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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

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

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2019

DOCTOR OF PHILOSOPHY DISSERTATION

OF

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2019

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, FeCl₂ mediated procedure to produce 3-substituted allylic alcohols from α,β -unsaturated ketones. The addition of an organolithium nucleophile produced tertiary allylic alcohol as an intermediate, which underwent a 1,3-OH migration assisted by FeCl₂. 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- α -carboline (A α C) and its interaction with DNA involved the synthesis of the A α C-DNA adduct. We report the synthesis of A α C and 2-nitro- α -carboline (A α C-NO₂) which also facilitate the synthesis of DNA adducts for biophysical 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 studies. Cyclization of the coupled product for the fluorinated analogue could not be achieved

due to the electron deficiency in the ring systems. A α C was obtained in good yields of 88%, and the A α C-NO₂ was obtained in 60% yield.

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'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 $\text{Fe}^{\text{I}}/\text{Fe}^{\text{III}}$ intermediate.

The second manuscript entitled “ FeCl_2 mediated allylic alcohol rearrangement” talks about a one pot procedure to produce 3-substituted allylic alcohols using FeCl_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 transition metals like chromium⁴ and rhenium⁵ 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 reagents⁷⁻¹², organocuprates¹³⁻¹⁶, organolithium reagent¹⁷⁻¹⁹, organozinc²⁰⁻²² and arylborates²³⁻²⁵ 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 Kumada²⁶⁻²⁸, Suzuki-Miyaura²⁹⁻³³, Heck³⁴⁻³⁷, Negishi³⁸⁻⁴¹ and Sonogashira.⁴²⁻⁴⁶ 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 bond¹. 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.^{1,2}

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^{47,48}, rhodium⁴⁹, iridium⁵⁰ and ruthenium.⁵¹ Most recent interest has been in iron⁵², cobalt¹ and nickel⁵³ 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 an intense investigation into its versatility. It is interesting to note that these iron catalyzed reactions are sometimes of better yields than their palladium counterparts⁵⁴ as shown in scheme 1.2.

Scheme 1.1: Nucleophilic molecular transformation methods

1. Kumada Coupling

2. Suzuki-Miyaura

3. Heck

4. Negishi

5. Sonogashira

Scheme 1.2: Comparison of iron and palladium catalyzed direct C-H activation

Mechanism for Iron Catalyzed C-H Activation

The mechanism for iron cross-coupled reactions has been studied extensively compared to direct C-H activation.^{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.⁵⁹

The pioneering works done by Nakamura et al^{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 organoborons⁶³ which utilizes general mechanism one. Other groups have confirmed this Fe(II)/Fe(III)^{64,65} though the mechanism involves a single electron transfer. Many of the proposed mechanism either goes through an Fe(I)/Fe(III) system¹¹ and other lower oxidation states of iron^{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(I)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 versatile⁵⁶. It has been shown to be comparable to palladium and in some cases, a better metal catalyst.⁶⁸ 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.⁶⁹ Iron catalyzed Negishi reactions were also found to be robust, highly reproducible and made studies for reaction mechanism manageable.⁴¹ 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 1.5.⁷⁰⁻⁷³ 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 ynones.^{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.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 reagents⁴ in synthesizing β substituted and α,β -disubstituted cyclic enones which are very important in the fragrance industry.⁷⁹ 1,3-Rearrangement of allylic alcohols has been used in the synthesis of anti-malarial target molecules⁸⁰, valerenic acid⁸¹(used for the treatment of dysfunction in the nervous system) (scheme 1.6) and two quinolone natural products isolated from *Pseudonocardia sp.*⁸²

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

Synthetic Method used for 1,3-Allylic Alcohol Rearrangement

Reagents such as transition metal complexes^{4,83-86} and transition metal oxo complexes^{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)^{3,81,89,90}, methanesulfonic acid⁹¹ iodoxybenzoic acid^{92,93}, Brønsted acids like boronic acid^{94,95} and radical based reagents like TEMPO^{83,96} have been explored, as shown in scheme 1.7. Recent methods involve the use of mild reagents such as water⁹⁷ and enzymes.⁹⁸

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

Transition metal oxo species

Radical based

Lewis acid

Transition metal complex

Iron has been involved in a few substitution reactions via π -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 α,β -unsaturated ketones, which then undergo a 1,3-rearrangement in the presence of 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- α -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).¹⁰⁵ Their structures and mutagenicity ($\times 10^3 \text{ rev}/\mu\text{g}$) 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 B₁ and benzo[α]pyrene.¹⁰⁸ Studies have also shown that these HAAs are principal causes of most cancers like lung, breast, colon, stomach and prostate.^{109–112} Alpha carboline, a subgroup of HAAs has been found in the core structure for some natural products^{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 chemistry¹¹⁵ and optoelectronic materials.¹¹⁶ They were isolated and identified several years ago and were found to be mutagenic against *Salmonella typhimurium* TA 98 (TA 98). They were different from its isomers, β -carboline and γ -carboline¹¹⁷ in structure and activity. The latter carbolines had been identified to exhibit anticancer, antimalarial and antidopamine¹¹⁸ effects, thus interest to find the therapeutic or mutagenicity of α -carboline intensified.

Figure 1.1: Examples of known and potential carcinogenic HAAs

Figure 1.2: A α C as a core structure in some natural products

Characteristics of 2-Amino- α -carboline (A α C)

2-Amino- α -carboline (A α C) and 2-amino-3-methyl- α -carboline (MeA α C) have been studied especially for their mutagenicity. A α C has been reported as the second most consumed HAA in the United State.¹¹⁹ A α 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 A α C has also shown antitumor activity towards Glioblastoma multiforme but unfortunately, the understanding of exactly how the HAA interact s 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-acetoxamine, which is easily transferred to DNA by the N-acetyltransferases found *in vivo*. Synthetically the best way to convert an amine to N-acetoxamine is by first converting the amine to nitro group, then partially reduce the nitro group to hydroxylamine, before acetylating the hydroxylamine. There has been a report though, of the use of a polyaniline nanofiber supported FeCl₃ to acetylate an alcohol or amine to an acetoxy group.¹²² To study the biophysical interaction between A α C and DNA and how this leads to mutation, we looked into the synthesis of A α C and then 2-nitro- α -carboline (A α C-NO₂).

Synthesis of Alpha-carboline

There have been various methods report for the synthesis of A α C (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 N₂ gas. This modified method has been used over the years to synthesis α -carbolines^{123,124} and indoloquinolines 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 al¹²⁷ 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.^{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.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.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^{133,134} with the most recent method involving unimolecular radical substitution of 3-halo-*N*-phenylpyridin-2-amine.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 its utility in synthesis ideal. In the synthesis of α -carboline, there have been reports of the use of Stille coupling¹³⁶, Suzuki coupling¹³⁷ and Heck reaction¹³⁸. Other reports involve one pot synthesis utilizing Buchwald-Hartwig¹³⁹ chemistry and the use of S_N2' monoalkylation of nitroarylacetonitriles with Baylis-Hillman-acetates to form α -carbolines.¹⁴⁰

DNA Adduct Synthesis

An important factor in determining the carcinogenic potential of a compound is its ability to form DNA adduct and A α 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 endonucleases¹⁴¹ but sometimes traces are left behind. These 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.^{120,142} There are two main synthetic routes for the synthesis of DNA adduct, the biomimetic and total synthesis.¹⁴³

Total synthesis

Total synthesis involves reacting the most reactive form of the A α 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 α 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 α 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 A α C 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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2 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 nickel¹ for these same reactions.

The use of iron for catalysis dates as far back as 1940² and 1970³ and these iron-catalyzed reactions are ideal because iron is economically sustainable due to its abundance,⁴ biologically nontoxic⁵ 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 waste⁶ 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 palladium⁷⁻⁹ and nickel based catalysis,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.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 transmetalation with a Grignard reagent before it reductively eliminates the product to give back the Fe(I) species.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.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.¹⁷ Other groups then researched into the mechanism for iron catalyzed C-H activation.^{18–20} It should also be noted that iron has been found to activate not just C(sp²)-H, but also C(sp)-H and C(sp³)-H bonds using Fe complexes to form Fe-C bonds in the presence or absence of directing groups.^{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.²³ 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.²⁴

The key step of interest was the reduction of $\text{Fe}(\text{acac})_3$ 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 $\text{Ph}_3\text{Fe}(\text{II})$ or $\text{Ph}_4\text{Fe}(\text{III})$ in THF.²⁵ 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.²⁶ Nakamura also proposed that the main intermediary species to be Fe(II)/Fe(III) system for a similar C-H activation using organoborons.²⁷ 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,^{28,29} Fe oxo species^{30,31} and Fe^{-1} species³² for other Fe-catalyzed processes.

Our group's previous work³³ 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 $\text{Fe}(\text{acac})_3$, were required for the reaction. Importantly, The Fe(II) catalyst precursor, $\text{Fe}(\text{acac})_2$, 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 FeX₃ (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 FeX_3 (**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.

Figure 2.1: Effect of bpy on $\text{Fe}(\text{acac})_3$

Figure 2.2: Effect of Phen on $\text{Fe}(\text{acac})_3$

It was established that there was no reaction observed when the $\text{Fe}(\text{acac})_3$ 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 $\text{Fe}(\text{acac})_3$ but within minutes a reaction occurred.

Figure 2.3: Effect of dtbpy on $\text{Fe}(\text{acac})_3$

The initial peak is converted into another peak for a different species as the Grignard reacts with the $\text{Fe}(\text{acac})_3$, confirming the hypothesis that the $\text{Fe}(\text{acac})_3$ thus reacts with the Grignard as proposed in our proposed mechanism. The effect of Grignard on $\text{Fe}(\text{acac})_3$ in the presence of ligand was also investigated. Grignard reacts with $\text{Fe}(\text{acac})_3$, 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 stabilize the Fe complex, preventing the reaction between $\text{Fe}(\text{acac})_3$ and the Grignard.

Following works done by Bedford et al.^{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 synthesized 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 were 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 $\text{Fe}(\text{acac})_3$

Figure 2.5: Investigating the reaction of $\text{Fe}(\text{acac})_3$ and Grignard in the presence of bpy

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 $\text{Fe}(\text{acac})_3$ set up. Even though after 12 hours the yield for the reaction involving Fe(I) species

increased, it was still lower than the $\text{Fe}(\text{acac})_3$. This implied the $\text{Fe}(\text{I})$ species might not be the active Fe species in this reaction as we initially proposed. We also confirmed that $\text{Fe}(\text{II})$ is definitely not the active species for this reaction. The nitrogen based ligand might not have afforded us the $\text{Fe}(\text{I})$ complexes but there was evidence to show the reduction of the $\text{Fe}(\text{acac})_3$ due to the formation of the biphenyl product.

Scheme 2.5: Synthesis of $\text{Fe}(\text{I})$ species by Bedford *et al.*

Scheme 2.6: Synthesis of $\text{Fe}(\text{I})$ 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 200 μ m x 0.33 μ m, 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 work³¹

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. ¹H 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)

FeCl₂·4H₂O (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: ^1H 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 ynones 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.*²⁰ Additionally one can envision that this rearrangement could be used to create artemisinin-like antimalarial drugs via Singh's synthetic (Scheme 3.1).²¹

Iron has recently been studied as a catalyst for a number of coupling reactions.^{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.^{22, 29,30} Even a few examples of substitution reactions via π -allyl iron intermediates have been reported.^{31–}

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Scheme 3.1: Application of allylic 1,3-migrations

1,2-Addition/1,3-migration

Applications of allylic 1,3-migration

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 α,β -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,^{30,36} we discovered that the addition of an organolithium reagent to an α,β -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 FeCl₂ 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 Et₂O, 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 FeCl₂ 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 ($^{\circ}\text{C}$)	Yield (%) 2	Yield (%) 3
1 ^a	FeCl_2	Et_2O	25	55	4
2	FeCl_2	Et_2O	25	87	17
3	$\text{Fe}(\text{OAc})_2$	Et_2O	25	35	27
4	FeF_3	Et_2O	25	25	40
5	$\text{Fe}(\text{acac})_2$	Et_2O	25	41	44
6	$\text{Fe}(\text{acac})_3$	Et_2O	25	30	29
7	FeCl_2	THF	25	-	5
8	FeCl_2	2-MeTHF	25	4	91
9	FeCl_2	MBTE	25	23	32
10	FeCl_2	Et_2O	-78	-	73
11 ^b	FeCl_2	Et_2O	25	36	-
12 ^c	FeCl_2	Et_2O	25	8	83
13 ^d	FeCl_2	Et_2O	25	71	-

Standard conditions: 0.2 M in Et_2O (stabilized with 5 ppm BHT), -78 $^{\circ}\text{C}$ to rt, 1 equiv of FeCl_2 and 3 equiv of nucleophile. ^a 1 equiv of the aryl lithium was used. ^b 1 equiv of BHT was added. ^c 10 mol % of FeCl_2 ^d Solvent was diethylether without BHT.

The scope and limitations of the addition-rearrangement with respect to both linear and cyclic α,β 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 α,β -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		 2 87%	
2		 4 53%	
3			 5 32%
4			 6 68%
5			 7 77%

Conditions: 0.2 M in Et₂O (stabilized with 5 ppm BHT), -78 °C to rt, 1 equiv of FeCl₂ and 3 equiv of nucleophile.

Table 3.3: Nucleophile scope

Entry	Nucleophile	Product
1	 8	 9 54%
2 ^a	 10	 11 98%
3 ^a	 12	 13 54%
4 ^a	 14	 87%
5 ^a	 16	 not observed

6 ^a	 18	 9 <i>trace</i>
7 ^a	 19	 20 5%
8 ^a	 21	 22 <i>trace</i>

Conditions: 0.2 M in Et₂O (stabilized with 5 ppm BHT), -78 °C to rt, 1 equiv of FeCl₂ and 3 equiv of nucleophile.

^a 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). Alkyl lithium 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.

Scheme 3.4: Proposed Mechanism for 1,3-OH migration

Scheme 3.5: Extent of OH-migration

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 α,β -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. ^1H 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 δ are reported relative to the residual solvent peaks (^1H , δ DMSO = 2.50 ppm; ^{13}C , δ DMSO = 39.52 ppm ^1H , δCDCl_3 = 7.26 ppm; ^{13}C , δ CDCl_3 = 77.16 ppm). All ^1H 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^{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 α,β -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 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). $^{13}\text{C}\{^1\text{H}\}$ 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 : $[\text{M} - \text{OH}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}^+$: 219.1168; found: 219.1154.

(E)-2-([1,1'-Biphenyl]-4-yl)-3-methylpent-3-en-2-ol (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). ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 : $[\text{M} - \text{OH}]^+$ Calcd for $\text{C}_{18}\text{H}_{19}^+$: 235.1487; found: 235.1481.

2-([1,1'-Biphenyl]-4-yl)-4-methylpent-3-en-2-ol (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). ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, DMSO- d_6) δ

149.90, 140.59, 138.01, 133.66, 133.61, 129.32, 127.58, 126.96, 126.42, 126.18, 72.77, 33.65, 27.18, 19.37. HRMS (ESI-TOF) m/z : $[M + Na]^+$ Calcd for $C_{18}H_{20}ONa^+$: 275.1412; found: 275.1406.

(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 μ L, 2 mmol) was added dropwise and stirred for 3 hours, after which, $FeCl_2$ (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, $DMSO-d_6$) 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). $^{13}C\{^1H\}$ 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 $C_{22}H_{20}ONa^+$: 323.1412; found: 323.1406

3-Phenylcyclohex-2-en-1-ol (9) According to Method B, 2-cyclohexen-1-one (97%, 29.1 μ L, 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 $FeCl_2$ (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-2-en-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). $^{13}C\{^1H\}$ 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 $C_{18}H_{20}ONa^+$: 197.0937; found: 197.0938.³⁷

4'-(Tert-butyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (11) According to Method A, 0.94 mL *n*-butyllithium (1.6M, 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 211.1093.¹⁷

(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). ¹H 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). ¹³C{¹H} 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, 37.21, 25.04, 19.49. HRMS (ESI-TOF) *m/z*: [M - OH]⁺ Calcd for C₁₆H₁₅⁺: 207.1174, found 207.1179.⁴⁰

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). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.91 (m, 1H), 5.96 (dq, *J* = 10.0, 1.9, 1.8, 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). $^{13}\text{C}\{^1\text{H}\}$ 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_7\text{H}_{11}\text{O}^+$: 111.0811; $[\text{M} + \text{H}]^+$ 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). ^1H 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): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{17}\text{O}^+$: 189.13; $[\text{M} + \text{H}]^+$ 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 (3S,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 ^1H 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). ^1H 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**). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 146.38, 141.52,

128.24, 127.24, 127.20, 126.53, 66.26, 30.93, 29.03, 27.13, 19.42. LRMS (ESI-TOF) m/z : $[M + H]^+$

Calcd for $C_{13}H_{17}O^+$: 189.13. $[M+H]^+$ found: 189.14

(E)-1,5,5-Triphenylpenta-2,4-dien-1-ol (33) and **(2E,4E)-1,1,5-Triphenylpenta-2,4-dien-1-ol (34)** 2

mL of anhydrous diethylether was added to cinnamylidieneacetophenone (234 mg, 1 mmol), and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. 1.6 mL of phenyllithium (3 mmol, 1.9 M) was then added dropwise, and the reaction mixture was stirred for 1 hour before FeCl_2 (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 **(E)-1,5,5-triphenylpenta-2,4-dien-1-ol (33)** was obtained as a yellow powder with 28% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 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 : $[M + \text{Na}]^+$ Calcd for $\text{C}_{23}\text{H}_{20}\text{ONa}^+$: 335.1412; found: 335.1406.

123 mg of **(2E,4E)-1,1,5-triphenylpenta-2,4-dien-1-ol (34)** was obtained as a yellow powder with 39% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 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 $\text{C}_{23}\text{H}_{21}\text{O}^+$: 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 (ω B97xD) 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**

Energy: -580.047023 hartrees			
Cartesian Coordinates (Angstroms)			
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

H20	2.003478	-0.32857	-1.0656
H21	3.157718	-2.4808	-0.80742
H22	-1.81982	1.607942	-1.20439
H23	-1.71494	4.064961	-1.16887
H24	0.267338	5.221105	-0.2204
H25	2.143069	3.879698	0.704454
H26	2.024548	1.409611	0.688473
H27	-1.38698	0.489992	1.92867
H28	-0.57854	-1.04173	2.284624
H29	-2.33884	-1.00118	2.05737

Table 3.5: Calculated energies and Cartesian coordinates **26**

Energy: -580.047673 hartrees			
Cartesian Coordinates (Angstroms)			
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: ^1H NMR of Compound 2

Figure 3.2: ^{13}C NMR of Compound **2**

Figure 3.3: COSY NMR of Compound 2

Chemical structure of 4-(4-phenylphenyl)cyclopent-1-en-1-ol. The molecule consists of a cyclopentene ring with a hydroxyl group (-OH) at position 1 and a 4-phenylphenyl group at position 4. The cyclopentene ring is colored red, and the hydroxyl group is also red. The 4-phenylphenyl group, consisting of two benzene rings connected by a single bond, is colored blue.

Figure 3.5: ^{13}C NMR of Compound 4

Figure 3.6: COSY NMR of Compound 4

Figure 3.7: ^1H NMR of Compound 5

Figure 3.8: ^{13}C NMR of Compound 5

Figure 3.9: COSY NMR of Compound 5

Figure 3.10: ^1H 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: ^1H NMR of Compound 7

Figure 3.14: ^{13}C NMR of Compound **7**

Figure 3.15: COSY NMR of Compound **7**

Figure 3.16: ^1H NMR of Compound **7b**

Figure 3.17: ^{13}C NMR of Compound **7b**

Figure 3.18: ^1H NMR of Compound **9**

Figure 3.19: ^{13}C NMR of Compound **9**

Figure 3.20: COSY NMR of Compound 9

Figure 3.21: ^1H NMR for compound **11**

Figure 3.22: ^{13}C NMR for Compound **11**

Figure 3.23: COSY NMR of Compound **11**

Figure 3.24: ^1H -NMR for Compound **13**

Figure 3.25: ^{13}C NMR for Compound **13**

Figure 3.26: COSY NMR of Compound **13**

Figure 3.27: ^1H NMR of Compound 15

Figure 3.28: ^{13}C NMR of Compound **15**

Figure 3.29: COSY NMR of Compound **15**

Figure 3.30: ^1H NMR of Compound **23**

Figure 3.31: ^{13}C NMR of Compound **23**

Figure 3.32: COSY NMR of Compound **23**

Figure 3.33: ^1H NMR of Compound **24**

Figure 3.34: COSY NMR of Compound **24**

Figure 3.35: NOESY NMR of Compound **24**

Figure 3.36: ^1H 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: ^1H NMR of Compound **33**

Figure 3.41: ^{13}C NMR of Compound **33**

Figure 3.42: COSY NMR of Compound **33**

Figure 3.43: ^1H NMR of Compound **34**

Figure 3.44: ^{13}C NMR of Compound **34**

Figure 3.45: COSY NMR of Compound **34**

4 SYNTHESIS OF 2-AMINO- α -CARBOLINE AND ANALOGUES RELEVANT FOR DNA ADDUCT FORMATION

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ABSTRACT

2-Amino- α -carboline, (A α C), 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 (A α C) interaction with DNA has involved the synthesis of the A α C-DNA adduct. We report the synthesis of A α C and 2-nitro- α -carboline A α C-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. A α C was obtained in good yields of 88% through the coupling of benzotriazole and 6-bromo-2-aminopyridine using the Graebe-Ullmann reaction. The A α C-NO₂ was obtained in an 60% yield by oxidation of A α C using dimethyldioxirane (DMDO) produced from oxone and acetone in basic medium.

INTRODUCTION

Alpha carbolines (α C) 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 grossularia*² 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 A α C 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 A α C 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,⁸ 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.⁹

Figure 4.1: Natural products with A α C as a backbone structure

2-Amino- α -carboline (A α C), 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,¹⁰ does not have enough biophysical data on its interaction with DNA. Though there has not been a definitive correlation between A α C and tumors in humans, studies in animals⁶ found a direct correlation between consumption of cooked meat and cancers.¹¹ The understanding of how A α C interacts with DNA and its resultant mutation needs to be unfolded. This makes looking into the biophysical study of the mechanism through which A α C cause these mutations, crucial.

The structure of A α C is very similar to the well-known and studied carcinogens 4-ABP and 2-aminofluorene 2-AF as shown in figure 4.2. What is known from recent findings is that A α C binds to the C-8 position of guanine⁶ which is a common characteristic of many DNA adducts of carcinogens. Reports indicate once A α C 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.¹²

Figure 4.2: Structures showing similarities between 4-ABP, 2-AF and A α C

The very first report of the attempt of synthesis of A α C using, Graebe-Ullmann coupling¹³, is as late 1920s¹⁴ 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 NaNO₃ to form a triazole before the cyclization to form the alpha carboline as shown in scheme 4.3. Several synthetic methods for synthesizing A α C involved many synthetic steps with high cost.^{15–17} Some recent developments involved [2+2+2] cycloaddition of functionalized alkyne-nitriles with ynamides,¹⁸ one-pot sequential palladium catalyzed aryl amination¹⁹ intramolecular arylation²⁰ and Suzuki cross coupling²¹ followed by a Cadogan reductive cyclization.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 A α C was a means to detect the DNA adduct formed after synthesis since, for small or minor DNA conformers, ¹H NMR is mostly not useful. ¹⁹FNMR is considered a powerful tool to help detect^{23,24} and track the molecule of our interest; hence fluorinated analogues of A α C were also synthesized.

The conventional means to form an N-acetoxamine from an arylamine is to partially reduce a nitro group to hydroxylamine before acylation thus nitro- α -carboline (A α C-NO₂) had to be synthesized to initiate the synthesis of the DNA adduct²⁵

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 A α C-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 A α C (**4**) was utilized, followed by oxidation to give A α C-NO₂ (pathway A). Product **3** can also be oxidized to give **7** before the thermal cyclization to give A α C-NO₂ (pathway B).

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

Scheme 4.4: Suzuki method for synthesis of A α C

Pathway **A** proved to be the best pathway for synthesis of A α C-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 (A α C-NO₂)

Scheme 4.6: Pathway C: synthesis of fluorinated nitro- α -carboline

Once the A α C 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)¹⁰ (scheme 4.7) and the use of Na_2WO_4 with H_2O_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**

Table 4.1: Methods of converting $\text{A}\alpha\text{C}$ to $\text{A}\alpha\text{C-NO}_2$

<i>Conditions</i>	<i>Observations</i>
$\text{H}_2\text{O}_2/\text{H}_2\text{SO}_4$, 0 °C, 36-48 h	Did not work
ACN, H_2O_2 , Buffer (K_2CO_3 and Na_2EDTA), rt	Did not work.
Na_2WO_4 MeOH/ H_2O_2 , 50-55 °C, 24 h	Purification was difficult. The Yield was low 10 % - 23 %
Oxone, acetone, NaHCO_3 , H_2O , 5-10 °C, 1 h	highest crude yield of 80 %, average yield was 60%

Scheme 4.7: Oxidation of A α C to A α C-NO₂

As mentioned above, there is the need to synthesize the fluorinated analogue of A α C-NO₂ to enable use of ¹⁹F NMR. The synthetic routes to obtain this product are outlined in scheme 4.8. This involves a Goldberg²⁷ 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 PivOH²⁸.

Scheme 4.8: Synthetic pathways to 7-fluoro-2-nitro- α -carboline

Scheme 4.9: Modification of pathway D for the synthesis of fluorinated A α C-NO₂

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 A α C-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 A α C-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 (A α C) and 2-nitro- α -carboline (A α C-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 A α C 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, δ CDCl₃ = 7.26 ppm; ¹³C, δ CDCl₃ = 77.16 ppm). All ¹H and ¹³C 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 K₃PO₄ (4.2 g, 20 mmol). N,N'-dimethylethylenediamine, (108 μ L, 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. ¹H 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). ¹³C 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 C₁₁H₁₀N₅⁺: 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 ¹H 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). ¹³C 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 C₁₁H₁₀N₃⁺: 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 NaHCO_3 , 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 NaHCO_3 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 NaHCO_3 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 NaHCO_3 . 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 Na_2SO_4 , ethyl acetate was removed and the product purified by Column chromatography. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 141.67, 131.53, 129.47, 123.06, 121.18, 121.12, 119.76, 112.44, 109.48. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ Calcd for $\text{C}_{11}\text{H}_6\text{N}_3\text{O}_2^-$: 212.0466; found: 212.0465.

N^2 -(3-fluorophenyl)pyridine-2,6-diamine (12), In the glovebox, 1.6 mL of 1-bromo-3-fluorobenzene (14.5 mmol), 3.2 g of 2,6-diaminopyridine (29 mmol), 2.5 g of K_2CO_3 (11.6 mmol) and 69 mg of CuI (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, $\text{DMSO}-d_6$) δ 8.83 (m, 1H), 7.86 (dt, J = 12.9, 2.3, 2.3 Hz, 1H), 7.23 (m, 3H), 6.58 (dddd, 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). ¹³C NMR (101 MHz, DMSO-d₆) δ 158.87, 155.43, 142.88, 138.70, 128.89, 119.96, 118.15, 97.82, 97.70. ¹⁹F 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: ^1H -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 CDCl₃

Figure 4.7: ^1H -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: ^1H NMR of compound **5** in DMSO

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PROTON DMSO {C:\Bruker\TopSpin3.5pl5} nmr 17

Figure 4.11: ^{13}C NMR of compound **5** in DMSO

Figure 4.12: COSY NMR of compound **5** in DMSO

Figure 4.13: ^1H 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

LabGroup DeBoef
F19 DMSO {C:\Bruker\TopSpin3.5pl5} nmr 17