmed the Fe(I) was not available as it had similar spectrum to the spectrum for the FeCl$_2$ species.
Figure 2.4: Reaction of Grignard with Fe(acac)₃

![Absorbance vs Wavelength](image)

Figure 2.5: Investigating the reaction of Fe(acac)₃ and Grignard in the presence of bpy

![Absorbance vs Wavelength](image)

The synthesized Fe(I) and Fe(II) however were subjected to the direct C-H activation reaction and we obtained results that showed as shown in table 2.1 that the Fe(II) and Fe(I) were not as efficient as the Fe(acac)₃ set up. Even though after 12 hours the yield for the reaction involving Fe(I) species
increased, it was still lower than the Fe(acac)$_3$. This implied the Fe(I) species might not be the active Fe species in this reaction as we initially proposed. We also confirmed that Fe(II) is definitely not the active species for this reaction. The nitrogen based ligand might not have afforded us the Fe(I) complexes but there was evidence to show the reduction of the Fe(acac)$_3$ due to the formation of the biphenyl product.

Scheme 2.5: Synthesis of Fe(I) species by Bedford et al.

Scheme 2.6: Synthesis of Fe(I) species using bidentate N-ligand dtbpy
Table 2.1: Comparison of catalyst species for direct C-H ortho arylation

| Iron Catalyst       | % GC yield | After 12 hrs |
|---------------------|------------|--------------|
| Fe(acac)₃           | 88.4       |              |
| Fe (II) complex     | 12.6       | 21.1         |
| Fe (I) complex      | 3.9        | 24.6         |

CONCLUSION

In summary, the probe into the mechanistic behavior of iron in direct arylation of ortho C-H bonds on heterocycles in the presence of Grignard based on Fe(I) was unsuccessful. The Fe(I) intermediate from our proposed mechanism could not be synthesized successfully. Future works will be looking at different ways to isolate the Fe intermediate or find another way to monitor the intermediary species during the reaction.

EXPERIMENTAL SECTION

Instrumentation:

A Perkin-Elmer Lambda 1050 spectrometer was employed for obtaining UV/Vis spectra. A Perkin-Elmer spectrum 100 FTIR spectrometer was used to make infrared measurements with scanning in the 650 to 4000 cm⁻¹. GC/MS analysis was carried out on an Agilent Technologies 6890 GC
system fixed with a 5973 mass selective detector. GC/MS Conditions: J & W Scientific DB-1, capillary 25.0m x 200µm x 0.33µm, 1.3 mL/min, 40 °C, hold 0.50 min, 12 °C/min to 320 °C, hold 6.0 min. NMR spectra were acquired with a Bruker Avance 300 MHz spectrometer

The imine((E)-N,1-diphenylethan-1-imine and arylamine product ((E)-N-([1,1'-biphenyl]-2-yl)-1-phenylethan-1-imine) were synthesized using the methods from previous work\textsuperscript{31}

**Synthesis of Imine**

To an oven dried 50 mL RBF with a stir bar was added 20 g of 3 Å molecular sieves and 30 mL of toluene. The aniline (60 mmol) and acetophenone (50 mmol) were added successively. The reaction was stirred at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The crude residue was purified using the Kugelrohr distillation apparatus. \textsuperscript{1}H NMR (300 MHz, Chloroform-d) δ 7.98 (m, 2H), 7.47 (d, J = 1.9 Hz, 2H), 7.45 (d, J = 2.1 Hz, 1H), 7.35 (dt, J = 2.1, 1.2, 1.2 Hz, 2H), 7.09 (t, J = 8.0, 1.9, 1.9 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 2.24 (s, 3H).

**Synthesis of Fe(II) complex (3)**

FeCl\textsubscript{2}.4H\textsubscript{2}O (1.00 mmol) was dissolved in 1 mL anhydrous acetone inside a Schleck tube and after stirring for 5 minutes, the solvent was removed with vacuum under nitrogen. This was repeated twice. Then the dtbpy (2.00 mmol) was added to the resulting iron complex with THF. Anhydrous acetone (25 mL) was then added and the mixture was stirred for 24 hours under nitrogen. The suspension obtained was then filtered with a Buchner funnel and washed with cold diethyl ether to yield an orange-red color.
**Synthesis of Fe (I) species (4)**

The Fe(II) complex (0.02 mmol) was dissolved in 1.5 mL of toluene (anhydrous) and cooled to -40 degrees, then the Grignard, tolyl MgBr (0.06 mmol) was added dropwise and the mixture was stirred for 20 minutes, then the mixture was allowed to warm to room temperature for 40 minutes under nitrogen. The solvent was removed to 2/3 its volume then the mixture was cooled to -20 degrees in order to obtain red crystals.

**Investigation of Iron Catalysts:**

For GC/MS analysis

An oven dried Schleck vial was evacuated using vacuum three times, the tube was filled with nitrogen intermittently. Iron catalyst (0.055 mmol) and 1,2-bis(diphenylphosphino)benzene (dppbz, 0.118 mmol) were added to the Schleck vial. Then PhMgBr Grignard (0.168 mmol) was added over 15mins. After 15 mins, 0.1 mL of the reaction mixture was taken into a GC vial and 990 mL of EtOAc was added for GC/MS analysis.

**Investigation of Iron Complexes for Direct C-H ortho Arylation**

The imine (0.55 mmol), chlorobenzene (2 mL), Iron complex (0.055 mmol) and the dppbz (0.118 mmol) were added to an oven dried Schleck vial sequentially. The vial was evacuated using vacuum three times, the tube was filled with nitrogen intermittently before the addition was done. The mixture was then cooled to -78 °C for 15 minutes. The Grignard (0.168 mmol) was added over 15mins. The reaction was then allowed to warm to room temperature. 0.1 mL of the reaction mixture was taken into a GC vial containing 990 mL of EtOAc and used for GC/MS analysis.
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2.2 Supporting Information

Figure 2.6: $^1$H NMR of imine ((E)-N,1-diphenylethan-1-imine)
Figure 2.7: $^{31}$P NMR comparison of different Fe species and their interaction with dppbz and Grignard
Figure 2.8: UV/VIS Spectrum comparison of synthesized Fe(I) and Fe(II) dtbpy complexes

Figure 2.9: IR spectrum comparison of synthesized Fe(I) and Fe(II) dtbpy complexes
Figure 2.10: EPR spectrum of synthesized Fe(II) dtbpy complex
Figure 2.11: EPR spectrum for synthesized Fe(I) complex
Figure 2.12: GS/MS spectrum of C-H activation reaction using Fe(II) dtbpy complex after an hour
Figure 2.13: GS/MS spectrum of C-H activation reaction using Fe(II) dtbpy complex after overnight
Figure 2.14: GS/MS spectrum of reaction of Fe(I) dtbpy complex after an hour.
Figure 2.15: GS/MS spectrum of the reaction of Fe(I) dtbpy complex overnight
Figure 2.16: GS/MS spectrum of reaction of Fe(acac)$_3$ dtbpy complex overnight
3 FECl₂ MEDIATED REARRANGEMENT OF TERTIARY ALLYLIC ALCOHOLS

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ABSTRACT

A mild, one-pot procedure to produce 3-substituted allylic alcohols from α,β-unsaturated ketones is described. The addition of an organolithium nucleophile produces a tertiary allylic alcohol as an intermediate, which undergoes a 1,3-OH migration assisted by FeCl$_2$. The proposed mechanism indicates that a syn-facial migration occurs for the major product. Yields as high as 98% for the one-pot reaction are reported.

INTRODUCTION

Allylic alcohols are indispensable functional groups in the synthesis of structurally complex organic molecules.$^{1-8}$ 3,3'-Disubstituted allylic alcohols, in particular, are often more difficult to synthesize than their mono-substituted counterparts. Though methods such as the conjugate addition of nucleophiles to yrones and the addition of organometallic reagents to propargylic alcohols have been described,$^{9-13}$ one method that has received little attention is the 1,3-migration of the hydroxy group in tertiary allylic alcohols. This transformation has been primarily catalyzed by oxo catalysts,$^{14-16}$ though oxidative palladium catalysis has also been employed to perform the migration and oxidize the allylic alcohol to a β-disubstituted enone.$^{17}$ This form of rearrangement can be done by enzymes to form enones.$^2$ Rhenium assisted rearrangement has also been used in the synthesis of semisquarates.$^{18}$ Trifluoroacetic acid has also been used to isomerize allylic alcohols, and this method has been applied to the synthesis of valerenic acid, which binds to both the GABA$_A$ and 5-HT$_{5A}$ receptors, and is used as a treatment of insomnia.$^{19}$ Acid assisted allylic
alcohol rearrangement was also used in the synthesis of two quinolone natural products isolated from *Pseudonocardia sp.*\textsuperscript{20} Additionally one can envision that this rearrangement could be used to create artemisinin-like antimalarial drugs via Singh’s synthetic (Scheme 3.1).\textsuperscript{21}

Iron has recently been studied as a catalyst for a number of coupling reactions.\textsuperscript{12–28} The most widely used of these processes are alternatives to traditional palladium-catalyzed transformations, such as the Kumada coupling and C–H arylation and alkylation reactions.\textsuperscript{22, 29, 30} Even a few examples of substitution reactions via π-allyl iron intermediates have been reported.\textsuperscript{31–35}

Scheme 3.1: Application of allylic 1,3-migrations

Iron is preferable to late transition metal catalysts due to its low expense and toxicity. Additionally, iron catalysts are often capable of performing synthetic steps that conventional late transition
metal catalysts cannot perform, such as breaking and functionalizing strong C–O bonds. Herein, we describe a one-pot addition of an organolithium reagent to an \( \alpha,\beta \)-unsaturated ketone, followed by an iron-mediated 1,3-rearrangement reaction. We propose that the novel reaction proceeds via the formal cleavage of a C–O bond and the intermediacy of an allylic cation.

RESULTS AND DISCUSSION

During the course of our studies on iron-mediated reactions involving organolithium and organomagnesium nucleophiles,\textsuperscript{30,36} we discovered that the addition of an organolithium reagent to an \( \alpha,\beta \)-unsaturated ketone in the presence of an iron salt, does not result in the expected 1,4-addition products, but rather an isomeric allylic alcohol is formed (2).

Cyclohex-2-enone, (1) was chosen as a reliable and simple substrate for reaction optimization (Table 3.1). A number of both iron(II) and iron(III) salts were selected, out of which FeCl\(_2\) was determined as the most efficient reagent. In general, iron(III) salts were inferior to iron(II) salts. Diethyl ether (with or without BHT stabilization) was the most desirable solvent for the rearrangement and the other common ethers solvents, THF and Me-THF, produced low or no yields of 2.

Colder temperatures (entry 10) allowed for the formation of the 1,2-addition product, 3, but hindered the formation of the desired rearranged product 2. While the reaction proceeded in both inhibited and purified Et\(_2\)O, the addition of one equiv of BHT further hindered the reaction (entry 11), indicating that the BHT preservative was not involved in the reaction and that commercial, stabilized ether was a suitable solvent for the addition/migration. Reduction of the loading of FeCl\(_2\) from one equiv to 10 mol% resulted in an 8% yield (entry 13), indicating that the reaction required a stoichiometric amount of the iron reagent.
Table 3.1: Evaluation of catalytic conditions

| Entry | Iron species | Solvent | Temp (°C) | Yield (%) 2 | Yield (%) 3 |
|-------|--------------|---------|-----------|-------------|-------------|
| 1<sup>a</sup> | FeCl<sub>2</sub> | Et<sub>2</sub>O | 25 | 55 | 4 |
| 2 | FeCl<sub>2</sub> | Et<sub>2</sub>O | 25 | 87 | 17 |
| 3 | Fe(OAc)<sub>2</sub> | Et<sub>2</sub>O | 25 | 35 | 27 |
| 4 | FeF<sub>3</sub> | Et<sub>2</sub>O | 25 | 25 | 40 |
| 5 | Fe(acac)<sub>2</sub> | Et<sub>2</sub>O | 25 | 41 | 44 |
| 6 | Fe(acac)<sub>3</sub> | Et<sub>2</sub>O | 25 | 30 | 29 |
| 7 | FeCl<sub>2</sub> | THF | 25 | - | 5 |
| 8 | FeCl<sub>2</sub> | 2-MeTHF | 25 | 4 | 91 |
| 9 | FeCl<sub>2</sub> | MBTE | 25 | 23 | 32 |
| 10 | FeCl<sub>2</sub> | Et<sub>2</sub>O | -78 | - | 73 |
| 11<sup>b</sup> | FeCl<sub>2</sub> | Et<sub>2</sub>O | 25 | 36 | - |
| 12<sup>c</sup> | FeCl<sub>2</sub> | Et<sub>2</sub>O | 25 | 8 | 83 |
| 13<sup>d</sup> | FeCl<sub>2</sub> | Et<sub>2</sub>O | 25 | 71 | - |

Standard conditions: 0.2 M in Et<sub>2</sub>O (stabilized with 5 ppm BHT), -78 °C to rt, 1 equiv of FeCl<sub>2</sub> and 3 equiv of nucleophile. <sup>a</sup> 1 equiv of the aryl lithium was used. <sup>b</sup> 1 equiv of BHT was added. <sup>c</sup> 10 mol % of FeCl<sub>2</sub> <sup>d</sup> Solvent was diethylether without BHT.
The scope and limitations of the addition-rearrangement with respect to both linear and cyclic $\alpha,\beta$ unsaturated ketone substrates were also investigated (Table 2). Cycloalkenones were found to be the best substrates, with cyclohex-2-enone (1) giving the highest yield. Linear $\alpha,\beta$-unsaturated ketones (entries 3-5) produced only the 1,2 addition product.

Table 3.2: Substrate scope

| Entry | Substrate | 1,3-Migration | 1,2-Addition |
|-------|-----------|---------------|--------------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | 2 87%        |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 4 53%        |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 5 32%        |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 6 68%        |
| 5     | ![Image](image9.png) | ![Image](image10.png) | 7 77%        |

Conditions: 0.2 M in Et$_2$O (stabilized with 5 ppm BHT), -78 °C to rt, 1 equiv of FeCl$_2$ and 3 equiv of nucleophile.
Table 3.3: Nucleophile scope

![Chemical structure](image)

| Entry | Nucleophile | Product |
|-------|-------------|---------|
| 1     | ![Structure](image) | ![Structure](image) 9 54% |
| 2<sup>a</sup> | ![Structure](image) | ![Structure](image) 11 98% |
| 3<sup>a</sup> | ![Structure](image) | ![Structure](image) 13 54% |
| 4<sup>a</sup> | ![Structure](image) | ![Structure](image) 87% |
| 5<sup>a</sup> | ![Structure](image) | not observed |
Aryllithium was synthesized via lithium-halogen exchange from the arylbromide and butyllithium.

We then investigated the scope and limitation of organolithium and Grignard nucleophiles (Table 3). Alkyllithium reagents did not yield any results, presumably due to their basicity. The naphthyllithium reagent produced only the 1,2-addition product 15, indicating that the 1,3 migration may be inhibited due to steric hindrance. Only trace amounts of the product were obtained from a Grignard reagent (entry 6). We investigated the feasibility of this method using heterocyclic aryllithiums, and we obtained only a trace amount of products 20 and 22.

To probe the mechanism of the reaction, the biphenyl lithium reagent was added to 1 and stirred for 3 hrs. Purification by flash chromatography gave 3. FeCl₂ (1 equiv) was then added to a solution
of 3 (1 equiv) and the reaction was stirred at room temperature for 3 hrs, providing 2 after column chromatography (Scheme 3.2). This confirmed that the tertiary allylic alcohol (3) was an intermediate for the rearrangement.

Scheme 3.2: Stepwise reaction

Furthermore, the use of a chiral α,β-unsaturated ketone indicated that the OH-migration was diastereoselective as shown in scheme 3.3. 6-Methylcyclohexenone, 23, was reacted with phenyllithium to produce a 1:1 mixture of diastereomers 24 and 25 (as judged by 1H NMR of the crude reaction mixture). Of the two possible diastereomers, only 24 could be isolated by flash chromatography. When this stereoisomer was reacted with FeCl₂, a 2:1 mixture of the two diastereomeric migration products (26 and 27) was obtained. NOESY NMR spectroscopy revealed that the major diastereomer retained the anti-relationship between the methyl group and the alcohol. This indicates that the 1,3-migration proceed primarily via a syn-facial pathway due to less energy needed for the iron-oxo species to approach from the same face of the allylic cation than to approach from the opposite face as the methyl group to give the syn product.

Based on these data and the previous work by McCubbin,³⁷ we propose the mechanism shown in Scheme 3.4. The organolithium reagent reacts with the α,β-unsaturated ketone to give the tertiary alkoxide (1,2-addition). The FeCl₂ coordinates to the alkoxide (28) and LiCl is formed. The iron-oxo species (29) cleaves the C–O bond, forming an allylic carbocation (30), and the iron-oxo species then attacks the 3-position of the allylic cation, forming a new C–O bond. The major product of
this process arises from the syn migration of the iron-oxo species. We hypothesize that the intimate ionic pair (30) could explain the formation of both diastereomers (26 and 27) and the preference for the trans isomer (26). DFT calculations indicate that both the trans (26) and cis (27) rearranged products have similar ground-state energies, so the observed 2:1 selectivity likely arises from kinetic control. When aryllithium nucleophiles are used, the final allylic alcohol is conjugated which we believe is the overall driving force for the reaction.

Scheme 3.3: Diastereoselective OH-migration

Finally, the extent of the OH-migration was investigated (scheme 3.5). Phenyllithium was added to a solution of the conjugated dieneone, 32, then after an hour, FeCl₂ was added. The mixture was then stirred at room temperature for 24 hours, producing 33, a 1,2-addition product, and 34, the product of a 1,5-OH migration. The 1,3-migration product (35) was not observed, likely because it was less conjugated than 33 or 34. This result corroborates the proposed OH-migration mechanism and confirms the overall driving force for the reaction is the creation of an extended conjugated system.
CONCLUSION

In summary, we have developed a novel iron-mediated process that isomerizes allylic alcohols. The system can be used to effect the transformation of cyclic $\alpha,\beta$-unsaturated enones to 3,3'-
disubstituted allylic alcohols. Future work in this field could involve the enhancement of the
diastereoselectivity of the process and its application to the synthesis of medicinal compounds.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under nitrogen atmosphere unless stated otherwise. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance 400 MHz and Bruker Avance 300 MHz spectrometers. NMR spectra were measured in DMSO and CDCl$_3$ solutions. The chemical shifts $\delta$ are reported relative to the residual solvent peaks ($^1$H, $\delta$ DMSO = 2.50 ppm; $^{13}$C, $\delta$ DMSO = 39.52 ppm $^1$H, $\delta$CDCl$_3$ = 7.26 ppm; $^{13}$C, $\delta$ CDCl$_3$ = 77.16 ppm). All $^1$H and $^{13}$C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; bs = broad signal. High-resolution mass spectrometry was performed using a Thermo Scientific LTQ Orbitrap XL$^\text{TM}$ instrument.

**General Procedure (Method A)** $^{38}$ n-Butyllithium (0.32 mL, 0.6 mmol, 3 equiv) was slowly added to the solution of arylhalide (1.0 equiv) in anhydrous diethylether (0.20 M) precooled to -78 °C. The resulting slightly turbid solution was stirred for 30 minutes allowing it to warm to ambient temperature. Then aryllithium solution was added to the substrate (1 equiv) dissolved in anhydrous diethylether in a glovebox dropwise and reaction mixture was stirred for 3 hrs and then iron species (1 equiv) was added to reaction mixture. The reaction was allowed to run overnight at room temperature. Silica was then added to the reaction. Purification by flash column chromatography using hexanes and ethyl acetate provided the desired 1,3-rearranged allylic alcohol.

**General Procedure (Method B)** $^{39}$ $\alpha,\beta$-unsaturated ketone (1.0 equiv) was dissolved in anhydrous diethylether (0.20 M) in a glovebox dropwise. Then aryllithium solution (3.0 equiv) was added to the substrate solution in a dropwise manner and reaction mixture was stirred for 3 hrs and FeCl$_2$
(1.0 equiv) was added. The reaction was allowed to run at room temperature overnight. Silica was then added to the reaction. Purification by flash column chromatograph using hexane and ethyl acetate provided the corresponding desired 1,3 rearranged allylic alcohols.

**3-Biphenylcyclohex-2-en-1-ol (2)** According to Method A, 1.44 mL n-butyllithium (1.6 M, 0.9 mmol) was slowly added to a solution of 4-bromobiphenyl (210 mg, 0.9 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was added to 2-cyclohexen-1-one (97%, 29.1 µL, 0.3 mmol) dropwise. After stirring for 3 hours, FeCl₂ (anhydrous, 37.9 mg, 0.3 mmol) was added to the reaction mixture. After 12 hours, purification (column chromatography: 17% ethyl acetate in hexane) of the reaction mixture after 12 hours gave 216 mg of 3-biphenylcyclohex-2-en-1-ol (2) as a white powder (87% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.51 (m, 4H), 7.37 (m, 4H), 7.26 (m, 1H), (dt, J = 3.6, 1.8, 1.8 Hz, 1H), 4.33 (bs, 1H), 2.51 (m, 1H), 2.42 (m, 1H), 1.86 (m, 2H), 1.65 (m, 2H). ¹³C{¹H} NMR (101 MHz, Chloroform-d) δ 140.68, 140.23, 139.67, 128.84, 128.78, 127.56, 127.39, 127.30, 127.05, 127.00, 126.97, 126.58, 125.78, 66.41, 31.74, 27.47, 19.48. HRMS (ESI-TOF) m/z: [M - OH]⁺ Calcd for C₁₈H₁₇⁺: 233.1325; found: 233.1322.

**3-[(1,1'-Biphenyl)-4-yl) cyclopent-2-en-1-ol (4)** According to Method A, 1.44 mL of n-butyllithium (1.6 M, 0.9 mmol) was slowly added to a solution of 4-bromobiphenyl (210 mg, 0.9 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C and stirred for 30 minutes. this solution was then added to 2-cyclohexen-1-one (97%, 29.1 µL, 0.3 mmol) dropwise. After stirring for 3 hours, FeCl₂ (anhydrous, 37.9 mg, 0.3 mmol) was added to the reaction mixture. After 12 hours, purification (column chromatography: 17% ethyl acetate in hexane) of the reaction mixture after 12 hours gave 38 mg of 3-[(1,1'-biphenyl)-4-yl) cyclopent-2-en-1-ol as a yellowish powder. (53% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.67 (t, J = 7.9, 7.9 Hz, 4H), 7.58 (d, J = 8.2 Hz, 2H) 7.46 (t, J = 7.6, 7.6 Hz, 2H), 7.36 (t, J = 7.3, 7.3 Hz, 1H), 6.30 (d, J = 1.9 Hz, 1H), 4.83 (s, 1H), 2.81 (m, 1H),
2.56 (m, 1H), 2.30 (m, 1H), 1.71 (m, 1H). $^{13}$C$^{1}$H NMR (101 MHz, DMSO-d$_6$) δ 143.05, 140.18, 140.07, 139.62, 135.31, 135.25, 130.20, 129.42, 127.94, 127.79, 127.26, 127.24, 127.07, 126.93, 126.91, 126.80, 76.36, 33.86, 31.38. HRMS (ESI-TOF) m/z: [M - OH]$^+$ Calcd for C$_{17}$H$_{15}$+: 219.1168; found: 219.1154.

(5) According to Method A, 1.88 mL n-butyllithium (1.6 M, 3 mmol) was slowly added to a solution of 4-bromobiphenyl (699 mg, 3 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was then added to 3-methyl-2-penten-1-one (98%, 99 µL, 1 mmol, 1eq) dropwise. After 3 hours, FeCl$_2$ (anhydrous, 126 mg, 1 mmol, 1eq) was added. After 12 hours, purification (column chromatography: 14% ethyl acetate in hexane) of reaction mixture gave 81 mg (0.32 mmol) of (E)-2-((1,1′-biphenyl)-4-yl)-3-methylpent-3-en-2-ol (5) as a white powder. (32% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.65 (m, 2H), 7.58 (m, 2H), 7.45 (m, 4H), 7.34 (t, $J = 7.3, 7.3$ Hz, 1H), 5.70 (m, 1H), 5.13 (s, 1H), 1.60 (m, 6H), 1.43 (s, 3H). $^{13}$C$^{1}$H NMR (101 MHz, DMSO-d$_6$) δ 147.79, 141.96, 140.60, 138.33, 129.31, 127.60, 126.99, 126.46, 126.41, 117.25, 76.08, 29.26, 13.69, 13.23. HRMS (ESI-TOF) m/z: [M - OH]$^+$ Calcd for C$_{18}$H$_{19}$+: 235.1487; found: 235.1481.

(6) According to Method A, 0.63 mL n-butyllithium (1.6 M, 3 mmol) was slowly added to a solution of 4-bromobiphenyl (699 mg, 3 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was then added to 4-methyl-2-penten-1-one (98%, 99 µL, 1 mmol) dropwise. After 3 hours, FeCl$_2$ (anhydrous, 126 mg, 1 mmol, 1eq) was added. After 12 hours, purification (column chromatography: 14% ethyl acetate in hexane) of reaction mixture gave 171 mg (0.68 mmol) of 2-((1,1′-biphenyl)-4-yl)-4-methylpent-3-en-2-ol (5) as a white powder. (68% yield). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.65 (m, 2H), 7.58 (m, 2H), 7.48 (m, 4H), 7.35 (m, 1H), 5.62 (p, $J = 1.4, 1.4, 1.4, 1.4$ Hz, 1H), 5.09 (s, 1H), 1.67 (d, $J = 1.4$ Hz, 3H), 1.52 (m, 6H). $^{13}$C$^{1}$H NMR (75 MHz, DMSO-d$_6$) δ
(E)-2-[[1,1'-Biphenyl]-4-yl]-4-phenylbut-3-en-2-ol (7) According to Method A, 1.26 mL n-butyllithium (1.6 M, 6 mmol) was slowly added to a solution of 4-bromobiphenyl (1250 mg, 6 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. 4-methyl-2-penten-1-one (98%, 294 µL, 2 mmol) was added dropwise and stirred for 3 hours, after which, FeCl₂ (anhydrous, 255 mg, 2 mmol) was added. After 12 hours, purification (column chromatography: 14% ethyl acetate in hexane) of reaction mixture gave 460 mg (1.5 mmol) of (E)-2-[[1,1'-biphenyl]-4-yl]-4-phenylbut-3-en-2-ol (7) as a white powder. (77% yield). 1H NMR (400 MHz, DMSO-d₆) δ 7.64 (m, 6H), 7.45 (m, 4H), 7.34 (m, 3H), 7.23 (m, 1H), 6.62 (d, J = 2.8 Hz, 2H), 5.53 (s, 1H), 1.66 (s, 3H). 13C{¹H} NMR (75 MHz, DMSO) δ 147.87, 140.54, 138.63, 138.45, 137.31, 129.34, 129.04, 127.68, 127.04, 126.74, 126.69, 126.26, 126.00, 73.47, 40.86, 40.58, 40.30, 40.03, 39.75, 39.47, 39.19, 31.14, 30.30. HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₂H₂₀ONa⁺: 323.1412; found: 323.1406

3-Phenylocxohex-2-en-1-ol (9) According to Method B, 2-cyclohexen-1-one (97%, 29.1 µL, 0.3 mmol) was dissolved in 2 mL of ether (stabilized with BHT) reacted with phenyllithium (2.1 mL, 1.9 M, 0.9 mmol). Reaction mixture was stirred for 3 hours and FeCl₂ (anhydrous, 38 mg, 0.3 mmol) was added. After 12 hours, purification (column chromatography: 17% ethyl acetate in hexane) of reaction mixture, gave 41 mg of 3-phenylcyclohex-2en-1-ol (9) as an off-white powder (54% yield). 1H NMR (400 MHz, Chloroform-d) δ 7.31 (m, 2H), 7.25 (m, 2H), 7.17 (m, 1H), 6.03 (dt, J = 3.6, 1.8, 1.8 Hz, 1H), 4.29 (bs, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 1.93 (s, 1H), 1.81 (s, 1H), 1.61 (m, 2H). 13C{¹H} NMR (101 MHz, Chloroform-d) δ 141.40, 140.03, 128.33, 127.43, 126.67, 125.41, 66.34, 31.69, 27.52, 19.53. HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₈H₂₀ONa⁺: 197.0937; found: 197.0938. 37
According to Method A, 0.94 mL n-butyllithium (1.6 M, 1.5 mmol) was slowly added to a solution of 4-bromotertbutylbenzene (320 mg, 1.5 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was added to 2-cyclohexen-1-one (97%, 49.0 µL, 0.5 mmol) and stirred for 3 hours and then FeCl₂ (anhydrous, 63 mg, 0.5 mmol) was added. Purification (column chromatography: 17% ethyl acetate in hexane) of reaction mixture after 12 hours gave 114 mg (0.49 mmol) of 4'-(tert-butyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (11) as a pale yellowish powder (98% yield).

**1H NMR** (300 MHz, Chloroform-d) δ 7.31 (s, 4H) 6.13 (dt, J = 3.6, 1.8, 1.8 Hz, 1H), 4.39 (bs, 1H), 2.51 (m, 1H), 2.42 (m, 1H), 1.92 (m, 2H), 1.72 (m, 2H), 1.33 (s, 9H).

**13C{1H} NMR** (75 MHz, Chloroform-d) δ 150.48, 139.88, 138.36, 125.86, 125.22, 125.04, 66.38, 34.50, 31.76, 31.32, 27.45, 19.45. HRMS (ESI-TOF) m/z: [M - OH]⁺ Calcd for C₁₆H₂₁⁺: 213.1638; found: 213.1634.

**4'-Methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (13)** According to Method A, 0.94 mL n-butyllithium (1.6 M, 6 mmol) was slowly added to a solution of 4-bromotoluene (72 µL mg, 0.6 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was added to 2-cyclohexen-1-one (97%, 17.0 µL, 0.2 mmol) and stirred for 3 hours and then FeCl₂ (anhydrous, 25 mg, 0.2 mmol) was added. Purification (column chromatography: 17% ethyl acetate in hexane) of reaction mixture after 12 hours gave 22 mg (0.12 mmol) of 4'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (13) as a white powder (59% yield).

**1H NMR** (300 MHz, Chloroform-d) δ 7.32 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.11 (dt, J = 3.5, 1.8, 1.8 Hz, 1H), 4.39 (bs, 1H), 2.51 (m, 1H), 2.42 (m, 1H), 2.35 (s, 3H), 1.92 (m, 2H), 1.70 (m, 2H). **13C{1H} NMR** (101 MHz, Chloroform-d) δ 150.49, 139.92, 138.35, 125.92, 125.82, 125.74, 125.23, 125.04, 124.71, 66.40, 37.29, 34.50, 31.75, 31.32, 31.19, 31.10, 27.97, 27.52, 27.45, 22.83, 19.45. HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₆H₂₁ONa⁺: 211.1099, found 211.1093.
**Naphthalen-1-yl cyclohex-2-en-1-ol (15)** According to Method A, 0.94 mL n-butyllithium (1.6 M, 1.5 mmol) was slowly added to solution of 1-bromonaphthalene (311 mg, 1.5 mmol) dissolved in anhydrous diethylether (0.20 M) and precooled to -78 °C. After 30 minutes, this solution was added to 2-cyclohexen-1-one (97%, 49.0 µL, 0.5 mmol) and stirred for 3 hours and then FeCl₂ (anhydrous, 63 mg, 0.5 mmol) was added. After 12 hours, purification (column chromatography: 14% ethyl acetate in hexane) of reaction mixture gave 97 mg (0.43 mmol) of (naphthalen-1-yl) cyclohex-2-en-1-ol (15) as a white powder. (87% yield). \(^1\)H NMR (400 MHz, Chloroform-d) δ 8.67 (dd, J = 7.4, 2.8 Hz, 1H), 7.89 (m, 1H), 7.80 (m, 2H), 7.47 (m, 3H), 6.11 (ddd, J = 10.0, 3.7, 3.7 Hz, 1H), 5.99 (dt, J = 10.0, 2.3, 2.3 Hz, 1H), 2.49 (ddd, J = 13.7, 10.6, 3.2 Hz, 1H), 2.24 (m, 3H), 2.11 (m, 1H), 1.91 (m, 1H), 1.64 (m, 1H). \(^13\)C\(^{1}\)H NMR (101 MHz, Chloroform-d) δ 142.15, 134.80, 133.87, 130.45, 129.97, 129.08, 128.49, 126.54, 125.20, 125.13, 124.89, 124.73, 73.51, 37.31, 25.04, 19.49. HRMS (ESI-TOF) m/z: [M - OH]⁺ Calcd for C₁₆H₁₅⁺: 207.1174, found 207.1179.

**6-Methylcyclohex-2-en-1-one (23)** Diisopropylamine (1.5 equiv) was dissolved in 3.2 mL of THF and placed in a sealed nitrogen filled vial with stir bar. The vial was cooled to 0 °C and n-butyllithium (1.6 M, 10.5 mmol) was added dropwise. After stirring for 20 minutes, the reaction was then cooled to -78 °C; then the cyclohexenone (1 equiv) was added dropwise and reaction was stirred for 30 minutes. At the same temperature, 1.3 mL methyl iodide was added, and the reaction was stirred for another 30 minutes. 6.3 mL of hexamethylphosphoramide (HMPA) was then added, and the reaction was then stirred for 2 hours. The reaction was then warmed to 0 °C before 8 mL of ether was added, and the organic layer was washed with saturated ammonium chloride (5 mL x 3) and saturated sodium chloride (5 mL x 3) and, then dried over sodium sulphate. 542 mg of the product 6-methylcyclohex-2-en-1-one (23) was obtained after purification by flash chromatography (10:1 Hex:EtOAc) as a clear solid. (47% yield). \(^1\)H NMR (400 MHz, Chloroform-d) δ 6.91 (m, 1H), 5.96 (dq, J = 10.0, 1.9, 1.8 Hz, 1H), 2.37 (m, 3H), 2.04 (dddd, J = 16.7, 13.2, 6.2,
4.9 Hz, 1H), 1.71 (dddd, J = 13.4, 12.0, 8.3, 6.8 Hz, 1H), 1.12 (dd, J = 6.8, 1.1 Hz, 3H). $^{13}$C($^1$H) NMR (101 MHz, Chloroform-$d$) δ 202.35, 149.71, 129.34, 41.60, 30.80, 25.50, 15.04. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_7$H$_{11}$O$: 111.0811; [M+H]$^+$ found: 111.0804.

2-Methyl-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (24) According to Method B, 0.2 mmol (22 µL) of 23 was dissolved in 1 mL of anhydrous diethylether (stabilized with BHT). Phenyllithium (316 µL, 1.9 M, 0.6 mmol) was added dropwise to the reaction mixture and stirred for 3 hours at room temperature. Purification (column chromatography: 17% ethyl acetate in hexane) of reaction mixture, gave 15 mg of 2-methyl-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol as a clear liquid (37% yield). $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.45 (m, 2H), 7.35 (m, 2H), 7.26 (m, 1H), 6.00 (m, 1H), 5.76 (dt, J = 9.9, 2.1, 2.1 Hz, 1H), 2.22 (m, 2H), 1.88 (m, 1H), 1.64 (dt, J = 3.9, 2.4, 2.4 Hz, 2H), 0.85 (d, J = 6.7 Hz, 3H). LRMS (ESI, m/z): [M + H]$^+$ Calcd for C$_{13}$H$_{17}$O$: 189.13; [M+H]$^+$ found: 189.14

6-Methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (26) and (27) 0.2 mmol of 24 was dissolved in 1 mL of anhydrous diethylether, and FeCl$_2$ (25 mg, 0.2 mmol) was then added in the glovebox. The reaction was stirred overnight at room temperature. Purification (column chromatography: 17% ethyl acetate in hexane) of the reaction mixture gave 20 mg of (3R,6R)-6-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (26) and (35,6R)-6-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (27) as a clear solid with 52 % yield. This diastereomeric mixture was impossible to separate by flash chromatography, but $^1$H NMR analysis of the crude mixture indicated a 2:1 ratio of the two isomers, 26 and 27 (determined by comparing the integrals of the two peaks corresponding to the methyl groups in each isomer). $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.24 (m, 5H) (both), 5.82 (dd, J = 3.7, 1.5 Hz, 2H) (26), 5.79 (dd, J = 3.7, 1.5 Hz 1H) (27), 4.26 (m, 1H) (both), 2.75 (m, 1H) (both), 1.97 (m, 1H) (both), 1.85 (m, 1H) (both), 1.60 (m, 1H) (both), 1.41 (m, 1H) (both), 0.90 (d, J = 7.1 Hz, 3H) (27), 0.83 (d, J = 7.1 Hz, 6H) (26). $^{13}$C($^1$H) NMR (101 MHz, Chloroform-$d$) δ 146.38, 141.52,
mL of anhydrous diethylether was added to cinnamyldieneacetophenone (234 mg, 1 mmol), and the solution was cooled to -78 °C. 1.6 mL of phenyllithium (3 mmol, 1.9 M) was then added dropwise, and the reaction mixture was stirred for 1 hour before FeCl₂ (126 mg, 1 mmol) was added in the glovebox. After 12 hours, purification (column chromatography: 14% ethyl acetate in hexane) of reaction mixture isolated two isomers.

87 mg of \(\text{(E)-1,5,5-Triphenylpenta-2,4-dien-1-ol (33)}\) was obtained as a yellow powder with 28% yield. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.31 (m, 9H), 7.22 (m, 4H), 7.16 (m, 3H), 6.81 (d, \(J = 11.0\) Hz, 1H), 6.29 (m, 1H), 6.09 (m, 1H), 5.51 (d, \(J = 4.3\) Hz, 1H), 5.08 (m, 1H). \(^{13}\)C\(^{(1)}\)H NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 144.73, 142.02, 141.79, 140.30, 139.63, 130.40, 129.04, 128.91, 128.79, 128.58, 127.93, 127.84, 127.43, 127.31, 126.60, 126.37, 73.24. HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C\(_{23}\)H\(_{20}\)ONa+: 335.1412; found: 335.1406.

123 mg of \(\text{(2E,4E)-1,5,5-Triphenylpenta-2,4-dien-1-ol (34)}\) was obtained as a yellow powder with 39% yield. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.47 (m, 6H), 7.34 (dd, \(J = 8.5, 6.8\) Hz, 6H), 7.25 (m, 3H), 7.09 (dd, \(J = 15.7, 10.6\) Hz, 1H), 6.62 (dd, \(J = 29.7, 15.4\) Hz, 2H), 6.43 (dd, \(J = 15.1, 10.6\) Hz, 1H), 6.18 (s, 1H). \(^{13}\)C\(^{(1)}\)H NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 147.72, 141.57, 137.55, 132.37, 129.21, 129.12, 129.07, 128.27, 127.92, 127.24, 127.07, 126.70, 78.23. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C\(_{23}\)H\(_{21}\)O+: 313.1587; found: 313.1583.

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3.2 Supporting Information

COMPUTATIONS

All quantum chemical computations were done using Spartan 16 software. [1] The energies of the structures were calculated using the Density Functional Theory method (ωB97x-D) and 6-31G* as the basis set. The charge was neutral. There were no imaginary frequencies. The calculated geometric energies for 26 and 27 were -580.047673 hartrees and -580.047023 hartrees respectively.

Job type: Geometry optimization.

Method: RWB97X-D

Basis set: 6-31G(D)

Number of basis functions: 242

Number of electrons: 102

[1] Spartan ’16; Wavefunction, Inc.: Irvine, CA, 2017. Version 3.0.2.
Table 3.4: Calculated energies and Cartesian coordinates for the 27

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| C0   | 1.4063| -1.78995| -1.98529 |
| C0   | -1.20651| -0.83509| 0.20358 |
| C1   | -1.2137| -2.33252| -0.14192 |
| C2   | 0.132569| -2.99241| 0.149836 |
| C3   | 1.215455| -2.36805| -0.71579 |
| C4   | 1.125878| -0.86201| -0.69844 |
| C5   | 0.060821| -0.15974| -0.29412 |
| O6   | 2.469698| -2.8198| -0.22249 |
| C7   | 0.105317| 1.328138| -0.27211 |
| C8   | -0.94976| 2.097763| -0.77635 |
| C9   | -0.88977| 3.487101| -0.76277 |
| C10  | 0.223062| 4.136179| -0.23488 |
| C11  | 1.27514| 3.383994| 0.279258 |
| C12  | 1.21361| 1.994567| 0.263727 |
| C13  | -1.38871| -0.58217| 1.708601 |
| H14  | -2.06283| -0.37168| -0.30439 |
| H15  | -2.01332| -2.83379| 0.415126 |
| H16  | -1.44727| -2.45486| -1.20811 |
| H17  | 0.416712| -2.84826| 1.198681 |
| H18  | 0.093271| -4.07145| -0.02886 |
| H19  | 1.08331| -2.71695| -1.7555 |

Energy: -580.047023 hartrees
Table 3.5: Calculated energies and Cartesian coordinates

| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| C0   | -1.31587| -0.32058| 0.503817|
| C1   | -1.90189| -1.73482| 0.393931|
| C2   | -0.85904| -2.80381| 0.711017|
| C3   | 0.28791 | -2.73335| -0.28893|
| C4   | 0.736215| -1.31359| -0.52617|
| C5   | 0.034326| -0.22487| -0.18483|
| O6   | -0.17009| -3.34176| -1.4975 |
| C7   | 0.59385 | 1.132552| -0.42803|
|   |   |   |   |
|---|---|---|---|
| C8 | -0.1836 | 2.153007 | -0.98905 |
| C9 | 0.357052 | 3.411442 | -1.22906 |
| C10 | 1.68406 | 3.679181 | -0.90386 |
| C11 | 2.4658 | 2.677602 | -0.33571 |
| C12 | 1.923858 | 1.418884 | -0.09854 |
| C13 | -1.20489 | 0.163492 | 1.958543 |
| H14 | -2.00462 | 0.364712 | -0.00754 |
| H15 | -2.7662 | -1.82629 | 1.06164 |
| H16 | -2.25942 | -1.90186 | -0.6283 |
| H17 | -0.45905 | -2.66713 | 1.723092 |
| H18 | -1.29924 | -3.80473 | 0.665604 |
| H19 | 1.143245 | -3.30964 | 0.098622 |
| H20 | 1.691421 | -1.18757 | -1.03745 |
| H21 | 0.383007 | -3.02081 | -2.21943 |
| H22 | -1.21649 | 1.957623 | -1.26264 |
| H23 | -0.26069 | 4.185191 | -1.67556 |
| H24 | 2.104003 | 4.663656 | -1.08721 |
| H25 | 3.498929 | 2.878437 | -0.06739 |
| H26 | 2.528896 | 0.646334 | 0.367355 |
| H27 | -0.80418 | 1.181095 | 2.004444 |
| H28 | -0.53841 | -0.48301 | 2.539662 |
| H29 | -2.18892 | 0.160616 | 2.439462 |
Figure 3.1: $^1$H NMR of Compound 2
Figure 3.2: $^{13}$C NMR of Compound 2
Figure 3.3: COSY NMR of Compound 2
Figure 3.4: $^1$H NMR of Compound 4
Figure 3.5: $^{13}$C NMR of Compound 4
Figure 3.6: COSY NMR of Compound 4
Figure 3.7: $^1$H NMR of Compound 5
Figure 3.8: $^{13}$C NMR of Compound 5
Figure 3.9: COSY NMR of Compound 5
Figure 3.10: $^1$H NMR of Compound 6 in DMSO
Figure 3.11: $^{13}$C NMR of Compound 6
Figure 3.12: COSY NMR of Compound 6
Figure 3.13: $^1$H NMR of Compound 7
Figure 3.14: $^{13}$C NMR of Compound 7
Figure 3.15: COSY NMR of Compound 7
Figure 3.16: $^1$H NMR of Compound 7b
Figure 3.17: $^{13}$C NMR of Compound 7b
Figure 3.18: $^1$H NMR of Compound 9
Figure 3.19: $^{13}$C NMR of Compound 9
Figure 3.20: COSY NMR of Compound 9
Figure 3.21: $^1$H NMR for compound 11
Figure 3.22: $^{13}$C NMR for Compound 11
Figure 3.23: COSY NMR of Compound 11
Figure 3.24: $^1$H-NMR for Compound 13

![NMR spectrum](image)
Figure 3.25: $^{13}$C NMR for Compound 13
Figure 3.26: COSY NMR of Compound 13
Figure 3.27: $^1$H NMR of Compound 15
Figure 3.28: $^{13}$C NMR of Compound 15
Figure 3.29: COSY NMR of Compound 15
Figure 3.30: $^1$H NMR of Compound 23
Figure 3.31: $^{13}$C NMR of Compound 23
Figure 3.32: COSY NMR of Compound 23
Figure 3.33: $^1$H NMR of Compound 24
Figure 3.34: COSY NMR of Compound 24
Figure 3.35: NOESY NMR of Compound 24
Figure 3.36: $^1$H NMR of Compound 26 and 27
Figure 3.37: $^{13}$C NMR of Compound 26 and 27
Figure 3.38: COSY NMR of Compound 26 and 27
Figure 3.39: NOESY NMR of Compound 26 and 27
Figure 3.40: $^1$H NMR of Compound 33
Figure 3.41: $^{13}$C NMR of Compound 33
Figure 3.42: COSY NMR of Compound 33
Figure 3.43: $^1$H NMR of Compound 34
Figure 3.44: $^{13}$C NMR of Compound 34
Figure 3.45: COSY NMR of Compound 34
SYNTHESIS OF 2-AMINO-α-CARBOLINE AND ANALOGUES RELEVANT FOR DNA ADDUCT FORMATION

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ABSTRACT

2-Amino-α-carboline, (AαC), a Heterocyclic Aromatic Amine (HAA), is known to be a probable carcinogen which forms an adduct with DNA. However, the extent and mechanism with which it causes mutation are yet to be fully understood. The study of 2-amino-α-carboline (AαC) interaction with DNA has involved the synthesis of the AαC-DNA adduct. We report the synthesis of AαC and 2-nitro-α-carboline AαC-NO₂ which will facilitate the synthesis of DNA adducts for biophysical and cellular studies. An attempt was made to synthesize the fluorinated 2-nitro-α-carboline which will enable the use of ¹⁹F-NMR for monitoring of these adduct. AαC was obtained in good yields of 88% through the coupling of benzotriazole and 6-bromo-2-aminopyridine using the Graebe-Ullmann reaction. The AαC-NO₂ was obtained in an 60% yield by oxidation of AαC using dimethyldioxirane (DMDO) produced from oxone and acetone in basic medium.

INTRODUCTION

Alpha carbolines (αC) are part of the family of aromatic compounds known as heterocyclic aromatic amines (HAAs). They are made up of a tricyclic moiety that is structurally related to indoles and carbazoles. Alpha carbolines are formed when protein based foods such as meat are subjected to high temperatures of cooking. They can also be found in diesel exhaust particles¹ and extracts from marine animals such as Dendroda grossularia² and Polycarpa aurata.³ The extracts containing grossularine and N,N'-didesmethylgrossularis and mescengricin, both known for anticancer properties, have alpha carboline as the core structure of the molecules isolated as shown in Figure 4.1.

Studies have shown the presence of AαC in the urine of smokers⁴ and that even its concentration in tobacco smoke is higher than the known carcinogen 4-aminobiphenyl, (4-ABP) (which is a well-known human bladder carcinogen).⁵ AαC has also been found to cause cancer of lungs in mice⁶ and also mutagenic towards Salmonella typhimurium.⁷ It is interesting to note that the isomer of
α-carboline, β-carboline has been found to have anti-cancer, anti-malaria and anti-dopaminergic activity. α-Carboline though, was not known for these properties until a recent study showed α-carboline as an antitumor agent against Glioblastoma multiforme.

**Figure 4.1:** Natural products with AαC as a backbone structure

2-Amino-α-carboline (AαC), isolated and identified from soybean several decades ago, though has been found to be the second most consumed HAA with a daily dietary intake of 5 ng/Kg/day, does not have enough biophysical data on its interaction with DNA. Though there has not been a definitive correlation between AαC and tumors in humans, studies in aminals found a direct correlation between consumption of cooked meat and cancers. The understanding of how AαC interacts with DNA and its resultant mutation needs to be unfolded. This makes looking into the biophysical study of the mechanism through which AαC cause these mutations, crucial.

The structure of AαC is very similar to the well-known and studied carcinogens 4-ABP and 2-aminoflourene 2-AF as shown in figure 4.2. What is known from recent findings is that AαC binds to the C-8 position of guanine which is a common characteristic of many DNA adducts of carcinogens. Reports indicate once AαC is consumed, it undergoes N-oxidation by human cytochrome P450, then N-acetylation to form the very reactive N-acetoxyamine. This N-acetoxyamine reacts with the C-8 of the base guanine thus binding to DNA as shown in scheme
4.1. These results in DNA adducts formation which, when not repaired properly will result in mutations.\textsuperscript{12}

**Figure 4.2:** Structures showing similarities between 4-ABP, 2-AF and AαC

![Structures](image)

4-Aminobiphenyl (4-ABP) 2-Aminofluorene (2-AF) 2-Amino-α-carboline (AαC)

The very first report of the attempt of synthesis of AαC using, Graebe-Ullmann coupling\textsuperscript{13}, is as late 1920s\textsuperscript{14} but there was difficulty in coupling to pyridine at the alpha position. (scheme 4.2) The modification was done to overcome this difficulty by coupling diaminobenzene to chloropyridine, then using NaNO\textsubscript{3} to form a triazole before the cyclization to form the alpha carboline as shown in scheme 4.3. Several synthetic methods for synthesizing AαC involved many synthetic steps with high cost.\textsuperscript{15–17} Some recent developments involved [2+2+2] cycloaddition of functionalized alkyne-nitriles with ynamides,\textsuperscript{18} one-pot sequential palladium catalyzed aryl amination\textsuperscript{19} intramolecular arylation\textsuperscript{20} and Suzuki cross coupling\textsuperscript{21} followed by a Cadogan reductive cyclization.\textsuperscript{22} (scheme 4.4) Graebe-Ullmann reaction has fewer steps and readily available starting materials.

A factor that needed to be considered in synthesizing fluorinated AαC was a means to detect the DNA adduct formed after synthesis since, for small or minor DNA conformers, \textsuperscript{1}H NMR is mostly not useful. \textsuperscript{19}FNMR is considered a powerful tool to help detect\textsuperscript{23,24} and track the molecule of our interest; hence fluorinated analogues of AαC were also synthesized.

The conventional means to form an N-acetoxyamine from an arylamine is to partially reduce a nitro group to hydroxylamine before acylation thus nitro-α-carboline (AαC-NO\textsubscript{2}) had to be synthesized to initiate the synthesis of the DNA adduct\textsuperscript{25}
Scheme 4.1: Formation of DNA adduct in vivo

Scheme 4.2: Initial attempt in the synthesis of alpha carbolines
RESULT AND DISCUSSION

Synthesis of 2-nitro-α-carboline

We proposed synthetic pathways involving shorter synthetic routes and readily available starting materials for the synthesis of AαC-NO₂. As shown in scheme 4.5, we employed a modified Graebe-Ullmann coupling reaction²⁶ to couple benzotriazole (1) to 2-amino-6-bromo pyridine (2) to give 3. A thermal cyclization using polyphosphoric acid PPA on 3 to give AαC (4) was utilized, followed by oxidation to give AαC-NO₂ (pathway A). Product 3 can also be oxidized to give 7 before the thermal cyclization to give AαC-NO₂ (pathway B).

Scheme 4.3: Modification of Graebe-Ullmann reaction to synthesize alpha carboline

Scheme 4.4: Suzuki method for synthesis of AαC

Pathway A proved to be the best pathway for synthesis of AαC-NO₂ as we obtained good yields for both Graebe-Ullmann reaction, in the presence of CuI, and the cyclization reactions. Another route involved the coupling of a fluorinated benzotriazole (7) with 2-nitro-6-bromopyridine (8) (pathway C). Pathway C did not give the desired product 6. It was enthralling to note from X-ray crystallography of product 9 showed that the NO₂ was a better leaving group in the reaction conditions leaving behind the Br. (figure 4.4) The very nitro group essential for the next step of
synthesis was no more available. This is because the Graebe-Ullmann coupling is a substitution nucleophilic aromatic reaction in which a leaving group is displaced, mostly an electron withdrawing group, in this case, the nitro group, which is more electron withdrawing than the Br.

Scheme 4.5: Synthetic pathways for 2-nitro-α-carboline (AαC-NO₂)

Once the AαC was obtained, several methods were considered for the oxidation of the NH₂ to NO₂. In most cases, the product 5 was not obtained or gave very low yield as shown in Table 4.1.

Most successful methods (entry 3 and 4) involved oxidation using potassium peroxymonosulfate.
(oxone) and acetone in the presence of a base (NaHCO$_3$)\textsuperscript{10} (scheme 4.7) and the use of Na$_2$WO$_4$ with H$_2$O$_2$ in MeOH though the latter had lower yields than the former and purification was difficult.

**Figure 4.3**: X-ray crystallography of product 9

![X-ray crystallography of product 9](image-url)

**Table 4.1**: Methods of converting A$\alpha$C to A$\alpha$C-NO$_2$

| Conditions                        | Observations                                      |
|----------------------------------|---------------------------------------------------|
| H$_2$O$_2$/H$_2$SO$_4$, 0 °C, 36-48 h | Did not work                                     |
| ACN, H$_2$O$_2$, Buffer (K$_2$CO$_3$ and Na$_2$EDTA), rt | Did not work.                                   |
| Na$_2$WO$_4$ MeOH/H$_2$O$_2$, 50-55 °C, 24 h | Purification was difficult. The Yield was low 10 % - 23 % |
| Oxone, acetone, NaHCO$_3$, H$_2$O, 5-10 °C, 1 h | highest crude yield of 80 %, average yield was 60% |
As mentioned above, there is the need to synthesize the fluorinated analogue of \( \alpha \)-C-NO\(_2\) to enable use of \( ^{19}\)F NMR. The synthetic routes to obtain this product are outlined in scheme 4.8. This involves a Goldberg\(^{27}\) coupling using 2,6-diaminopyridine (10) and 3-fluoro-1-bromobenzene (11) to help incorporate fluorine right from the starting materials as shown in scheme 4.8. Having a fluorinated starting material was helpful since initial investigations showed the difficulty in adding a fluorine atom to starting materials or product. The product 12 was subjected to Fagnou carboline cyclization using Pd(OAc)\(_2\) and PivOH\(^{28}\).

Scheme 4.8: Synthetic pathways to 7-fluoro-2-nitro-\( \alpha \)-carboline

Scheme 4.9: Modification of pathway D for the synthesis of fluorinated A\( \alpha \)-C-NO\(_2\)
This method involves concerted metalation deprotonation, CMD or a double C-H activation. Though this proposed scheme has many advantages, inexpensive starting materials, and fewer steps, many challenges were faced during the experimental. The Goldberg coupling gave low yields of the desired product 12, due to the formation of other side products. Cyclization was also not achieved due to the absence of electron donating groups on the rings. In order to increase the efficiency of this pathway, the modification as shown in scheme 4.9 can be done.

**DNA ADDUCT REACTION**

Our biomimetic synthesis for DNA adduct formation imitates the pathway for the metabolism of HAA as explained above. The AαC-NO₂ is partially reduced to hydroxylamine. The hydroxylamine will be acetylated using acetic acid or trifluoroacetic acid to form the very reactive acetamide as shown in scheme 4.10.

Scheme 4.10: Biomimetic pathway for synthesis of DNA adduct
In order to obtain the reactive N-acetoxy-α-carboline, the AαC-NO₂ will be partially reduced using Pd/C and hydrazine to obtain the hydroxylamine, which is then acetylated to obtain the N-acetoxy-α-carboline using Acyl chloride as shown in scheme 4.11.

Scheme 4.11: Synthetic pathway to form N-acetoxy-α-carboline

**CONCLUSION**

In summary, we have synthesized 2-amino-α-carboline (AαC) and 2-nitro-α-carboline (AαC-NO₂) with high yields. Future works would involve synthesizing the fluorinated analogue and DNA adduct for studies into the thermodynamic stability and other biophysical parameters of the adduct to ascertain how the carcinogen AαC interaction with DNA leads to mutation.

**EXPERIMENTAL SECTION**

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere unless stated otherwise. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance 400 MHz and Bruker Avance 300 MHz spectrometers. NMR spectra were measured in DMSO and CDCl₃ solutions. The chemical shifts δ are reported relative to the residual solvent peaks (¹H, δ DMSO = 2.50 ppm; ¹³C, δ DMSO = 39.52 ppm ¹H, δCDCl₃ = 7.26 ppm; ¹³C, δ CDCl₃ = 77.16 ppm). All ¹H and ¹²C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; bs = broad signal. High-resolution mass spectrometry was performed using a Thermo Scientific LTQ Orbitrap XL™ instrument.
6-(1H-benzo[d][1,2,3]triazol-1-yl)pyridin-2-amine (3) In the glovebox, an oven-dried 50 mL round bottom flask with a small stir-bar was charged with benzotriazole, (1.2 g, 10 mmol), 2-amino-6-bromopyridine (2.1 g, 12 mmol), CuI (5 mol%), and K$_3$PO$_4$ (4.2 g, 20 mmol). N,N'-dimethylethylenediamine, (108 µL, 10 mol%) and 3 mL of DMF were mixed and added to the reaction flask. The round bottom was placed into an oil bath at 90 °C and stirred for 24 hours. Workup to be done by adding DI-H2O. The product crashes out of solution. The product was used without further purification as the product was obtained with little or no impurity. 2.0 g of brown solid (95 % yield) was obtained. The product can be purified using chromatography of the 20 % EtOAc/hexane mobile phase. $^1$H NMR (300 MHz, DMSO-d6) δ 8.76 (dt, J = 8.4, 1.0, 1.0 Hz, 1H), 8.16 (dt, J = 8.4, 1.0, 1.0 Hz, 1H), 7.67 (m, 2H), 7.52 (ddd, J = 8.2, 7.7, 1.1 Hz, 1H), 7.29 (dd, J = 7.7, 0.7 Hz, 1H), 6.57 (s, 2H), 6.51 (dd, J = 8.2, 0.7 Hz, 1H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 157.59, 150.41, 146.68, 140.30, 131.55, 128.30, 124.58, 119.75, 114.75, 106.52, 103.97. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{11}$H$_{10}$N$_5$: 212.0931; found: 212.0918.

9H-pyrido[2,3-b]indol-2-amine, (4) Polyphosphoric acid, PPA, 7.8 g (20 equiv) was added to a 100 mL RB flask via glass stirring rod. 844 mg (4 mmol) of 3 is then added and the flask is transferred to a preheated 180 °C bath. The reaction was allowed to run for between 90 to 120 min until no more bubbles can be seen (the viscous mixture turns from yellowish to green to black once there is no bubble). The reaction was allowed to cool overnight. The mixture is neutralized with 10% sodium carbonate solution (pH of 8). Product was purified by recrystallization using acetone and water affording 682 mg of product (88 %) as a very dark solid $^1$H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.18 (td, J = 7.9, 7.6, 1.3 Hz, 1H), 7.06 (td, J = 7.5, 7.5, 1.3 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 6.05 (s, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 157.04, 151.66, 136.96, 130.70, 124.30, 122.34, 120.02, 119.12, 110.65, 107.80, 101.58. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{11}$H$_{10}$N$_5$: 184.0869; found: 184.0857.
**2-nitro-9H-pyrido[2,3-b]indole**, (5) 2-amino-α-carboline (0.45 mmol) was dissolved in 8 mL of acetone in a 3-neck flask RBF. 20 mL of DI water was used to dissolve 1.8 g of NaHCO₃, and 10 mL of that solution was added to the SM solution. The oxone (8.9 mmol) was grounded in a mortar with a pestle (a solid addition flask can also be used for the addition). The SM mixture was placed under nitrogen and placed in an ice bath. 20 mL of acetone was then added to the NaHCO₃ solution. This mixture and the oxone were added simultaneously to the SM solution slowly with stirring (a dropping funnel can also be used to add the acetone and NaHCO₃ mixture). Additional 7 mL of acetone was added to rinse, and the reaction was allowed to run for one hour. After an hour, about 150 mL of water was added to dissolve the excess NaHCO₃. The product is extracted three times using ethyl acetate (100 mL portions). The organic layer was washed with brine then the organic layer dried with Na₂SO₄, ethyl acetate was removed and the product purified by Column chromatography. ¹H NMR (400 MHz, DMSO-d₆) δ 12.52 (s, 1H), 8.90 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 7.9 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.63 (t, J = 1.3, 1.3 Hz, 1H), 7.62 (d, J = 1.0 Hz, 1H), 7.36 (ddd, J = 8.1, 4.8, 3.4 Hz, 1H). ¹³C NMR (101 MHz, DMSO-d₆) δ 141.67, 131.53, 129.47, 123.06, 121.18, 121.12, 119.76, 112.44, 109.48. HRMS (ESI-TOF) m/z: [M - H]⁺ Calcd for C₁₁H₆N₃O₂: 212.0466; found: 212.0465.

**N²-(3-fluorophenyl)pyridine-2,6-diamine** (12), In the glovebox, 1.6 mL of 1-bromo-3-fluorobenzene (14.5 mmmol), 3.2 g of 2,6-diaminopyridine (29 mmol), 2.5 g of K₂CO₃ (11.6 mmol) and 69 mg of Cul (8 mol%) were placed in a pressure tube inside a glovebox and run neat. Reaction was stirred at 180 °C for 48hrs. Flash chromatography was performed with hexane and ethyl acetate 1:2 (stepwise 10%, 55%, 75%) to afford 832 mg (31 % yield) brick red viscous oil as product. ¹H NMR (300 MHz, DMSO-d₆) δ 8.83 (m, 1H), 7.86 (dt, J = 12.9, 2.3, 2.3 Hz, 1H), 7.23 (m, 3H), 6.58 (ddddd, J = 8.9, 8.0, 2.6, 1.2 Hz, 1H), 6.00 (dd, J = 7.8, 0.7 Hz, 1H), 5.89 (dd, J = 7.9, 0.7 Hz,
1H), 5.76 (s, 2H). $^{13}$C NMR (101 MHz, DMSO-d6) δ 158.87, 155.43, 142.88, 138.70, 128.89, 119.96, 118.15, 97.82, 97.70. $^{19}$F NMR (376 MHz, DMSO-d6) δ -112.41 (dt, $J$ = 13.0, 7.8, 7.8 Hz).

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4.2 Supporting Information

Figure 4.4: $^1$H-NMR of compound 3 in CDCl$_3$
Figure 4.5: $^{13}$C-NMR of compound 3 in CDCl$_3$
Figure 4.6: COSY-NMR for compound 3 in CDCl$_3$
Figure 4.7: $^1$H-NMR of compound 4 in DMSO
Figure 4.8: $^{13}$C-NMR of compound 4 in CDCl$_3$
Figure 4.9: COSY NMR of compound 4 in DMSO
Figure 4.10: $^1$H NMR of compound 5 in DMSO
Figure 4.11: $^{13}$C NMR of compound 5 in DMSO
Figure 4.12: COSY NMR of compound 5 in DMSO
Figure 4.13: $^1$H NMR of compound 12 in DMSO
Figure 4.14: $^{13}$C NMR of compound 12 in DMSO
Figure 4.15: COSY NMR of compound 12 in DMSO
Figure 4.16: $^{19}$F Decoupled NMR of compound 12 in DMSO
Figure 4.17: $^{19}$F NMR of compound 12 in DMSO