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Synthesis of Cationic TetraNHC Complexes of Cobalt, Chromium, Iron, and Platinum for Oxidative Group Transfer

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I am submitting herewith a dissertation written by Calvin L. Keller entitled "Synthesis of Cationic TetraNHC Complexes of Cobalt, Chromium, Iron, and Platinum for Oxidative Group Transfer." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

David Jenkins, Major Professor

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Synthesis of Cationic TetraNHC Complexes of Cobalt, Chromium, Iron, and Platinum for Oxidative Group Transfer

A Dissertation Presented for the

Doctor of Philosophy

Degree

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Calvin L. Keller

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DEDICATION

I dedicate this work to my parents, Calvin and Connie Keller. They educated me and taught me hard work and dedication. Without their efforts and support, I would not have accomplished this work.

I dedicate this work to my wife, Lydia Keller. She has been by my side and supported me in this work. Her love and support have been invaluable.

Finally, I dedicate this work to my Lord and Savior Jesus Christ.

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I would also like to thank Dr. Xian Powers for her willingness to help proofread and edit my dissertation. I greatly appreciated her efforts.

Finally, I would like to acknowledge Joseph DeJesus and Kristina Valonis for their friendship and advice. Thanks for everything, we make a great team.

ABSTRACT

Aziridines are the nitrogen analogue of epoxides, and like epoxides, this functional group is an intermediate in numerous syntheses. Additionally, they are found in several natural products with anticancer activity. Despite their chemical applications, aziridine synthesis faces two big challenges: functional group tolerance is limited and a large excess of one reagent is often needed. This research is focused on ameliorating these two limitations.

Previous research demonstrated that square planar, strong donor metal complexes, such as porphyrin or macrocyclic tetracarbene complexes were capable of catalyzing aziridination. In our efforts to develop an ideal catalyst for aziridination, we chose to screen a series of transition metals with our tetracarbene ligand to determine which would be most effective for aziridination.

A cobalt(II) tetracarbene complex was synthesized by transmetallation and tested for C_2 + N_1 catalytic aziridination. The complex was unable to catalyze aziridination; furthermore, it showed no reactivity towards organic azides. The oxidative chemistry of the cobalt complex was explored, and a series of cobalt(III) tetracarbene complexes were synthesized. These complexes proved ineffective at aziridination and were unsuitable for further oxidation to a cobalt(IV) complex.

A chromium(III) tetracarbene dichloride complex was tested as an aziridination catalyst. The complex proved capable of performing catalytic aziridination at low alkene substrate loadings and performed aziridination with alkenes and azides containing protic functional groups, such as alcohols. The

axial chloride ligand on the chromium was proposed as the key to successful catalysis. This complex represents the first ever C_2 + N_1 aziridination catalyst on a group 6 metal.

Following our hypothesis of the penta-coordinated catalyst, an iron(II) pentacarbene complex was synthesized and characterized for aziridination catalysis. While the complex proved an effective catalyst for aziridination at low alkene loadings, the synthesis of the iron complex proved irreproducible.

A series of azidoalkenes compounds were synthesized to study the organic chemistry of ring closing intramolecular aziridination. The aziridination reactions had high conversion of the starting materials. However, the reactions proved to be non-catalytic as the control and catalytic yields were identical.

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INTRODUCTION

The Significance of $C_2 + N_1$ Catalytic Aziridination

Aziridines are the nitrogen analogue of epoxides: a three-membered ring with two carbons and one nitrogen.[1] Epoxides are commonly used as reactive intermediates in organic synthesis due to their ring strain. They can undergo enantioselective ring opening reactions to give a variety of useful products including chiral aminoalcohols,[2, 3] 1,2-diols,[4] azidoalcohols[5]. In a similar manner, aziridines also can be useful synthetic intermediates in organic synthesis. They can be ring opened enantioselectively to give optically pure aminoalcohols,[6, 7] 1,2-diamines,[7, 8] and aminoethers,[7, 9] to give a few examples. In addition, aziridines have demonstrated their versatility in total synthesis, being used as intermediates in the syntheses of myriad drugs and their synthetic intermediates, including oseltamivir phosphate (Tamiflu).[10, 11, 12, 13, 14, 15, 16, 17] The aziridine ring is also present in a modest number of of natural products, the most important families are azinomycins[18] and mitomycins.[19] Due to the strained aziridine ring, these natural products have demonstrated activity against various cancer lines and mitomycin C is approved in the treatment of bladder and intestinal cancers.[19] Finally, aziridines have been used to alkylate DNA in a ring opening reaction.[20]

In spite of the efficacy of aziridines, their synthesis is in its infancy compared to the synthesis of epoxides. There are a few traditional reactions to synthesize aziridines, such as the Wenker synthesis, the cyclization of an amino-alcohol;[1] and the Blum aziridine synthesis, a reaction between an epoxide, sodium azide, and triphenylphosphine.[1] However, both of these reactions have significant

disadvantages. The Wenker synthesis requires the use of an aminoalcohol as the starting material (**Figure I.1**).[1] The most common way to synthesize these is by the Sharpless oxyamination reaction.[21] This reaction uses alkenes as the starting material, but it requires the use of a chloramine and osmium tetroxide.[21] Both these compounds are hazardous to handle and can be expensive, making this synthesis undesirable. Alternatively, the aminoalcohol can be synthesized by ring opening of an epoxide,[2, 3] but this method again often requires the use of metal catalysts to synthesize the epoxide.[22] In a like manner, the Blum aziridine synthesis starts with an epoxide (**Figure I.1**),[1] which are commonly made by transition metal catalyzed oxygen transfer reactions on alkenes.[1, 22] Both these methods require significant efforts to prepare the starting material, often involving transition metal catalysis, which hurt the atom economy of these syntheses.

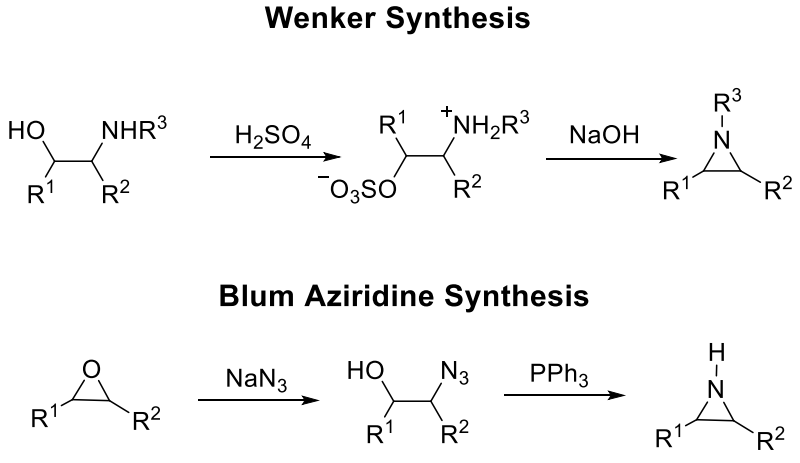


Figure I.1: Methods of Aziridine Synthesis.[1]

We desire to be able to eliminate the intermediate chemistry and synthesize aziridines directly from cheap starting materials *via* transition metal catalysis, using first row transition metals. This reliance on first row transition metals will cut down on cost of synthesis in two ways. First, by eliminating heavy transition metals, this will reduce the purification required, as there is a much lower tolerance for the heavy transition metal contaminants in consumer products than there is for the first row transition metals.[23] Second, cutting down on reaction steps will decrease the cost by reducing the number of reagents needed and eliminating the use of expensive heavy metals. Therefore, implementation of a general catalytic method to synthesize aziridines directly from alkenes would be a significant improvement over traditional organic synthesis.

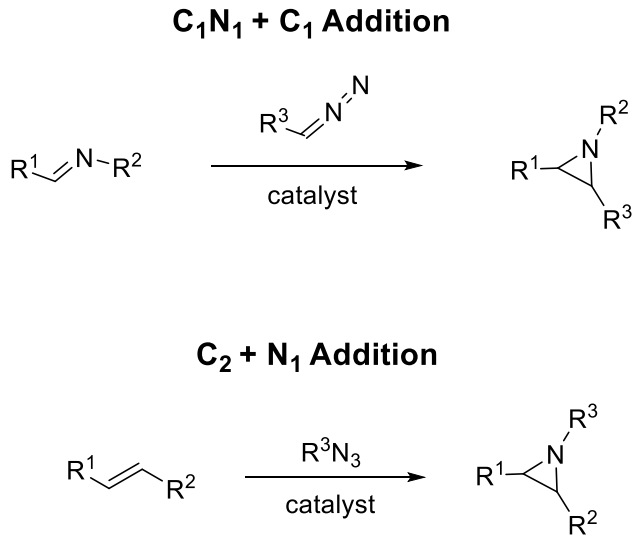


Figure I.2: Types of Catalytic Reactions to Form Aziridines.[1]

There are two common methods for synthesizing aziridines via catalysis. These methods are: (1) the $C_1N_1 + C_1$ method[1, 24] and (2) the $C_2 + N_1$ method (**Figure I.2**).[1, 24] The $C_1N_1 + C_1$ method is the addition of a carbene or a carbenoid, often generated from a diazoalkane, to an imine.[24] This method is less preferable, since most imines are not very stable, thus leaving a small pool of potential reagents and hurting the generalizability of this reaction class. Additionally, the C_1 fragment is usually formed from a diazo compound, many of which can be toxic or explosive.[25]

In contrast to this method, $C_2 + N_1$ aziridination is much more viable. The $C_2 + N_1$ reaction is the addition of a nitrene to an alkene.[24] The use of alkenes gives this reaction a significant advantage over the $C_1N_1 + C_1$ method, as alkenes are much more widely available and much cheaper than imines.[24] The nitrene can be generated by a variety of chemical reagents, but the most preferable nitrene source is an organic azide.[24, 26] These compounds react to give a nitrene and molecular nitrogen (N_2) in the presence of catalysts.[27] Overall, this reaction is much more generalizable than the $C_1N_1 + C_1$ method, since a large library of both alkenes and organic azides are available.[24, 28]

Previous Research on $C_2 + N_1$ Aziridination

The earliest $C_2 + N_1$ catalytic reaction using organic azides was reported by the Cenini group in 1999.[29] They used a ruthenium(II) porphyrin catalyst to catalyze the reaction of aliphatic alkenes with *p*-nitrophenyl azide. In addition to the aziridination products, they also found amination side products for many of the

reactions.[29] Later, Cenini discovered that the same ruthenium porphyrin and a similar cobalt porphyrin were capable of performing catalytic aziridination on styrenes with aromatic azides functionalized with electron withdrawing groups (**Figure I.3**).[27] Additionally, the same catalyst was capable of performing aziridination on conjugated dienes to yield the corresponding vinyl aziridines.[30]

Later examples by X. Peter Zhang and coworkers included aziridination of alkenes and sufonyl azides,[31] and enantioselective aziridination of styrenes with diphenylphosphoryl azide,[32] all with cobalt(II) porphyrin catalysts. These reactions were proposed to work through a metal imide intermediate.[31] The metal imide would then reductively transfer the nitrene moiety to an alkene. Other work included the synthesis of aziridines from styrenes with sulfonyl and some aryl azides by a series of porphyrin catalysts under microwave conditions, performed by Liu and Che.[33]

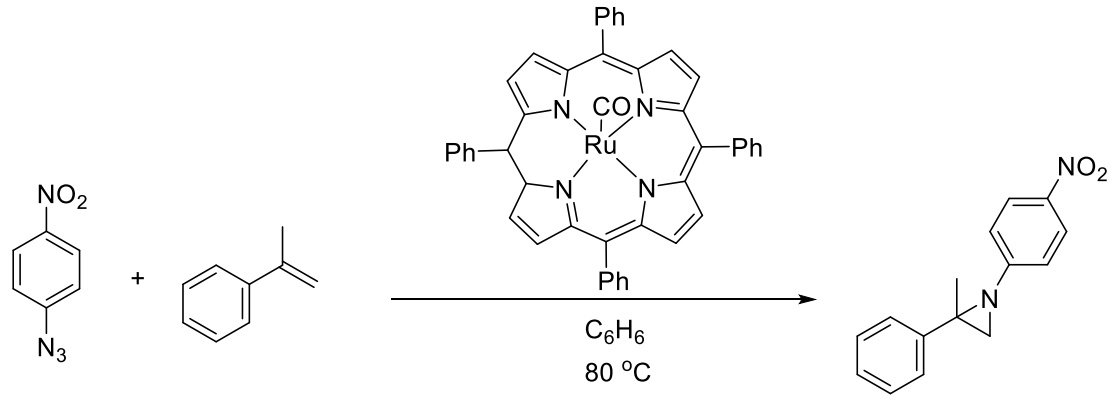


Figure I.3: Cenini's Catalytic Aziridination.[27]

The Jenkins group first developed a tetracarbene ligand, ($^{Me,Et}TC^{Ph}$)$(PF_6)_2$ (**1**), in order to imitate the structural features of porphyrins, while featuring the enhanced electron donating abilities of carbenes.[34] From this ligand, the Jenkins group synthesized an iron(II) tetracarbene complex, [($^{Me,Et}TC^{Ph}$)$Fe(NCCH_3)_2$]$(PF_6)_2$ (**2**) (**Figure I.4**).[35] This complex proved capable of catalyzing aziridination with aliphatic alkenes and aromatic azides in high yields (**Figure I.5**); it also proved an effective catalyst for tri and tetrasubstituted alkenes.[35] Unfortunatly, the catalyst required a high alkene loading in order to perform effective catalysis, limiting its utility to inexpensive alkenes. Further experimentation showed that the complex had a modest functional group tolerance; however, it was not capable of aziridination when the substrates had protic functional groups, such as alcohols or amines. These two shortcomings must be overcome for a general synthesis of aziridines from alkenes and organic azides to be viable for synthetic chemists.

In order to gain insight into the reaction mechanism, the Jenkins group sought to isolate the proposed intermediate in the reaction, an iron(IV) imide. Intriguingly, an imide complex of the reaction of **2** with an organic azide could not be isolated, even at low temperatures. Instead, an iron(IV) tetrazene complex, [($^{Me,Et}TC^{Ph}$)$Fe((p\text{-}tolyl)N_4(p\text{-}tolyl))](PF_6)_2$, was isolated (**Figure I.6**).[36] Tetrazene ligands are known to be the product of the reaction of metal imides with azides, so the product supported the formation of a metal imide as a potential reaction intermediate.[36] Upon heating, the tetrazene would decompose to diazine and **2**. This side reaction could explain why complex **2** required a large excess of alkene

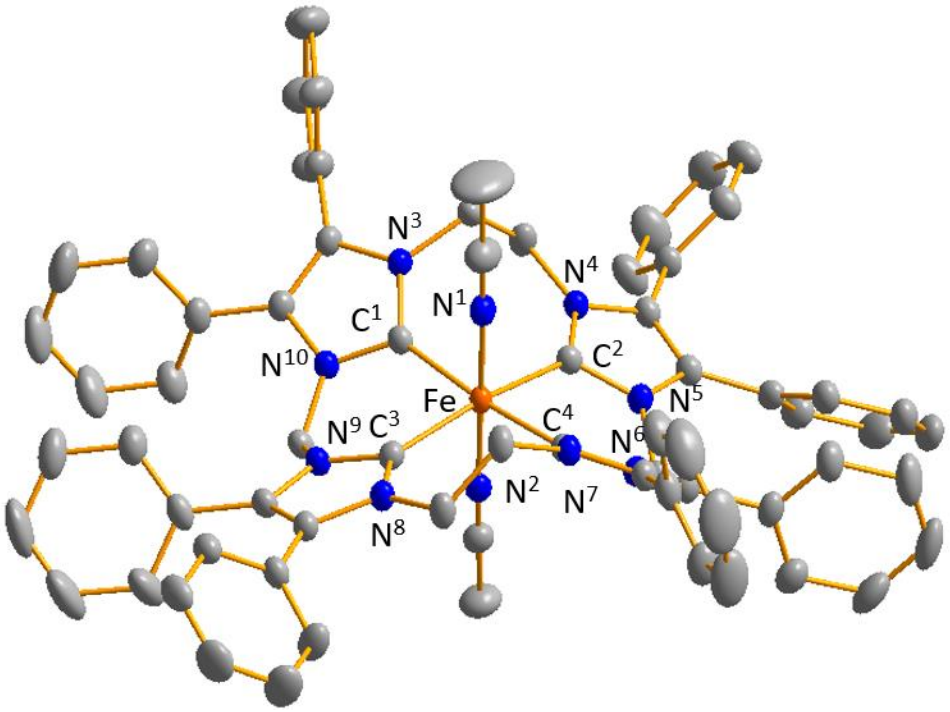


Figure I.4: Crystal Structure of [($^{Me,Et}TC^{Ph}$)Fe(NCCH$_3$)$_2$](PF$_6$)$_2$ (2),[35] Orange, gray, and blue ellipsoids represent iron, carbon, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

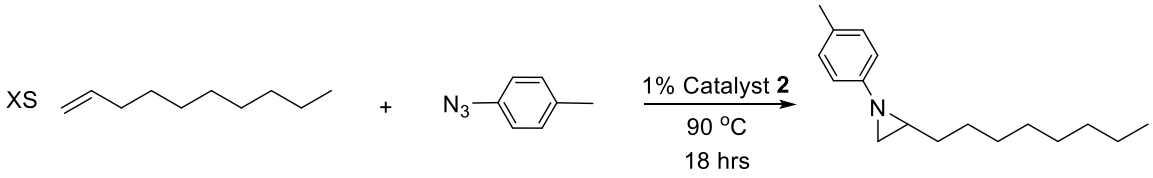


Figure I.5: Representative Catalysis with Catalyst 2.[35]

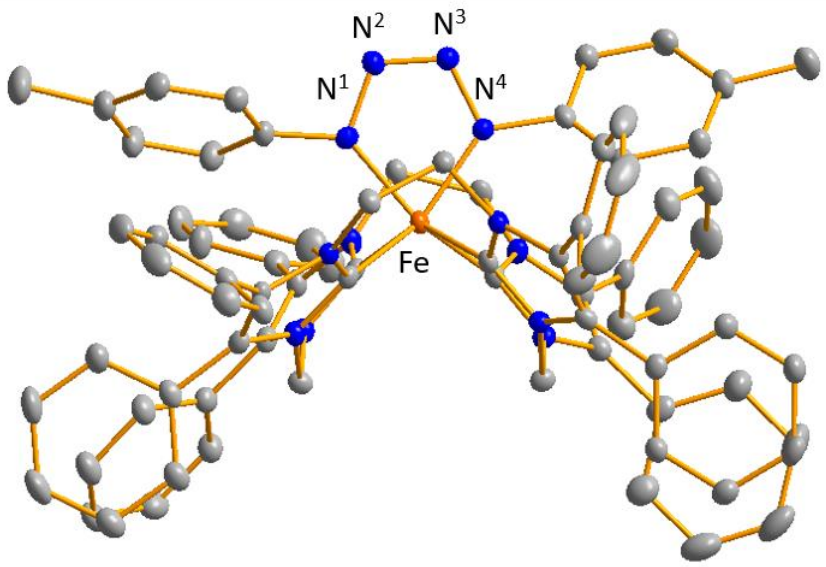


Figure I.6: Crystal Structure of [($^{Me,Et}TC^{Ph}$)Fe((p-tolyl)N_4(p-tolyl))]$(PF_6)_2$.[36] Orange, gray, and blue ellipsoids represent iron, carbon, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

to perform aziridination.[36] In light of this data, the catalytic cycle was revised so the tetrazene formation was considered a competing side reaction with aziridination.

The Jenkins group further developed a next generation tetracarbene ligand that had borate moieties in the ligand, resulting in a dianionic macrocycle.[37] Anionic ligands reduce the overall charge of a metal complex, allowing for stabilization of high oxidation compounds.[37, 38] Both transition metal complexes and main group metal complexes were synthesized with this new ligand.[37, 39] One

of the metal complexes made with this ligand, an iron(II) complex, [($^{BMe_2,Et}TC^{Ph}$)Fe], proved effective at aziridination with fully alkyl azides and alkenes which was a significant breakthrough.[40] Unfortunately, this complex still required the alkene in a large excess in order to effectively perform catalytic aziridination and like the first catalyst was not effective with protic functional groups.

Additional research on C_2 + N_1 aziridination includes more work by the Zhang group. They used a chiral cobalt(II) porphyrin complex to catalyze the enantioselective addition of aryl azides to styrenes with good *ee*.[41] In contrast to previous examples of aziridination, the Zhang group were able to use their azide as the limiting reagent. However, their catalytic system did have one critical drawback: it was limited to *ortho*-fluorinated azides and styrenes (**Figure I.7A**).[41] Later, using the same catalyst, Zhang and coworkers were able to perform ring-closing aziridination on functionalized allyl azidoformates to give fused three and five membered rings.[42] The aziridine rings were then ring opened *in situ* by addition of a nucleophile, but they also isolated a few pure aziridines (**Figure I.7B**). Again, these reactions proceeded in high enantiomeric excess (*ee*). Other research by the Betley group showed that an iron(II) dipyrromethene complex catalyzed the reaction of aryl azides with styrenes (**Figure I.8**).[43] The reaction intermediate was identified as an iron(III) imidyl radical.

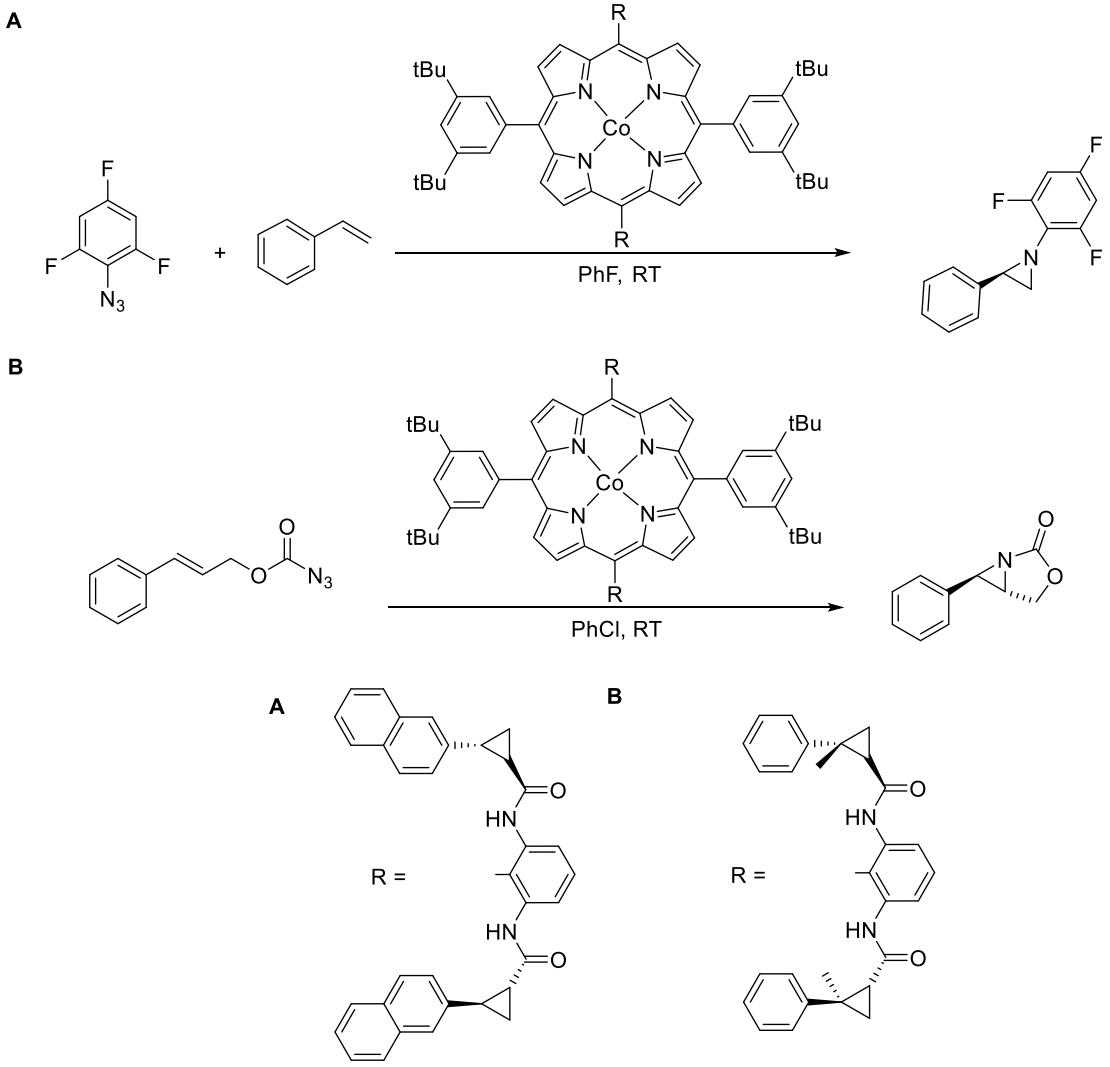


Figure I.7: Zhang's Catalytic Aziridination.[41, 42]

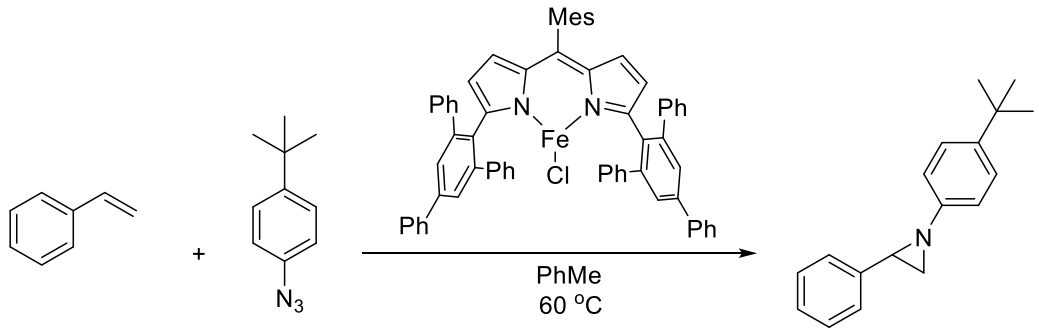


Figure I.8: Betley's Catalytic Aziridination.[43]

Another example of C_2 + N_1 aziridine synthesis comes from the world of biochemistry. Frances Arnold and coworkers synthesized aziridines from styrenes and tosyl azide using a Cytochrome P450 variant as a catalyst.[44] The reactions gave high enantiomeric excess andwhile the highest yield was 70%, main substrates yielded only at 10-15%,[44] demonstrating decreased efficiency versus homogenous aziridination catalysts in the literature.[27, 30, 35] To date, this constitutes the only example of C_2 + N_1 aziridination using an enzyme as the catalyst.

By evaluating the reported catalysts in the literature to date, several conclusions can be drawn. First, the vast majority of reported catalysts for C_2 + N_1 aziridination are based on tetradentate, equatorial ligands such as porphyrins.[27, 30, 35] Second, the proposed intermediate in catalytic aziridination is a high valent metal imide complex,[35, 45] and porphyrins and similar ligands have been shown to stabilize these high valent complexes.[45, 46] Notably, porphyrins complexes catalyze epoxidation reactions,[46, 47, 48, 49] which are isoelectronic to aziridination.[1] The tetracarbene ligand the Jenkins group uses is modeled after a porphyrin ligand, except it uses the stronger donating NHC ligands to impart greater stability to the resulting high valent metal imide intermediate.[34, 35]

The effectiveness of four-coordinate planar ligands for aziridination stands in stark contrast to similar reactions with tridentate ligands as the auxiliary ligand. A number of tridentate ligands have been used to support the synthesis of metal imides, but the resulting products metal imide complexes are non-reactive towards

oxidative group transfer[50, 51, 52] or only show non-catalytic group transfer of the imide.[53] In contrast, there are a few examples of aziridine synthesis using metal complexes with bidentate ligands. Most notably, Betley's iron complex was capable of catalyzing aziridination, but only on unhindered styrenes, whereas on any other alkene, it performed amination.[43] Another bidentate metal imide complex synthesized by Hillhouse was capable of aziridination, but the complex could not be formed from azides, requiring multiple synthetic steps to form the imide,[54] which makes the complex not suited for catalysis. Overall, bidentate and, particularly, tridentate ligands are inferior to tetradentate ligands in catalytic aziridination.

Much progress has been made in $C_2 + N_1$ aziridination since Cenini's work. Today, there are several catalysts capable of synthesizing aziridines in high yields; however, these systems have three key limitations. One, many catalysts are only capable of performing aziridination on styrene.[27, 32, 35, 41, 42] This problem is less urgent, as the Jenkins group has already developed catalysts capable of performing aziridination with non-conjugated alkenes.[35, 40] The second problem is related to the first; many catalysts, particularly ones that use aliphatic alkenes, require a large excess of alkene for the aziridination to work.[33, 35, 40] In order for $C_2 + N_1$ aziridination to be practical for synthesis, the reaction must be able to work at equivalency or nearly so. Three, most aziridination catalysts have poor functional group tolerance. Most $C_2 + N_1$ catalytic systems only report reactions with relatively inert functional groups, such as nitros and chloros,[27, 30, 40, 55] and some have not reported any experiments with functional groups.[35] If $C_2 + N_1$ aziridination

is to move forward, we need catalysts with a large functional group tolerance that also are effective with a wide variety of alkenes at low alkene loading.

Our research goals were to solve these limitations on $C_2 + N_1$ aziridination. We desired to make catalysts capable of synthesizing aziridines at reduced alkene loadings. While reaching equivalency would be outstanding, even the reduction of the alkene loading to a five-fold, or even a three-fold excess would be a significant improvement over most current systems, particularly with any alkene other than styrene. Additionally, we wanted to develop catalysts capable of performing aziridination with protic functional groups, such as alcohols. Protic functional groups are quite common in pharmaceutical chemistry so this is critical to moving the reaction into the mainstream for practicing synthetic chemists. In order to achieve these goals, we set out to explore the reactivity of other transition metal tetracarbene complexes developed by the Jenkins group with organic azides and explore their group transfer chemistry. To achieve these goals, we explored modifications to existing ligands and metal complexes synthesized previously by the Jenkins lab to enhance their catalytic activity. The results of these studies are described in this dissertation.

CHAPTER I

SYNTHESIS AND REACTIVITY OF COBALT TETRACARBENE COMPLEXES

Abstract

In order to screen different transition metal complexes for catalytic aziridination, syntheses for cobalt(II) and cobalt(III) tetracarbene complexes were developed. These complexes exhibited no activity as aziridination catalysts. Further research probed the redox and coordination chemistry of these complexes.

Introduction

Previously, the Jenkins group established the catalytic activity of an iron(II) tetracarbene complex, (**2**), mimicking the structure of known ruthenium aziridination catalysts.[35] After this, the Jenkins group sought to test a series of transition metal tetracarbene complexes to determine which metal made the best aziridination catalyst. An ruthenium(II) complex isostructural to complex **2** was synthesized and tested as an aziridination catalyst.[56] This complex proved to be ineffective at catalytic aziridination, due to the difficulty in activating the acetonitrile ligands present on the metal center.[56] After testing ruthenium for aziridination catalysis, the Jenkins group wanted to determine if better results could be achieved using a first-row transition metal not from group eight. For this goal, the Jenkins group developed the synthesis for a variety of complexes with the original tetracarbene ligand, including cobalt, nickel, and chromium.[57]

Cobalt(II) porphyrin complexes have previously been shown to perform catalytic aziridination.[55, 58] However, a cobalt(II) tetracarbene complex previously synthesized by the Jenkins group had been tested as an aziridination catalyst and

was found to be ineffective.[59] This complex, however, had triflates as counteranions, one of which, was shown to bind to the metal center through X-ray crystallography. Synthesis of a complex with non-binding anions, such as hexafluorophosphate, could potentially make a better catalyst, since the metal could have a site more open to reactivity.

Synthesis and Characterization of a Cobalt(II) Tetracarbene Complex

The Jenkins group has previously developed the synthesis of a tetracarbene ligand (1) with hexafluorophosphate anions.[34] From this ligand, a dimeric silver tetracarbene complex (3) was synthesized *via* a weak base approach.[57] These silver complexes were capable of transmetallating the tetracarbene ligand to other transition metals, including cobalt. Starting from the silver(I) tetracarbene hexafluorophosphate complex, cobalt iodide was added in a tetrahydrofuran and methylene chloride solution to yield a green solution, which we identified as a cobalt(II) tetracarbene hexafluorophosphate complex, $[(^{Me,Et}TC^{Ph})Co(Solvent)_x](PF_6)_2$. This compound was purified by vapor diffusion of diethyl ether into the reaction solution, yielding pale green crystals. Characterization of this complex by single crystal X-ray diffractometry (SCXRD) showed that the complex was actually a mixture of a square planar complex and a square pyramidal complex with a bound tetrahydrofuran ligand. Running the same reaction with acetonitrile as the solvent gave exclusively a square pyramidal

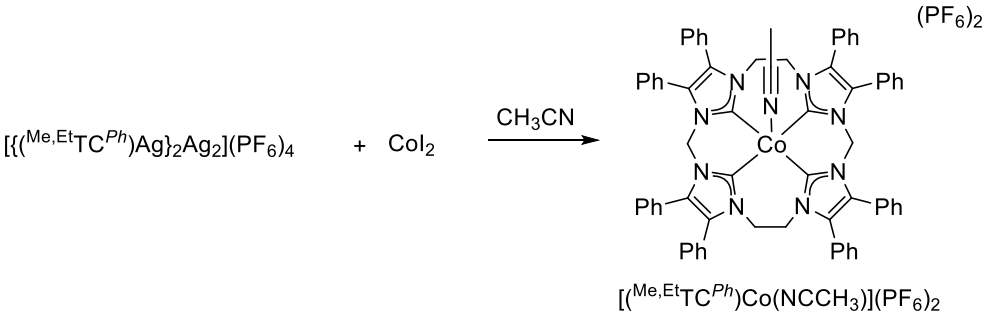


Figure 1.1: Synthesis of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)](PF$_6$)$_2$ (4).

cobalt(II) complex with a single bound acetonitrile ligand, [($^{Me,Et}TC^{Ph}$)Co(NCCH$_3$)](PF$_6$)$_2$ (**4**) (**Figure 1.1**). The square pyramidal structure of this complex is analogous to the one previously synthesized by our group,[57] but at odds with some other cobalt(II) tetracarbene structures in the literature.[60, 61] A dicationic cobalt(II) tetracarbene complex synthesized by Mo and coworkers had a square planar geometry,[60] while another cobalt(II) tetracarbene complex synthesized by Park and coworkers was tetrahedral.[61] This reaction was purified as before, giving a 70 % yield. This complex was characterized by ^{1}H NMR, ESI-MS, and single crystal XRD (**Figure 1.2**).

After characterization was completed, complex **4** was tested as a catalyst (**Figure 1.3**). Using *p*-tolyl azide as the nitrene source, the cobalt complex was tested with 1-decene, cyclooctene, and 1-methylcyclohexene (**Table 1.1**). We refrained from testing styrenes as the styrene would polymerize at the chosen temperatures. The results of the attempted catalysis were negative. All attempted catalysis reactions gave yields equivalent to the control reactions, about 30 %. As a further test, iodosobenzene and (3,5-trifluoromethyl)-1-azidobenzene were added to solutions of **3** in tetrahydrofuran and acetonitrile. The solutions with the azide showed no reactivity; however, a color change from green to yellow was observed in the reactions of **4** with iodosobenzene. The observed color change lead us to explore the oxidative chemistry of **4**.

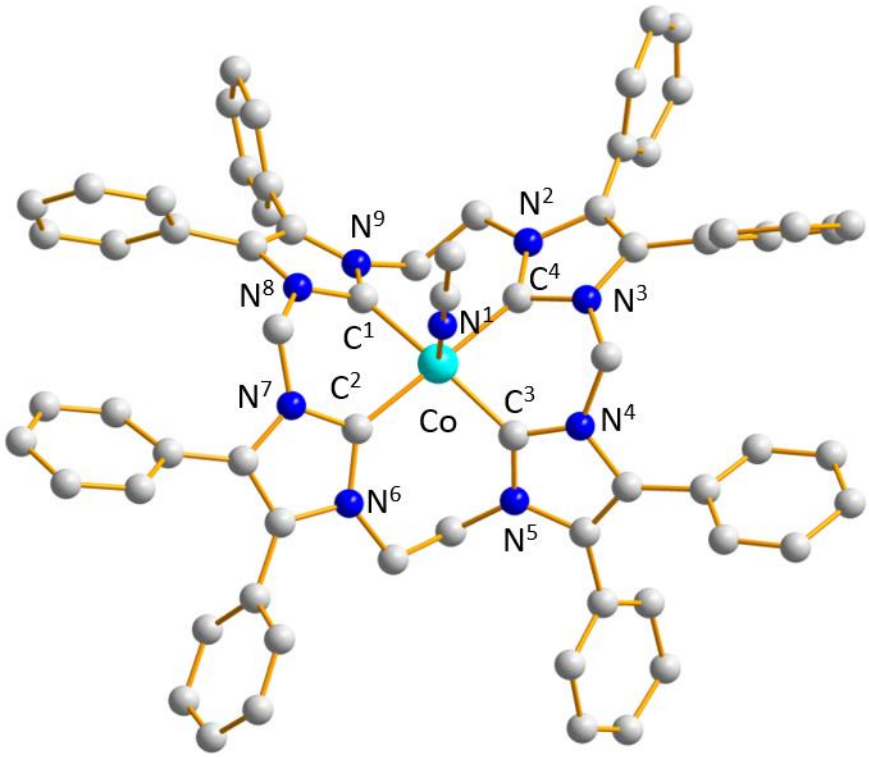


Figure 1.2: Crystal Structure of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)](PF$_6$)$_2$ (4). Cyan, gray, and blue ellipsoids represent cobalt, carbon, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

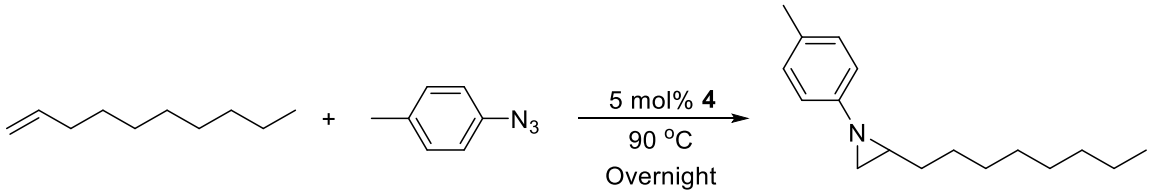
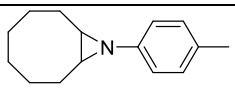
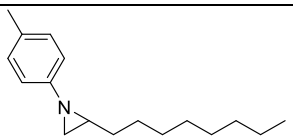
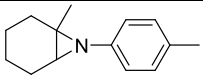


Figure 1.3: Sample Aziridination Reaction with [($^{Me,Et}TC^{Ph}$)Co(NCCH$_3$)](PF$_6$)$_2$ (4).

Table 1.1: Catalytic Aziridination Test with [($^{Me,Et}TC^{Ph}$)Co($NCCH_3$)](PF_6)$_2$ (4).

Aziridine	Yield	Control Yield
	38 %	30 %
	30 %	30 %
	NR	NR

Synthesis and Characterization of a Cobalt(III) Tetracarbene Complex

As part of the studies on aziridination with **4**, we were interested in its the oxidation chemistry. In a serendipitous crystallization of a cobalt(II) sample, a number of large yellow crystals were obtained *via* vapor diffusion of diethyl ether into an acetonitrile solution. These were identified by single crystal XRD as a cobalt(III) tetracarbene *bis*-acetonitrile complex, $[(^{Me,Et}TC^{Ph})Co(NCCH_3)_2](PF_6)_3$ (**5**) (**Figure 1.4**). Given that the cobalt(II) complex was ineffective at aziridination, and the cobalt(III) complex was isoelectronic to the iron(II) complex that had proved to be an effective aziridination catalyst, we decided to explore the chemistry of this new complex. Since the crystallization that yielded the cobalt(III) complex was performed under air, it was initially assumed that the cobalt(III) complex had been formed by air oxidation. However, when a solution of the pure cobalt(II) complex in acetonitrile was exposed to air, no oxidation was observed for up to a week. In light of this evidence, we decided that the oxidation was likely performed by residual silver(I) ions from the transmetallation reaction with **3**. Analysis of **4** by cyclic voltammetry demonstrated that ferrocenium would be strong enough to oxidize the cobalt(II) complex. Thus, we reacted **4** with one equivalent of ferrocenium hexafluorophosphate. This gave the desired cobalt(III) complex (**5**) in a 60% yield after crystallization (**Figure 1.5**). This complex was further characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

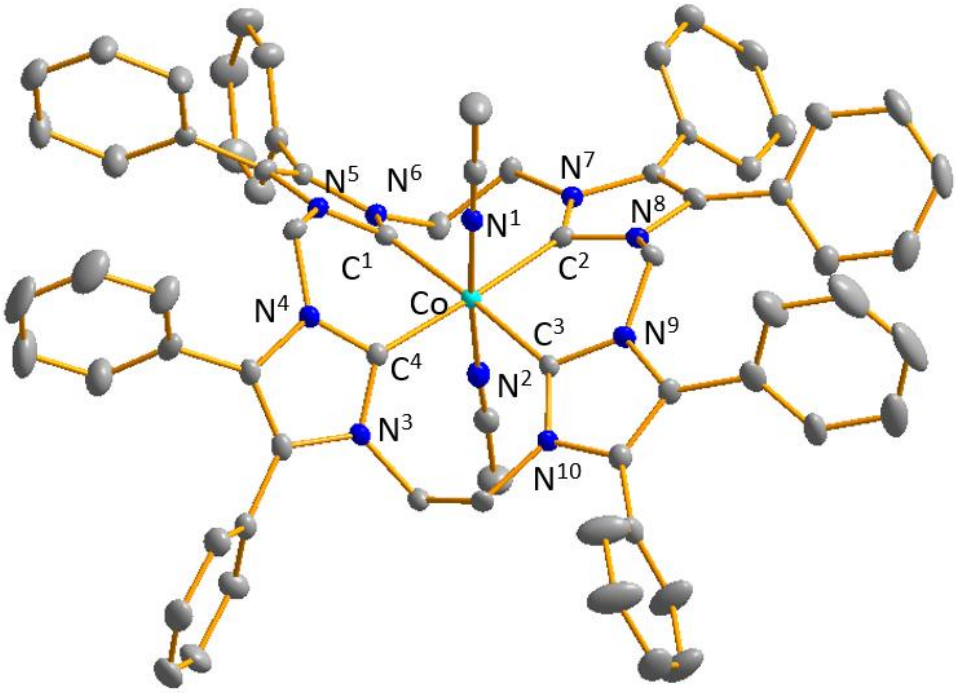


Figure 1.4: Crystal Structure of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)$_2$](PF$_6$)$_3$ (5), Cyan, gray, and blue ellipsoids represent cobalt, carbon, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

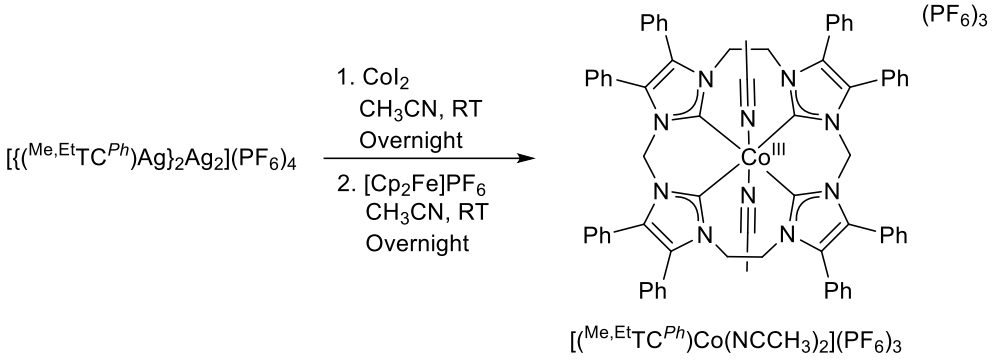


Figure 1.5: Synthesis of [($^{Me,Et}TC^{Ph}$)Co(NCCH$_3$)$_2$](PF$_6$)$_3$ (5).

Complex **5** could potentially be employed for aziridination but would need to be further oxidized to perform catalysis. Since the complex was diamagnetic, its reactions with various oxidants were followed by ^{1}H NMR. Reaction of the cobalt(III) complex with organic azides, iodosobenzene, and tosylimino iodobenzene are resulted in no reaction. The failure of the oxidation reactions was likely because the cobalt complex was tricationic, and the oxidation reactions we attempted would have resulted in a tricationic cobalt(V) complex, which would have been very unstable. This begged the question: could a cobalt(IV) or (V) complex be synthesized by addition of anionic ligands to reduce the overall charge?

Axial Ligand Chemistry of a Cobalt(III) Tetracarbene Complex

In order to try and stabilize a high oxidation cobalt tetracarbene complex, synthetic methods were developed to try and exchange the neutral acetonitrile ligands for anionic ligands. The axial ligands would also serve to decrease the overall charge of the molecule and therefore increase its solubility in non-polar solvents. We targeted chlorides as our axial ligands of choice, due to the difficulty in oxidizing them to chlorine. Another advantage is that if further ligand metathesis reactions were attempted, the chlorides could easily be precipitated from non-polar solvents as a salt. The first reaction attempted was a metathesis reaction between the cobalt complex (**5**) and tetrabutylammonium chloride in acetonitrile. No reaction was observed at room temperature, but on heating to 40 ^{o}C, rapid color change from yellow to green was observed, presumably due to ligand exchange. Single crystal XRD revealed that the reaction product was a cobalt(III) tetracarbene

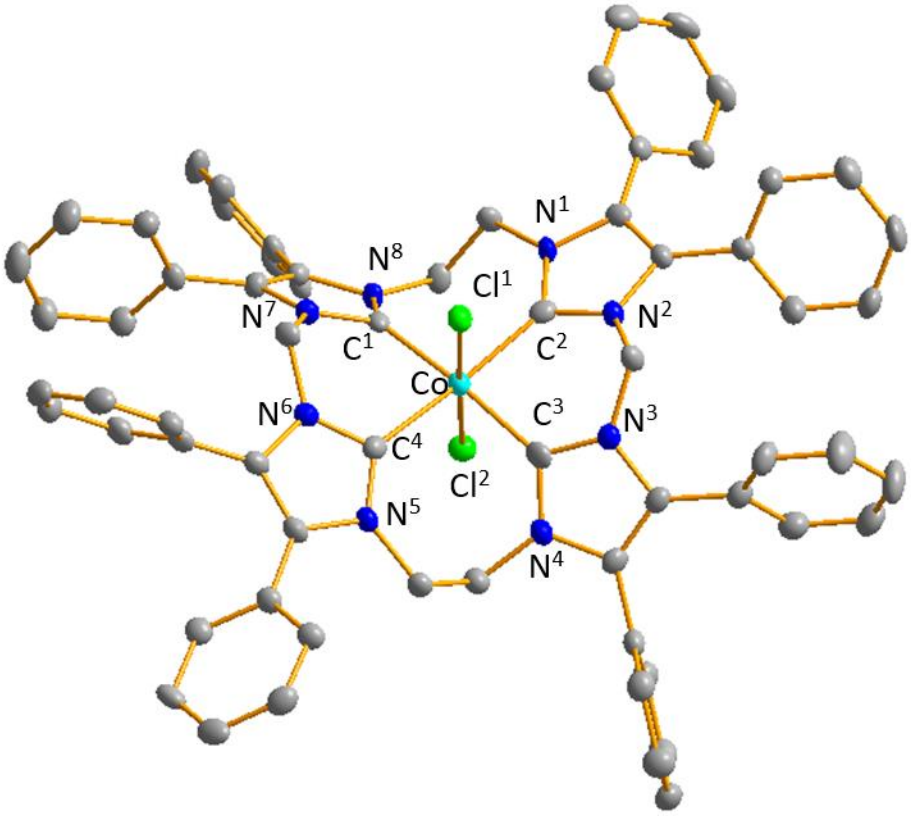


Figure 1.6: Crystal Structure of [(^{Me,Et}TC^{Ph})Co(Cl)$_2$](PF$_6$) (6). Cyan, gray, blue, and green ellipsoids represent cobalt, carbon, nitrogen, and chloride, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

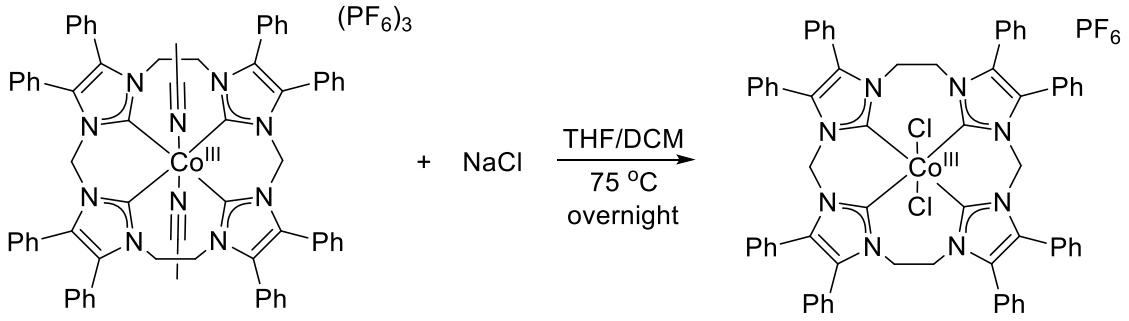


Figure 1.7: Synthesis of [($^{Me,Et}TC^{Ph}$)$Co(Cl)_2$](PF_6)

complex, [($^{Me,Et}TC^{Ph}$)$Co(Cl)_2$](PF_6), with two axial chloride ligands (**6**) (**Figure 1.6**). Unfortunately, the product was contaminated with the tetrabutylammonium hexafluorophosphate side product. Despite multiple efforts of purification by crystallization, a pure sample of **6** was not able to be isolated, and an accurate yield was unable to be determined for this synthesis.

A new reaction was developed to synthesize **6** that excluded the tetrabutyammonium ion. An excess of sodium chloride was added to a THF/DCM mixture with **5**. The reaction was heated at 70 ^{o}C overnight and filtered over Celite to give an 82% yield of [($^{Me,Et}TC^{Ph}$)$Co(Cl)_2$](PF_6) (**Figure 1.7**). Cyclic voltammetry on this complex showed a reduction at about -1800 mV, but no clear oxidation wave was seen. In order to better stabilize a high oxidation state, an axial ligand with stronger electron donation was sought.

Using **6** as a starting material, we reacted it with two equivalents of sodium phenoxide in THF (**Figure 1.8**). This gave a rapid color change at room temperature from green to red. Single crystal XRD confirmed the product was a cobalt(III) complex with *bis*-phenoxide ligands, [($^{Me,Et}TC^{Ph}$)$Co(OPh)_2$](PF_6) (**7**) (**Figure 1.9**).

Analysis of this complex indicated that, it too, was a poor candidate for oxidation to a cobalt(IV) species. At this point, we decided that we were unlikely to obtain a cobalt(IV) species via this approach, and we decided that this project was unlikely to yield any publishable results.

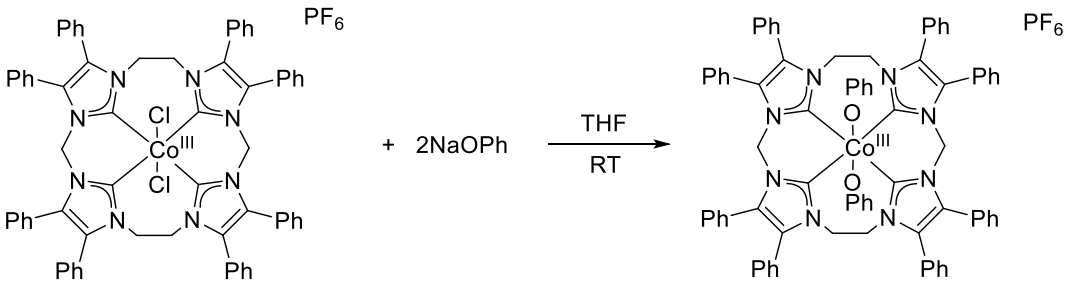


Figure 1.8: Synthesis of [(^{Me,Et}TC^{Ph})Co(OPh)$_2$](PF$_6$).

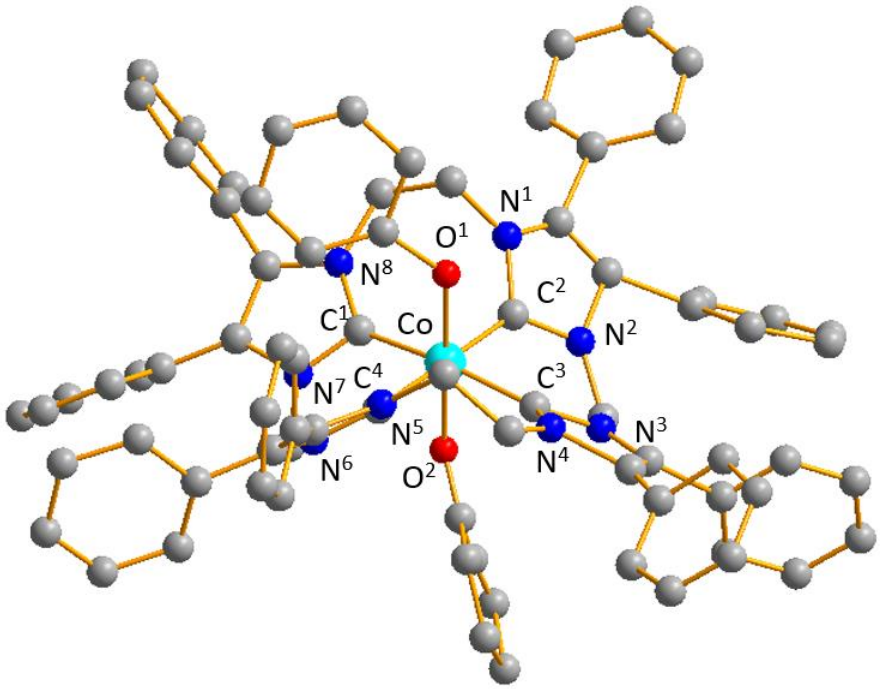


Figure 1.9: Crystal structure of [(^{Me,Et}TC^{Ph})Co(OPh)$_2$](PF$_6$) (7). Cyan, gray, red, and blue ellipsoids represent cobalt, carbon, oxygen, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

Conclusion

In conclusion, we have synthesized a new cobalt(II) tetracarbene monoacetonitrile complex, $[(^{Me,Et}TC^{Ph})Co(NCCH_3)](PF_6)_2$ and three new cobalt(III) tetracarbene complexes, one with *bis*-acetonitrile ligand, $[(^{Me,Et}TC^{Ph})Co(NCCH_3)_2](PF_6)_3$; one with *bis*-chloride ligands, $[(^{Me,Et}TC^{Ph})Co(Cl)_2](PF_6)$; and one with *bis*-phenoxide ligands, $[(^{Me,Et}TC^{Ph})Co(OPh)_2](PF_6)$. The cobalt(II) complex and the cobalt(III) *bis*-acetonitrile complex were tested for catalytic aziridination and found to be inactive. Finally, all the cobalt(III) complexes were found to be unsuitable for further oxidation.

Experimental

Synthesis of the organic compounds used were performed under atmospheric conditions. All reactions with the silver and cobalt complexes were performed under a nitrogen atmosphere in a glovebox. Solvents were dried on an Innovative Technologies (Newburgport, MA) Pure Solv MD-7 Solvent Purification System, and they were degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use, then dried over activated molecular sieves. Acetonitrile-d_3 was purchased from Cambridge Isotope Lab and degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves, followed by storage in a glovebox. Synthesis of the macrocyclic tetracarbene[34] and the silver(I) tetracarbene complex[57] were performed following our published procedures. All other reagents were purchased from commercial vendors and used without further purification.

^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury 300 MHz or a Varian VNMRS 500 MHz narrow-bore broadband system. ^{1}H and ^{13}C NMR chemical shifts were referenced to the residual solvent. All mass spectrometry analyses were conducted at the Mass Spectrometry Center located in the Department of Chemistry at the University of Tennessee. The ESI-MS analyses were performed using a QSTAR Elite quadrupole time-of-flight (QTOF) mass spectrometer with an electrospray ionization source from AB Sciex (Concord, Ontario, Canada). Mass spectrometry sample solutions of organometallic compounds were prepared in solutions of acetonitrile. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. Cyclic voltammetry measurements were made inside a dry glovebox using a BAS Epsilon electrochemical analyzer with a platinum working electrode, platinum wire counter electrode, and $Ag/AgNO_3$ reference electrode. All potentials were measured versus an external standard of ferrocene. Carbon, hydrogen, and nitrogen analyses were obtained from Atlantic Microlab, Norcross, GA.

X-ray Structure Determinations. X-ray diffraction measurements were performed on single crystals coated with Paratone oil and mounted on glass fibers. Each crystal was frozen under a stream of N2 while data were collected on a Bruker APEX diffractometer. A matrix scan using at least 12 centered reflections was used to determine initial lattice parameters. Reflections were merged and corrected for Lorenz and polarization effects, scan speed, and background using

SAINT 4.05. Absorption corrections, including odd and even ordered spherical harmonics were performed using SADABS, if necessary. Space group assignments were based upon systematic absences, E statistics, and successful refinement of the structure. The structures were solved by S7 direct methods with the aid of successive difference Fourier maps, and were refined against all data using the SHELXTL 5.0 software package.

Synthesis of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)](PF$_6$)$_2$, 4. **3** (0.3097 g, 0.106 mmol) was weighed out in a 20 mL vial, and dissolved in a solution of acetonitrile. Cobalt(II) iodide (0.0660 g, 0.211 mmol) was dissolved in acetonitrile and added to the solution of **3** dropwise at room temperature with stirring. The reaction rapidly turned green, and a white precipitate of silver(I) iodide formed. The reaction stirred overnight at room temperature. After completion of the reaction, the solution was filtered over Celite, and crystalized by vapor diffusion of diethyl ether into the acetonitrile solution to yield the product in 0.199 g, 70 %. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 34.39 (s, 4H), 24.74 (bs, 40H), -3.22 (bs, 8H). IR: 2926.41, 2296.08, 1627.64, 1488.50, 1445.12, 1377.61, 1230.04, 1181.44, 1075.03, 1025.57, 925.64, 826.15, 763.89, 732.81, 697.85 cm^{-1}. ESI/MS (m/z): $[M\text{-}PF_6]^+$ 1160.31, $[M\text{-}2PF_6]^{2+}$ 507.68. Electrochemistry (vs. ferrocene in CH_3CN with (TBA)(PF_6) as supporting electrolyte): -29 mV (irr.), -568 mV, (irr.) -1497 mV (rev.). Anal. Calced for $C_{136}H_{110}AgCo_2F_{24}IN_{18}P_4$ (**4**•0.5AgI): C, 55.77; H, 3.79; N, 8.61. Found: C, 55.75; H, 4.20; N, 8.41.

Synthesis of [($^{Me,Et}TC^{Ph}$)Co($NCCH_3$)$_2$](PF_6)$_3$, 5. **4** (0.0792 g, 0.061 mmol) was weighed out and added to a 20 mL vial. It was dissolved in acetonitrile, and ferrocenium hexafluorophosphate was added (0.0201g, 0.061mmol). The reaction turned a dark blue color and stirred overnight. Upon completion of the reaction, the resulting solution was crystalized by vapor diffusion of diethyl ether into the reaction solution. The product was collected as bright yellow crystals suitable for X-ray diffraction, 0.0577 g, 62 % yield. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 7.41 (m, 20H), 7.35 (m, 4H), 7.20 (m, 16H), 5.89 (s, 4H), 4.46 (s, 8H). Anal. Calcd for $C_{70}H_{58}CoF_{18}N_{10}P_3$: C, 54.84; H, 3.81; N, 9.14. Found: C, 55.54; H, 4.40; N, 8.63.

Synthesis of [($^{Me,Et}TC^{Ph}$)Co($Cl)_2$](PF_6), 6. **5** (0.1322 g, 0.086 mmol) was weighed out and added to a 20 mL vial. It was dissolved in acetonitrile, heated to 40 ^oC, and tetrabutylammonium chloride was added (0.0479 g, 0.173 mmol). The reaction was let stir overnight, and following this, the solution was crystalized by vapor diffusion of diethyl ether into the reaction solution. The product was collected as green crystals and co-crystalized with white needles of tetrabutylammonium hexafluorophosphate.

Synthesis of [($^{Me,Et}TC^{Ph}$)Co($Cl)_2$](PF_6), 6. **5** (0.0803 g, 0.052 mmol) was weighed out and added to a 20 mL vial. It was dissolved in a 50:50 mixture of tetrahydrofuran and methylene chloride, and sodium chloride was added (0.0245 g, 0.42 mmol). The reaction was let stir overnight at 75 ^oC. On completion of the reaction, the solution was filtered over Celite, and crystalized by vapor diffusion of diethyl ether into the reaction solution. The product was collected as green

crystals, 0.0529 g, 82 % yield. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 7.41 (m, 20H), 7.33 (m, 4H), 7.21 (m, 16H), 6.43 (bs, 4H), 4.90 (bs, 8H). IR: 2926.41, 2296.08, 1627.64, 1488.50, 1445.12, 1377.61, 1230.04, 1181.44, 1075.03, 1025.57, 925.64, 826.15, 763.89, 732.81, 697.85 cm^{-1}. ESI/MS (m/z): $[M\text{-}PF_6]^+$ 1085.34, $[M\text{-}Cl\text{-}PF_6]^{2+}$ 525.19. Electrochemistry (vs. ferrocene in THF with (TBA)(PF_6) as supporting electrolyte): -1800 mV. Anal. Calced for $C_{68}H_{56}Cl_6CoF_6N_8P$ (**5**•$2CH_2Cl_2$): C, 58.26; H, 4.03; N, 7.99. Found: C, 58.57; H, 4.20; N, 8.26.

Synthesis of [($^{Me,Et}TC^{Ph}$)Co(OPh)$_2$](PF$_6$), 7. 6 (0.1789 g, 0.145 mmol) was added to a solution of THF. Sodium phenoxide (0.0482 g, 0.415 mmol) was added as a solid. The reaction was stirred at room temperature overnight. After completion of the reaction, the solution was filtered over Celite. Crystals suitable for XRD were grown by vapor diffusion of diethyl ether into a solution of tetrahydrofuran. The product was found to be very impure; hence, no accurate yield could be determined. ESI/MS (m/z): $[M\text{-}PF_6]^+$ 1201.47.

Select NMRs of Novel Products Synthesized in this Work

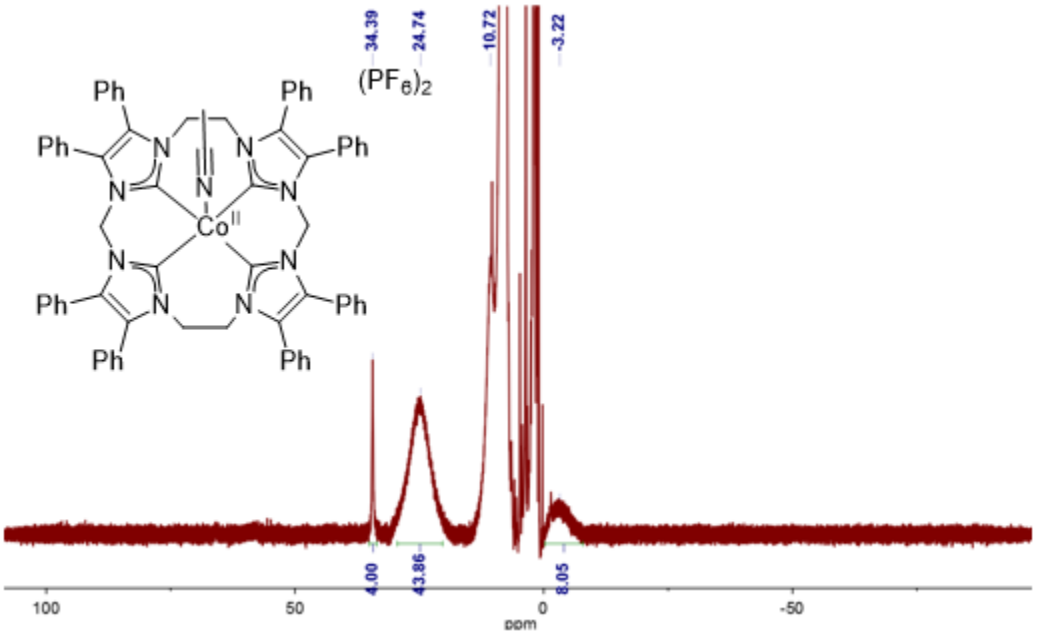


Figure 1.10: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)](PF$_6$)$_2$, 4.

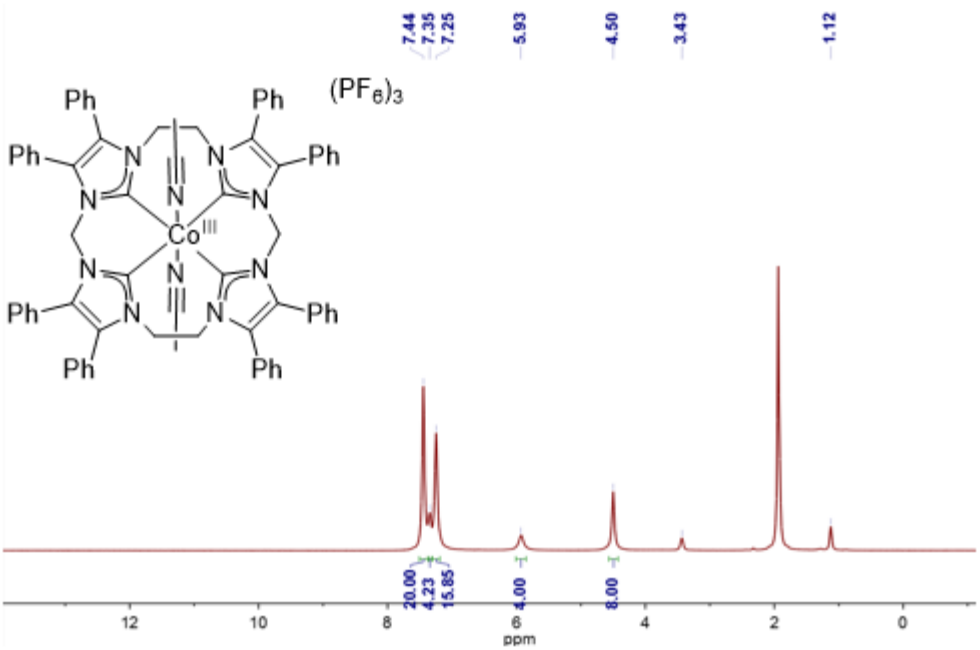


Figure 1.11: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Co(NCCH$_3$)$_2$](PF$_6$)$_3$, 5.

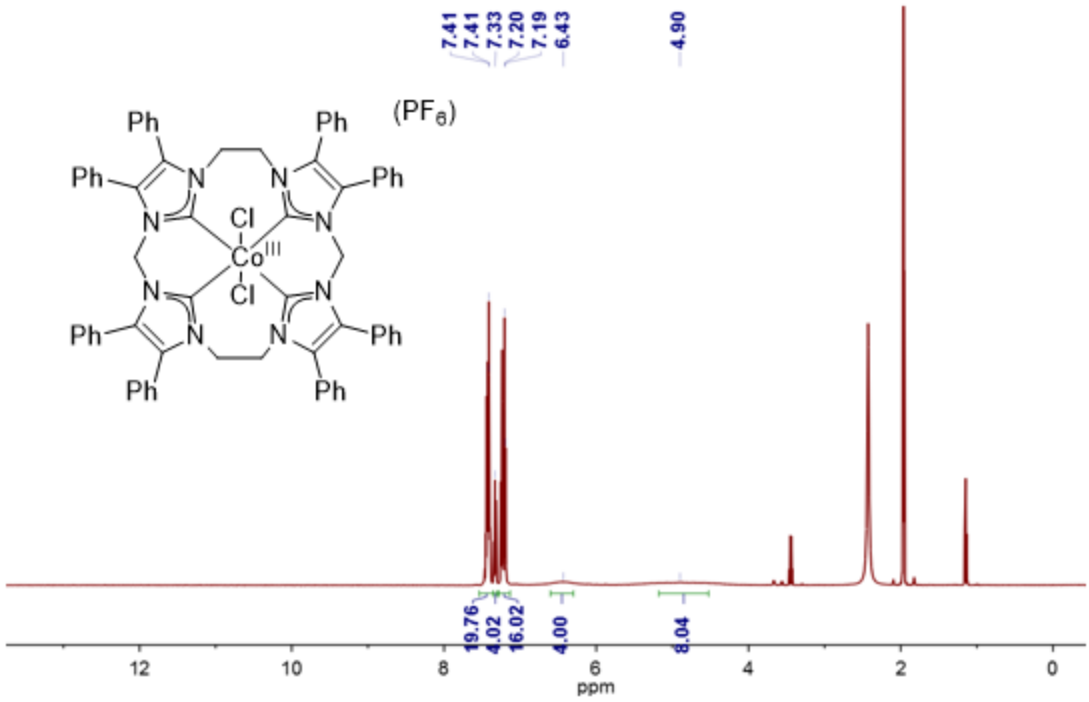


Figure 1.12: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Co(Cl)$_2$](PF$_6$), 6.

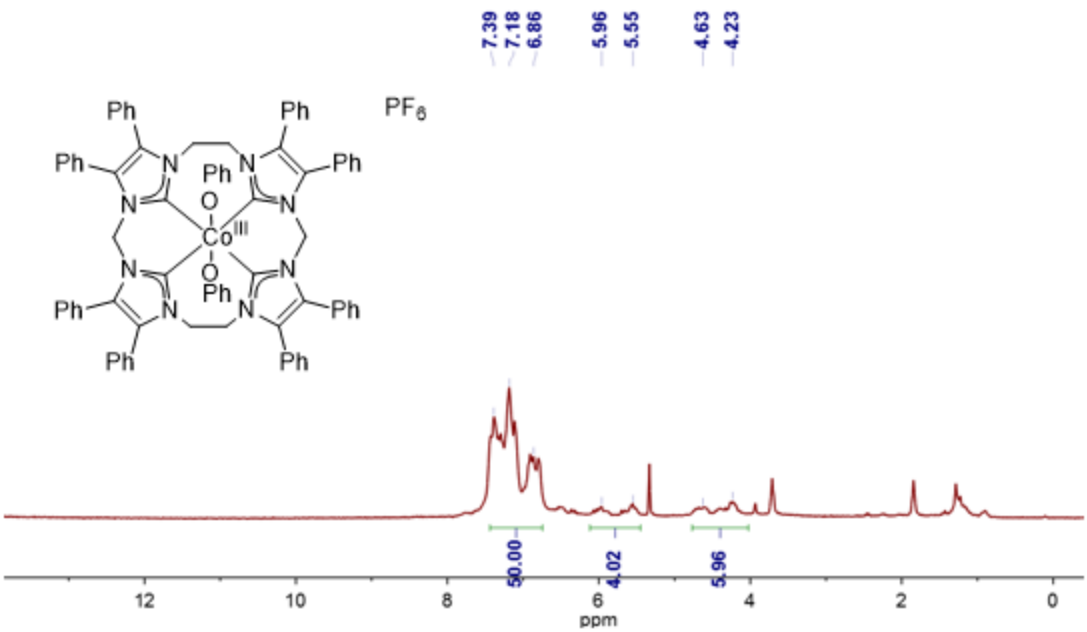


Figure 1.13: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Co(OPh)$_2$](PF$_6$), 7.

CHAPTER II

CHROMIUM CATALYZED AZIRIDINATION CHEMISTRY

A version of this chapter was originally published by C Luke Keller, Jesse L. Kern, Bradley D. Terry, Sharani Roy, and David M. Jenkins. All calculations were performed by Jesse L. Kern and Bradley D. Terry; all other work was performed by C. Luke Keller:

Keller, C Luke; Kern, Jesse L.; Terry, Bradley D.; Roy, Sharani; Jenkins, David M. “Catalytic Aziridination of Alcoholic Substrates *via* a Chromium Tetracarbene Catalyst.” *Chemical Communications*, **2018**, *54* (12), 1429-1432. DOI: 10.1039/C7CC08928G.

Abstract

A chromium(III) complex previously synthesized by the Jenkins group was found to catalyze aziridination at low alkene loadings.[62] This is the first examples of $C_2 + N_1$ catalytic aziridination on chromium or any other group six metal. The reactivity was tested across a wide variety of solvents and alkene loadings. The complex was able to give modest isolated yields of aziridines utilizing alkenes and azides with non-protic functional groups. It was also found to catalyze aziridination with unprotected alcohols and amines, albeit with low isolated yields. This is the first generalizable catalytic system for the aziridination of alcohol-containing substrates, and the first reported example of catalytic aziridination with unprotected amines. Mechanistic and percent conversion experiments showed that the protic aziridine reactions had comparable yields to the unfunctionalized examples, and the reduction in yield was likely due to the difficulty in purifying the aziridines.

Calculations on the catalytic cycle showed that an axial chloride ligand is key for performing aziridination.

Introduction

Since iron was successful as an aziridination catalyst,[35] and cobalt was not, we chose to continue screening different tetracarbene complexes for catalytic aziridination. Manganese was the next obvious choice, as it is closely related to iron, and the Jacobsen epoxidation system utilizes a manganese metal center.[63] Unfortunately, despite numerous efforts by previous group members, a manganese complex of tetracarbene ligand **1** has not been isolated, either by transmetallation, or by direct deprotonation. The most favorable oxidation state for manganese is +2, giving a d_5 complex.[64, 65] This configuration favors high spin complexes, due to electronic repulsion.[64, 65] N-heterocyclic carbene ligands are strong donor ligands, favoring low spin complexes. Low spin manganese(II) complexes are quite rare,[66] making carbenes a fairly incompatible ligand for manganese.[64] To date, there are no examples of tetracarbene complexes on manganese, and few examples of manganese complexes with more than one carbene ligand.[66, 67] Many manganese(II) *bis*-NHC complexes utilize anionic ligands to enhance stability of the complex.[66] Additionally, reports of catalysis by manganese carbene complexes are few and far between.[66, 67, 68] Since manganese complexes of ligand **1** have not been isolated, we chose to bypass group 7 and test the reactivity of a chromium(III) tetracarbene *bis*-chloride complex (**8**), [($^{Me,Et}TC^{Ph}$)Cr(Cl)$_2$](PF$_6$), previously synthesized by the Jenkins group.[57]

Complex **8** is prepared by transmetallation of **3** with chromium(II) chloride, undergoing oxidation with the silver(I) chloride side product to give a chromium(III) complex.[57] There is some literature precedence for group transfer catalysis on chromium(III). Some chromium(III) complexes, notably salens, have been reported as catalysts for epoxidation,[69, 70] *via* group transfer of an oxo, but the yields are poor. A few chromium(V) imides have reported group transfer of an imide to a phosphine, but not to an alkene.[71, 72] A chromium(IV) imide prepared by our group proved capable of performing group transfer with an alkene to make an aziridine, but the reaction was non-catalytic.[73]

Test Conditions for Aziridination

Complex **8** was isolated according to the literature.[57] It was dissolved in a solution of acetonitrile, and 1-decene and *p*-tolyl azide were added in equivalency. The reaction was heated at 85 ^{o}C. The reaction was monitored by GC/MS for consumption of the azide. After three days, complete consumption of the azide was not attained. The reaction was halted, and the product was isolated by chromatography. 2-octyl-1-(*p*-tolyl)aziridine (**9**) was isolated in a 26 % yield, compared to a 5 % control. The characterization of **9** was in accord with the literature.[35]

Further reactions were run to determine the ideal conditions for aziridination catalysis. Running the aziridination at a 3:1 alkene to azide ratio gave roughly a three-fold increase in both the control and the catalytic yields, 12 % and 61 %, respectively. The ideal conditions were determined to be a 3:1 alkene to azide

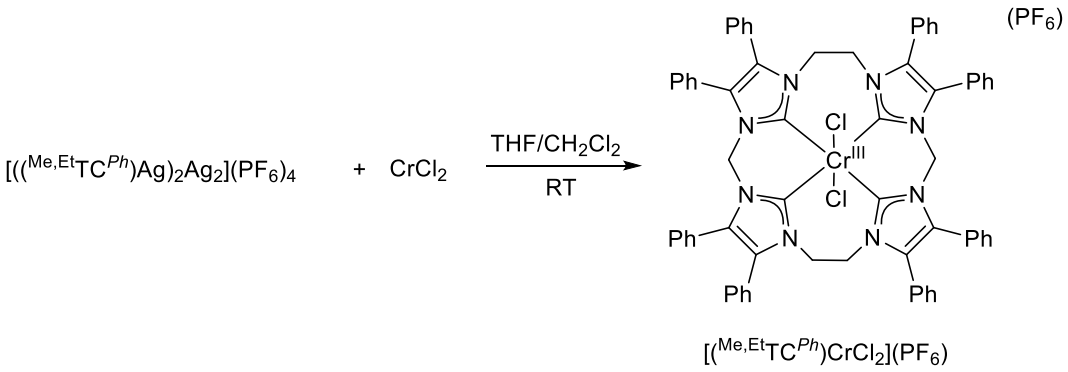


Figure 2.1: Synthesis of [($^{Me,Et}TC^{Ph}$)Cr(Cl)$_2$](PF$_6$), (8).

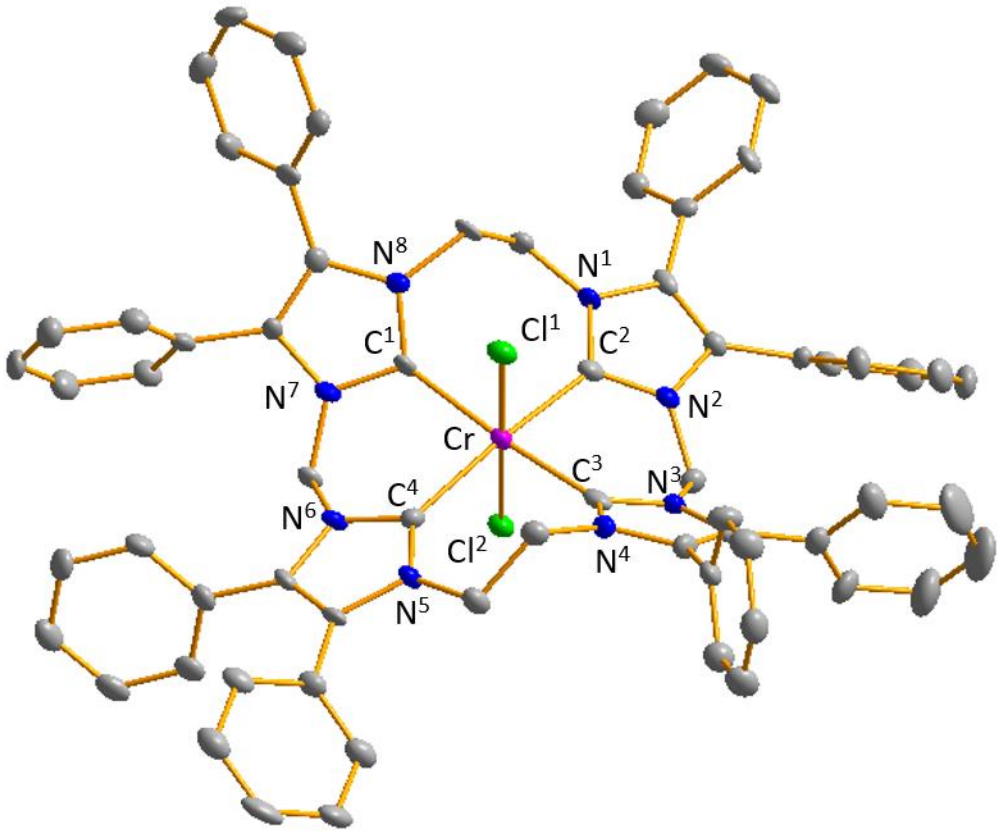


Figure 2.2: Crystal structure of [($^{Me,Et}TC^{Ph}$)Cr(Cl)$_2$](PF$_6$), (8), published previously.[2] Purple, gray, blue, and green ellipsoids represent chromium, carbon, nitrogen, and chloride, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for Cl.

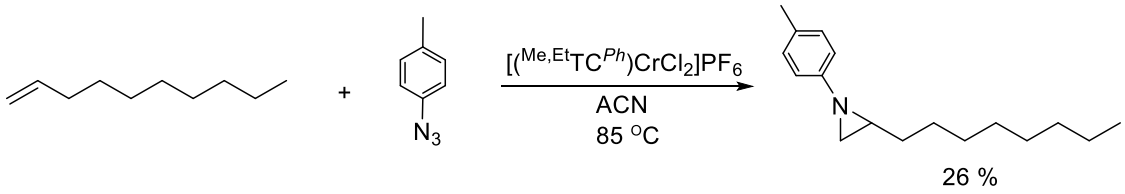


Figure 2.3: Synthesis of Aziridine 9.

ratio gave roughly a three-fold increase in both the control and the catalytic yields, 12 % and 61 %, respectively. The ideal conditions were determined to be a 3:1 alkene to azide ratio with a 2 % loading of **8** as the catalyst. These results are summarized in **Table 2.1**.

Since the catalyst has axial chloride ligands blocking both sites, it likely activates one of the chromium-chloride bonds to generate a five-coordinate chromium(III) complex with a single axial chloride ligand as the active catalyst. We therefore attempted to react **8** with halide abstractors to generate such a chromium complex *in situ*. These reaction conditions, to our surprise, generated no catalysis whatsoever. Using a twofold excess of silver(I) hexafluorophosphate as a halide abstracting reagent gave a yield consistent with a control reaction under the current conditions (4 %). Using a single equivalent of silver(I) hexafluorophosphate gave a yield of 18 %, while using thallium(I) hexafluorophosphate a yield of 23 %. These results are summarized in **Table 2.2**.

Solvent Effects

We next pursued a series of test reactions to determine the ideal solvent

Table 2.1: Test Catalysis Condition for Aziridination with 8.

Entry	Aziridine	Alkene:Azide	Time/Temperature/Cat. loading	Yield[a]
1	**9**	1:1	3 days/85 ^{o}C/2 %	26 %
2	**9**	1:1	3 days/85 ^{o}C/0 %	5 %
3	**9**	3:1	3 days/85 ^{o}C/2 %	61 %
4	**9**	3:1	3 days/85 ^{o}C/0 %	12 %
5	**9**	10:1	3 days/85 ^{o}C/2 %	67 %

catalytic aziridination. Acetonitrile had been our first choice, and we decided to screen a series of solvent across the polarity range and see which would be best. Acetonitrile gave a 61 % yield for aziridination, so we tried dimethylformamide next. This reaction gave a 46 % yield, not a control result, but distinctly inferior to the reaction in acetonitrile. Dimethyl sulfoxide, gave a 13 % yield of aziridine, while pyridine gave a 31 % yield (**Table 2.3**).

Synthesis of Non-protic Functionalized Aziridines

With the ideal conditions for our catalytic system determined, we decided to expand the substrate scope for our catalytic system. Reaction of *p*-tolyl azide with cyclooctene gave the aziridine 9-(*p*-tolyl)-9-azabicyclo[6.1.0]nonane, (**10**), in 52 % yield. Its characterization matched what was previously reported.[35] Reaction of *p*-tolyl azide with a trisubstituted alkene, 1-methylcyclohexene, gave no identifiable aziridine product. In light of this result, we decided that it would be futile to test any tetrasubstituted alkenes. Catalytic reactions of 1-decene with 1-azido-4-methoxybenzene and 1-azido-4-chlorobenzene gave the corresponding aziridines **11** and **12** in 56 % and 35 % yields, respectively. The products were identified by comparison to the literature.[74] While chloride functional groups have some limited use in organic synthesis, neither chlorides or methoxides are especially useful reagents. We decided to test more synthetically relevant functional groups. We were especially interested to see how tolerant **8** is of oxygen-containing functional functional groups. These functional groups are often found on aziridine containing natural products, so tolerance of these functional groups would be important for a

Table 2.2: Halide Abstractor Effects on Aziridination Catalysis with 8.

Entry	Aziridine	Additive	Loading	Yield[a]
1	**9**	Thallium Hexafluorophosphate	1 %	23 %
2	**9**	Silver Hexafluorophosphate	1 %	18 %
3	**9**	Thallium Hexafluorophosphate	2 %	4 %
4	**9**	Silver Hexafluorophosphate	2 %	4 %

Table 2.3: Solvent Effects on Aziridination Catalysis with 8.

Entry	Aziridine	Solvent	Yield[a]
1	**9**	Acetonitrile	61 %
2	**9**	Dimethylformamide	46 %
3	**9**	Dimethyl sulfoxide	13 %
4	**9**	Pyridine	31 %

Reactions run under the conditions of **Table 2.1: Entry 3**, unless otherwise noted.
[a]All reported yields are isolated.

practical aziridination catalyst. Using 4-azidobenzaldehyde as our azide, we were pleased to discover that we could synthesize 4-(2-octylaziridin-1-yl)benzaldehyde (**13**) from 1-decene in 40 % yield. As this product had not been reported before, we published its full characterization. In order to further test the stability of **8** vs carbonyls, we reacted *p*-tolyl azide with ethyl 10-undecenoate under the established conditions. From the reaction, we were able to isolate the predicted aziridine product, ethyl 9-(1-(*p*-tolyl)aziridin-2-yl)nonanoate (**14**). Unfortunately, it was in a poor yield, 23 %. **14** also has never been previously synthesized, so we reported its characterization. The results are all summarized in **Table 2.4**.

Synthesis of Protic Aziridines

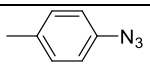
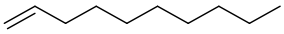
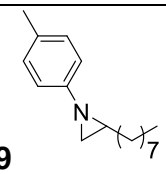
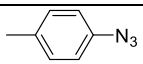
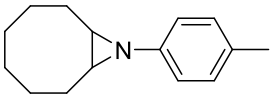
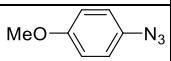
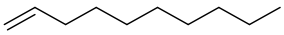
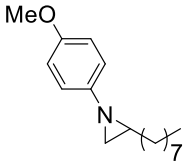
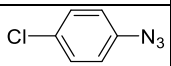
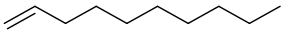
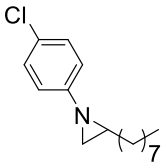
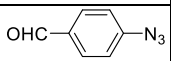
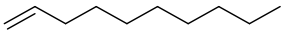
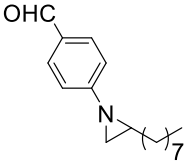
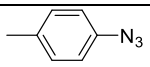
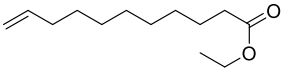
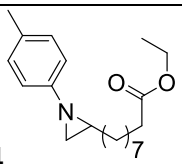
Previous examples in the literature of catalytic aziridination have largely been limited to non-protic functional groups, such as chloride and nitro groups.[27, 30, 33, 35, 40] There is only one prior published example of aziridination with an unprotected alcohol by Cenini, but the product isolated was barely characterized.[29] However, many aziridine-containing natural products and reactive intermediates contain alcohols or amines. The lack of effective catalysts for this transformation represents a distinct problem for aziridine synthesis, and we sought to alleviate this deficiency. Given that **8** had shown catalysis with polar functional groups, we decided to test its reaction with alcohol functionalized azides and alkenes.

4-pentenol was reacted with *p*-tolyl azide using **8** as a catalyst; we obtained a 41% yield of an oil that was initially assigned as the aziridine. However, on closer examination of the spectra and careful search of the literature, we determined that

the product was actually 4-methyl-N-((tetrahydrofuran-2-yl)methyl)aniline (**15**), previously synthesized by Antilla and Buchwald.[75] We postulated that the aziridine was formed during the course of the reaction, but **8** acted as a Lewis acid catalyst for a nucleophilic attack on the aziridine ring by the alcohol, yielding the observed product. The literature contains some prior reports of aziridine and epoxide ring opening by nucleophiles catalyzed by early transition metals.[76, 77] In order to prevent ring opening so we could isolate the aziridine, we discarded 4-pentenol and replaced it with 9-decenol. With **8** as a catalyst, we reacted *p*-tolyl azide with 9-decenol and isolated 8-(1-(*p*-tolyl)aziridin-2-yl)octanol (**16**) in 32% yield. We saw the same behavior with phenolic alkenes, 4-allylphenol gave the corresponding aziridine, 4-((1-(*p*-tolyl)aziridin-2-yl)methyl)phenol (**17**), in a 26% yield, while 2-allylphenol made the ring opened product, N-((2,3-dihydrobenzofuran-2-yl)methyl)-4-methylaniline (**18**), in a 39% yield.

Having explored the reactivity of aziridines functionalized on the alkene portion, we turned our attention to aziridines functionalized with alcohols on the azide portion. We reacted 4-azidophenol with 1-decene under catalytic conditions to try and make the corresponding aziridine, but we were not able to detect any aziridine product. Upon further investigation, we discovered that 4-azidophenol decomposed rapidly upon heating, so we switched to 3-azidophenol. Using 3-azidophenol, we were able to synthesize the aziridine 3-(2-octylaziridin-1-yl)phenol (**19**), in a 35% yield.

Table 2.4: Substrate Scope for Catalytic Aziridination.

Entry	Azide	Alkene	Aziridine	Yield[a]
1			 **9**	61%
2			 **10**	52%
3			 **11**	56%
4			 **12**	35%
5			 **13**	40%
6			 **14**	23%

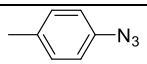
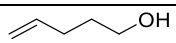
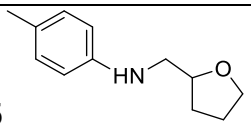
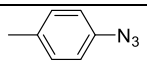
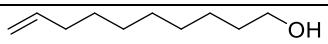
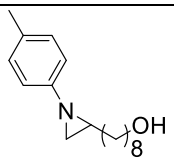
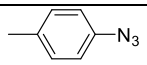
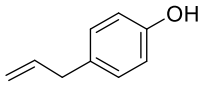
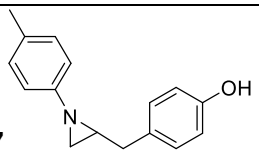
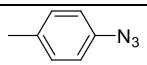
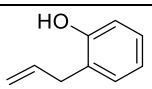
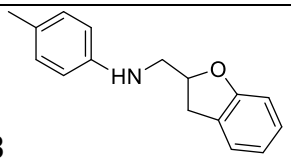
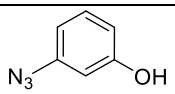
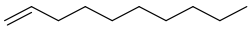
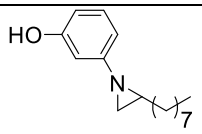
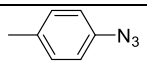
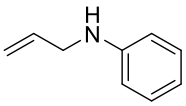
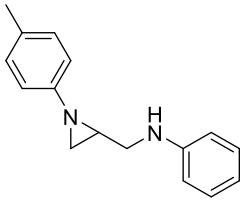
Reactions run under the conditions of **Table 1: Entry 3**, unless otherwise noted.
[a]All reported yields are isolated.

Since we had been able to synthesize a series of alcohol-functionalized aziridines, we decided to test and see if we could do the same with amine-functionalized aziridines. We reacted N-allylaniline with *p*-tolyl azide under the catalytic conditions and isolated N-((1-(*p*-tolyl)aziridin-2-yl)methyl)aniline (**20**) in a 30% yield. In a moment of grand extravagance, we tested the reaction of *p*-tolyl azide with 9-decenoic acid to see if the catalyst was tolerant of carboxylic acids. No aziridine product was detected in the reaction, and no ring opened products were detected either. The results for protic aziridination catalysis are summarized in **Table 2.5**.

One disadvantage with our current catalytic system has been the low yields compared to previous catalysts. However, catalyst **2** used previously by the Jenkins group required a large excess of alkene to get the observed yields. How would **2** fare in a head-to-head matchup with **8** under the current reaction conditions? Complex **8** gave a 61% yield of **9** under catalytic conditions, when **2** was tested under the same conditions, the resulting yield was only 10%, roughly a control yield. Additionally, **8** was able to synthesize aziridines functionalized with alcohols, while **2** formed no aziridine products or ring-opened products under similar conditions.

In order to better understand the observed decrease in yields for alcohol-functionalized aziridines, we performed two internal conversion experiments *via* ^{1}H NMR on the syntheses of aziridines **16** and **19**. During these experiments, we determined that the percent conversion of the aziridines in the reaction was

Table 2.5: Results for Aziridination Catalysis with Protic Substrates.

Entry	Azide	Alkene	Product	Yield[a]
1			 **15**	41%
2			 **16**	32%
3			 **17**	26%
4			 **18**	39%
5			 **19**	35%[b]
6			 **20**	30%

Reactions run under the conditions of **Table 1: Entry 3**, unless otherwise noted.
[a] All reported yields are isolated. [b] Reaction was run for five days

significantly higher than the isolated yields, likely due to the difficulty associated with separating organic products containing alcohols. Compound **16**, isolated in a 32% yield, had a conversion of 50%, *in situ*. The alkene had two and a half equivalents remaining, and the azide had a 30% remainder. Of the remaining 20% of the azide, 18% had been reduced to the corresponding aniline, which has been observed previously,[55, 58] leaving 2% of the azide unaccounted for. This is within the expected error of 5 % for this experiment. The synthesis of **19** gave similar results, with 44% conversion to **19**. Additionally, 2.3 equivalents of the alkene were left over along with 28% of the azide, with 28% conversion to aniline. Again, the expected error on the experimental integration is 5 %. We presume that the *in situ* yields are representative for the catalysis of protic substrates.

Mechanistic Studies

The obvious question is why is **8** an effective catalyst at low alkene loadings when **2** is ineffective under the same conditions? Previous examples of chromium(V) imide complexes have never been reported to do nitrene group transfer to an alkene. In order to answer these concerns, we asked our collaborators in the Roy group, Dr. Jesse Kern and Bradley Terry, to perform calculations for us on our proposed catalytic cycle. They discovered that the key to our catalysis was the presence of an axial chloride ligand.[62] Calculations run with a five coordinate chromium species showed that formation of the imide species was favorable with a ΔE of -54 kcal/mol. At this point, the imide complex could either form a tetrazene or an aziridine. Aziridine formation was slightly higher

in energy than imide formation (ΔE of -44 kcal/mol vs ΔE of -54 kcal/mol), but it was distinctly favorable vs tetrazene synthesis, which had an energy reduction ΔE of -33 kcal/mol. Without the axial chloride ligand, the energy of the imide was at a ΔE of -83 kcal/mol and the energy of the tetrazene had a ΔE of -73 kcal/mol, significantly below the energy of aziridination. These results both explain why **8** is an effective aziridination catalyst as opposed to other chromium complexes, and why the catalysis had significantly reduced effectiveness when silver(I) or thallium(I) salts are added.

Conclusion

In conclusion, we have developed the use of a chromium(III) tetracarbene *bis*-chloride complex (**7**) as a catalyst for C_2 + N_1 aziridination. This catalyst represents the first group 6 metal complex to perform C_2 + N_1 catalytic aziridination. Complex **8** proved capable of performing catalytic aziridination at low alkene loadings and is the most effective catalyst at low loadings for aliphatic alkenes to date. Additionally, it also proved capable of performing aziridination on unprotected alcohols and amines, a largely unattained achievement. The key feature of this catalyst was the presence of a fifth axial ligand in the catalytic cycle, which suggests the addition of a single axial ligand to existing aziridination catalysts could enhance their reactivity. Furthermore, the ring-opening reactions seen on 4-pentenol and 2-allylphenol suggests this phenomena is worth further study, to see if conditions could be developed for aziridination and subsequent ring opening to the corresponding secondary amines.

Experimental

All reactions were performed under a dry nitrogen atmosphere in a glovebox. Solvents were dried on an Innovative Technologies (Newburgport, MA) Pure Solv MD-7 Solvent Purification System and degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves. Chloroform-d and acetonitrile-d3 were purchased from Cambridge Isotope Lab and used without further purification. All azides were synthesized by the procedure developed by Smith and Brown.[28] The compounds *p*-tolyl azide,[28] 4-azidobenzaldehyde,[78] 1-azido-4-methoxybenzene,[79] 1-azido-4-chlorobenzene,[80] and 3-azidophenol[81] were prepared from literature procedures or as described previously. The compounds $[(^{Me,Et}TC^{Ph})Cr(Cl)_2](PF_6)$ and $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ were prepared as previously described in the literature.[57] All other reagents were purchased from commercial vendors and degassed by three freeze-pump-thaw cycles and dried over activated molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury 300 MHz or a Varian VNMRS 500 MHz narrow-bore broadband system. ^{1}H and ^{13}C NMR chemical shifts were referenced to the residual solvent. DEPT, HSQC, and COSY were performed on a Varian VNMRS 500 MHz narrowbore broadband system. All mass spectrometry analyses were conducted at the Mass Spectrometry Center located in the Department of Chemistry at the University of Tennessee. The DART analyses were performed using a JEOL AccuTOF-D time-of-flight (TOF) mass spectrometer with a DART (direct analysis

in real time) ionization source from JEOL USA, Inc. (Peabody, MA). Mass spectrometry sample solutions of organic compounds from catalysis reactions were prepared in chloroform or acetonitrile. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance.

General Catalytic Reaction: [(^{Me,Et}TC^{Ph})Cr(Cl)$_2$](PF$_6$) (**8**) was added to a 20 mL vial, along with 4 mL of acetonitrile as the solvent. The solution was stirred at room temperature until dissolution was achieved. Three equivalents of alkene and one equivalent of azide were added, and the reaction was heated at 85 °C for three days, unless otherwise noted. Then the reaction solution was filtered over Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using gradient dilution unless otherwise noted.

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 2 % catalyst loading: 1-decene (0.998 g, 7.11 mmol), *p*-tolyl azide (0.0947 g, 0.711 mmol), and **8** (0.0174 g, 0.0142 mmol) were used in the General Catalytic Reaction, purification was achieved using 1 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.117 g, 67%. The characterization (^{1}H and ^{13}C NMR) matched the literature data[35].

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 0 % catalyst loading: 1-decene (0.104 g, 0.722 mmol) and *p*-tolyl azide (0.103 g, 0.723 mmol) were used in the General Catalytic Reaction, purification was achieved using 1 % ethyl acetate in

hexanes on a silica gravity column, resulting in a yield of 0.0086 g, 5 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 0 % catalyst loading: 1-decene (0.294 g, 2.09 mmol) and *p*-tolyl azide (0.0954 g, 0.698 mmol) were used in the General Catalytic Reaction, purification was achieved using 1 % ethyl acetate in hexanes on a silica gravity column, resulting in a yield of 0.0217 g, 12 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 2 % catalyst loading: 1 was isolated from a recrystallization of a reaction stored in a -30 °C freezer. 1-decene (0.2198 g, 1.567 mmol), *p*-tolyl azide (0.0696 g, 0.522 mmol), and **8** (0.0128 g, 0.0104 mmol) were used in the General Catalytic Reaction, purification was achieved using 1 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0711 g, 55 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 2 % catalyst loading: 1-decene (0.3078 g, 2.194 mmol), *p*-tolyl azide (0.0974 g, 0.731 mmol), and **8** (0.0179 g, 0.0146 mmol) were used in the General Catalytic Reaction, substituting DMF for acetonitrile, purification was achieved using 5 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0832 g, 46 %. (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 2 % catalyst loading: 1-decene (0.310 g, 2.209 mmol), *p*-tolyl azide (0.0991 g, 0.744 mmol), and **8** (0.0182 g,

0.0149 mmol) were used in the General Catalytic Reaction, substituting DMSO for acetonitrile, purification was achieved using 1 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0231 g, 13 %. (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 2 % catalyst loading: 1-decene (0.288 g, 2.05 mmol), *p*-tolyl azide (0.0911 g, 0.684 mmol), and **8** (0.0168g, 0.0137 mmol) were used in the General Catalytic Reaction, substituting pyridine for acetonitrile, purification was achieved using 5 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0525 g, 31 %. (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 9-(*p*-tolyl)-9-azabicyclo[6.1.0]nonane, 10. 2 % catalyst loading: ciscyclooctene (0.296 g, 2.68 mmol), *p*-tolyl azide (0.119 g, 0.895 mmol), and **8** (0.0219 g, 0.0179 mmol) were used in the General Catalytic Reaction, purification was achieved using 5 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.101 g, 52 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 1-(4-methoxyphenyl)-2-octylaziridine, 11. 2 % catalyst loading: 1-decene (0.349 g, 2.49 mmol), 1-azido-4-methoxybenzene (0.124 g, 0.829 mmol), and **8** (0.0203 g, 0.0166 mmol) were used in the General Catalytic Reaction, purification was achieved using 20 % ethyl acetate in hexanes, resulting in a yield of 0.122 g, 56 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[40]

Synthesis of 1-(4-chlorophenyl)-2-octylaziridine, 13. 2 % catalyst loading: 1-decene (0.352 g, 2.51 mmol), 1-azido-4-chlorobenzene (0.128 g, 0.831 mmol), and **8** (0.0207 g, 0.0169 mmol) were used in the General Catalytic Reaction, purification was achieved using purification was achieved using 1 % ethyl acetate in hexanes, resulting in a yield of 0.0767 g, 35 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[40]

Synthesis of 4-(2-octylaziridin-1-yl)benzaldehyde, 12. 2 % catalyst loading: 1-decene (0.313 g, 2.23 mmol), 4-azidobenzaldehyde (0.110 g, 0.745 mmol), and **8** (0.0196 g, 0.0160 mmol) were used in the General Catalytic Reaction, purification was achieved using 10 % ethyl acetate in hexanes, resulting in a yield of 0.0769 g, 40 % ^{1}H NMR ($CDCl_3$, 499.74 MHz): δ 9.86 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.3Hz, 2H), 2.18 (s, 2H), 2.15, (m, 1H), 1.58 (m, 4H), 1.31 (m, 10H), 0.89 (t, J = 7.1Hz, 3H). ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 191.05, 161.19, 131.34, 131.15, 121.05, 40.67, 34.34, 33.10, 31.99, 29.69, 29.64, 29.39, 27.70, 22.79, 14.24. IR: 2923, 2853, 1694, 1596, 1570, 1506, 1463, 1406, 1302, 1212, 1156, 836, 721 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 260.20059 (found); $[C_{17}H_{26}NO]^+$ 260.20144 (calcd).

Synthesis of ethyl 9-(1-(*p*-tolyl)aziridin-2-yl)nonanoate, 14. 2 % catalyst loading: ethyl 10-undecenoate (0.402 g, 1.89 mmol), *p*-tolyl azide (0.0840 g, 0.631 mmol), and **8** (0.0155 g, 0.0127 mmol) were used in the General Catalytic Reaction, purification was achieved using 10 % ethyl acetate in hexanes, resulting in a yield of 0.0465 g, 23 %. ^{1}H NMR ($CDCl_3$, 499.74 MHz): δ 7.01 (d, J = 8.2 Hz,

2H), 6.88 (d, J = 8.3 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.29 (t, J = 7.6 Hz, 2H), 2.27 (s, 3H), 2.02 (m, 3H), 1.58 (m, 6H), ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 152.55, 131.56, 129.50, 120.66, 63.00, 40.38, 34.18, 33.29, 32.88, 29.67, 29.56, 29.47, 27.78, 25.84, 20.77. IR: 3334, 2924, 2853, 1510, 1291, 1055, 820 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 262.21693 (found); $[C_{17}H_{28}NO]^+$ 262.21654 (calcd).

Synthesis of 4-methyl-N-((tetrahydrofuran-2-yl)methyl)aniline, 15. 2 % catalyst loading: 4-pentenol (0.197 g, 2.29 mmol), *p*-tolyl azide (0.102 g, 0.762 mmol), and **8** (0.0180 g, 0.0147 mmol) were used in the General Catalytic Reaction, purification was achieved using 50% ethyl acetate in hexanes, resulting in a yield of 0.0602 g, 41 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[75]

Synthesis of 8-(1-(*p*-tolyl)aziridin-2-yl)octanol, 16. 2 % catalyst loading: 9-decenol (0.312 g, 2.00 mmol), *p*-tolyl azide (0.0887 g, 0.666 mmol), and **8** (0.0163 g, 0.0133 mmol) were used in the General Catalytic Reaction, purification was achieved using 20 % ethyl acetate in hexanes, resulting in a yield of 0.0555 g, 32 %. ^{1}H NMR ($CDCl_3$, 499.74 MHz): δ 7.01 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 3.60 (q, J = 6.5 Hz, 2H), 2.26 (s, 3H), 2.01 (m, 3H), 1.79 (t, J = 4.9 Hz, 1H), 1.55 (m, 6H), 1.34 (m, 8H). ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 152.55, 131.56, 129.50, 120.66, 63.00, 40.38, 34.18, 33.29, 32.88, 29.67, 29.56, 29.47, 27.78, 25.84, 20.77. IR: 3334, 2924, 2853, 1510, 1291, 1055, 820 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 262.21693 (found); $[C_{17}H_{28}NO]^+$ 262.21654 (calcd).

Synthesis of 4-((1-(*p*-tolyl)aziridin-2-yl)methyl)phenol, 17. 2 % catalyst loading: 4-allylphenol (0.308 g, 2.30 mmol), *p*-tolyl azide (0.102 g, 0.765 mmol), and **8** (0.0188 g, 0.0153 mmol) were used in the General Catalytic Reaction, purification was achieved using 20 % ethyl acetate in hexanes, resulting in a yield of 0.0478 g, 26 %. ^{1}H NMR ($CDCl_3$, 499.74 MHz): δ 7.15 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 2.84 (dd, J_1 = 14.2 Hz, J_2 = 4.5Hz, 1H), 2.80 (dd, J_1 = 14.2 Hz, J_2 = 7.5 Hz, 1H), 2.32 (m, 1H), 2.25 (m, 4H), 2.15 (d, J = 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 154.82, 151.28, 132.29, 130.83, 130.08, 129.64, 120.83, 115.73, 42.39, 38.48, 34.35, 20.79. IR: 3311, 2919, 1612, 1509, 1239, 1110, 908, 770, 729 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 240.13900 (found); $[C_{16}H_{18}NO]^+$ 240.13829 (calcd).

Synthesis of N-((2,3-dihydrobenzofuran-2-yl)methyl)-4-methylaniline, 18. 2 % catalyst loading: 2-allylphenol (0.397 g, 2.96 mmol), *p*-tolyl azide (0.131 g, 0.987 mmol), and **8** (0.0242 g, 0.0198 mmol) were used in the General Catalytic Reaction, purification was achieved using a gravity column with chloroform as the eluent, resulting in a yield of 0.0922 g, 39 %. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 7.19 (d, J = 7.3 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.83 (t, J = 7.9 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 8.2 Hz, 2H), 4.96 (dtd, J_1 = 9.2 Hz, J_2 = 7.0 Hz, J_3 = 4.7 Hz, 1H), 4.38 (s br, 1H), 3.33 (m, 3H), 3.02 (dd, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 1H), 2.18 (s, 3H). ^{13}C NMR (CD_3CN, 125.66 MHz): δ 160.36, 147.36, 130.53, 128.83, 128.05, 126.98, 126.15, 121.33, 113.82, 110.04, 82.53,

49.00, 33.67, 20.40. IR: 3397, 2917, 2103, 1614, 1519, 1478, 1226, 806, 747 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 240.13826 (found); $[C_{16}H_{18}NO]^+$ 240.13829 (calcd).

Synthesis of 3-(2-octylaziridin-1-yl)phenol, 19. 2 % catalyst loading: 1-decene (0.316 g, 2.25 mmol), 3-azidophenol (0.101 g, 0.750 mmol), and **8** (0.0184 g, 0.0150 mmol) were used in the General Catalytic Reaction, the reaction ran for five days instead of three. Purification was achieved using 1 % methanol in chloroform, resulting in a yield of 0.0649 g, 35 %. ^1H NMR ($CDCl_3$, 499.74 MHz): δ 7.05 (t, J = 7.9 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.46 (m, 2H), 2.11 (m, 1H), 2.06 (d, J = 3.8 Hz, 1H), 2.03 (d, J = 6.4 Hz, 1H) 1.54 (m, 4H), 1.27 (m, 10H), 0.89 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 156.91, 155.22, 130.07, 113.08, 110.61, 108.79, 41.11, 34.38, 32.83, 32.01, 29.69, 29.62, 29.41, 27.77, 22.81, 14.26. IR: 3339, 3059, 2923, 2853, 1590, 1458, 1178, 1153, 856, 755, 691 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 248.20005 (found); $[C_{16}H_{26}NO]^+$ 248.20089 (calcd).

Synthesis of N-((1-(*p*-tolyl)aziridin-2-yl)methyl)aniline, 20. 2 % catalyst loading: N-allylaniline (0.301 g, 2.26 mmol), *p*-tolyl azide (0.100 g, 0.752 mmol), and **8** (0.0184 g, 0.0150 mmol) were used in the General Catalytic Reaction, purification was achieved using 10 % ethyl acetate in hexanes, resulting in a yield of 0.0538 g, 30 %. ^1H NMR ($CDCl_3$, 499.74 MHz): δ 7.34 (m, 2H), 7.15 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.4 Hz, 2H), 6.87 (m, 3H), 4.19 (br s, 1H), 3.67 (d, J = 12.9 Hz, 1H), 3.37 (dd, J_1 = 12.3 Hz, J_2 = 6.0 Hz, 1H), 2.53 (m, 1H), 2.41 (s, 3H), 2.38 (m, 1H), 2.21 (d, J = 6.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.66 MHz): δ 151.95, 148.18, 131.97, 129.63, 129.42, 120.55, 117.84, 113.32, 46.08, 39.01, 32.38, 20.78. IR:

3394, 3021, 2918, 1600, 1507, 1313, 1255, 809, 750, 612 cm^{-1}. DART HR MS (m/z): $[M+H]^+$ 239.15394 (found); $[C_{16}H_{19}N_2]^+$ 239.15428 (calcd). 14 was found to be thermodynamically unstable, decomposing within a week.

Comparison aziridination reactions with $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ (2) under general catalytic conditions:

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, 9. 2 % **2** loading: 1-decene (0.310 g, 2.21 mmol), *p*-tolyl azide (0.0979 g, 0.735 mmol), and **2** (0.0204 g, 0.0147 mmol) were used in the General Catalytic Reaction (substituting **2** for **8**), purification was achieved using 5 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0176 g, 10 %. The characterization (^1H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 8-(1-(*p*-tolyl)aziridin-2-yl)octanol, 16. 2 % **2** loading: 9-decenol (0.344 g, 2.20 mmol), *p*-tolyl azide (0.0977 g, 0.734 mmol), and **2** (0.0203 g, 0.0147 mmol) were used in the General Catalytic Reaction (substituting **2** for **8**), no aziridine product or byproduct was identified in the reaction.

Synthesis of 3-(2-octylaziridin-1-yl)phenol, 19. 2 % **2** loading: 1-decene (0.313 g, 2.23 mmol), 3-azidophenol (0.101 g, 0.744 mmol), and **2** (0.0206 g, 0.0149 mmol) were used in the General Catalytic Reaction (substituting **2** for **8**), no aziridine product or byproduct was identified in the reaction.

Comparison aziridination reactions with 1 with additional halide abstraction reagents:

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, 9. 1-decene (0.110 g, 0.787 mmol), *p*-tolyl azide (0.109 g, 0.816 mmol), silver(I) hexafluorophosphate (0.0083 g, 0.033 mmol) and **8** (0.0200 g, 0.0163 mmol) were used in the General Catalytic Reaction, purification was achieved using 5 % ethyl acetate in S7 hexanes on a silica flash column, resulting in a yield of 0.0077 g, 4 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, 9. 1-decene (0.315 g, 2.24 mmol), *p*-tolyl azide (0.098 g, 0.748 mmol), thallium(I) hexafluorophosphate (0.0051 g, 0.0145 mmol) and **8** (0.0179 g, 0.0146 mmol) were used in the General Catalytic Reaction, purification was achieved using 5% ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0423 g, 23 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, 9. 1-decene (0.271 g, 1.93 mmol), *p*-tolyl azide (0.087 g, 0.644 mmol), silver(I) hexafluorophosphate (0.0033 g, 0.013 mmol) and **8** (0.0163 g, 0.0133 mmol) were used in the General Catalytic Reaction, purification was achieved using 1 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.0289 g, 18 %. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[35]

Aziridination reactions for quantitative ^{1}H NMR analysis:

Synthesis of 8-(1-(*p*-tolyl)aziridin-2-yl)octanol, 16. 9-decenol (0.266 g, 1.70 mmol), *p*-tolyl azide (0.0756 g, 0.568 mmol), and **8** (0.009 g, 0.0073 mmol) were used in the General Catalytic Reaction, with CD_3CN substituted for the solvent.

CH_2Br_2 (0.040 mL, 0.568 mmol) was added as an internal standard for integration. ^1H NMR integration showed the following products to be present: **16**, 50 % conversion; *p*-tolyl azide, 30 %; *p*-toluidine, 18 %. The integrations have a 5 % error associated with them. Additionally, 2.5 equivalents of 9-decenol were found to be present.

Synthesis of 3-(2-octylaziridin-1-yl)phenol, 19. 1-decene (0.227 g, 1.61 mmol), 3-azidophenol (0.073 g, 0.539 mmol), and **8** (0.0132 g, 0.0108 mmol) were used in the General Catalytic Reaction, with CD_3CN substituted for the solvent. CH_2Br_2 (0.038 mL, 0.539 mmol) was added as an internal standard for integration. ^1H NMR integration showed the following products to be present: **19**, 44 %, 3-azidophenol 28 %, 3-aminophenol 28 %. The integrations have a 5 % error associated with them. Additionally, 2.3 equivalents of 1-decene were found to be present.

Select NMRs of Novel Products Prepared in this Work.

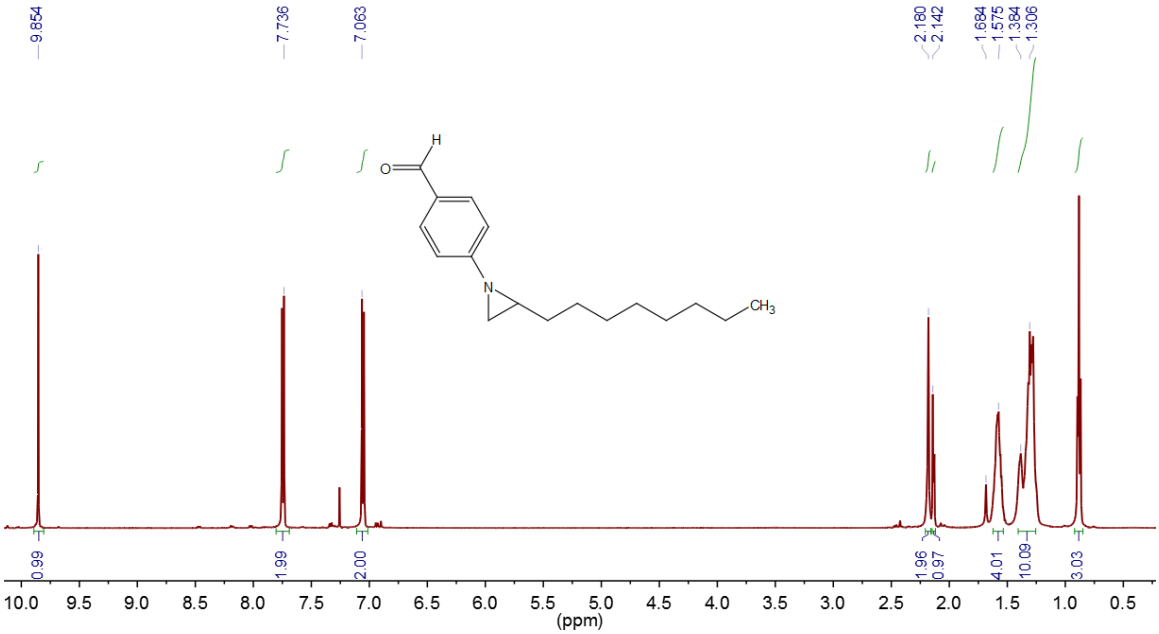


Figure 2.4: ^{1}H NMR of of 4-(2-octylaziridin-1-yl)benzaldehyde, 12.

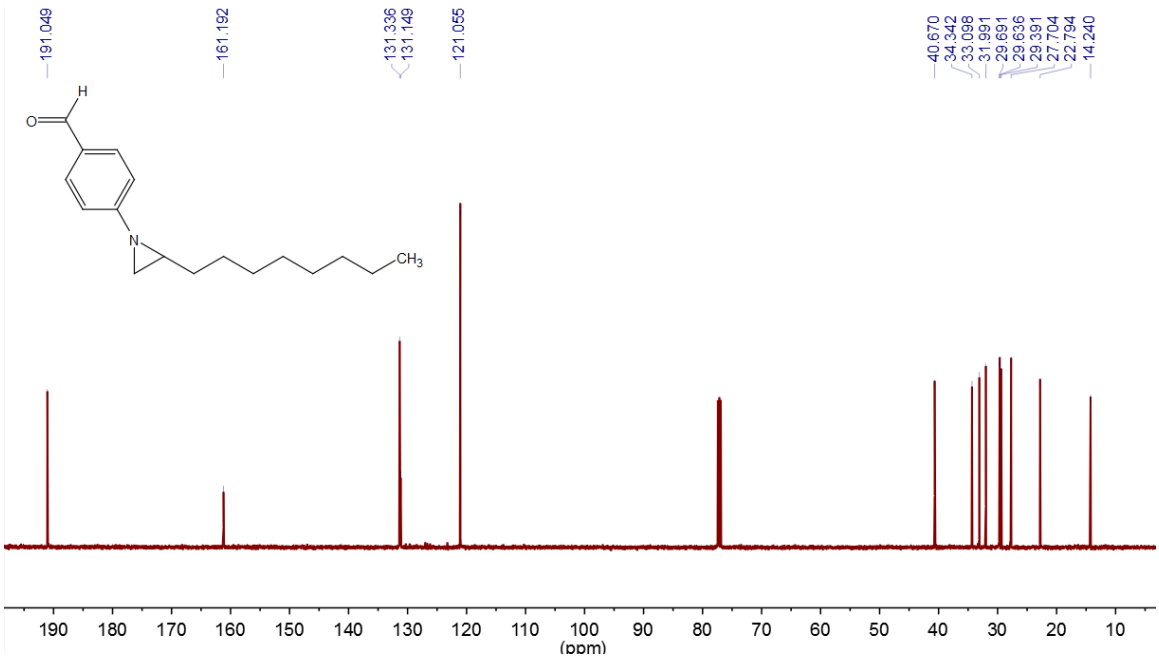


Figure 2.5: ^{13}C NMR of of 4-(2-octylaziridin-1-yl)benzaldehyde, 12.

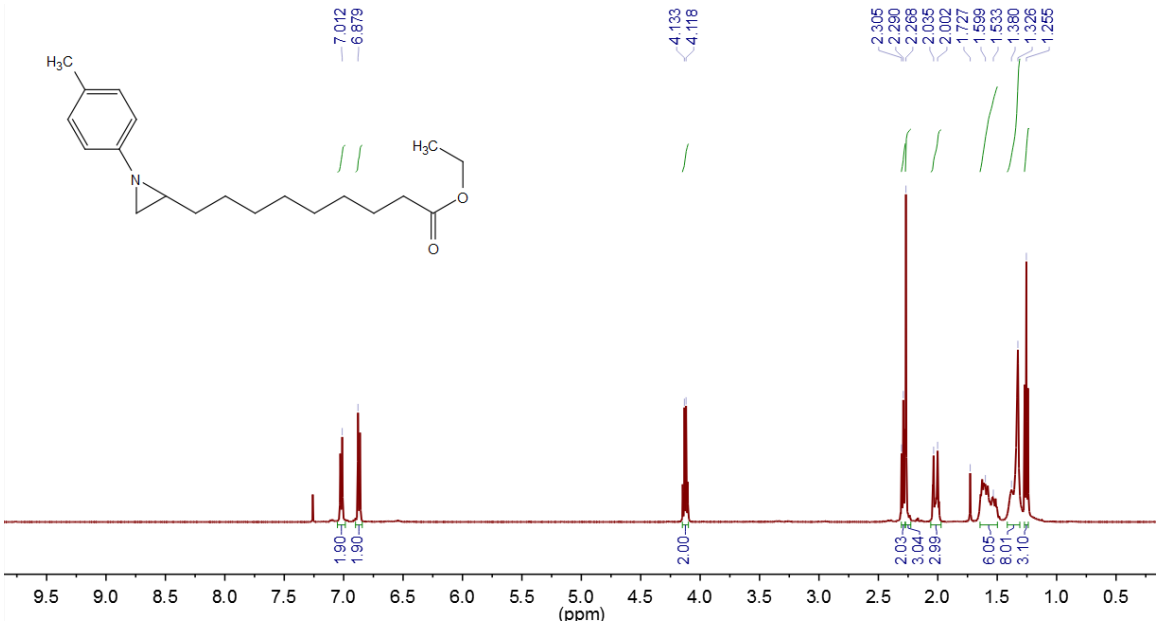


Figure 2.6: ^{1}H NMR of ethyl 9-(1-(p-tolyl)aziridin-2-yl)nonanoate, 14.

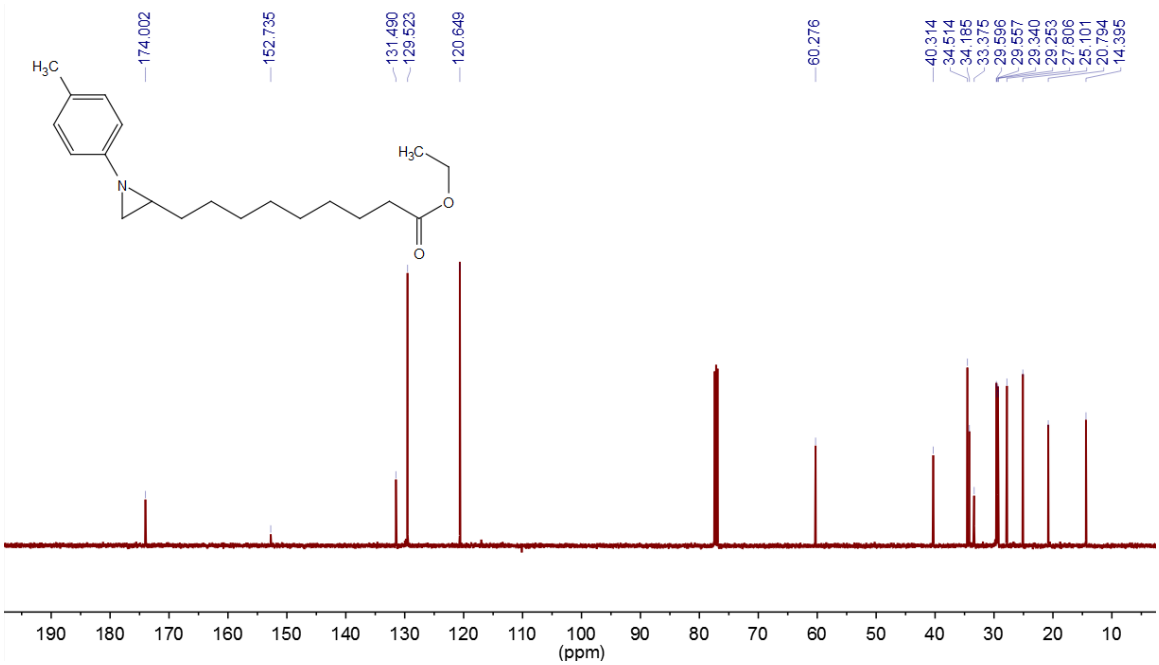


Figure 2.7: ^{13}C NMR of ethyl 9-(1-(p-tolyl)aziridin-2-yl)nonanoate, 14.

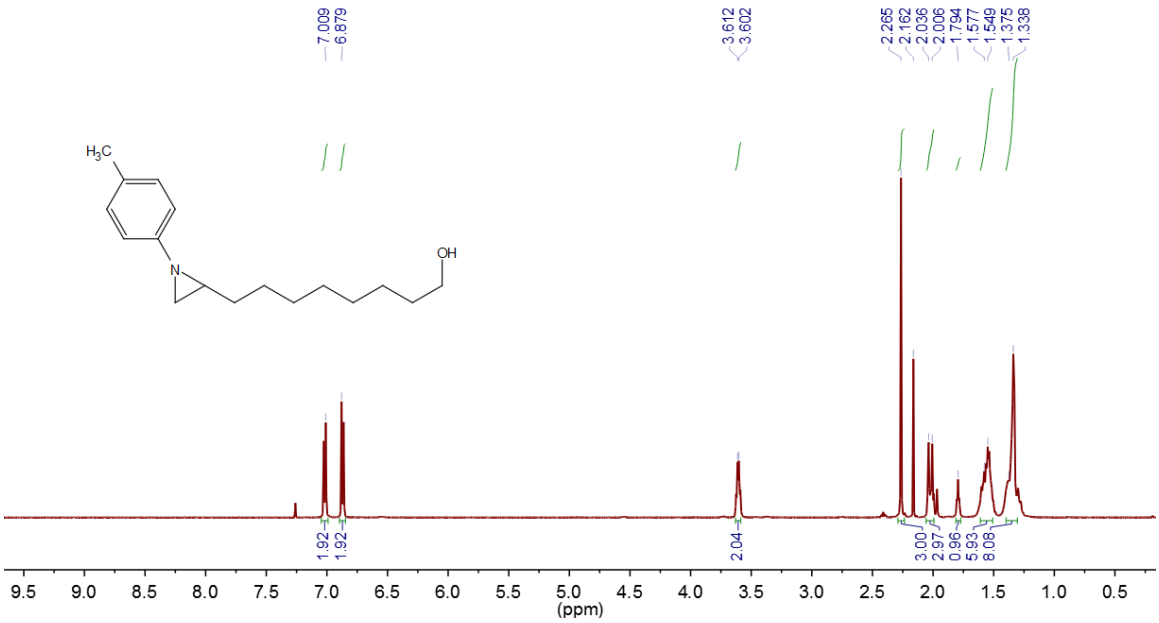


Figure 2.8: ^{1}H NMR of 8-(1-(p-tolyl)aziridin-2-yl)octanol, 16.

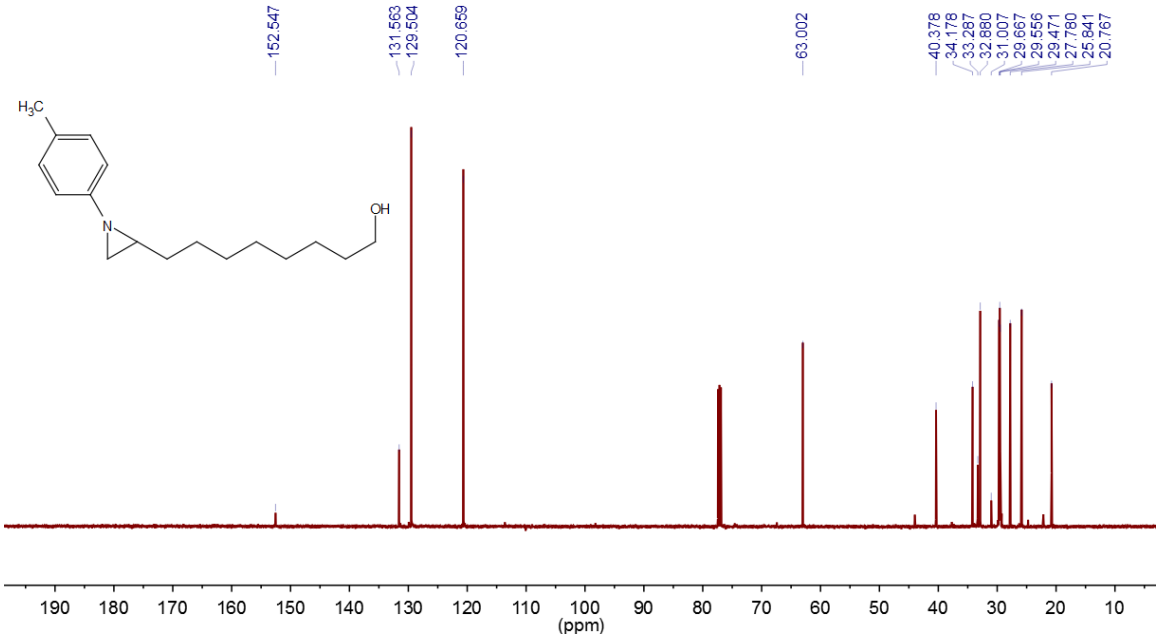


Figure 2.9: ^{13}C NMR of 8-(1-(p-tolyl)aziridin-2-yl)octanol, 16.

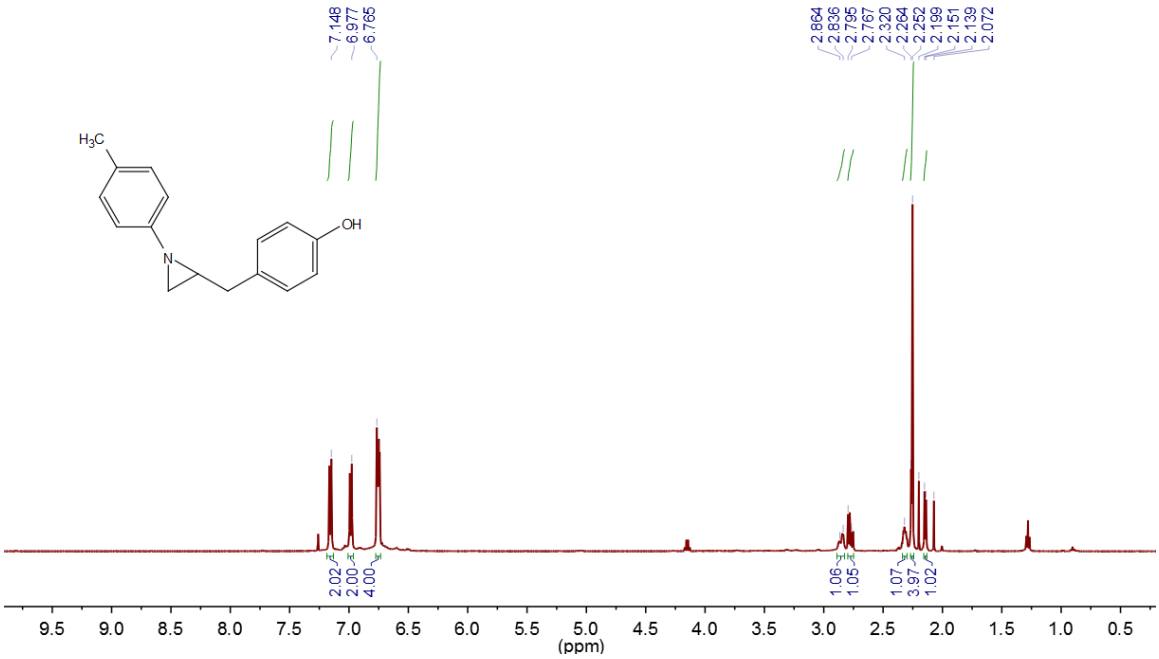


Figure 2.10: ^{1}H NMR of 4-((1-(p-tolyl)aziridin-2-yl)methyl)phenol, 17.

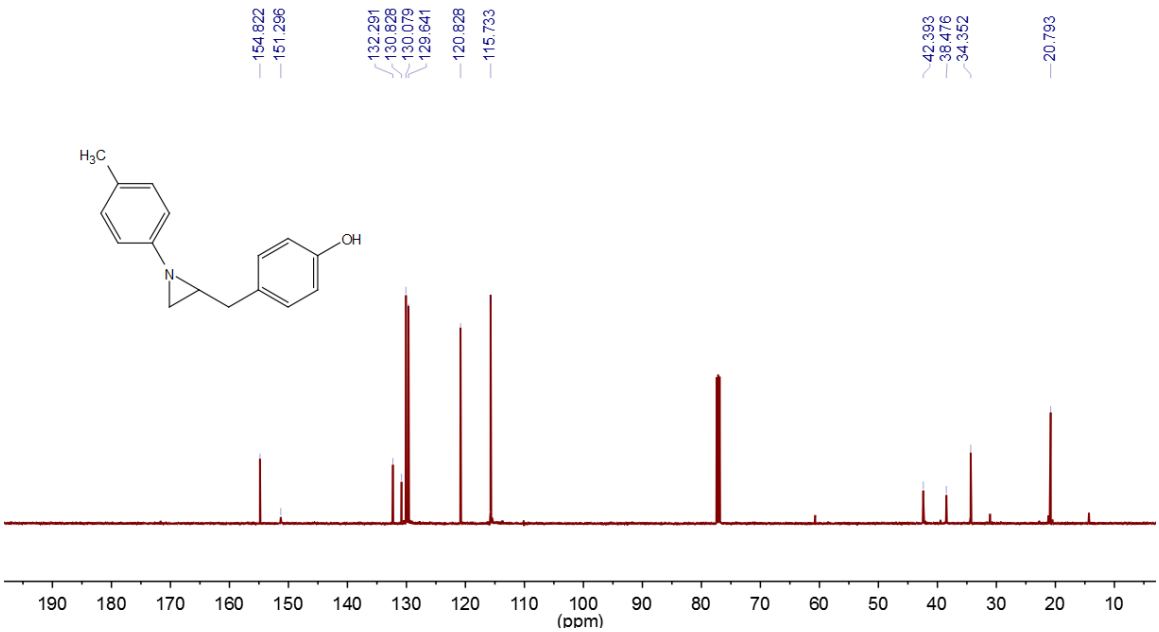


Figure 2.11: ^{13}C NMR of 4-((1-(p-tolyl)aziridin-2-yl)methyl)phenol, 17.

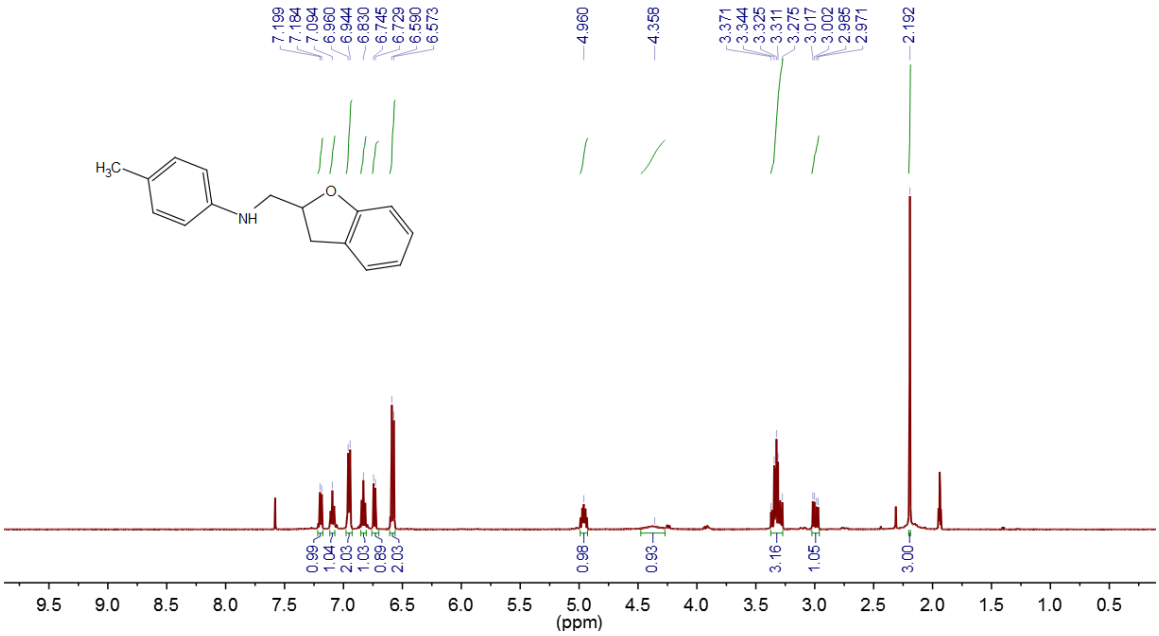


Figure 2.12: ^{1}H NMR of N-((2,3-dihydrobenzofuran-2-yl)methyl)-4-methylaniline, 18.

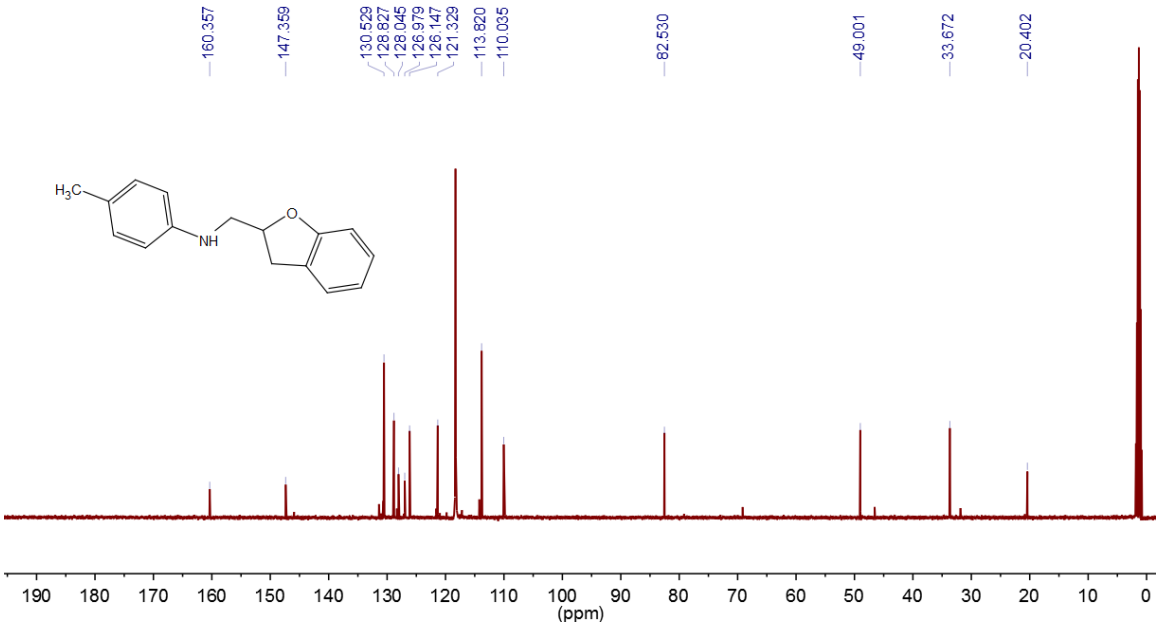


Figure 2.13: ^{13}C NMR of N-((2,3-dihydrobenzofuran-2-yl)methyl)-4-methylaniline, 18.

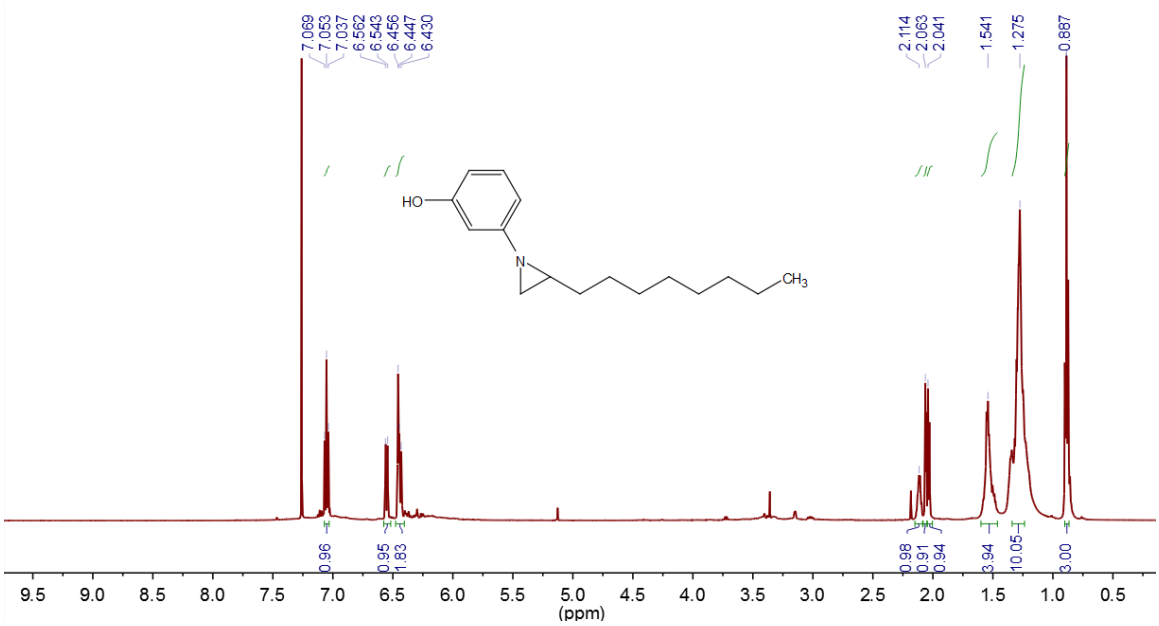


Figure 2.14: ^{1}H NMR of 3-(2-octylaziridin-1-yl)phenol, 19.

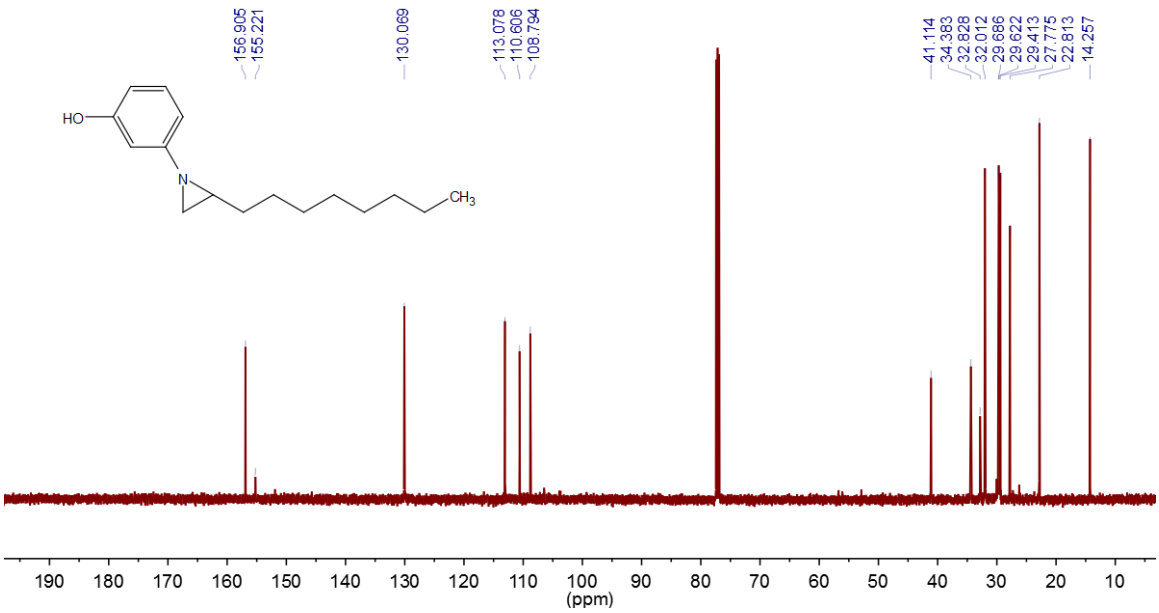


Figure 2.15: ^{13}C NMR of 3-(2-octylaziridin-1-yl)phenol, 19.

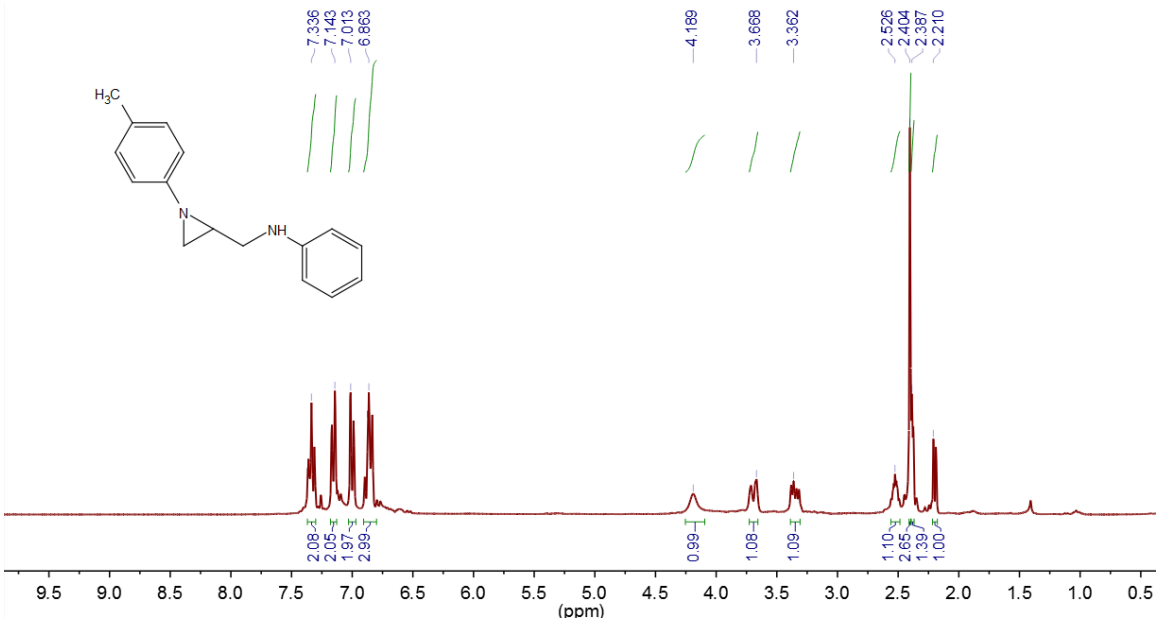


Figure 2.16: ^{1}H NMR of N-((1-(p-tolyl)aziridin-2-yl)methyl)aniline, 20.

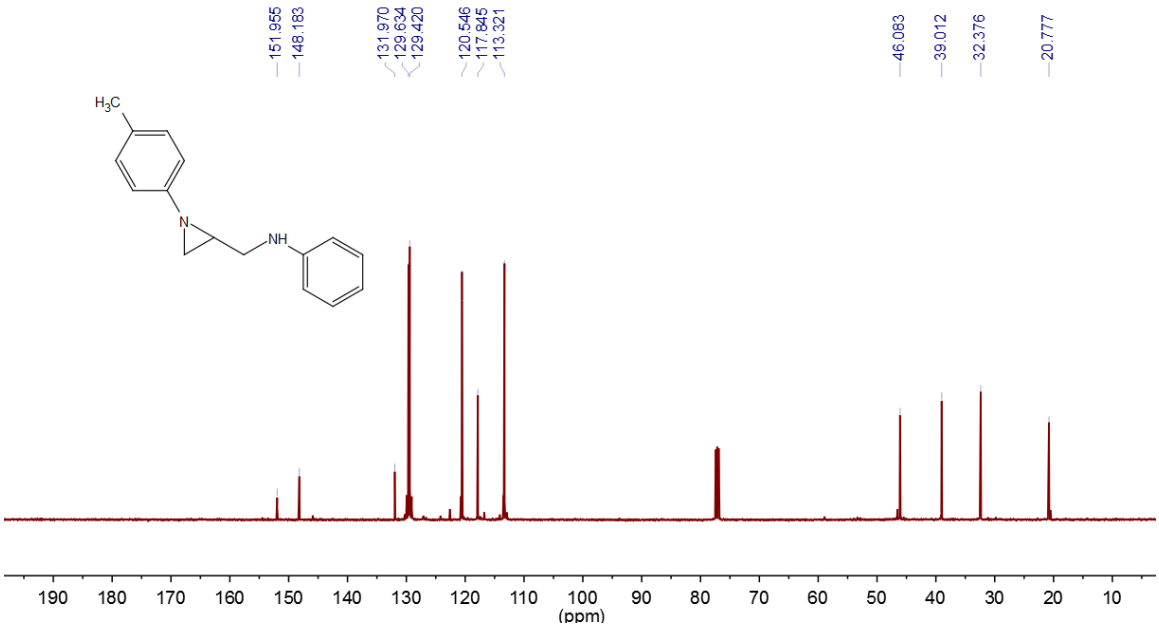


Figure 2.17: ^{13}C NMR of N-((1-(p-tolyl)aziridin-2-yl)methyl)aniline, 20.

CHAPTER III

SYNTHESIS OF MACROCYCLIC IRON COMPLEXES WITH ADDITIONAL AXIAL NHC LIGANDS

Abstract

[(^{Me,Et}TC^{Ph})Fe(NCCH$_3$)$_2$](PF$_6$)$_2$, complex **2**, was used as a starting material to attempt to synthesize an iron(II) complex with a fifth NHC ligand in the axial position. A macrocyclic tetracarbene complex was isolated with a fifth carbene ligand in the axial position. This complex was shown to be an effective catalyst for aziridination at low alkene loadings. Unfortunately, the initial synthesis proved to be irreproducible. Further efforts to synthesize a similar complex resulted in the formation of iron(II) tetracarbene complexes with two axial carbene ligands. Work on this project, including the effect of phosphine ligands on catalysis, is still ongoing at the time of this writing.

Introduction

Previously, complex **2** had been shown to perform aziridination with a large excess of alkene, typically around fifty-fold.[35] Further research showed that the excess of alkene was required to outcompete the formation of a tetrazene side product.[36] While the aziridination yields were high, a reaction that requires a fifty-fold excess of one reactant is not going to be practical for synthesis, especially when the reactant is very expensive, such as an intermediate in the synthesis of aziridine-containing therapeutic agents.[12] In our previous work with [(^{Me,Et}TC^{Ph})Cr(Cl)$_2$](PF$_6$), complex **8**, we were able to perform aziridination at low loadings, due to the presence of an axial ligand that destabilized a tetrazene product.[62] In light of this, we decided to try and redesign complex **2** as a five coordinate species with a single axial ligand to block tetrazene formation. Complex

2 showed little inclination to bind halide ions, so we attempted to synthesize an NHC ligand we could bind to one of the axial positions.

Synthesis of a Pentacarbene Iron(II) Complex

In order to synthesized a carbine adduct of **2**, we decided to use a carbon dioxide adduct of a carbene as our carbene source for these reactions. These adducts have been reported in the literature as a good precursor for carbene complexes.[82] For example, Albrecht and coworkers used a carbene-CO_2 adduct to synthesize a cobalt porphyrin complex with a single axial carbine ligand, analogous to our target molecule.[83]

Complex **2** was synthesized according to published procedures.[57] The carbene adduct was synthesized, starting from 1-methylimidazole. The imidazole was reacted with one equivalent of methyl iodide in ethyl acetate, giving the dimethylimidazolium iodide salt (**21**) in nearly quantitative yield.[84] The imidazolium salt was dried and brought into the glovebox, where it was deprotonated with potassium *bis*(trimethylsilyl)amide in tetrahydrofuran.[85] The THF solution was bubbled with carbon dioxide; a white precipitate was observed. The precipitate was collected and dried; it was then used without further purification. ^{1}H NMR identified the product as a bicarbonate salt of the carbene (**22**).

Alternatively, **22** could be synthesized by a reaction of 1-methylimidazole with dimethylcarbonate.[85] Complex **2** was reacted with **21** to give a mixture of carbene adducts, which, on crystallization, gave an iron(II) tetracarbene complex with a single axial carbene ligand (**23**). Complex **23** was characterized by ^{1}H

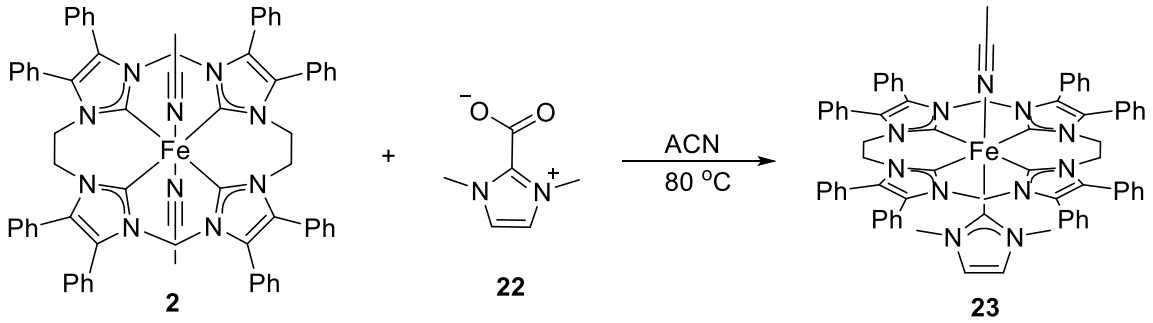


Figure 3.1: Synthesis of [(^{Me,Et}TC^{Ph})Fe(^{Me_2}NHC^{H})(NCCH$_3$)](PF$_6$)$_2$ (23).

NMR and single crystal XRD. This complex was used as a catalyst for C_2 + N_1 aziridination under the standard reaction conditions for catalysis with complex **8**, except that the catalyst loading was only 0.1%. This reaction gave a 50% crude yield of aziridine. Notably, no diazine or tetrazene products were observed. We pursued the synthesis of complex **23**, but our efforts were met with frustration. We were able to synthesize **23** only one other time; the majority of the time we either got no reaction, or we got another carbene adduct product. Analysis of the ^{1}H NMR of the second product suggested that it was an abnormal carbene, meaning an imidazolium bound through the 4-carbon and not the 2-carbon. This is not impossible since the rearrangement of sterically crowded carbenes to abnormal carbenes has been reported before.[86, 87] Unfortunately, we were unable to grow crystals of the reaction product to confirm our assignment. We next attempted to use a strong base approach to deprotonate the carbenes and add them to complex **2**, but they reacted with the acetonitrile ligands. Thus, the synthesis of an iron(II) complex of macrocycle **1** with open sites was targeted.

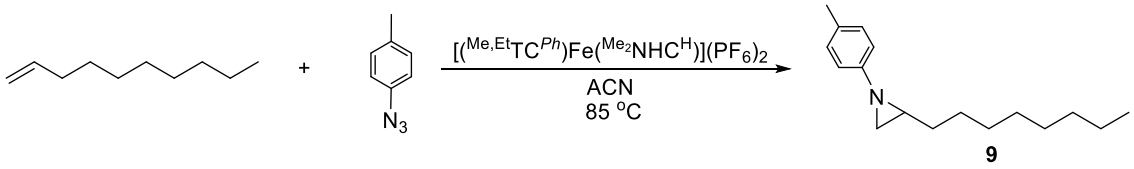


Figure 3.2: Synthesis of Aziridine 9.

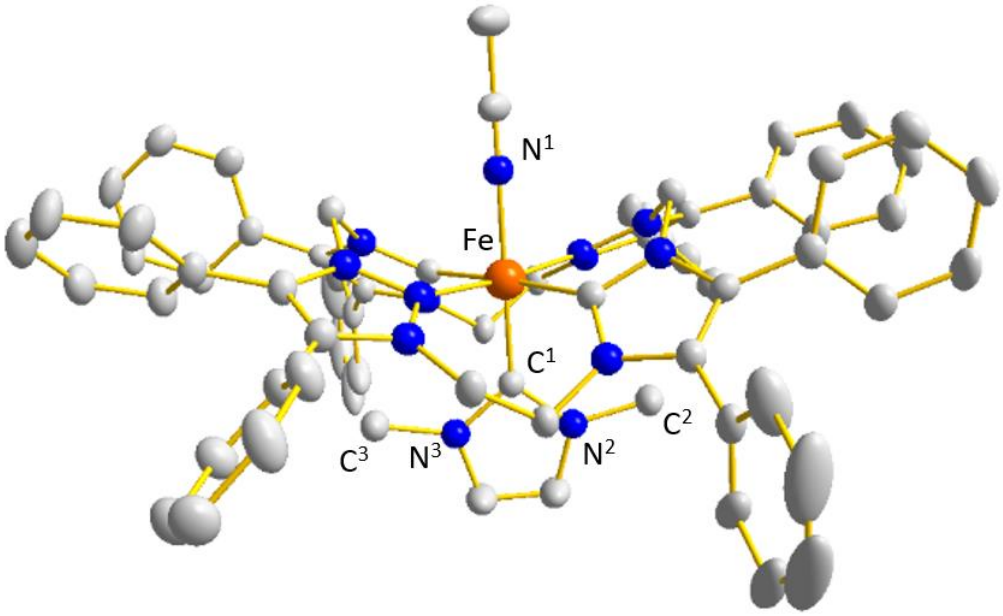


Figure 3.3: Crystal Structure of [(^{Me,Et}TC^{Ph})Fe(^{Me_2}NHC^{H})(NCCH$_3$)](PF$_6$)$_2$, (23). Orange, gray, and blue ellipsoids represent iron, carbon, and nitrogen, respectively. Hydrogen atoms, counteranions, and solvent molecules omitted for clarity.

Using a strong base approach, a new synthesis was performed. Iron(II) chloride was reacted with potassium *bis*(trimethylsilyl)amide in tetrahydrofuran at room temperature. Once the iron(II) chloride was fully dissolved, it was cooled to -30 ^{o}C in the freezer. Ligand **1** was added to tetrahydrofuran and cooled to -30 ^{o}C in the freezer. The solution of iron and the base was added to **1** dropwise. The solution gradually turned yellow as the reaction stirred overnight. On completion, the reaction was filtered over Celite, and the solvent was removed under vacuum to yield a yellow solid in an 80% yield (**24**). ^{1}H NMR in acetonitrile matched the published data for **2**, and a paramagnetic ^{1}H NMR was obtained for the open site complex. Complex **24** was dissolved in tetrahydrofuran and reacted with imidazolium salt **21**. **21** was dissolved in tetrahydrofuran, and potassium *bis*(trimethylsilyl)amide was added. After the reaction was complete, it was filtered over Celite, and the solvent was removed under vacuum to isolate the free carbene. The product was dissolved in tetrahydrofuran and added to a THF solution of **24**. Based on ^{1}H NMR analysis, the reaction did not yield the monocarbene adduct **23**, but a mixture of what appeared to be a dicarbene adduct and residual complex **2**. Addition of two equivalents of the carbene to a solution of **2** gave a ^{1}H NMR of a single product matching the proposed dicarbene adduct from before. Current efforts on this project are focusing on the effect of phosphine ligands on catalysis, and the reactivity of mono- and di-phosphine adducts of complex **2**.

Conclusion

A tetracarbene iron(II) complex with a single axial carbene ligand was synthesized, but not reproducibly. This complex proved capable of performing catalytic aziridination at low alkene loadings, confirming the observations of the benefit of an additional axial ligand. While the use of carbon dioxide adducts of carbenes was capable of yielding a monocarbene adduct of complex **2**, synthesis of a free carbene and addition of it to an iron(II) complex gave the dicarbene adduct. Future efforts in this area will focus on using hemi-labile ligands to block a single coordination sight. Further work on the synthesis of these transition metal complexes is ongoing.

Experimental

Synthesis of the organic compounds used were performed under atmospheric conditions. All reactions with the silver and cobalt complexes were performed under a nitrogen atmosphere in a glovebox. Solvents were dried on an Innovative Technologies (Newburgport, MA) Pure Solv MD-7 Solvent Purification System, and they were degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves. Acetonitrile-d_3, dichloromethane-d_2, and chloroform-d were purchased from Cambridge Isotope Lab and degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves, followed by storage in a glovebox. 1,3-dimethylimidazolium iodide and 1,3-dimethylimidazolium bicarbonate were synthesized by the published

procedures.[84, 85] Synthesis of the macrocyclic tetracarbene, and the iron(II) and silver(I) tetracarbene complexes were performed following our published procedures.[34, 57] All other reagents were purchased from commercial vendors and used without further purification. ^{1}H, ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury 300 MHz or a Varian VNMRS 500 MHz narrow-bore broadband system. ^{1}H and ^{13}C NMR chemical shifts were referenced to the residual solvent. All mass spectrometry analyses were conducted at the Mass Spectrometry Center located in the Department of Chemistry at the University of Tennessee. The ESI-MS analyses were performed using a QSTAR Elite quadrupole time-of-flight (QTOF) mass spectrometer with an electrospray ionization source from AB Sciex (Concord, Ontario, Canada). Mass spectrometry sample solutions of organometallic compounds were prepared in solutions of acetonitrile. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. Carbon, hydrogen, and nitrogen analyses were obtained from Atlantic Microlab, Norcross, GA.

Synthesis of [(^{Me,Et}TC^{Ph})Fe(^{Me_2}NHC^{H})(NCCH$_3$)](PF$_6$)$_2$, 23. Complex **2** (0.031 g, 0.023 mmol) was added to an acetonitrile solution. Carbene **22** (0.003 g, 0.023 mmol) was added. The reaction heated at 80 ^{o}C overnight, going from orange to yellow. The reaction was purified by vapor diffusion of diethyl ether into an acetonitrile solution of the crude product. Complex **23** was isolated as yellow crystals suitable for XRD in a yield of 0.0013 g, 4 % yield. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 7.41 (m, 10H), 7.35 (m, 8H), 7.24 (m, 6H), 7.13 (m, 8H), 7.00 (s, 2H), 6.95

(m, 8H), 5.65 (d, J = 13.7 Hz, 2H), 4.93 (dd, J_1 = 8.6 Hz, J_2 = 16.0 Hz, 4H), 4.28 (dd, J_1 = 8.3 Hz, J_2 = 15.7 Hz, 4H), 3.50 (d, J = 13.7 Hz, 2H), 2.92 (s, 6H).

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, **9**. 0.1 % catalyst loading: 1-decene (0.380 g, 2.71 mmol), *p*-tolyl azide (0.122 g, 0.903 mmol), and **23** (0.001 g, 0.0009 mmol) were added to acetonitrile and heated for 3 days at 85 ^{o}C, purification was achieved using 5 % ethyl acetate in hexanes on a silica flash column, resulting in a yield of 0.1152 g, 51 %. (^{1}H and ^{13}C NMR) matched the literature data.[35]

Synthesis of [(^{Me,Et}TC^{Ph})Fe](PF$_6$)$_2$, 24. $FeCl_2$ (0.043g, 0.341 mmol) and KHMDS (0.146 g, 0.731 mmol) were added to THF at room temperature. Upon complete dissolution of the $FeCl_2$, this solution was cooled to -30 ^{o}C in the freezer. **1** (0.251 g, 0.163 mmol) was weighed out and added to THF and cooled to -30 ^{o}C in the freezer. The solution of $FeCl_2$ and KHMDS was added dropwise to **1**; the reaction stirred overnight and warmed to room temperature. Upon completion of the reaction, the solution was filtered over Celite. The THF was removed under vacuum, and a yellow solid was isolated, for a yield of 0.1775 g, 84 % yield. (^{1}H and ^{13}C NMR) matched the literature data.[35]

Select NMRs of Novel Products Prepared in this Work

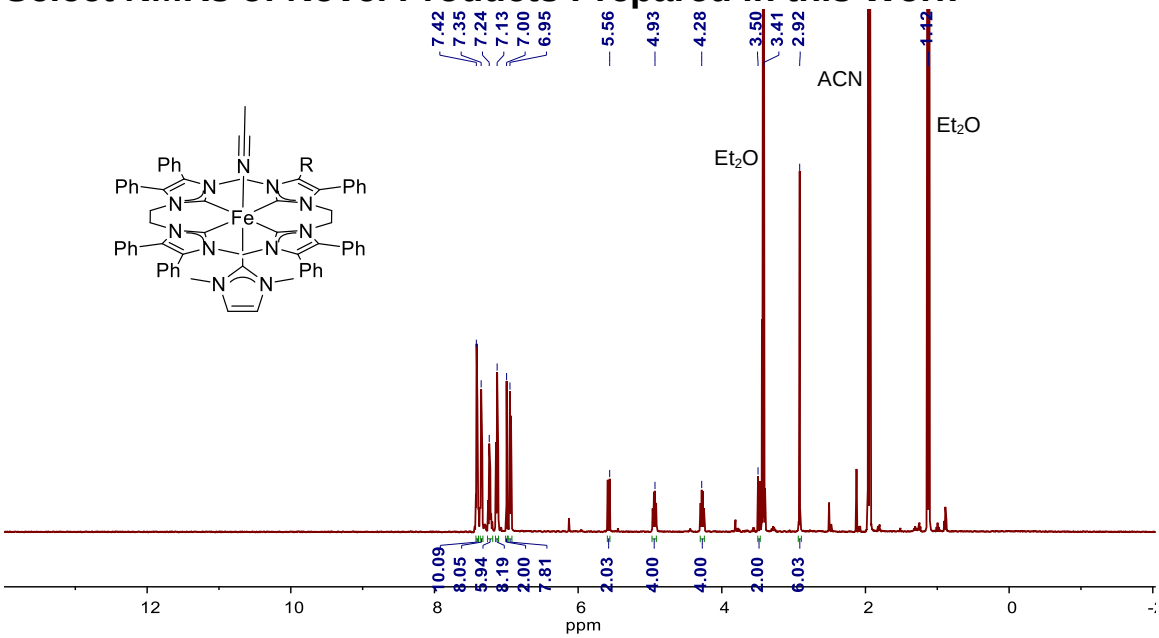


Figure 3.4: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Fe(^{Me_2}NHC^{H})(NCCH$_3$)](PF$_6$)$_2$, 23.

CHAPTER IV

RING CLOSING AZIRIDINATION

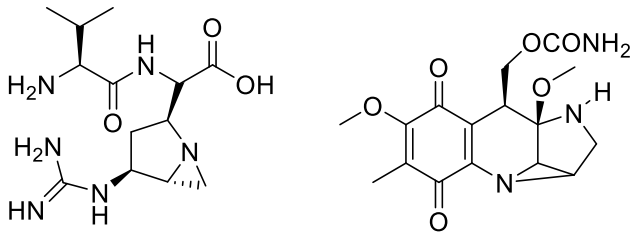
The synthesis of **33** was performed by Dr. S. Alan Cramer; all other work was performed by C. Luke Keller.

Abstract

A series of substrates containing an azide and an alkene were synthesized for ring-closing $C_2 + N_1$ aziridination to synthesize tertiary bicyclic aziridines. These compounds were tested using a tetracarbene iron complex as a catalyst. A study of the reactivity of the aziridine precursors showed that the rate of reactivity was unaffected by the presence of the iron complex. Further studies with known aziridination catalysts gave similar results.

Introduction

Tertiary bicyclic aziridines are aziridines with one or more fused ring systems. These structures are found in several natural products, including



Ficellomycin **Isomitomycin A**

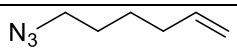
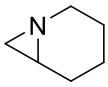
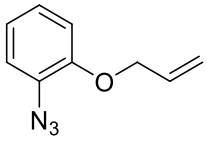
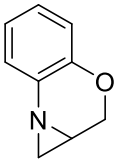
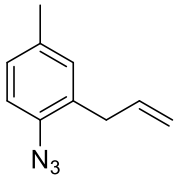
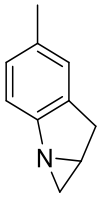
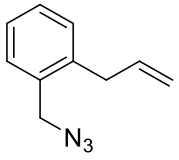
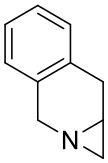
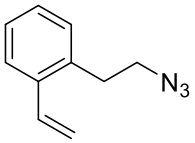
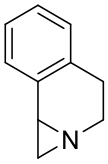
Figure 4.1: Structures of Ficellomycin[1] and Isomitomycin A.[2]

ficellomycin[88] and isomitomycin A.[89]

The only method to synthesize bicyclic aziridines using C_2 + N_1 aziridination is *via* a ring closing intramolecular aziridination reaction. On examination of the literature, most previous examples of catalytic aziridination are of intermolecular reactions, i.e. reactions where the alkene and the azide are on different molecules. To date, there are only two papers that report intramolecular aziridination. The first one, from the Jenkins group, reports the ring closing of two fully alkyl azidoalkenes to give the corresponding fused ring systems.[40] The other report comes from Peter Zhang and coworkers, where they reported the synthesis of aziridines from allyl azidoformates *via* ring closing C_2 + N_1 aziridination.[42] However, neither of these papers focused on ring closing aziridination. The work by the Jenkins group focused largely on intermolecular aziridination,[40] and the work by Zhang ring focus on the ring opening of the aziridines *in situ* to yield oxazolindinones.[42] We wished to undertake the first systematic study of C_2 + N_1 aziridination.

In order to perform this study, we designed a series of substrates to test the generalizability of the catalysis. We proposed a series of azidoalkenes containing of alkyl, benzyl, and aryl azides. Additionally, we also wished to test the effects of conjugated vs nonconjugated alkenes on the reaction. The possible aziridine targets were broken down into five classes along with the azidoalkene precursors as shown in **Table 4.1**.

Table 4.1: Aziridination Classes for Intramolecular Aziridination.

Entry	Class	Azidoalkene	Aziridine
1	Fully Alkyl		
2	Aryl 6-carbon ring		
3	Aryl 5-carbon ring		
4	Benzyl 6-carbon ring		
5	Fused ring alkyl		

Catalyst Selection

Previous research by the Jenkins group demonstrated that metal complexes with the 18 atom ring sized ligands were flexible enough to allow the imide intermediates to react with a second equivalent of azide and form a metallotetrazene.[36] However, calculations performed by our collaborators in the Roy group at the University of Tennessee suggested that a smaller macrocycle would destabilize a tetrazene by decreasing the flexibility of the ligand. Dr. Gaya Elpitiya and Dr. Markus Anneser developed a synthesis for a 16 atom iron(II) complex with a dianionic ligand, [($^{BMe_2,Me}TC^{H}$)Fe], (25) as shown in **Figure 4.2**, this complex is currently part of a separate journal submission. We believed this complex was likely to be the most effective catalyst for the chemistry we were undertaking.

Synthesis of Substrates for Intramolecular Aziridination

As we had determined our desired approach for this chemistry, we set about

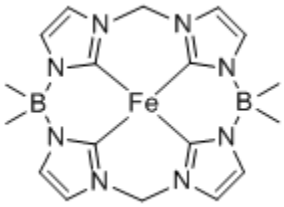


Figure 4.2: Structure of [($^{BMe2,Me}TC^{H}$)Fe] (25).

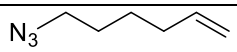
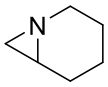
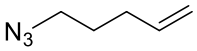
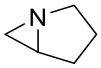
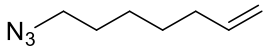
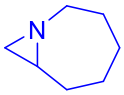
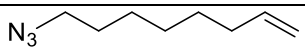
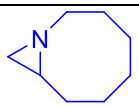
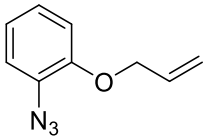
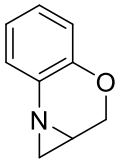
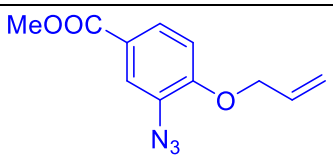
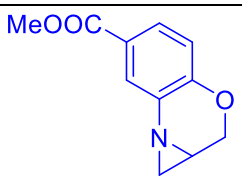
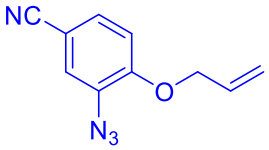
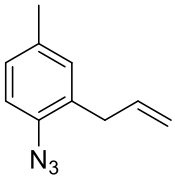
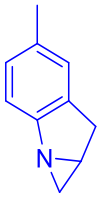
deciding which substrates we wanted to test catalysis on. Previously, our group has reported the synthesis of aziridines with fused five- and six-membered rings using 5-azidopent-1-ene and 6-azidohex-1-ene.[40] Initially, we decided to use these compounds from Group 1 as test cases for our chemistry. Additionally, we wished to pursue aziridines with larger rings from the same class. Following this, we would pursue examples of aziridines from the other classes. We compiled a list of azidoalkenes from each group for synthesis and testing. The compounds are shown in **Table 4.2**.

Synthesis of Starting Materials for Ring-closing Aziridination

Synthesis of the class **1** azidoalkenes proved to be straight forward. Following a procedure from the Betley group,[43] the corresponding alkyl bromides were added to a solution of DMF with an excess of sodium azide and heated at 40 ^{o}C. This reaction yielded the corresponding alkyl azides in good yields, see **Figure 4.3**. The compounds from class **2** were synthesized by a three-step procedure. Starting from the corresponding nitrophenols, a Williamson Ether Synthesis was performed using allyl bromide and potassium carbonate in acetonitrile.[90] This procedure gave the corresponding allyloxynitro compounds in high yields. After this, the nitro was reduced to the anilines using iron powder in a mixture of ethanol and aqueous ammonium chloride.[91] Finally, the anilines were converted to the azides following the procedure of Smith and Brown (**Figure 4.4**).[28]

The compound in class **3** was synthesized by reacting *p*-toluidine with allyl bromide and potassium carbonate in dimethylformamide, yielding N-allyl-4-

Table 4.2: Azidoalkenes for Intramolecular Aziridination.

Entry	Class	Azidoalkene	Aziridine
1	**1**	 **26**	 **34**
2	**1**	 **27**	 **35**
3	**1**	 **28**	 **36**
4	**1**	 **29**	 **37**
5	**2**	 **30**	 **38**
6	**2**	 **31**	 **39**
7	**2**	 **32**	 **40**
8	**3**	 **33**	 **41**

Structures in blue have not been reported before

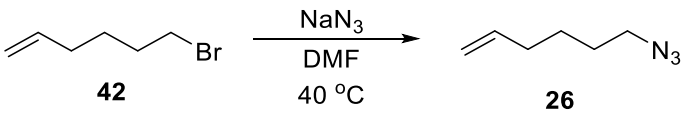
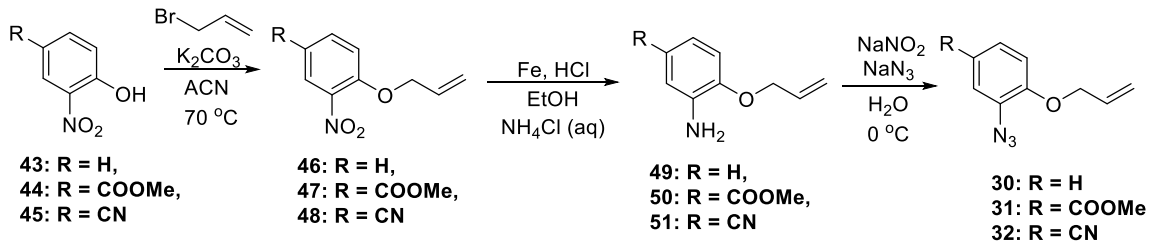


Figure 4.3: Sample Synthesis of Azides from Class 1.



43: R = H,
44: R = COOMe,
45: R = CN

46: R = H,
47: R = COOMe,
48: R = CN

49: R = H,
50: R = COOMe,
51: R = CN

30: R = H
31: R = COOMe
32: R = CN

Figure 4.4: Sample Synthesis of Azides from Class 2.

methylaniline.[92] Next, an Aza-Cope Rearrangment was performed by refluxing the product with borontrifluoride etherate in *o*-xylene.[92] Finally, the azide was synthesized by following the method of Smith and Brown (**Figure 4.5**).[28]

In order to synthesize our lead in compound in class **4**, we pursued a synthesis using a Stille coupling to install the allyl moiety on the aryl ring,[93] followed by metathesis of the chloride with sodium azide (**Figure 4.6**).[94] To our surprise, instead of reacting with the aryl bromide, the Stille coupling added the allyl group to the benzyl chloride position. In spite of our efforts, we were unable to find a successful coupling partner for this reaction.

The proposed synthesis of our lead compound in class **5** was as follows: a Stille coupling to synthesize the styrene,[95] followed by tosylation of the alcohol and metathesis with sodium azide (**Figure 4.7**).[96] The Stille reaction was run with an excess of the tin reagent and gave a good yield of product; however, the reaction could be run at equivalency by replacing triphenylphosphine with XANTPHOS. Unfortunately, the product had a propensity to polymerize, and we were unable to get the tosylation to work effectively.

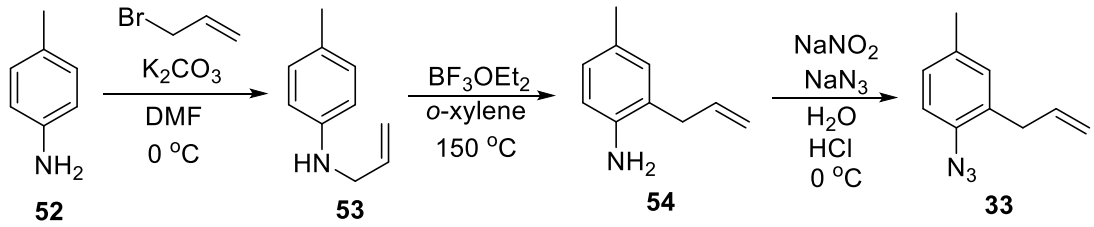


Figure 4.5: Synthesis of Azide in Class 3.

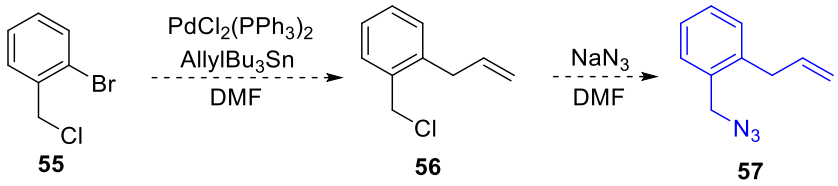
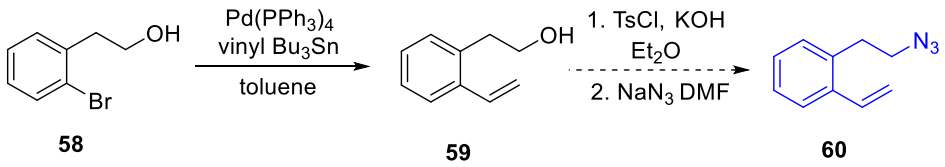


Figure 4.6: Synthesis of Azide in Class 4.

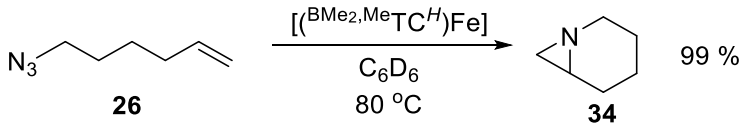


58 **59** **60**

Figure 4.7: Synthesis of Azide in Class 5.

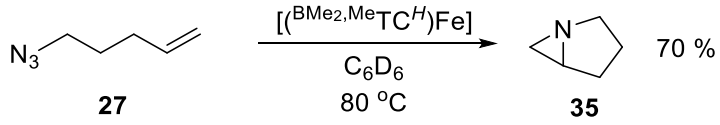
Aziridine Synthesis *via* Ring-closing with Complex 25

Using azidoalkene **26** as out starting material, we added it to benzene-d_6 with a 1 % loading of **25**. The reaction was heated at 80 °C overnight. ^{1}H NMR confirmed the complete consumption of the starting material. Aziridine **34** was identified as the sole product, in a 99 % yield (**Figure 4.8**). Using azidoalkene **27** as a starting material under the same conditions gave aziridine **35** as the major product, in a 70 % yield (**Figure 4.9**). Both yields were determined by integration of ^{1}H NMR. We ran some test reactions to see if larger rings could be synthesized this way. Azidoalkene **29** showed no reactivity towards aziridination; however, **28** showed an ^{1}H NMR potentially consistent with aziridine **36** after refluxing in toluene-d_8, but the sample was impure. In spite of our efforts, we were unable to positively identify the presence of aziridine **36** as a reaction product. We decided to test the effectiveness of aryl azides from class **2** for ring closing aziridination. 1-allyloxy-2-azidobenzene (**30**) was added to a solution of benzene, a 1 % loading of **25** was added. The reaction stirred at 80 °C overnight, yielding the desired aziridine product, 1a,2-dihydro-1*H*-azirino[1,2-*d*]benzo[b][1,4]oxazine (**38**), as well as an imine, 3-methyl-2*H*-benzo[b][1,4]oxazine (**61**).



26 **34**

Figure 4.8: Synthesis of 34.



27 35

Figure 4.9: Synthesis of 35.

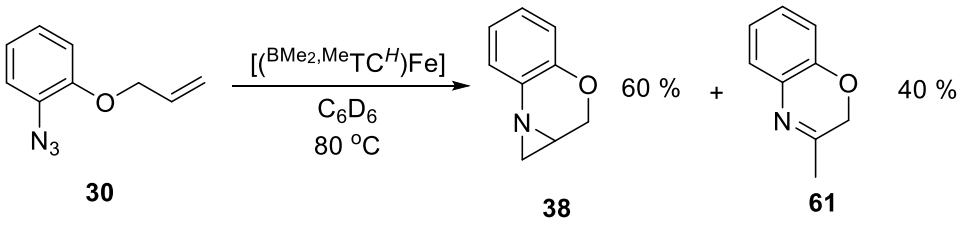


Figure 4.10: Synthesis of 38 and 42.

A non-catalytic version of this reaction has been reported before, yielding the same products.[97] Using complex **25** as a catalyst at 80 °C, compound **30** was converted to compounds **38** and **42** in a 60 % yield and a 40 % yield, respectively. The yield was determined by integration of ^{1}H NMR vs an internal standard. Methyl 4-allyloxy-3-azidobenzoate (**31**) was found to give similar aziridination products, with a 57% yield of the aziridine (**39**), and a 19% yield of the corresponding imine (**43**). Further testing showed that this reaction was complete after one hour at 80 °C. On lowering the temperature to 70 °C, the reaction was found to be complete after 2 hours. Aziridine **39** was isolated in a 50 % yield, and imine **43** was isolated in a 16 % yield.

We next focused on the synthesis of aryl aziridines from class **3**. Using 2-allyl-*p*-tolyl azide (**33**) as a starting material, we reacted it with **25**. The reaction went for 1 day in benzene-d_6. Two products were identified in the reaction, one was the desired aziridine product, 5-methyl-7,7a-dihydro-1*H*-azirino[1,2-*a*]indole (**41**), and the other was an indole, 2,5-dimethyl-1*H*-indole (**44**). Integration of the

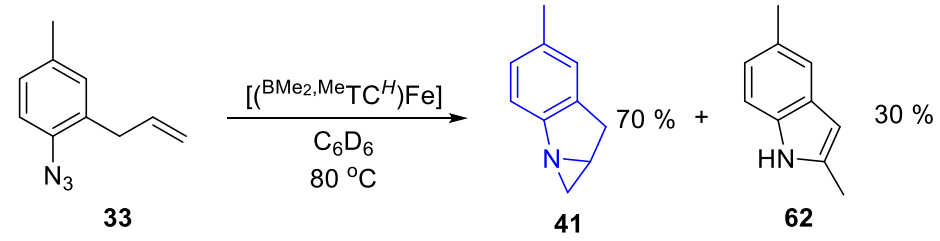


Figure 4.11: Synthesis of 41 and 44.

^{1}H NMR gave a 70 % yield of **41**, and a 30% yield of **44**. Efforts to alter the product distribution by adjusting the temperature or catalyst loading showed no effect on the product distribution.

Indole **44** was isolated in a 35% yield *via* chromatography, but **41** was found to be unstable on silica and alumina. Isolating **41** proved to be a challenge, but it was finally purified by distillation, in a 24% yield.

We had been attempting to synthesize classes **4** and **5** to this point; however, we had yet to isolate the pure azides for testing.

Control Reactions of Ring Closing Aziridination

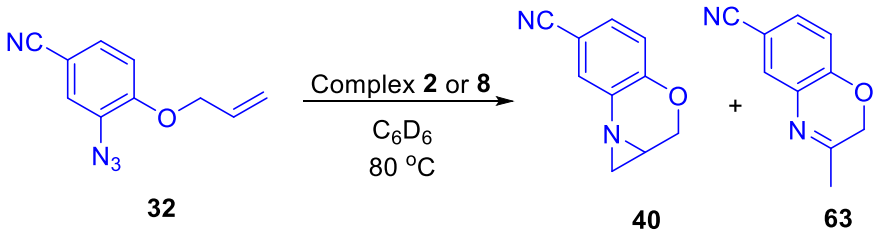
In order to get a firm grasp on the chemistry of ring closing aziridination, we set out to test control reactions for this chemistry. The first one tested was the ring closing of **30**. The literature reported that the control took six hours.[69] However, monitoring the reaction *in situ* by ^{1}H NMR showed that at 80 ^{o}C, the reaction went to completion in an hour with roughly the same product distribution. The ring closing of **33** went to completion in one day at 80 ^{o}C, giving a *in situ* yield of aziridine **41** of 75%, with the remained being **44**. Finally, we ran a control on the synthesis of aziridine **26,** giving 90% yield *via* ^{1}H NMR.

Ring Closing Aziridination with Different Catalysts

Since complex **25** proved to be an ineffective catalyst, we turned to some of the previous catalysts used by our group. We wanted to see if we could exclusively form aziridine products. As the control reaction for azidoalkene **30** was

faster than the catalytic reactions with our previous catalysts, we deemed it too reactive to use. Instead, we used 5-cyano-1-allyloxy-2-azidobenzene, **32**, as our starting material. The reactions were run in acetonitrile, analogous to the General Catalytic Reaction from Chapter II. We ran control reactions in acetonitrile and discovered that the control reaction for **32** went to completion in acetonitrile in 2 hours, yielding both an aziridine (**40**) and an imine (**45**), analogous to the reaction of **30**.

Using [($^{Me,Et}TC^{Ph}$)$Cr(Cl)_2$](PF_6) (**2**) and [($^{Me,Et}TC^{Ph}$)$Fe(NCCH_3)_2$]$(PF_6)_2$ (**8**) as catalysts, we reacted **32** at 85 °C, 50 °C, and room temperature. At 85 °C, both reactions gave product distributions virtually identical to the control reactions. At 50 °C, the reactions went to completion in 18 hours, yielding a product distribution largely the same as the reaction at 85 °C. Both reactions at room temperature failed to form a significant amount of either product (**Figure 4.12**). Since the control reaction for the allyloxyazides is so rapid, we switched our focus to **33**, to see if it



32 **40** **63**

Figure 4.12: Synthesis of Aziridine 40.

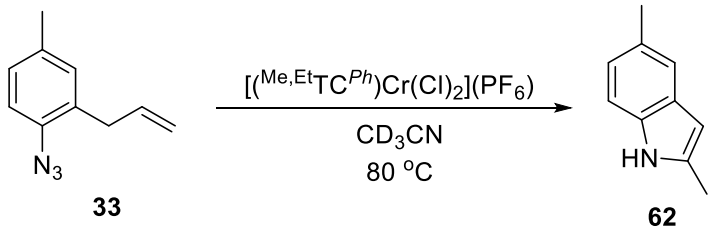


Figure 4.13: Synthesis of 44 using 2 as a catalyst.

only formed the aziridine. A reaction of **33** with **2** as a catalyst resulted in complete decomposition of the starting material. However, the reaction of **33** with **8** gave exclusively indole **44**. We propose that this reaction gave a significant yield of aziridine *in situ*, but complex **8** acted as a Lewis acid and catalyzed the decomposition of **41** to **44**.

Due to the high yields obtained from the control reactions, we determined that further pursuit of the synthesis of azides in classes **4** and **5** was superfluous.

Conclusion

A series of substrates containing an azide and an alkene were synthesized for $C_2 + N_1$ aziridination. Catalytic testing showed that the ring closing in the control reaction was equal to or faster than the fastest reported catalysis with any catalyst tested, rendering them ineffective on the reaction results. With such a rapid control reaction, as opposed to the previously reported control reactions for aziridination,[35, 40, 62] there must be a significant mechanistic difference to account for this reaction. The most likely explanation is that five and six membered rings are formed in the transition states and intermediates. These rings would impart significant stabilization to the intermediates and lower the energy of the transition states, thus lowering the overall energy barrier for the reaction.

Experimental

All organic syntheses were performed under atmospheric conditions. All attempted catalytic reactions were performed under a dry nitrogen atmosphere in

a glovebox. Solvents were dried on an Innovative Technologies (Newburgport, MA) Pure Solv MD-7 Solvent Purification System and degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves. Chloroform-d, benzene-d_6 and acetonitrile-d3 were purchased from Cambridge Isotope Lab and degassed by three freeze-pump-thaw cycles on a Schlenk line to remove oxygen prior to use and dried over activated molecular sieves. The compounds 6-azidohex-1-ene and 5-azidopent-1-ene were prepared by the method of King *et al*.[43] All allyoxyanilines were prepared following the method of Ouyang *et al.*[91] The compounds 2-(allyloxy)aniline,[91] methyl 4-allyloxy-3-aminobenzoate,[91] and 4-(allyloxy)-3-aminobenzonitrile[98] were prepared as described previously. All aryl azides were synthesized from the corresponding anilines by the procedure developed by Smith and Brown.[28] The compounds 1-allyloxy-2-azidobenzene[97] and 2-allyl-*p*-tolyl azide[99] were prepared as described previously. The compounds $[(^{Me,Et}TC^{Ph})Cr(Cl)_2](PF_6)$ and $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ were prepared as previously described in the literature.[57] All other reagents were purchased from commercial vendors and degassed by three freeze-pump-thaw cycles and dried over activated molecular sieves. ^1H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury 300 MHz or a Varian VNMRS 500 MHz narrow-bore broadband system. ^1H and ^{13}C NMR chemical shifts were referenced to the residual solvent. All mass spectrometry analyses were conducted at the Mass Spectrometry Center located in the Department of Chemistry at the University of Tennessee. The DART

analyses were performed using a JEOL AccuTOF-D time-of-flight (TOF) mass spectrometer with a DART (direct analysis in real time) ionization source from JEOL USA, Inc. (Peabody, MA). Mass spectrometry sample solutions of organic compounds from catalysis reactions were prepared in chloroform or acetonitrile. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance.

Synthesis of methyl 4-(allyloxy)-3-azidobenzoate, 31. Methyl 4-allyloxy-3-aminobenzoate (0.793 g, 3.83 mmol) was dissolved in 100 mL of H_2O and 30 mL of HCl at 0 ^oC. Sodium nitrate (0.340 g, 4.92 mmol) was added as a solid. The reaction was stirred for 30 minutes, and sodium azide (0.320 g, 4.92 mmol) was added. Significant bubbling was observed, and the reaction was let warm to room temperature overnight. The reaction was neutralized with sodium bicarbonate, and the crude product was isolated by extraction with ethyl acetate. The product was purified by dissolving it in chloroform and adding pentane until a precipitate was observed. The precipitate was removed by filtration, and the solvent was removed under reduced pressure. **31** was isolated as a red solid (0.521 g, 58 % yield). ^1H NMR (C_6D_6, 499.74 MHz): δ 7.85 (dd, J_1 = 2.1 Hz, J_2 = 8.5 Hz, 1H), 7.81 (d, J_1 = 2.1 Hz, 1H), 6.27 (d, J_1 = 8.6 Hz, 1H), 5.63 (m, 1H), 5.14 (m, 1H), 4.99 (m, 1H), 3.87 (m, 2H), 3.49, (s, 1H).

Synthesis of 4-(allyloxy)-3-azidobenzonitrile, 32. 4-(Allyloxy)-3-aminobenzonitrile (1.506 g, 8.65 mmol) were dissolved in 100 mL of water and 10 mL of HCl. The solution was cooled to 0 ^oC. Sodium nitrate (0.754 g, 10.92 mmol)

was added as a solid. The reaction was stirred for 30 minutes, and sodium azide (0.693 g, 10.92 mmol) was added. Significant bubbling was observed, and the reaction was let warm to room temperature overnight. The reaction was neutralized with sodium bicarbonate, and the product was isolated by extraction with ethyl acetate. **32** was isolated as a red solid (1.366 g, 79 % yield). ^{1}H NMR (C_6D_6, 499.74 MHz): δ 6.73 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz 1H), 6.66 (d, J = 2.0 Hz, 1H), 5.92 (d, J = 8.5 Hz, 1H), 5.56 (m, 1H), 5.07 (m, 1H), 4.97 (m, 1H), 3.73 (m, 2H). ^{13}C NMR (C_6D_6, 125.66 MHz): δ 155.02, 131.96, 130.13, 129.97, 124.85, 118.64, 118.59, 113.40, 105.79, 69.91. IR: 3217.55, 3000.65, 2226.62, 2121.44, 1601.18, 1503.10, 1411.52, 1300.39, 1280.06, 1251.55, 1099.17, 982.30, 917.71, 814.01, 742.00 cm^{-1}.

Synthesis of 1- azabicyclo[4.1.0]heptane, 34. 6-Azidohex-1-ene (**26**) (0.021 g, 0.139 mmol) were added to a 20 mL vial. Complex **25** (0.0006 g, 0.0013 mmol) was weighted out and dissolved in 4 mL of C_6D_6. The resulting solution was added to **3**, and the reaction heated at 80 ^{o}C overnight. On completion of the reaction, the solution was filtered over Celite and removed from the glovebox. 1,2,4,5-tetrachlorobenzene (0.030 g, 0.139 mmol) was added as an internal standard. The product was identified by ^{1}H NMR and quantified by integration of the spectrum vs the standard. **34** was found in a 99 % yield. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[40]

Synthesis of 1-azabicyclo[3.1.0]hexane, 35. 5-Azidopent-1-ene (**27**) (0.014 g, 0.129 mmol) were added to a 20 mL vial. Complex **25** (0.0006 g, 0.0013 mmol)

was dissolved in C_6D_6. The resulting solution was added to **27**, and the reaction heated at 80°C overnight. On completion of the reaction, the solution was filtered over Celite and removed from the glovebox. 1,2,4,5-tetrachlorobenzene (0.028 g, 0.129 mmol) was added as an internal standard. The product was identified by ^{1}H NMR and quantified by integration of the spectrum vs the standard. **35** was found in a 70 % yield. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[40]

Synthesis of 1a,2-dihydro-1*H*-azirino[1,2-*d*]benzo[b][1,4]oxazine, 38. 1-Allyloxy-2-azidobenzene (**30**) (0.2875 g, 1.591 mmol) was dissolved in C_6H_6. Complex **25** (0.0068 g, 0.0159mmol) was added to the solution. The reaction heated at 70°C for 2 hours. After completion, the solvent was removed under vacuum. Reaction purification was achieved using 5% triethylamine in diethyl ether on a silica flash column. 0.0384 g of **61** were isolated, for a 16 % yield, and 0.1201 g of **38** were isolated, for a 50 % yield. The characterization (^{1}H and ^{13}C NMR) matched the literature data.[97]

Synthesis of methyl 1a,2-dihydro-1H-azirino[1,2-d]benzo[b][1,4]oxazine-6-carboxylate, 39. Methyl 4-allyloxy-3-azidobenzoate (**31**) (0.1716 g, 0.736 mmol) was weighed out in a 20 mL vial. Complex **25** (0.0032 g, 0.0074 mmol) was dissolved in C_6H_6 (4 mL). The reaction heated at 80°C for 18 hrs. On completion of the reaction, the solution was filtered over Celite and removed from the glovebox. The solvent was removed under vacuum. Reaction purification was

achieved using 10 % triethylamine in diethyl ether on a silica flash column, yielding 0.0862 g of **39**, for a 57 % yield.

Synthesis of 2,5-dimethyl-1*H*-indole, 62. 2-Allyl-*p*-tolyl azide (**33**) (0.2475 g, 1.428 mmol) was weighed out in a 20 mL vial. Complex **25** (0.0061 g, 0.0143 mmol) was dissolved in C_6H_6. The resulting solution was added to **33**, and the reaction heated at 75 ^oC for 1 day. On completion of the reaction, the solution was filtered over Celite and removed from the glovebox. Purification of the reaction was achieved using 5% ethyl acetate in hexanes on a silica flash column. Aziridine **41** was found to be unstable on silica. 0.0712 g of indole **62** were isolated, for a 34 % yield. The characterization (^1H and ^{13}C NMR) matched the literature data.[100]

Synthesis of 5-methyl-7,7a-dihydro-1*H*-azirino[1,2-*a*]indole, 41. 2-Allyl-*p*-tolyl azide (**33**) (0.4394 g, 2.537 mmol) was weighed out in a 20 mL vial. Complex **25** (0.0109 g, 0.0025 mmol) was dissolved in C_6H_6. The resulting solution was added to **33**, and the reaction heated at 80 ^oC overnight. Upon completion of the reaction, the reaction was filtered and removed from the glovebox. The solvent was removed under vacuum, and the crude product underwent vacuum distillation. Aziridine **41** distilled at 70 mtorr and 55 ^oC, yielding 0.0895 g of the pure oil, for a 24 % yield. ^1H NMR (C_6D_6, 499.74 MHz): δ 7.27 (d, J = 7.7 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.74 (s, 1H), 2.84 (m, 2H), 2.57 (m, 1H), 2.11 (s, 3H), 2.07 (d, J = 5.3 Hz, 1H), 0.94 (d, J = 3.8 Hz, 1H). ^{13}C NMR (C_6D_6, 125.66 MHz): δ 156.75, 136.22, 133.76, 128.02, 126.69, 119.59, 39.91, 38.86, 32.93, 21.08. IR: 2917.08, 1483.03,

1457.93, 1256.76, 1190.75, 1078.35, 953.57, 820.87, 772.19, 755.50, 710.53, 676.24 cm^{-1}.

Synthesis of 5-methyl-7,7a-dihydro-1*H*-azirino[1,2-*a*]indole, 41. 2-Allyl-*p*-tolyl azide (**33**) (0.0221 g, 0.128 mmol) was weighed out in a 20 mL vial. Complex **25** (0.0005 g, 0.0013 mmol) was dissolved in C_6D_6. The resulting solution was added to **37**, and the reaction heated at 80 ^oC overnight. On completion of the reaction, the solution was filtered over Celite and removed from the glovebox. 1,2,4,5-Tetrachlorobenzene (0.028 g, 0.128 mmol) was added as an internal standard. Two different products were identified in the solution, **41** and **62**. The two products were quantified by integration of the spectrum vs the standard, giving a yield of 70% for **41** and 30 % for **62**.

Select NMRs from Novel Products Prepared in this Work

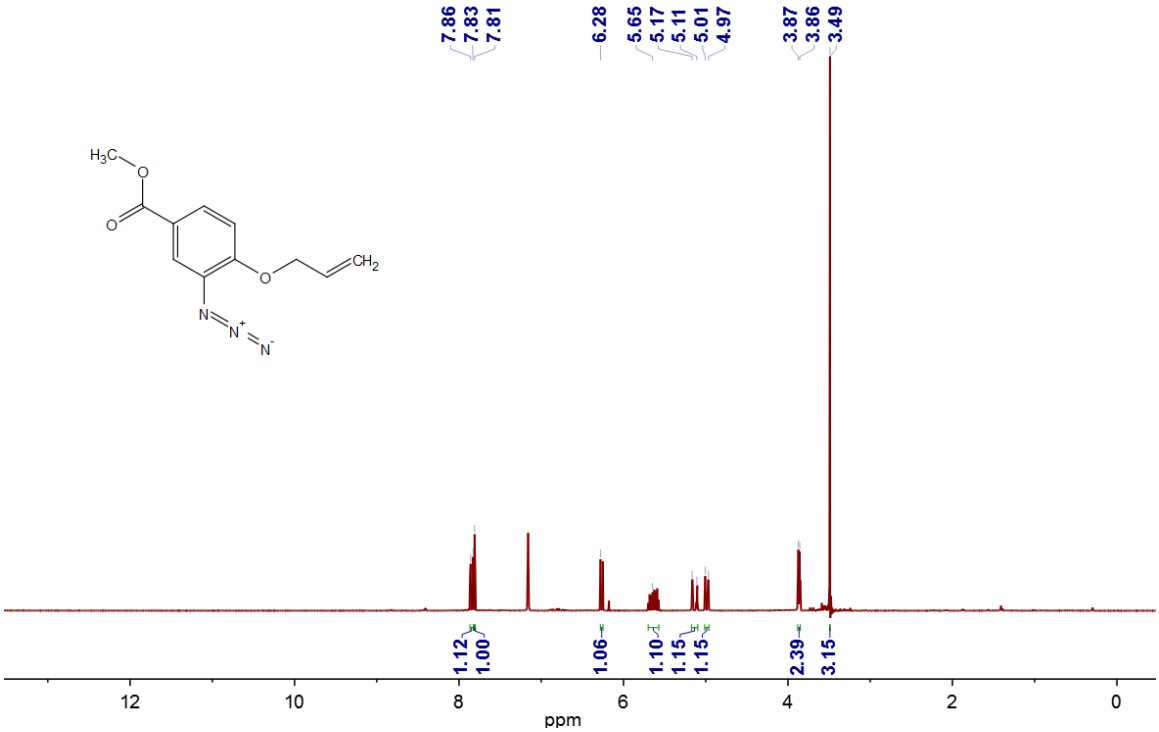


Figure 4.14: ^{1}H NMR of methyl 4-(allyloxy)-3-azidobenzoate, 31.

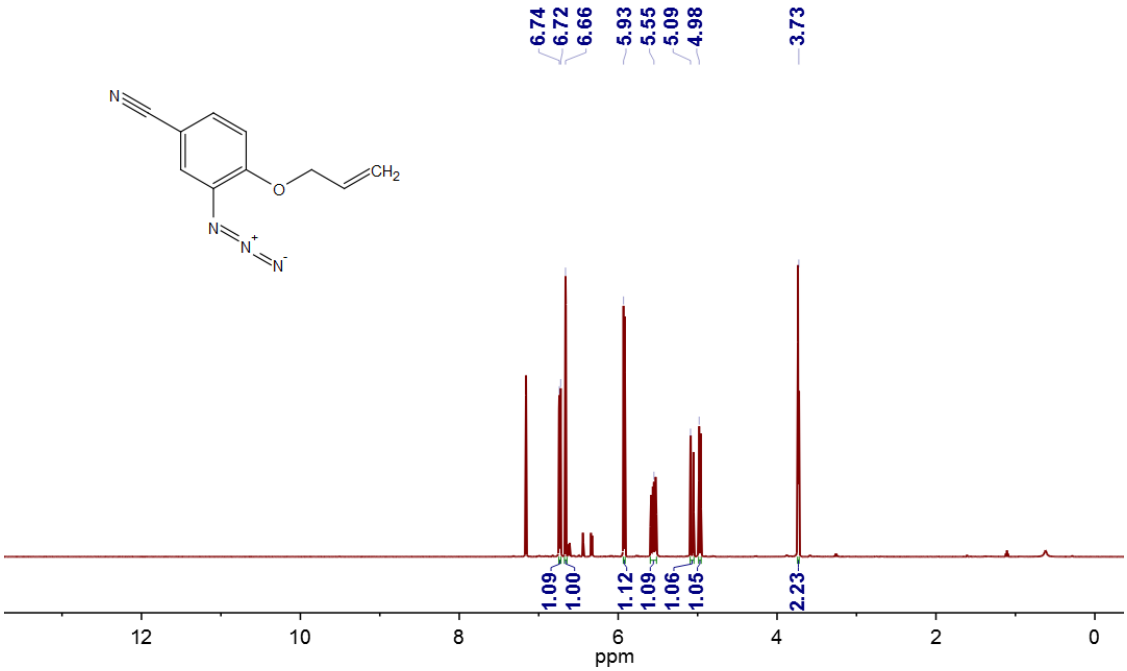


Figure 4.15: ^{1}H NMR of 4-(allyloxy)-3-azidobenzonitrile, 32.

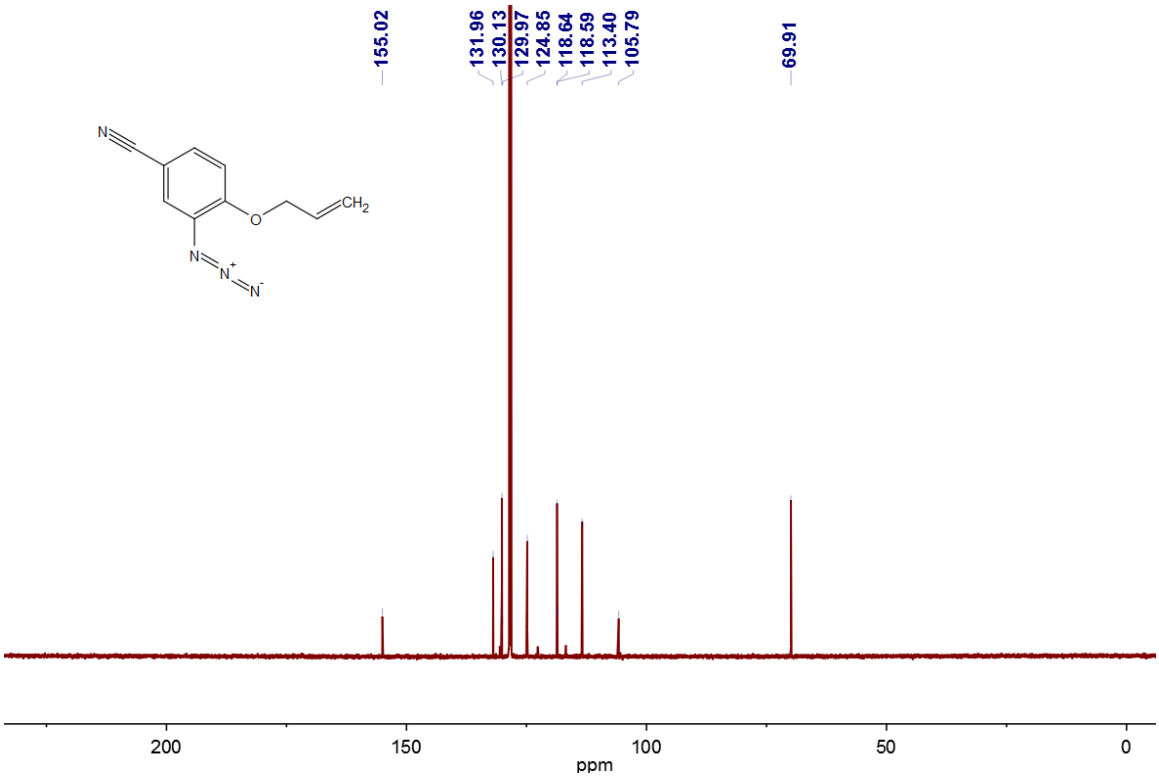


Figure 4.16: ^{13}C NMR of 4-(allyloxy)-3-azidobenzonitrile, 32.

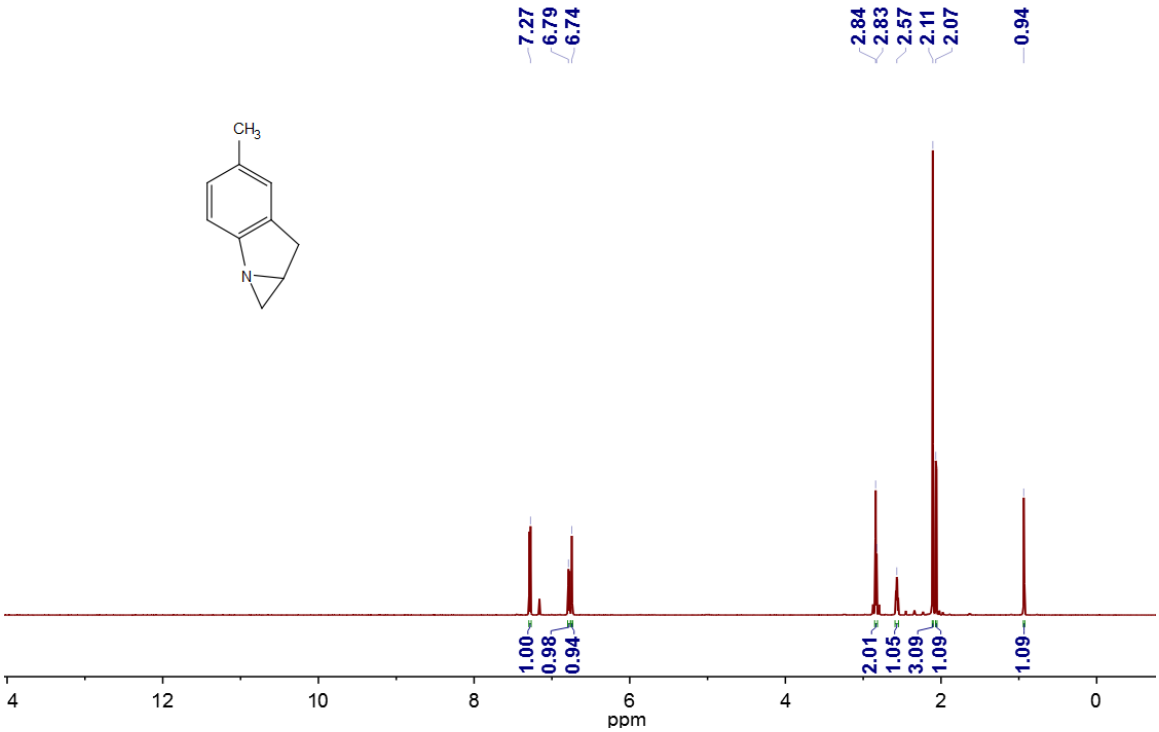


Figure 4.17: ^{1}H NMR of 5-methyl-7,7a-dihydro-1H-azirino[1,2-a]indole, 41.

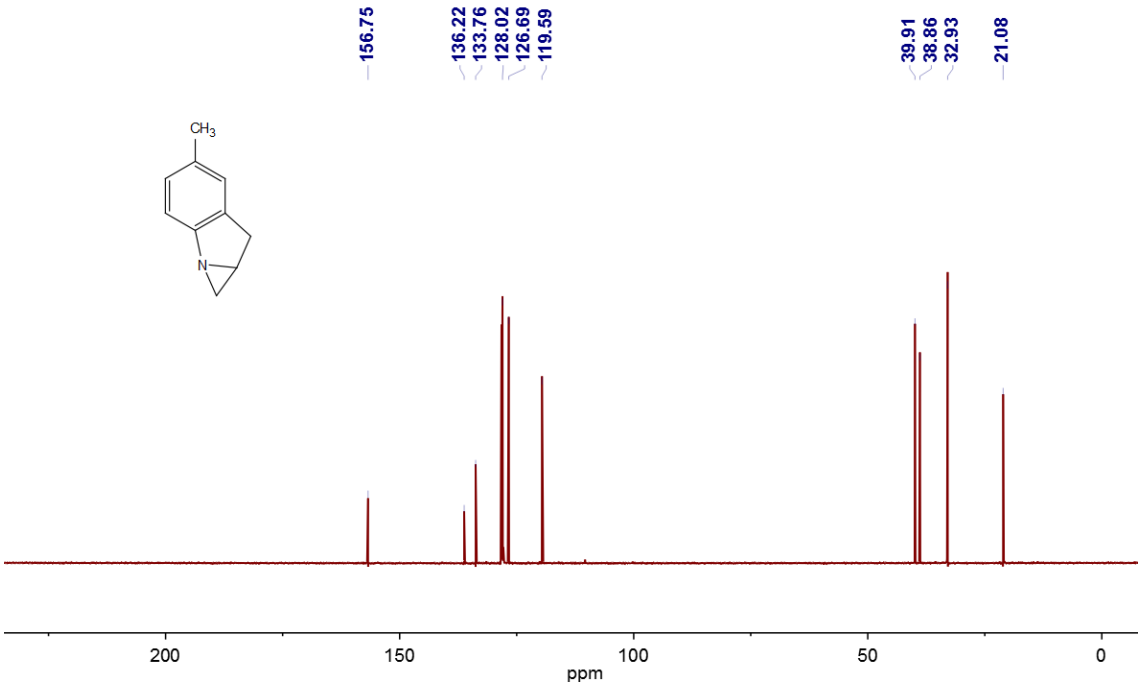


Figure 4.18: ^{13}C NMR of 5-methyl-7,7a-dihydro-1H-azirino[1,2-a]indole, 41.

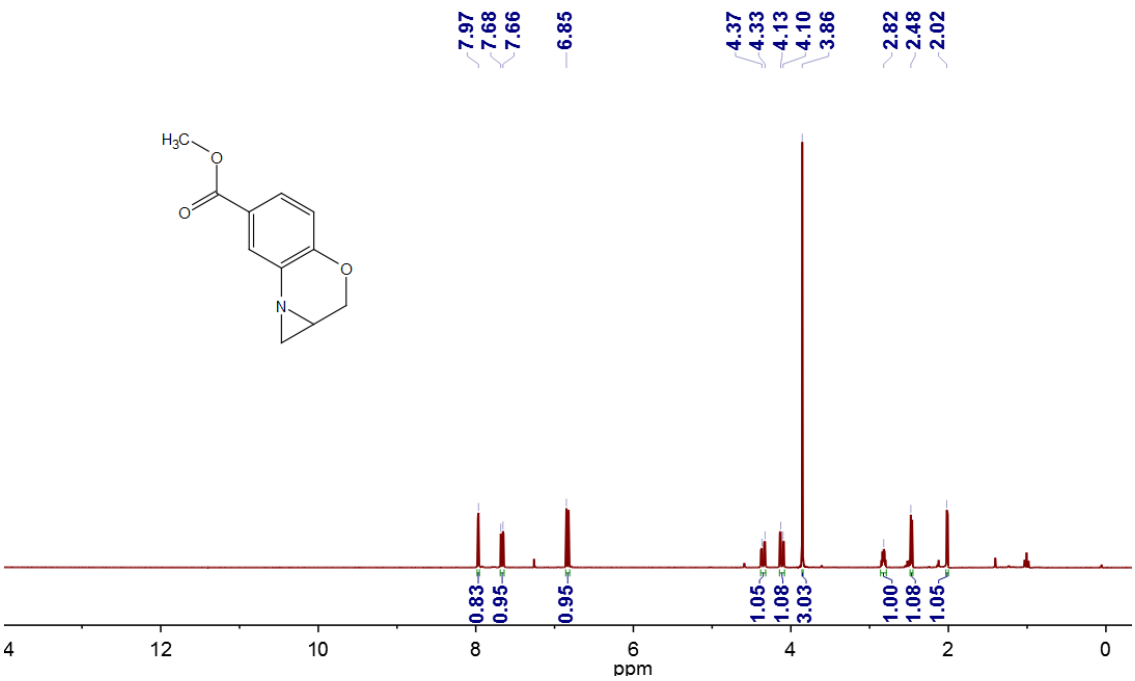


Figure 4.19: ^{1}H NMR of methyl 1a,2-dihydro-1H-azirino[1,2-d]benzo[b][1,4] oxazine-6-carboxylate, 39.

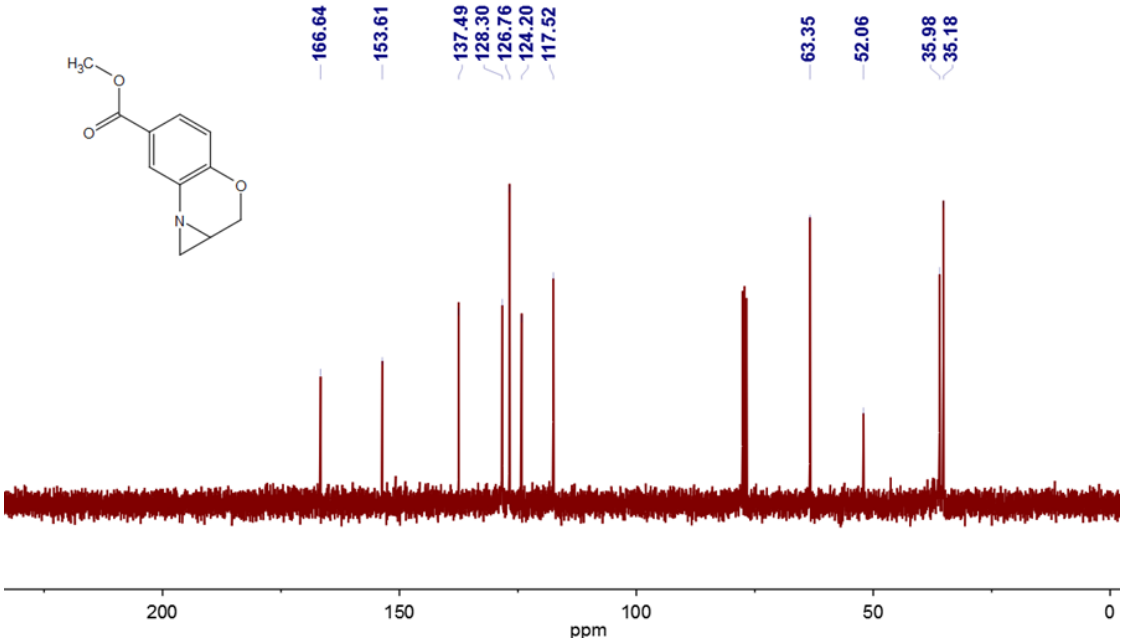


Figure 4.20: ^{13}C NMR of methyl 1a,2-dihydro-1H-azirino[1,2-d]benzo[b][1,4] oxazine-6-carboxylate, 39.

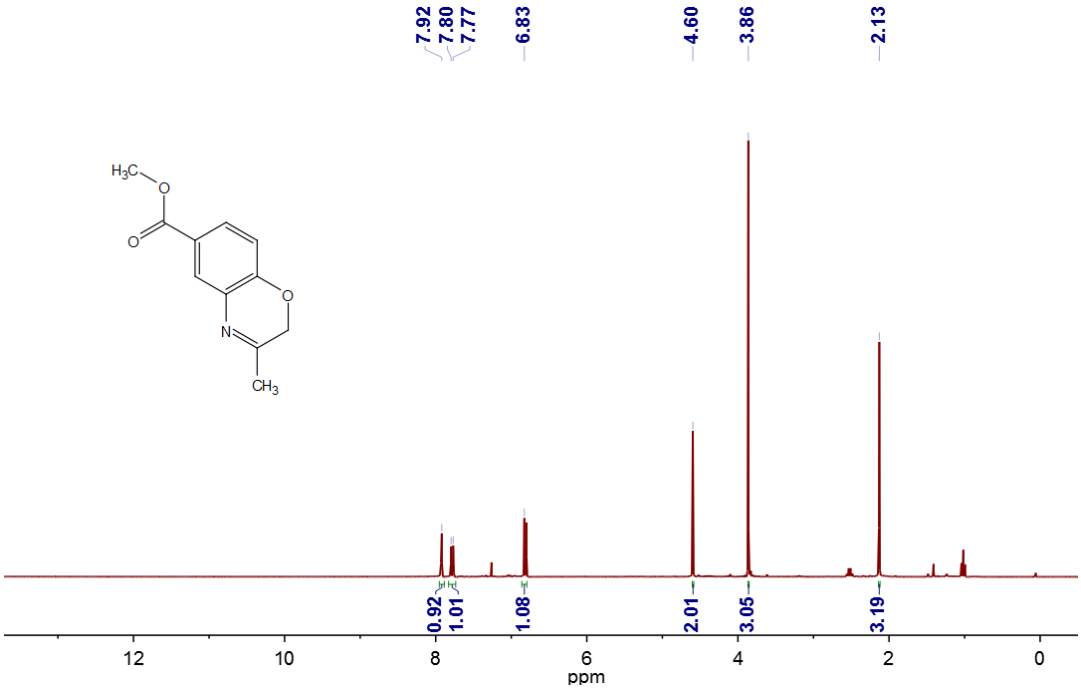


Figure 4.21: ^{1}H NMR of methyl 3-methyl-2H-benzo[b][1,4]oxazine-6-carboxylate, 43.

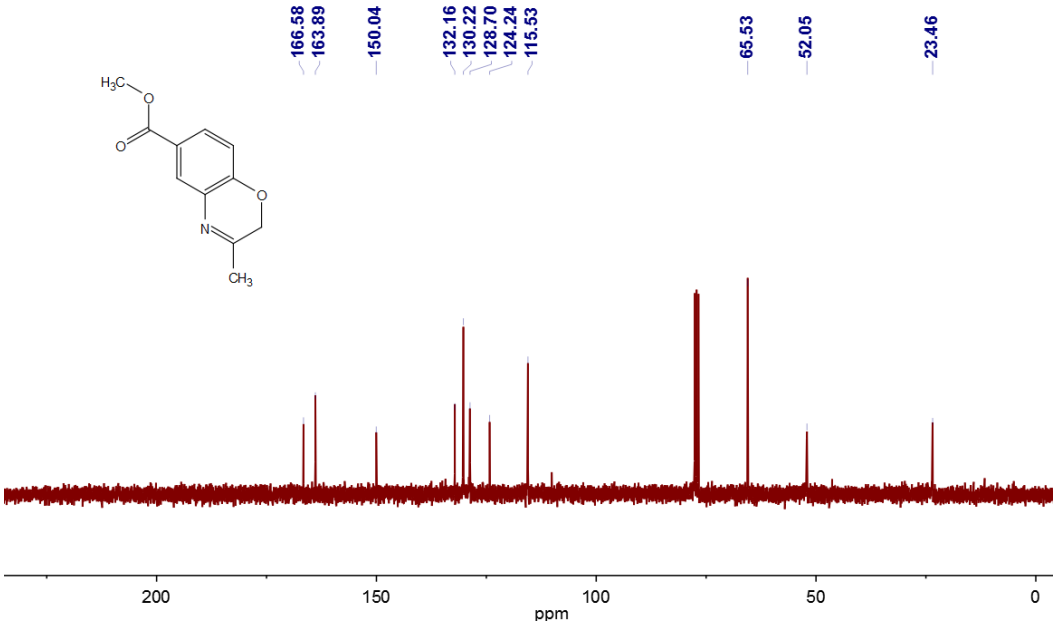


Figure 4.22: ^{13}C NMR of methyl 3-methyl-2H-benzo[b][1,4]oxazine-6-carboxylate, 43.

CHAPTER V

MISCELLANEOUS SYNTHETIC CHEMISTRY

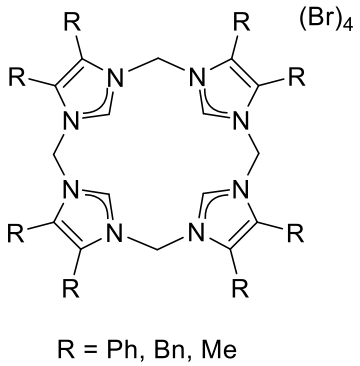
Abstract

Three novel tetracarbene macrocycles were synthesized and characterized. Due to various challenges in their syntheses, we chose not to pursue these macrocycles any further.

In addition to the synthesis of the macrocycles, the synthesis of a platinum(IV) tetracarbene dibromide complex is discussed. This complex successfully demonstrated oxidative halogen transfer to an alkene, showing the viability of this approach. However, we chose not to pursue this reaction, as the yields were low.

Introduction

The tetrazene side product was an undesirable side-product in the catalytic aziridination cycle.[36] Based off of our crystal structures of the iron tetrazenes, we believed that the flexibility of the 18-atom ligand was contributing to the reaction.[36] In order prevent tetrazene formation, we attempted to synthesized macrocycles with 16 atoms in the backbone of the macrocycle, analogous to the porphyrin aziridination catalysts (**Figure 5.1**). Previously, Kwang Kim and coworkers had prepared [calix[4]imidazolium]Br_4, a 16-atom tetracarbene macrocycle with protons on the imidazole backbone *via* a tetrabutylammonium chloride template.[101] We decided to use this basic procedure to synthesize tetraimidazolium macrocycles functionalized on the imidazolium backbone (the 4 and 5 positions), for two reasons. First, protons in the four and five positions



R = Ph, Bn, Me

Figure 5.1: Target Macrocycle Structure.

on imidazolium can be deprotonated under the right conditions. Second, imidazolium macrocycles with aryl or alkyl groups in the four and five positions show enhanced solubility as compared to macrocycles with protons in those positions.[34]

Synthesis of 4- and 5-Substituted Tetraimidazolium Macrocycles

In order to synthesize tetracarbene macrocycles, we refluxed *bis*(4,5-diphenyl-1*H*-imidazol-1-yl)methane in methylene bromide. Tetrabutylammonium chloride as a templating reagent to synthesize exclusively the tetraimidazolium salt. The desired macrocycle, ($^{Me,Me}TC^{Ph}$)$(Br)_4$ (**64**), precipitated out of the reaction solution in high purity (**Figure 5.2A**). The product was characterized by ^{1}H and ^{13}C NMR. Unfortunately, the reaction yield was only 1%! This extremely low yield precluded us from pursuing this research avenue further.

Our next effort was targeted at benzimidazole. Using the same method, we reacted *bis*(1*H*-benzo[*d*]imidazole-1-yl)methane with dibromomethane to close the ring and synthesized the corresponding macrocycle, ($^{Me,Me}TC^{Bn}$)$(Br)_4$ (**65**)(**Figure 5.2B**). We isolated a white solid that gave a large downfield peak in ^{1}H NMR, likely due to the formation of the benzimidazolium macrocycle. Unfortunately, the reaction product proved to be unstable, decomposing within 24 hours in organic solvents, so more complete characterization proved impossible. Similar tetrameric macrocycles have been shown to decompose in the presence of water and air.[102] We finally turned our attention to the synthesis of a macrocycle functionalized with methyl on the imidazole backbone. Starting from *bis*(4,5-dimethyl-1*H*-imidazol-1-

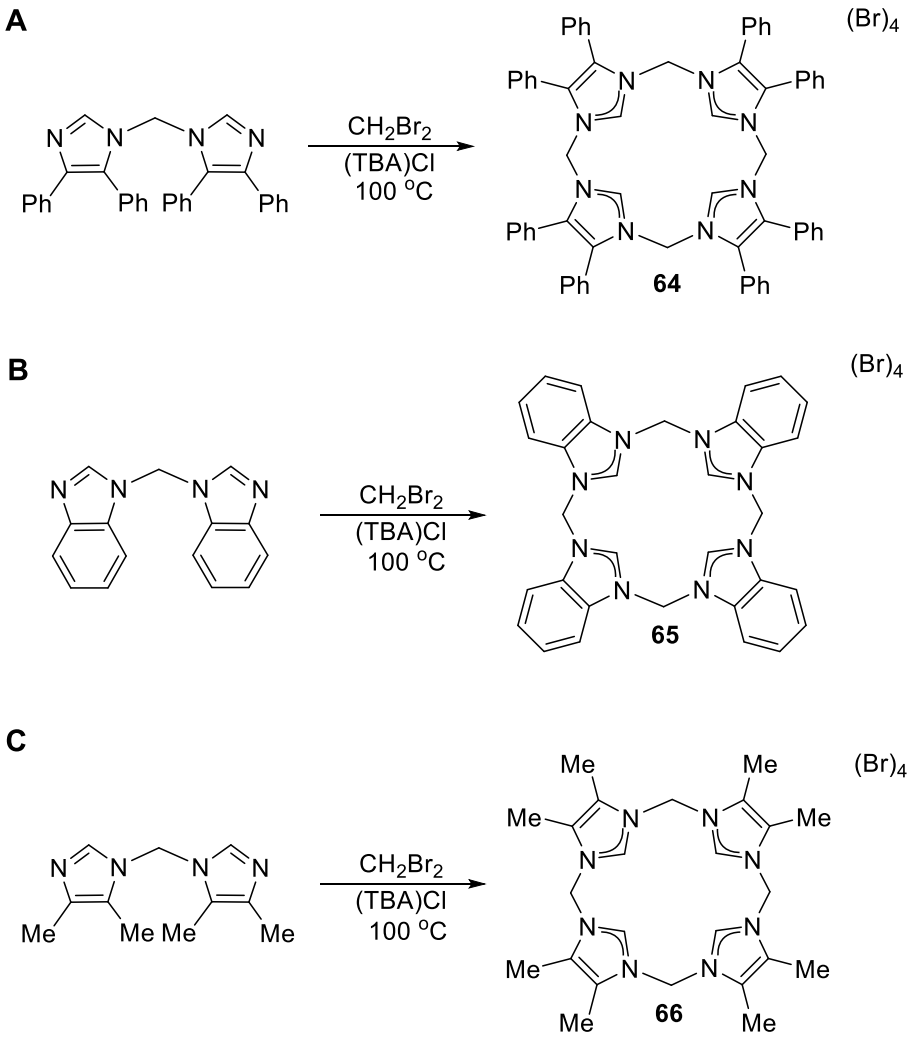


Figure 5.2: Synthesis of macrocycles 64, 65, and 66.

yl)methane, we followed a similar procedure as the previous reactions. The diimidazole was refluxed in dibromomethane with tetrabutyl ammonium chloride for three days. The reaction yielded a white solid. The product, possibly ($^{Me,Me}TC^{Me}$)$(Br)_4$ (**66**)(**Figure 5.2C**), was characterized by ^1H NMR, the NMR data was consistent with tetraimidazolium macrocycles. However, the product was impure, and all attempted methods of purification were unsuccessful. Since we were unable to purify the product, this macrocycle was also rejected as a potential ligand. Thus, all three new macrocycles were not compatible with new NHC chemistry.

Oxidative Bromine Transfer

Bromination reactions are important in modern synthetic chemistry; organobromines are versatile starting materials for organometallic synthesis,[103] palladium coupling reactions,[103, 104] and nucleophilic displacement reactions.[103] Additionally, these reactions are of commercial importance since organobromines are commonly used as flame retardants[103, 105] and biocides.[103] While bromination with the pure halogen is more selective than chlorination,[104] alternative reagents, such as N-bromosuccinimide (NBS) are preferred, due to bromine's volatility and toxicity.[103] However, NBS is not ideal in terms of atom economy. Previously, the Kraft group has established that chlorination reactions can be performed under more controlled conditions using palladium(IV) tetrachloride complexes with chelating *bis*-NHC ligands.[106, 107] However, an analogous reaction with high valent

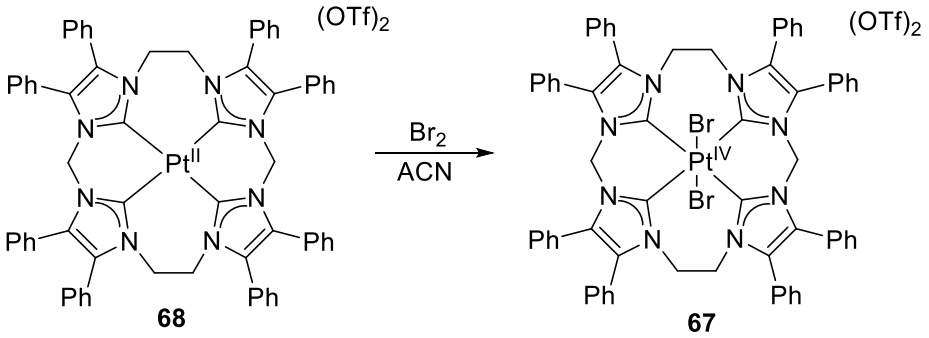


Figure 5.3: Synthesis of complex 67.

bromine complexes is unknown. Therefore, we attempted synthesize a high valent group 10 metal bromide complex for oxidative bromine transfer. To this end, we developed a synthesis of a platinum(IV) tetracarbene *bis*-bromide complex, [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$ (**67**), from elemental bromine. Starting from a platinum(II) tetracabene complex previously synthesized by the Jenkins group,[57] [(^{Me,Et}TC^{Ph})Pt](OTf)$_2$ (**68**), we reacted it with one equivalent of bromine in acetonitrile at room temperature. Removal of volatiles under vacuum gave complex **67** in an 82% yield. This complex was characterized by ^{1}H and ^{13}C NMR. Additionally, a single crystal XRD structure was obtained of this complex by a previous post-doc.

We next tested the complex's reactivity towards alkenes; [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$ was added to an acetonitrile solution with one equivalent of cyclohexene. The reaction was refluxed in acetonitrile, and a GC/MS was taken of the reaction solution. Based on the data, complex **49** did perform halogen transfer, in a 30% yield. In spite of this limited success, we decided that the reaction was not worth pursuing, since much better yields could be obtained by conventional methods.[104] Any future efforts on this work should focus on testing conditions for radical bromination, to see if this could be viable.

Conclusion

We synthesized a series of 16-atom tetraimidazolium macrocycles as potential NHC ligands for catalysis. Unfortunately, all the ligands had difficulties with their synthesis and all proved to be of untenable utility for as NHC ligands.

Additionally, we synthesized a platinum(IV) tetracarbene *bis*-bromide complex and did limited tested for this complex for oxidative bromine transfer.

Experimental

Synthesis of the organic compounds used were performed under atmospheric conditions. Dimethylsulfoxide-d_6 and acetonitrile-d_3 were purchased from Cambridge Isotope Lab and used without further purification. The compounds *bis*(4,5-diphenyl-1*H*-imidazol-1-yl)methane,[34] *bis*(4,5-dimethyl-1*H*-imidazol-1-yl)methane,[37] and *bis*(1*H*-benzo[*d*]imidazole-1-yl)methane,[108] and complex **50**[57] were synthesized by the published procedures. All other reagents were purchased from commercial vendors and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Mercury 300 MHz or a Varian VNMRS 500 MHz narrow-bore broadband system. ^{1}H and ^{13}C NMR chemical shifts were referenced to the residual solvent. All mass spectrometry analyses were conducted at the Mass Spectrometry Center located in the Department of Chemistry at the University of Tennessee. The ESI-MS analyses were performed using a QSTAR Elite quadrupole time-of-flight (QTOF) mass spectrometer with an electrospray ionization source from AB Sciex (Concord, Ontario, Canada). Mass spectrometry sample solutions of organometallic compounds were prepared in solutions of acetonitrile. GC/MS analysis was performed using a Hewlett and Packard 6890 gas chromatography system with Hewlett Packard 5973 mass spectrometer. Mass spectrometry sample solutions of organic compounds from the halogen transfer reactions were

prepared in solutions of acetonitrile. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance.

Synthesis of ($^{Me,Me}TC^{Ph}$)$(Br)_4$ (64): *Bis*(4,5-diphenyl-1*H*-imidazol-1-yl)methane (2.350 g, 5.19 mmol) was added to a solution of methylene bromide (50mL). Tetrabutylammonium chloride (0.144 g, 0.519 mmol) was then added. The reaction was heated at 95 ^oC for three days. After completion, the reaction was filtered over a fine frit. A white solid was collected, which was purified by washing with diethyl ether and drying the resulting solid on the Schlenk line, resulting in a yield of 0.0347 g, 1%. ^1H NMR (DMSO-d_6), 499.74 MHz): δ 11.60 (s, 4H), 7.39 (m, 40H), 6.55 (s, 8H). ^{13}C NMR (DMSO-d_6), 125.66 MHz): δ 137.20, 132.24, 131.05, 130.77, 128.87, 122.87, 56.91. IR: 3458.40, 2908.04, 1555.42, 1444.82, 1212.19, 1193.05, 1022.86, 860.38, 696.04 cm^{-1}.

Synthesis of ($^{Me,Me}TC^{Bn}$)$(Br)_4$ (65): *Bis*(1*H*-benzo[*d*]imidazole-1-yl)methane (0.712 g, 2.869 mmol) was added to a solution of methylene bromide (50 mL). Tetrabutylammonium chloride (0.078 g, 0.287 mmol) was then added. The reaction heated at 95 ^oC for three days. After completion, the reaction was filtered over a fine frit. A white solid was collected, which was purified by washing with diethyl ether and drying the resulting solid on the Schlenk line. The product degraded within 24 hours, preventing accurate characterization.

Synthesis of ($^{Me,Me}TC^{Me}$)$(Br)_4$ (66): *Bis*(4,5-dimethyl-1*H*-imidazol-1-yl)methane (0.098 g, 0.481 mmol) was added to a solution of methylene bromide (50 mL). Tetrabutylammonium chloride (0.016 g, 0.048 mmol) was added. The reaction

heated at 95 °C for three days. After completion, the reaction was filtered over a fine frit. A white solid was collected, which was purified by washing with diethyl ether and drying the resulting solid on the Schlenk line. The product was found to be very impure; hence, no accurate yield could be determined. ^{1}H NMR (DMSO-d_6), 499.74 MHz): δ 10.17 (s, 4H), 6.94 (s, 8H), 2.40 (s, 24H).

Synthesis of [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$, (67): **68** (0.093 g, 0.064 mmol) was added to 10 mL of acetonitrile. Bromine (5.4 μL, 0.064 mmol) was added by pipet. The resulting orange solution was stirred at room temperature for 20 min. After completion of the reaction, the solution was filtered over Celite, and the solvent was removed under vacuum. [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$ 0.0846 g was isolated as an orange solid, resulting in a yield of 0.0846 g, 82%. ^{1}H NMR (CD_3CN, 499.74 MHz): δ 7.43 (m, 12H), 7.34 (m, 12H), 7.23 (m, 8H), 7.18 (m, 8H), 6.44 (s, 4H), 4.91 (s, 8H). ^{13}C NMR (CD_3CN, 125.66 MHz): δ 136.85, 134.63, 133.18, 132.56, 131.99, 131.93, 130.70, 130.63, 129.69, 127.57, 126.51, 59.34, 48.71. ESI/MS (*m*/*z*): [M-OTf]$^{+}$ 1460.18, [M-2OTf]$^{2+}$ 655.63.

Oxidative Bromine Transfer to Cyclohexene: [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$ (0.0846 g, 0.052 mmol) was dissolved in acetonitrile. Cyclohexene (5.3 μL, 0.052 mmol) was added by pipet. The reaction heated at 60 °C overnight. The reaction was analyzed by GC/MS, giving approximately a 30% yield of 1,2-dibromocyclohexane by integration.[109]

Select NMRs for Products Discussed in this Chapter

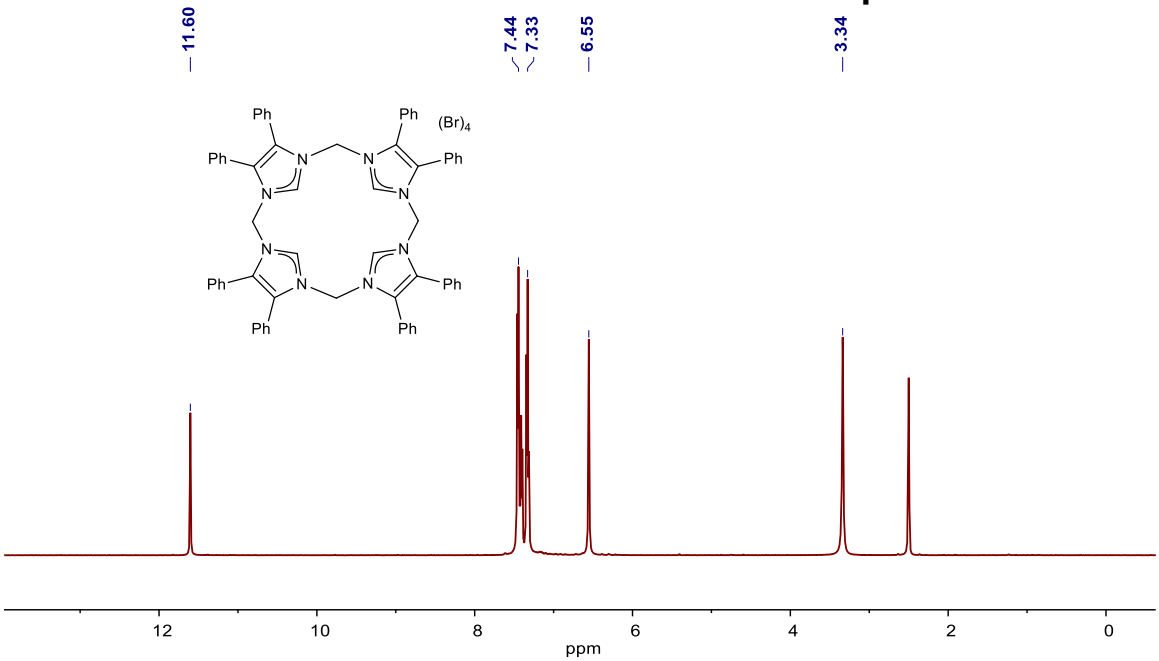


Figure 5.4: ^{1}H NMR of (^{Me,Me}TC^{Ph})(Br)$_4$.

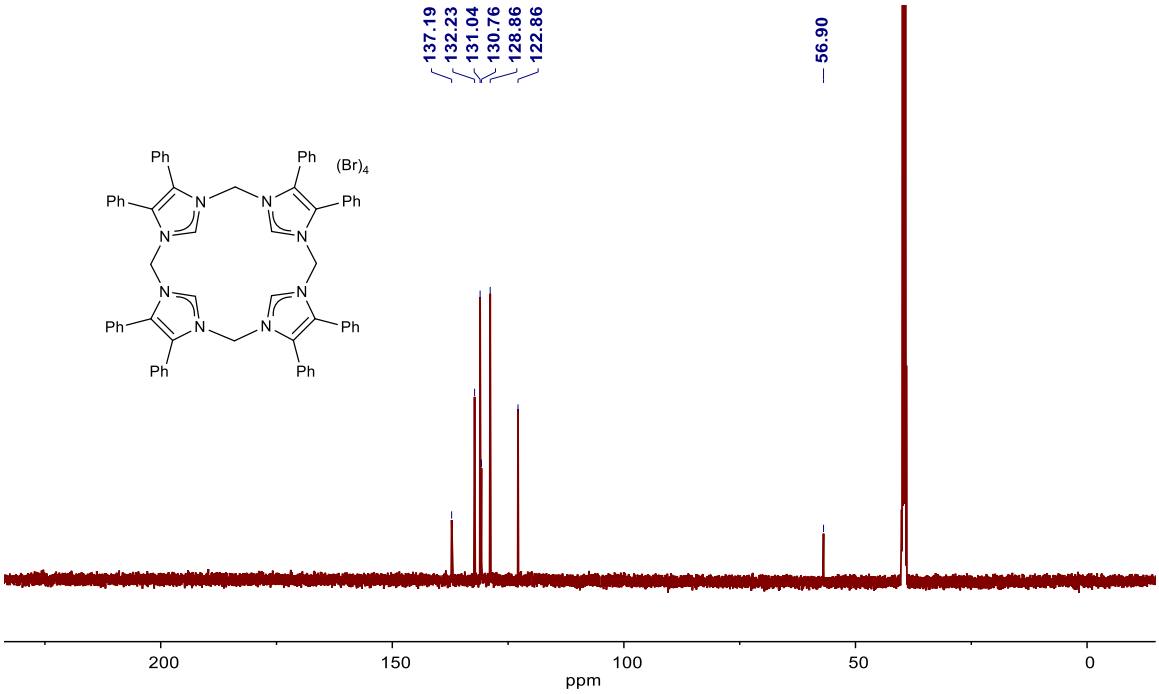


Figure 5.5: ^{13}C NMR of (^{Me,Me}TC^{Ph})(Br)$_4$.

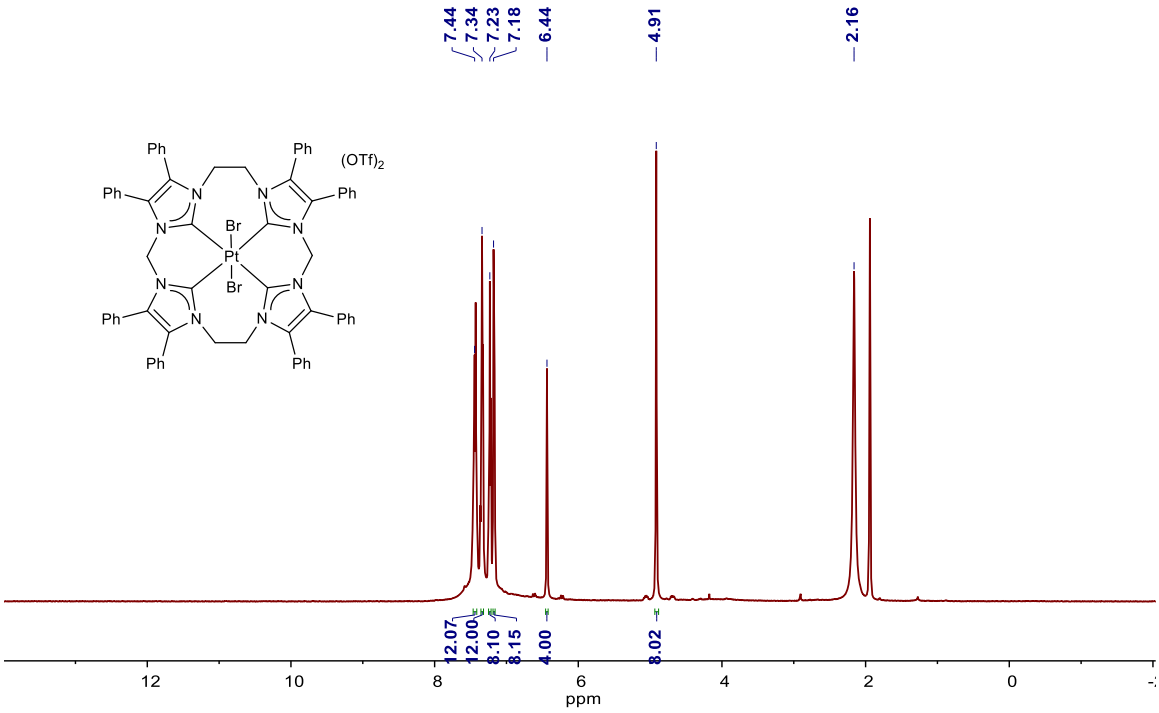


Figure 5.6: ^{1}H NMR of [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$.

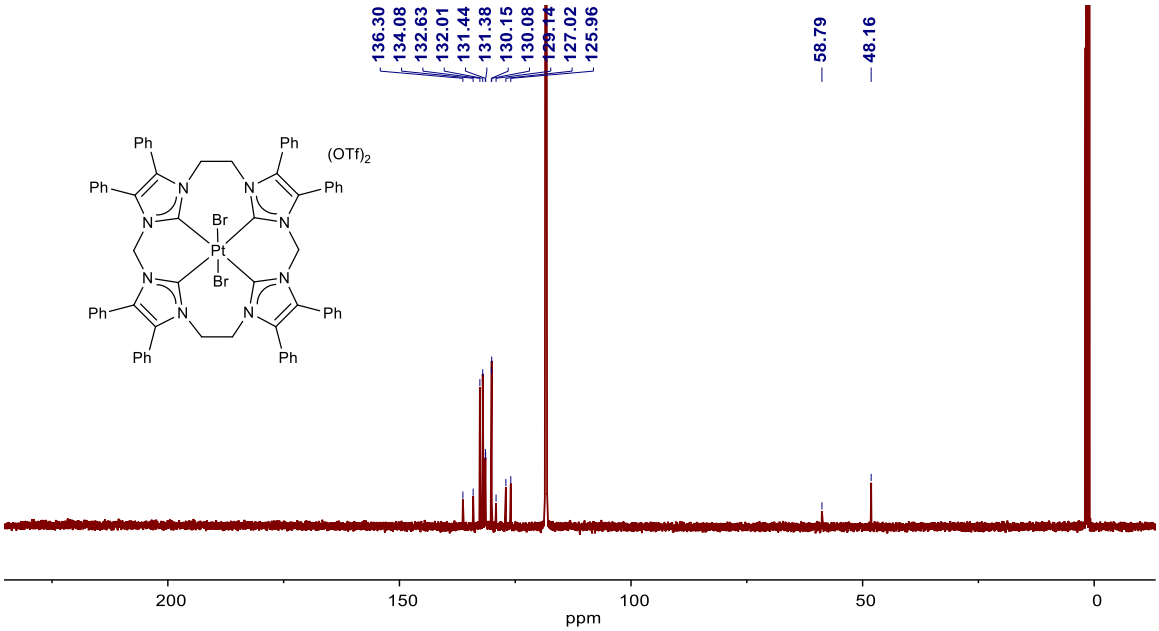


Figure 5.7: ^{13}C NMR of [(^{Me,Et}TC^{Ph})Pt(Br)$_2$](OTf)$_2$.

CONCLUSION

Results of Aziridination Research

Prior to this research, while there were several known $C_2 + N_1$ aziridination catalysts using cobalt or a group eight metal, such as iron or ruthenium, there were no published examples of any type of aziridination using chromium as a catalyst. Indeed, no examples of catalytic $C_2 + N_1$ aziridination were known on any group six metal. Furthermore, examples of catalytic aziridination using protic functional groups were few and far between.

We first synthesized and tested a cobalt(II) complex as an aziridination catalyst, $[(^{Me,Et}TC^{Ph})Co(NCCH_3)](PF_6)_2$. This complex showed no reactivity towards azides, and, consequently, no aziridination. The oxidative chemistry of this complex was explored, and a cobalt(III) complex was synthesized and isolated, $[(^{Me,Et}TC^{Ph})Co(NCCH_3)_2](PF_6)_3$. This complex was inert to further oxidation, whether by azides or other oxidants. A pair of additional cobalt(III) complexes were synthesized, $[(^{Me,Et}TC^{Ph})Co(Cl)_2](PF_6)$ and $[(^{Me,Et}TC^{Ph})Co(OPh)_2](PF_6)$, and neither of these complexes were reactive towards oxidants.

In an additional effort at catalytic aziridination, we demonstrated that with proper ligand design, not only was catalytic aziridination on chromium possible, it could even outperform known group eight catalysts in terms of substrate loading and functional group tolerance. $[(^{Me,Et}TC^{Ph})Cr(Cl)_2](PF_6)$ was used as a catalyst for aziridination at low alkene loadings. This complex was effective as a catalyst using only a threefold excess of alkene. Additionally, we successfully performed

catalytic aziridination using substrates containing unprotected alcohols on both the alkene (C_2 fragment), such as 9-decenol and 4-allylphenol, and on the azide (N_1 fragment). Additionally, we successfully performed catalytic aziridination on a substrate containing an unprotected secondary amine, N-allylaniline. Previous catalysts have only been able to perform aziridination with either protected amines or tertiary amines. Based on calculations performed by our collaborators, the key structural feature of the active catalyst was the axial chloride ligand, which prevented tetrazene formation and enabled group transfer. This work was published in *Chemical Communications.*

Based on the previous research, we attempted to synthesize an iron(II) complex that had a fifth ligand in an axial coordination site to improve the catalysis of our original iron complex, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$. This complex was reacted with a carbon dioxide adduct of an NHC, yielding $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)(^{Me}NHC^{H})](PF_6)_2$. This complex proved successful at aziridination; however, we were unable to reproduce its synthesis.

In spite of our failure to develop an improved iron catalyst, we still believed that there was more work to be done in the field of catalytic $C_2 + N_1$ aziridination, namely intramolecular aziridination. Tertiary aziridines are structures found in a few natural products, such as ficellomycin. The only way to synthesize these molecules using a $C_2 + N_1$ aziridination would be by performing a ring-closing intramolecular reaction. This topic had been largely unexplored, and we set out to make the first systematic study of catalytic intramolecular aziridination. We

synthesized a series of azidoalkenes for ring closing aziridination and isolated several novel aziridines. Unfortunately, the yields of the control reactions were identical to the catalytic yields with metals, showing that we were getting no practical catalysis.

Based on calculations performed by our collaborators in the Roy group, we attempted to synthesize a series of 16-atom tetra NHC macrocycles from the corresponding diimidazoles. We were able to synthesize three macrocycles with different functional group on the 4- and 5-positions on the imidazole, but they all proved to be unusable for tetracarbene chemistry.

Finally, as a side note, we synthesized a platium(IV) dibromide tetra NHC complex from a platinum(II) tetra NHC starting material using bromine. This complex was capable of performing halogen transfer to an alkene, but the yield was too low to be synthetically useful.

REFERENCES

1. Yudin, A. K., *Aziridines and Epoxides in Organic Synthesis*. Wiley: Weinheim, Germany, 2006.
2. Hou, X.; Zhang, H.; Chen, B.-C.; Guo, Z.; Singh, A.; Goswami, A.; Gilmore, J. L.; Sheppeck, J. E.; Dyckman, A. J.; Carter, P. H.; Mathur, A., Regioselective Epoxide Ring Opening for the Stereospecific Scale-Up Synthesis of BMS-960, A Potent and Selective Isoxazole-Containing S1P1 Receptor Agonist. *Organic Process Research & Development* **2017,** *21* (2), 200-207.
3. Pujala, B.; Rana, S.; Chakraborti, A. K., Zinc Tetrafluoroborate Hydrate as a Mild Catalyst for Epoxide Ring Opening with Amines: Scope and Limitations of Metal Tetrafluoroborates and Applications in the Synthesis of Antihypertensive Drugs (RS)/(R)/(S)-Metoprolols. *The Journal of Organic Chemistry* **2011,** *76* (21), 8768-8780.
4. Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E., An Oxidation and Ring Contraction Approach to the Synthesis of (±)-1-Deoxynojirimycin and (±)-1-Deoxyaltronojirimycin. *Organic Letters* **2010,** *12* (1), 136-139.
5. Jacobsen, E. N., Asymmetric Catalysis of Epoxide Ring-Opening Reactions. *Accounts of Chemical Research* **2000,** *33* (6), 421-431.
6. Liu, H.; Pattabiraman, V. R.; Vederas, J. C., Stereoselective Syntheses of 4-Oxa Diaminopimelic Acid and Its Protected Derivatives via Aziridine Ring Opening. *Organic Letters* **2007,** *9* (21), 4211-4214.
7. Moens, M.; De Kimpe, N.; D'hooghe, M., Selective Synthesis of cis- and trans-2-(Methyl/phenyl)-3-(trifluoromethyl)aziridines and Their Regio- and Stereospecific Ring Opening. *The Journal of Organic Chemistry* **2014,** *79* (12), 5558-5568.
8. Kelley, B. T.; Joullié, M. M., Ring Opening of a Trisubstituted Aziridine With Amines: Regio- and Stereoselective Formation of Substituted 1,2-Diamines. *Organic Letters* **2010,** *12* (19), 4244-4247.
9. Li, P.; Forbeck, E. M.; Evans, C. D.; Joullié, M. M., Trisubstituted Aziridine Ring-Opening by Phenol Derivatives: Stereo- and Regioselective Formation of Chiral Tertiary Alkyl-Aryl Ethers. *Organic Letters* **2006,** *8* (22), 5105-5107.
10. Wu, Y.-C.; Zhu, J., Asymmetric Total Syntheses of (−)-Renieramycin M and G and (−)-Jorumycin Using Aziridine as a Lynchpin. *Organic Letters* **2009,** *11* (23), 5558-5561.
11. Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S., Synthesis and Reactivity of 2-(Carboxymethyl)aziridine Derivatives. *Chemical Reviews* **2014,** *114* (16), 7954-8015.
12. Oh, H.-S.; Kang, H.-Y., Synthesis of (−)-Oseltamivir Phosphate (Tamiflu) Starting from cis-2,3-Bis(hydroxymethyl)aziridine. *The Journal of Organic Chemistry* **2012,** *77* (19), 8792-8796.
13. Rivinoja, D. J.; Gee, Y. S.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T., The Diastereoselective Synthesis of Pyrroloindolines by Pd-Catalyzed Dearomative Cycloaddition of 1-Tosyl-2-vinylaziridine to 3-Nitroindoles. *ACS Catalysis* **2017,** *7* (2), 1053-1056.

14. Mulcahy, J. V.; Walker, J. R.; Merit, J. E.; Whitehead, A.; Du Bois, J., Synthesis of the Paralytic Shellfish Poisons (+)-Gonyautoxin 2, (+)-Gonyautoxin 3, and (+)-11,11-Dihydroxysaxitoxin. *Journal of the American Chemical Society* **2016,** *138* (18), 5994-6001.
15. Liew, S. K.; Kaldas, S. J.; Yudin, A. K., A Linchpin Synthesis of 6-Hydroxyceramides from Aziridine Aldehydes. *Organic Letters* **2016,** *18* (24), 6268-6271.
16. Feng, J.-J.; Zhang, J., Synthesis of Unsaturated N-Heterocycles by Cycloadditions of Aziridines and Alkynes. *ACS Catalysis* **2016,** *6* (10), 6651-6661.
17. Wang, L.; Yang, D.; Han, F.; Li, D.; Zhao, D.; Wang, R., Catalytic Asymmetric Construction of Pyrroloindolines via an in Situ Generated Magnesium Catalyst. *Organic Letters* **2015,** *17* (2), 176-179.
18. Coleman, R. S.; Kong, J.-S., Stereocontrolled Synthesis of the Fully Elaborated Aziridine Core of the Azinomycins. *Journal of the American Chemical Society* **1998,** *120* (14), 3538-3539.
19. Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M., DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic acids research* **2018,** *46* (D1), D1074-d1082.
20. Musser, S. M.; Pan, S. S.; Egorin, M. J.; Kyle, D. J.; Callery, P. S., Alkylation of DNA with aziridine produced during the hydrolysis of N,N',N''-triethylenethiophosphoramide. *Chemical Research in Toxicology* **1992,** *5* (1), 95-99.
21. Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A., New reaction. Stereospecific vicinal oxyamination of olefins by alkyl imido osmium compounds. *Journal of the American Chemical Society* **1975,** *97* (8), 2305-2307.
22. Wang, L.-Y.; Gu, G.-G.; Yue, T.-J.; Ren, W.-M.; Lu, X.-B., Semiaromatic Poly(thioester) from the Copolymerization of Phthalic Thioanhydride and Epoxide: Synthesis, Structure, and Properties. *Macromolecules* **2019**.
23. Marcotrigiano, G. O.; Storelli, M. M. J. V. R. C., Heavy Metal, Polychlorinated Biphenyl and Organochlorine Pesticide Residues in Marine Organisms: Risk Evaluation for Consumers. **2003,** *27* (1), 183-195.
24. Chandrachud, P. P.; Jenkins, D. M., Transition Metal Aziridination Catalysts. In *Encyclopedia of Inorganic and Bioinorganic Chemistry*.
25. Maas, G., New Syntheses of Diazo Compounds. **2009,** *48* (44), 8186-8195.
26. Jenkins, D. M., Atom-Economical C2 + N1 Aziridination: Progress towards Catalytic Intermolecular Reactions Using Alkenes and Aryl Azides. *Synlett* **2012,** *23* (09), 1267-1270.
27. Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Cenini, S., The (Porphyrin)ruthenium-Catalyzed Aziridination of Olefins Using Aryl Azides as Nitrogen Sources. *European Journal of Organic Chemistry* **2007,** *2007* (36), 6053-6059.

28. Smith, P. A. S.; Brown, B. B., The Reaction of Aryl Azides with Hydrogen Halides1,2. *Journal of the American Chemical Society* **1951,** *73* (6), 2438-2441.
29. Cenini, S.; Tollari, S.; Penoni, A.; Cereda, C., Catalytic amination of unsaturated hydrocarbons: reactions of p-nitrophenylazide with alkenes catalysed by metallo-porphyrins. *Journal of Molecular Catalysis A: Chemical* **1999,** *137* (1), 135-146.
30. Piangiolino, C.; Gallo, E.; Caselli, A.; Fantauzzi, S.; Ragaini, F.; Cenini, S., The [Ru(CO)(porphyrin)]-Catalyzed Synthesis of N-Aryl-2-vinylaziridines. *European Journal of Organic Chemistry* **2007,** *2007* (5), 743-750.
31. Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P., A Highly Effective Cobalt Catalyst for Olefin Aziridination with Azides: Hydrogen Bonding Guided Catalyst Design. *Organic Letters* **2008,** *10* (10), 1995-1998.
32. Jones, J. E.; Ruppel, J. V.; Gao, G.-Y.; Moore, T. M.; Zhang, X. P., Cobalt-Catalyzed Asymmetric Olefin Aziridination with Diphenylphosphoryl Azide. *The Journal of Organic Chemistry* **2008,** *73* (18), 7260-7265.
33. Liu, Y.; Che, C.-M., [FeIII(F20-tpp)Cl] Is an Effective Catalyst for Nitrene Transfer Reactions and Amination of Saturated Hydrocarbons with Sulfonyl and Aryl Azides as Nitrogen Source under Thermal and Microwave-Assisted Conditions. *Chemistry – A European Journal* **2010,** *16* (34), 10494-10501.
34. Bass, H. M.; Cramer, S. A.; Price, J. L.; Jenkins, D. M., 18-Atom-Ringed Macrocyclic Tetra-imidazoliums for Preparation of Monomeric Tetra-carbene Complexes. *Organometallics* **2010,** *29* (15), 3235-3238.
35. Cramer, S. A.; Jenkins, D. M., Synthesis of Aziridines from Alkenes and Aryl Azides with a Reusable Macrocyclic Tetracarbene Iron Catalyst. *Journal of the American Chemical Society* **2011,** *133* (48), 19342-19345.
36. Cramer, S. A.; Hernandez Sanchez, R.; Brakhage, D. F.; Jenkins, D. M., Probing the role of an FeIV tetrazene in catalytic aziridination. *Chemical Communications* **2014,** *50* (90), 13967-13970.
37. Bass, H. M.; Cramer, S. A.; McCullough, A. S.; Bernstein, K. J.; Murdock, C. R.; Jenkins, D. M., Employing Dianionic Macrocyclic Tetracarbenes To Synthesize Neutral Divalent Metal Complexes. *Organometallics* **2013,** *32* (7), 2160-2167.
38. Scepaniak, J. J.; Harris, T. D.; Vogel, C. S.; Sutter, J.; Meyer, K.; Smith, J. M., Spin Crossover in a Four-Coordinate Iron(II) Complex. *Journal of the American Chemical Society* **2011,** *133* (11), 3824-3827.
39. Cramer, S. A.; Sturgill, F. L.; Chandrachud, P. P.; Jenkins, D. M., Overcoming NHCs neutrality: installing tetracarbenes on group 13 and 14 metals. *Dalton Transactions* **2014,** *43* (21), 7687-7690.
40. Chandrachud, P. P.; Bass, H. M.; Jenkins, D. M., Synthesis of Fully Aliphatic Aziridines with a Macrocyclic Tetracarbene Iron Catalyst. *Organometallics* **2016,** *35* (11), 1652-1657.
41. Jin, L.-M.; Xu, X.; Lu, H.; Cui, X.; Wojtas, L.; Zhang, X. P., Effective Synthesis of Chiral N-Fluoroaryl Aziridines through Enantioselective Aziridination

of Alkenes with Fluoroaryl Azides. *Angewandte Chemie International Edition* **2013,** *52* (20), 5309-5313.
42. Jiang, H.; Lang, K.; Lu, H.; Wojtas, L.; Zhang, X. P., Asymmetric Radical Bicyclization of Allyl Azidoformates via Cobalt(II)-Based Metalloradical Catalysis. *Journal of the American Chemical Society* **2017,** *139* (27), 9164-9167.
43. King, E. R.; Hennessy, E. T.; Betley, T. A., Catalytic C−H Bond Amination from High-Spin Iron Imido Complexes. *Journal of the American Chemical Society* **2011,** *133* (13), 4917-4923.
44. Farwell, C. C.; Zhang, R. K.; McIntosh, J. A.; Hyster, T. K.; Arnold, F. H., Enantioselective Enzyme-Catalyzed Aziridination Enabled by Active-Site Evolution of a Cytochrome P450. *ACS Central Science* **2015,** *1* (2), 89-93.
45. Zdilla, M. J.; Abu-Omar, M. M., Mechanism of Catalytic Aziridination with Manganese Corrole: The Often Postulated High-Valent Mn(V) Imido Is Not the Group Transfer Reagent. *Journal of the American Chemical Society* **2006,** *128* (51), 16971-16979.
46. Sorokin, A. B., Phthalocyanine Metal Complexes in Catalysis. *Chemical Reviews* **2013,** *113* (10), 8152-8191.
47. Zhang, K.; Farha, O. K.; Hupp, J. T.; Nguyen, S. T., Complete Double Epoxidation of Divinylbenzene Using Mn(porphyrin)-Based Porous Organic Polymers. *ACS Catalysis* **2015,** *5* (8), 4859-4866.
48. Liu, C.-J.; Yu, W.-Y.; Che, C.-M.; Yeung, C.-H., A Mechanistic Investigation of Alkene Epoxidation by Sterically Encumbered trans-Dioxoruthenium(VI) Porphyrins. *The Journal of Organic Chemistry* **1999,** *64* (20), 7365-7374.
49. Chan, W.-K.; Wong, M.-K.; Che, C.-M., Metalloporphyrin-Catalyzed Diastereoselective Epoxidation of Allyl-Substituted Alkenes. *The Journal of Organic Chemistry* **2005,** *70* (11), 4226-4232.
50. Jenkins, D. M.; Betley, T. A.; Peters, J. C., Oxidative Group Transfer to Co(I) Affords a Terminal Co(III) Imido Complex. *Journal of the American Chemical Society* **2002,** *124* (38), 11238-11239.
51. Bowman, A. C.; Milsmann, C.; Bill, E.; Turner, Z. R.; Lobkovsky, E.; DeBeer, S.; Wieghardt, K.; Chirik, P. J., Synthesis and Electronic Structure Determination of N-Alkyl-Substituted Bis(imino)pyridine Iron Imides Exhibiting Spin Crossover Behavior. *Journal of the American Chemical Society* **2011,** *133* (43), 17353-17369.
52. Blake, A. J.; Collier, P. E.; Gade, L. H.; Mountford, P.; Lloyd, J.; Pugh, S. M.; Schubart, M.; Skinner, M. E. G.; Trösch, D. J. M., Group 4 Imido Complexes Stabilized by a Tridentate Diamido-Donor Ligand. *Inorganic Chemistry* **2001,** *40* (5), 870-877.
53. Brown, S. D.; Betley, T. A.; Peters, J. C., A Low-Spin d5 Iron Imide: Nitrene Capture by Low-Coordinate Iron(I) Provides the 4-Coordinate Fe(III) Complex [PhB(CH2PPh2)3]Fe:N-p-tolyl. *Journal of the American Chemical Society* **2003,** *125* (2), 322-323.

54. Mindiola, D. J.; Hillhouse, G. L., Terminal Amido and Imido Complexes of Three-Coordinate Nickel. *Journal of the American Chemical Society* **2001,** *123* (19), 4623-4624.
55. Caselli, A.; Gallo, E.; Fantauzzi, S.; Morlacchi, S.; Ragaini, F.; Cenini, S., Allylic Amination and Aziridination of Olefins by Aryl Azides Catalyzed by CoII(tpp): A Synthetic and Mechanistic Study. *European Journal of Inorganic Chemistry* **2008,** *2008* (19), 3009-3019.
56. Chandrachud, P. P., Catalysis of Fully Alkyl Aziridines with a Borate-containing Macrocyclic N-Heterocyclic Tetracarbene Iron Complex. **2016**.
57. Lu, Z.; Cramer, S. A.; Jenkins, D. M., Exploiting a dimeric silver transmetallating reagent to synthesize macrocyclic tetracarbene complexes. *Chemical Science* **2012,** *3* (10), 3081-3087.
58. Caselli, A.; Gallo, E.; Ragaini, F.; Ricatto, F.; Abbiati, G.; Cenini, S., Chiral porphyrin complexes of cobalt(II) and ruthenium(II) in catalytic cyclopropanation and amination reactions. *Inorganica Chimica Acta* **2006,** *359* (9), 2924-2932.
59. Bass, H. M., Developing 16- and 18-Atom Ringed Macrocyclic Tetracarbene Complexes. **2013**.
60. Mo, Z.; Li, Y.; Lee, H. K.; Deng, L., Square-Planar Cobalt Complexes with Monodentate N-Heterocyclic Carbene Ligation: Synthesis, Structure, and Catalytic Application. *Organometallics* **2011,** *30* (17), 4687-4694.
61. Park, S. R.; Findlay, N. J.; Garnier, J.; Zhou, S.; Spicer, M. D.; Murphy, J. A., Electron transfer activity of a cobalt crown carbene complex. *Tetrahedron* **2009,** *65* (52), 10756-10761.
62. Keller, C. L.; Kern, J. L.; Terry, B. D.; Roy, S.; Jenkins, D. M., Catalytic aziridination with alcoholic substrates via a chromium tetracarbene catalyst. *Chemical Communications* **2018,** *54* (12), 1429-1432.
63. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N., Enantioselective epoxidation of unfunctionalized olefins catalyzed by salen manganese complexes. *Journal of the American Chemical Society* **1990,** *112* (7), 2801-2803.
64. Saha, A.; Majumdar, P.; Goswami, S., Low-spin manganese(II) and cobalt(III) complexes of N-aryl-2-pyridylazophenylamines: new tridentate N,N,N-donors derived from cobalt mediated aromatic ring amination of 2-(phenylazo)pyridine. Crystal structure of a manganese(II) complex*Journal of the Chemical Society, Dalton Transactions* **2000,** (11), 1703-1708.
65. Shriver, D.; Atkins, P., *Inorganic Chemistry*. 5th ed.; W. H. Freeman: 2009.
66. Hock, S. J.; Schaper, L.-A.; Herrmann, W. A.; Kühn, F. E., Group 7 transition metal complexes with N-heterocyclic carbenes. *Chemical Society Reviews* **2013,** *42* (12), 5073-5089.
67. Díez-González, S.; Marion, N.; Nolan, S. P., N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chemical Reviews* **2009,** *109* (8), 3612-3676.
68. Mukherjee, A.; Milstein, D., Homogeneous Catalysis by Cobalt and Manganese Pincer Complexes. *ACS Catalysis* **2018,** *8* (12), 11435-11469.
69. Siddall, T. L.; Miyaura, N.; Huffman, J. C.; Kochi, J. K., Isolation and molecular structure of unusual oxochromium(V) cations for the catalytic

epoxidation of alkenes. *Journal of the Chemical Society, Chemical Communications* **1983,** (21), 1185-1186.
70. Hess, J. S.; Leelasubcharoen, S.; Rheingold, A. L.; Doren, D. J.; Theopold, K. H., Spin Surface Crossing in Chromium-Mediated Olefin Epoxidation with O2. *Journal of the American Chemical Society* **2002,** *124* (11), 2454-2455.
71. Edwards, N. Y.; Eikey, R. A.; Loring, M. I.; Abu-Omar, M. M., High-Valent Imido Complexes of Manganese and Chromium Corroles. *Inorganic Chemistry* **2005,** *44* (10), 3700-3708.
72. Leung, W.-H.; Danopoulos, A. A.; Wilkinson, G.; Hussain-Bates, B.; Hursthouse, M. B., tert-Butylimido complexes of chromium and vanadium. X-Ray crystal structures of Cr(NBut)Cl3(MeOCH2CH2OMe), Cr[C6H4(NH)2-o]Cl2(PMe2Ph)2, Cr(NBut)2(OSiPh3)2, Cr(NBut)-Cl(OC9H6N)2 and [(PPh3)2][Cr(NBut){S2C2(CN)2}2]. *Journal of the Chemical Society, Dalton Transactions* **1991,** (8), 2051-2061.
73. Elpitiya, G. R.; Malbrecht, B. J.; Jenkins, D. M., A Chromium(II) Tetracarbene Complex Allows Unprecedented Oxidative Group Transfer. *Inorganic Chemistry* **2017,** *56* (22), 14101-14110.
74. Chandrachud, P. P.; Jenkins, D. M., High valent FeIV chemistry in sustainable oxidation catalysis. *Tetrahedron Letters* **2015,** *56* (19), 2369-2376.
75. Antilla, J. C.; Buchwald, S. L., Copper-Catalyzed Coupling of Arylboronic Acids and Amines. *Organic Letters* **2001,** *3* (13), 2077-2079.
76. Arai, K.; Lucarini, S.; Salter, M. M.; Ohta, K.; Yamashita, Y.; Kobayashi, S., The Development of Scalemic Multidentate Niobium Complexes as Catalysts for the Highly Stereoselective Ring Opening of meso-Epoxides and meso-Aziridines. *Journal of the American Chemical Society* **2007,** *129* (26), 8103-8111.
77. Liu, Y.; Guo, J.-Z.; Lu, H.-W.; Wang, H.-B.; Lu, X.-B., Making Various Degradable Polymers from Epoxides Using a Versatile Dinuclear Chromium Catalyst. *Macromolecules* **2018,** *51* (3), 771-778.
78. Walton, R.; Lahti, P. M., An Efficient, Simple Synthesis of 4-Azidobenzaldehyde. *Synthetic Communications* **1998,** *28* (6), 1087-1092.
79. Thomas, J.; John, J.; Parekh, N.; Dehaen, W., A Metal-Free Three-Component Reaction for the Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles. *Angewandte Chemie* **2014,** *126* (38), 10319-10323.
80. Zilla, M. K.; Nayak, D.; Vishwakarma, R. A.; Sharma, P. R.; Goswami, A.; Ali, A., A convergent synthesis of alkyne–azide cycloaddition derivatives of 4-α,β-2-propyne podophyllotoxin depicting potent cytotoxic activity. *European Journal of Medicinal Chemistry* **2014,** *77*, 47-55.
81. Demeter, O.; Fodor, E. A.; Kállay, M.; Mező, G.; Németh, K.; Szabó, P. T.; Kele, P., A Double-Clicking Bis-Azide Fluorogenic Dye for Bioorthogonal Self-Labeling Peptide Tags. *Chemistry – A European Journal* **2016,** *22* (18), 6382-6388.
82. Lee, E.; Lee, J.; Yandulov, D. V., On the Mechanism of the Oxidative Cleavage of N-Heterocyclic-Carbene–Palladium Bonds with Iodine. *European Journal of Inorganic Chemistry* **2017,** *2017* (13), 2058-2067.

83. Albrecht, M.; Maji, P.; Häusl, C.; Monney, A.; Müller-Bunz, H., N-Heterocyclic carbene bonding to cobalt porphyrin complexes. *Inorganica Chimica Acta* **2012,** *380*, 90-95.
84. Das, R.; Banerjee, M.; Rai, R. K.; Karri, R.; Roy, G., Metal-free C(sp2)–H functionalization of azoles: K2CO3/I2-mediated oxidation, imination, and amination. *Organic & Biomolecular Chemistry* **2018,** *16* (23), 4243-4260.
85. de Robillard, G.; Devillers, C. H.; Kunz, D.; Cattey, H.; Digard, E.; Andrieu, J., Electrosynthesis of Imidazolium Carboxylates. *Organic Letters* **2013,** *15* (17), 4410-4413.
86. Day, B. M.; Pugh, T.; Hendriks, D.; Guerra, C. F.; Evans, D. J.; Bickelhaupt, F. M.; Layfield, R. A., Normal-to-Abnormal Rearrangement and NHC Activation in Three-Coordinate Iron(II) Carbene Complexes. *Journal of the American Chemical Society* **2013,** *135* (36), 13338-13341.
87. Day, B. M.; Pal, K.; Pugh, T.; Tuck, J.; Layfield, R. A., Carbene Rearrangements in Three-Coordinate N-Heterocyclic Carbene Complexes of Cobalt(II) Bis(trimethylsilyl)amide. *Inorganic Chemistry* **2014,** *53* (19), 10578-10584.
88. Chen, G.; He, Z.; Yudin, A. K., Synthesis of Functionalized 1-azabicyclo[3.1.0]hexanes : Studies Towards Ficellomycin and its Analogs. *Heterocycles : an international journal for reviews and communications in heterocyclic chemistry* **2014,** *88* (2), 1299-1310.
89. Fukuyama, T.; Yang, L., Total synthesis of (.+-.)-mitomycins via isomitomycin A. *Journal of the American Chemical Society* **1987,** *109* (25), 7881-7882.
90. Hartmann, M.; Studer, A., Cyclizing Radical Carboiodination, Carbotelluration, and Carboaminoxylation of Aryl Amines. **2014,** *53* (31), 8180-8183.
91. Ouyang, J.; Su, X.; Chen, Y.; Yuan, Y.; Li, Y., Copper-catalyzed carbochlorination or carbobromination via radical cyclization of aryl amines. *Tetrahedron Letters* **2016,** *57* (13), 1438-1441.
92. Theodorou, A.; Kokotos, C. G., Green Organocatalytic Synthesis of Indolines and Pyrrolidines from Alkenes. *Advanced Synthesis and Catalysis* **2017,** *359* (9), 1577-1581.
93. Bell, H. P. Palladium-Catalyzed Dominocyclizations in the Efficient Total Synthesis of Tatracycline Antibiotics. The Geog-August University of Goettingen, Goettingen, Germany, 2004.
94. Blastik, Z. E.; Voltrová, S.; Matoušek, V.; Jurásek, B.; Manley, D. W.; Klepetářová, B.; Beier, P., Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition. **2017,** *56* (1), 346-349.
95. Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vézina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Déziel, R.; Peeters, T.; Fraser, G. L., Discovery of a New Class of Macrocyclic Antagonists to the Human Motilin Receptor. *Journal of Medicinal Chemistry* **2006,** *49* (24), 7190-7197.

96. Shing, K.-P.; Liu, Y.; Cao, B.; Chang, X.-Y.; You, T.; Che, C.-M., N-Heterocyclic Carbene Iron(III) Porphyrin-Catalyzed Intramolecular C(sp3)–H Amination of Alkyl Azides. **2018,** *57* (37), 11947-11951.
97. Fusco, R.; Garanti, L.; Zecchi, G., Intramolecular 1,3-dipolar cycloadditions of aryl azides bearing alkenyl, alkynyl, and nitrile groups. *The Journal of Organic Chemistry* **1975,** *40* (13), 1906-1909.
98. Joachim Telser, P. D., Ulrike Wachendorff-Neumann, Pierre Cristau, Philippe Rinolfi Fungicidal Pyrazole Derivatives. 2016/01/28, 2016.
99. Konev, M. O.; McTeague, T. A.; Johannes, J. W., Nickel-Catalyzed Photoredox-Mediated Cross-Coupling of Aryl Electrophiles and Aryl Azides. *ACS Catalysis* **2018,** *8* (10), 9120-9124.
100. Ambrogio, I.; Cacchi, S.; Fabrizi, G.; Prastaro, A., 3-(o-Trifluoroacetamidoaryl)-1-propargylic esters: common intermediates for the palladium-catalyzed synthesis of 2-aminomethyl-, 2-vinylic, and 2-alkylindoles. *Tetrahedron* **2009,** *65* (44), 8916-8929.
101. Chun, Y.; Jiten Singh, N.; Hwang, I.-C.; Woo Lee, J.; Yu, S. U.; Kim, K. S., Calix[n]imidazolium as a new class of positively charged homo-calix compounds. *Nature Communications* **2013,** *4*, 1797.
102. Rivera, A.; Maldonado, M., Unexpected behavior of 6H,13H-5:12,7:14-dimethanedibenzo[d,i][1,3,6,8]tetraazecine (DMDBTA) toward phenols. *Tetrahedron Letters* **2006,** *47* (42), 7467-7471.
103. Ioffe, D.; Kampf, A., Bromine, Organic Compounds. In *Kirk-Othmer Encyclopedia of Chemical Technology*.
104. Bruice, P., *Organic Chemistry*. 6th ed.; Prentice Hall: Boston, 2011.
105. Alaee, M.; Arias, P.; Sjödin, A.; Bergman, Å., An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. *Environment International* **2003,** *29* (6), 683-689.
106. McCall, A. S.; Wang, H.; Desper, J. M.; Kraft, S., Bis-N-heterocyclic Carbene Palladium(IV) Tetrachloride Complexes: Synthesis, Reactivity, and Mechanisms of Direct Chlorinations and Oxidations of Organic Substrates. *Journal of the American Chemical Society* **2011,** *133* (6), 1832-1848.
107. McCall, A. S.; Kraft, S., Pyridine-Assisted Chlorinations and Oxidations by Palladium(IV). *Organometallics* **2012,** *31* (9), 3527-3538.
108. Ahmed, N.; Shirinfar, B.; Youn, I. S.; Yousuf, M.; Kim, K. S., Selective detection of guanosine-5′-triphosphate and iodide by fluorescent benzimidazolium-based cyclophanes. *Organic & Biomolecular Chemistry* **2013,** *11* (37), 6407-6413.
109. Ren Tang, R.; Hua Gong, N., *The Rapid and Efficient Synthesis of Bromohydrins from Olefins under HBr/H2O2 System by Visible Light Induced*. 2009; Vol. 30, p 1832-1834.

VITA

C. Luke Keller was born on December 3, 1990 in San Diego, California. He grew up in California, Connecticut, and Tennessee. Homeschooled his entire life, he applied to University of Tennessee at Chattanooga (UTC) after graduation. He was accepted and awarded the Provost's Scholarship.

At UTC, Luke studied chemistry and started research in his third year under the tutelage of Dr. Robert Mebane, studying transfer hydrogenation using Raney nickel and isopropanol. After a year of research, Luke was accepted into the 2012 UTC summer REU program. There, he did research into C-H activation under Dr. Gregory Grant and Dr. John Lee. With their support, Luke successfully applied for the Provost Student Research Award. The research in C-H activation eventually lead to his first publication. After the REU concluded, he joined the research group of Dr. John Lee and synthesized a series of palladium and platinum thioether phosphine complexes. During this time, Luke was awarded the Murray Raney Scholarship, as well as the ACS Outstanding Senior Award.

As he completed his degree, Luke applied to several graduate schools, and decided to accept the University of Tennessee's offer. On entry, he was awarded the Calvin Buehler Fellowship. At UT, he joined the lab of Dr. David Jenkins and studied catalytic aziridination, publishing his work on chromium catalyzed aziridination in 2018. Luke has presented at two ACS meetings and has two publications to his name.