

**Catalytic Aziridination with a Borate-Containing *N*-
Heterocyclic Tetracarbene Iron Complex**

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Doctor of Philosophy

Degree

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I want to dedicate this dissertation to my parents and sister. I am fortunate to be the daughter of Aai and Baba who love and care for me. This degree has only been possible because of the freedom and trust they have given me. My sister has always inspired me, by example, to never give up. This dissertation is a tiny token of love to them.

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ABSTRACT

Aziridines, the nitrogen analog of epoxides, are an important class of compounds. They are present in many biologically active compounds having antibacterial and antitumor properties. Along with biological significance, it can also be considered as a synthetic tool for various functional group transformations. Being an important functional group we focused on the development of synthetic methodology using alkenes as substrates and organic azides as the nitrene source [C_2 (carbon₂)+ N_1 (nitrogen₁) addition reaction].

For the potential use as an aziridination catalyst a macrocyclic *N*-heterocyclic tetracarbene (NHC) ligand system was developed. First, the neutral NHC ligand was used to synthesize ruthenium(II) complex that was found catalytically inactive for aziridination. Due to the limitations such as poor solubility, the second generation, borate-containing dianionic NHC ligand was developed. Using this 18-atom ring ligand cobalt(II) and manganese(III) and iron(III) complexes with neutral charge were synthesized.

Further, iron(III) complex was reduced to form the square planar iron(II) neutral complex. This complex successfully performed fully aliphatic aziridination involving functional group tolerance. In order to check the versatility of the catalyst it was also tested with aliphatic alkenes and aryl azide, which resulted in high yields of corresponding aziridines. Finally, the catalyst successfully

performed intramolecular $C_2 + N_1$ aziridination to form five- and six-membered bicyclic aziridines.

Another aspect of the project was to investigate the mechanism of the catalytic $C_2 + N_1$ aziridination reaction for this tetracarbene system. We were able to isolate an iron(IV) tetrazene complex that support the argument of a reactive iron(IV) imide as an intermediate in the catalytic cycle. In order to explore the reaction pathway from imide to aziridine we carried out reactions with *p*-tolyl azide in presence of *cis*- and *trans*- alkenes that formed the *syn*- and *anti*-aziridines. This observation suggested the formation of radical intermediate, which was also supported by DFT [density functional theory] calculations.

Lastly, we also synthesized *N*-carbamate aziridines from carbamate azides with boc-, fmoc-, and cbz- groups and aliphatic alkenes. Deprotection and nucleophilic ring opening reactions on these carbamate aziridines will be carried out in future.

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CHAPTER ONE

INTRODUCTION

Aziridines are the organic functional group that is the nitrogen analog of epoxides. Though epoxidation and cyclopropanation have been studied extensively, aziridination lags behind due to absence of a convenient synthetic method.¹ Aziridines are an important functional group due to their presence in many biologically active compounds such as mitomycin C, azinomycin, and azicemicin (Figure 1.1).² Studies on these compounds suggest that the *anti*-tumor and *anti*-bacterial properties of these compounds are due to the presence of the aziridine functional group.^{2a} Figure 1.1 illustrates examples of such compounds including primary aziridines in mitomycin C and tertiary aziridine in azinomycin.

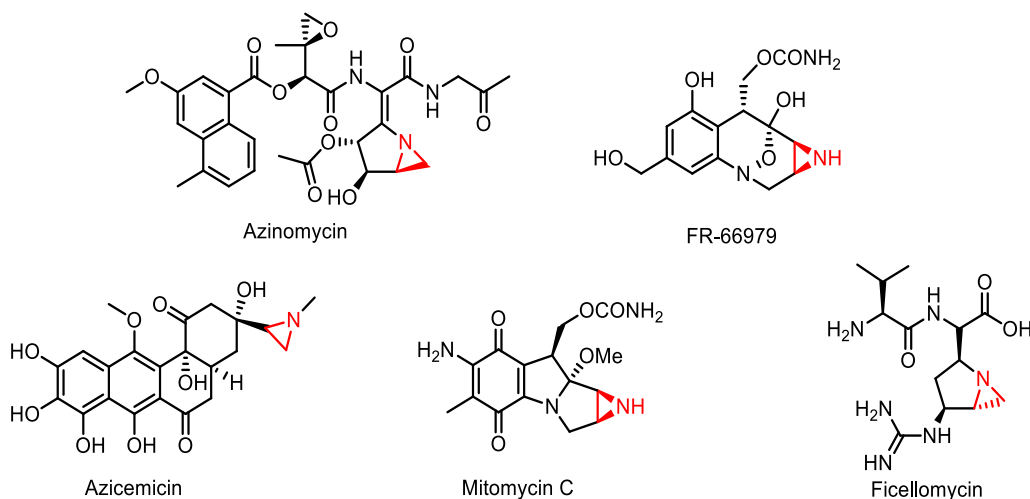


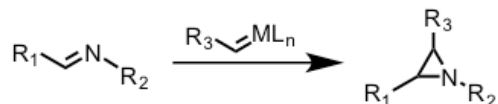
Figure 1.1. Biologically active compounds containing aziridine.

Apart from biological significance, aziridines can also be treated as synthetic tool for functional group transformations. Aziridines, being three-membered strained rings, react easily to undergo various reactions including ring opening via nucleophilic attack.³ They can also undergo ring expansion reactions to form more stable five- or six- membered rings.^{3e, 4} Recently, aziridines have been shown to be useful reagents for the synthesis of pyrrolindolines, which are important due to their presence in many natural products.⁵

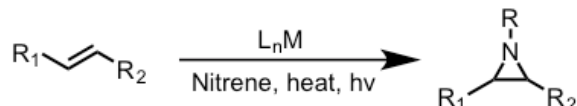
The synthesis of aziridines is feasible through non-catalytic methods such as Wenker synthesis⁶ and Blum aziridine synthesis.⁷ The disadvantage of these methods is that they are not generalizable techniques. Apart from lower yields, these synthetic methods have specific starting materials such as hydroxy amines or epoxides. The more useful approach is through catalytic addition reactions.^{1b} The first among these addition reactions is the $C_1N_1 + C_1$ addition reaction (Scheme 1.1A) involving the addition of carbene to an imine.⁸ Another approach is the $C_2 + N_1$ approach which involves addition of a nitrene to an alkene (Scheme 1.1B). We believe this is a more practical approach because there are ample alkenes that are available through synthesis or that can be found in nature as compared to imine. Hence the $C_2 + N_1$ could be the most generalizable way of synthesis of aziridines.

Scheme 1.1. Catalytic addition reactions to form aziridines.

A. C₁N₁ + C₁ approach



B. C₂ + N₁ approach



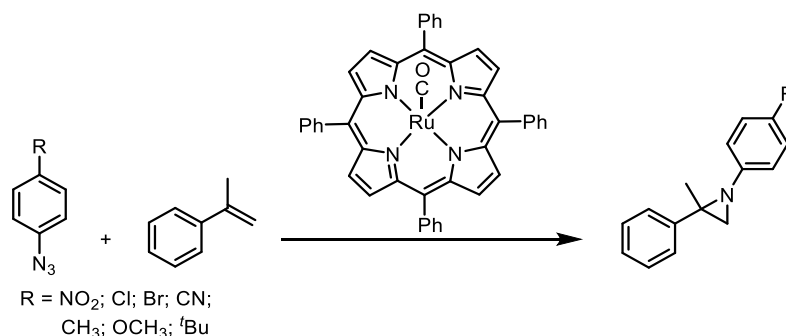
There have been multiple nitrene sources previously employed for aziridination such as hypervalent iodine PhI=NTs reagent,⁹ tosyl azide,¹⁰ and chloramine-T.^{10b} Though these reagents successfully form functionalized aziridines, there are some major disadvantages associated with them. First, it reduces the atom economy of the reaction because the tosyl group needs to be removed for the synthesis of primary aziridines before functionalizing it. Second, while deprotecting the tosyl group, there is a possibility of aziridine degrading due to the use of harsh reagents.¹¹ An alternative class of nitrene reagents is organic azides,¹² which is beneficial since N₂ is the only byproduct from the reaction. This approach is thus more environmentally friendly as well as atom economical. The nitrogen is functionalized prior to aziridination and therefore not only a deprotection step is avoided but also ring degradation possibility is minimized.

Finally, several organic azides are easy to synthesize from cheap starting materials.

The Cenini group used azides as a nitrene source on styrene derivatives for aziridination utilizing a ruthenium porphyrin catalyst (Scheme 1.2).¹² This catalytic system only works with conjugated alkene and aryl azides with electron-withdrawing functional groups. Therefore, though the reaction shows the first use of organic azides for aziridination, it has a limited substrate scope.

The Jenkins group has been working on developing a more versatile and synthetically useful methodology for aziridines synthesis. Initially, an 18-atom neutral macrocyclic tetra *N*-heterocyclic carbene (NHC) ligand was developed.¹³ NHCs are preferred over many other ligands such as phosphines due to their stability towards oxidizing conditions.¹⁴ Also, carbenes are strong σ electron-donors resulting in the higher electron density at the metal center.¹⁵ This would help to stabilize high oxidation states on the metal center of the tetracarbene complexes resulting in expected better catalytic activity.

Scheme 1.2. Catalytic aziridination by Cenini group.



The first catalyst synthesized was an iron(II) complex, $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$, based on a neutral tetra-NHC ligand (Figure 1.2).¹⁶ The ligand contains imidazolium derivatives that are connected by alternate methylene and ethylene bridges. Once macrocyclic precursor denoted as, $(^{\text{Me,Et}}\text{TC}^{\text{Ph}})(\text{I})_4$, is deprotonated using a base, the carbenes can bind to the iron center in the equatorial plane. $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$ catalyzed aziridination using aryl azides and aliphatic alkenes. The best results were obtained when the reaction was heated at 90°C in *neat* alkenes. The reaction yields were higher for the azides with electron-donating functional groups on aryl azide unlike examples by Cenini.¹² This reusable catalyst was specifically successful as it was the first catalyst to perform aziridination on tri- and tetra-substituted aliphatic alkenes. The important catalysis results are illustrated in Table 1.1

My goal in this project was to develop and test a tetra-NHC catalytic system for improved aziridination. This included the synthesis of fully aliphatic aziridines and the investigation of the functional group tolerance of the catalytic reaction. These objectives were achieved by the synthesis of various metal complexes, characterization and examination of their catalytic activity. One of the aspects of this project that I worked on is the investigation of the aziridination pathway of our catalytic system by isolation of possible intermediates and stereospecific compounds.

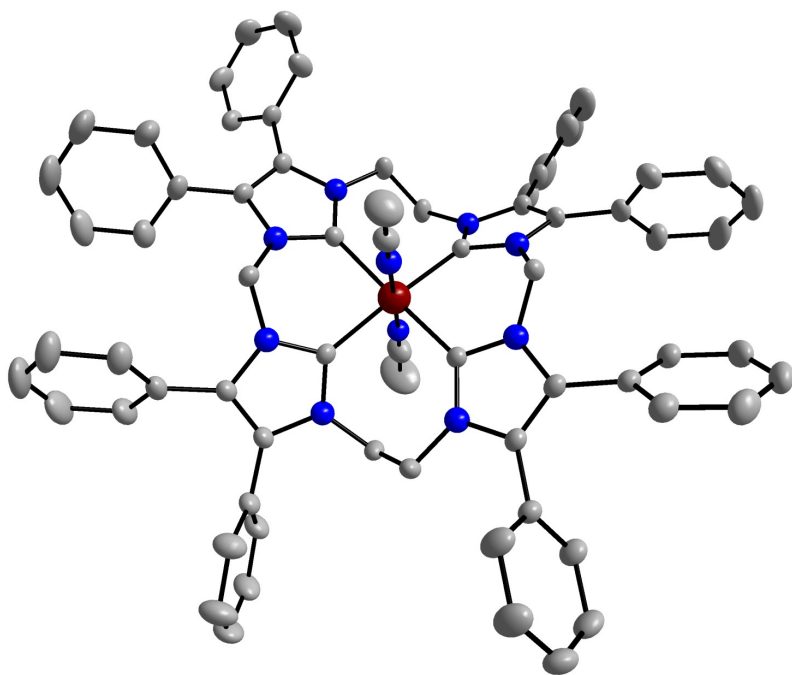
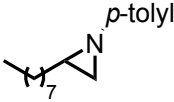
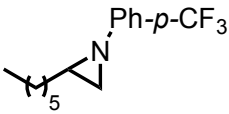
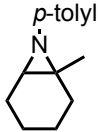
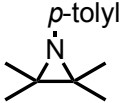


Figure 1.2. Iron (II) catalyst, $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$, supported by a neutral tetra-NHC ligand. Gray, blue, and red ellipsoids (50% probability) represent carbon, nitrogen, and iron respectively. Hydrogens, counteranions, and solvents are omitted for clarity.

Table 1.1. Results of catalytic aziridination by $[(^{\text{Me},\text{Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$.

Alkene	Azide R-group	Catalyst loading (mol %)	Temp (°C)	Time (h)	Aziridine	Yield
1-decene	CH ₃	0.1	90	18		70%
1-octene	CF ₃	0.1	90	18		37%
1-methyl cyclohexene	CH ₃	1	90	144		39%
2,3-dimethyl-2-butene	CH ₃	0.1	70	160		20%

CHAPTER TWO
EFFORTS TO IMPROVE AZIRIDINATION WITH NEUTRAL
MACROCYCLIC COMPLEXES

The DFT calculations in this chapter are done by Alan S. Cramer.

Abstract

We synthesized a neutral tetra *N*-heterocyclic carbene (NHC) ligand structurally similar but electronically distinct from a porphyrin ligand. Complexes supported by porphyrin and its derivatives are shown to be catalytically active for various reactions including aziridination. In order to develop a generalizable synthetic method to form tetra-NHC metal complexes, we synthesized a silver transmetallating reagent using this macrocyclic tetra-NHC ligand. Utilizing this transmetallating reagent, the ruthenium complex $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$ was synthesized analogous to the iron catalyst. We also attempted to make a chiral D_2 symmetric 24-atom neutral ligand, which did not have promising future based on theoretical calculations.

Introduction

There are a limited number of macrocyclic ligands synthesized apart from porphyrin and its derivatives.¹⁷ Macrocyclic ligands incorporating *N*-heterocycles, such as cyclam, have proven critical for metal–ligand multiple bond stabilization in high valent metal complexes.¹⁸ One type of *N*-heterocyclic ligands that has received significant attention in the last decade is *N*-heterocyclic carbenes (NHCs). NHCs are strong σ - electron donating ligands and therefore can stabilize high oxidation states on metals. Another distinct advantage is that NHCs are

significantly more resistant towards oxidizing conditions compared to phosphines. As a result, NHC metal complexes are robust enough to persist in diverse reaction conditions. Polydentate NHC ligands, which include mono-, bi- and tridentate ligands, as well as macrocyclic variations are synthesized.¹⁹ These ligands are used for synthesizing complexes useful for near-UV-phosphorescent emitters,²⁰ radiopharmaceuticals,²¹ and catalyst precursors.²²

We have previously reported a neutral 18-atom tetra macrocyclic NHC ligand (^{Me,Et}TC^{Ph})(PF₆)₄ synthesized in a five step reaction that forms monomeric metal complexes.¹³ A silver tetra-NHC complex was synthesized expecting it to serve as a transmetallating reagent to form other monomeric transition metal complexes.²³ Transmetallation has been successful before with mono-,²⁴ bi-²⁵ as well as polydentate NHC ligands.²⁶ However, the dimeric silver complex made by Murphy and Spicer did not demonstrate transmetallation to other metals from silver.²⁷ The Jenkins group has synthesized a dimeric silver complex shown to transmetalate the tetra-NHC ligand to transition metals from first, second, and third row of the periodic table.²³

Previously reported [^{Me,Et}TC^{Ph})Fe(NCCH₃)₂](PF₆)₂ complex functioned as an aziridination catalyst for aliphatic alkenes and aryl organic azides. In order to examine the mechanism of the catalytic aziridination of our system the catalyst was reacted with *p*-tolyl azide only to get ESI MS of the imide. Therefore, [^{Me,Et}TC^{Ph})Ru(NCCH₃)₂](PF₆)₂ was synthesized hoping to stabilize high oxidation

states on the metal and to isolate the imide intermediate. Unfortunately, the Ru complex was not reactive towards multiple azides. Due to its catalytic inactivity, work with this complex was halted.

A valuable advancement in catalytic aziridination would be development of methodology for synthesis of chiral aziridines. The ideal comparison to our tetracarbene catalytic system would be chiral porphyrinoids used for asymmetric epoxidation and cyclopropanation.²⁸ Therefore, a 24-atom chiral ligand precursor based on chiral binaphthyl group was synthesized. The DFT calculated structure showed the change in the geometry of the ligand due to larger ring size and is unlikely to favor enantioselectivity for aziridination.

Synthesis of silver transmetallating reagent,



The use of a silver transmetallating reagent has significant advantages from synthetic perspective. The byproduct of the reaction will be a silver halide that is easy to separate. Additionally, strong base is not required to make carbenes, which results in milder reaction conditions. The dimeric silver complex, $[\{(\text{Me},\text{EtTC}^{Ph})\text{Ag}\}_2\text{Ag}_2](\text{PF}_6)_4$, is able to make monomeric complexes with Pt, Pd, Rh, Ni, Fe, Cr, Co, Ru and Au in high yields. The yield of $[(\text{Me},\text{EtTC}^{Ph})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$ synthesis was drastically improved to 92% from 11% using $[\{(\text{Me},\text{EtTC}^{Ph})\text{Ag}\}_2\text{Ag}_2](\text{PF}_6)_4$ as compared to the use of a strong base.

Scheme 2.1. Synthesis of the silver transmetallating reagent.

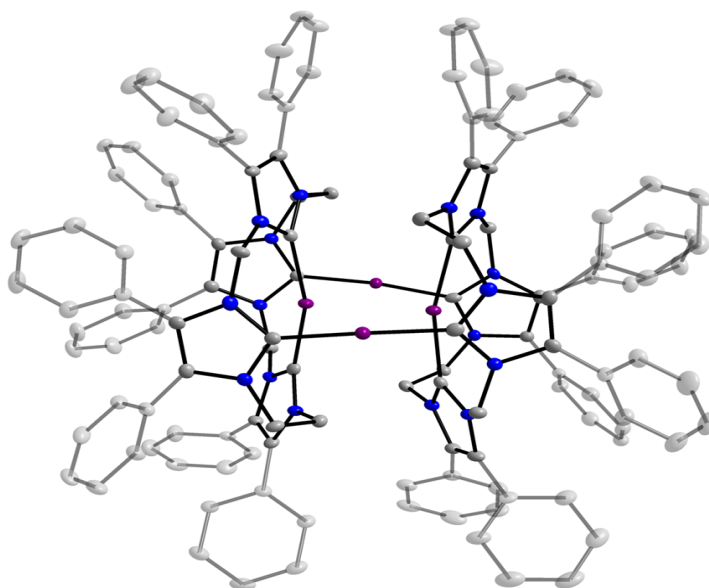
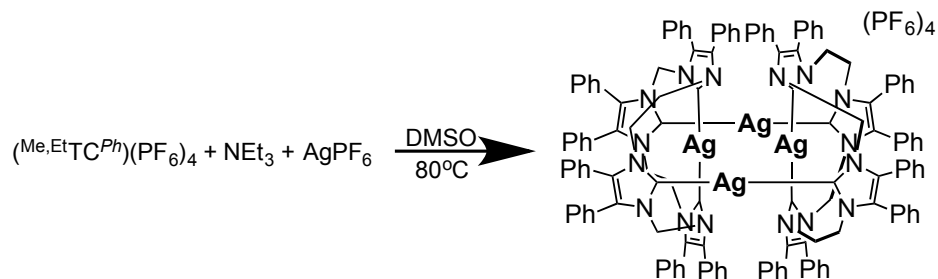


Figure 2.1. Crystal structure of $[(\text{Me},\text{EtTC}^{\text{Ph}})\text{Ag}]_2\text{Ag}_2(\text{PF}_6)_4$. Gray, blue, and silver ellipsoids (50% probability) represent carbon, nitrogen, and silver atoms respectively. Hydrogen atoms, counteranions and solvent molecules are omitted for clarity.

As reported previously, $(^{Me,Et}TC^{Ph})(PF_6)_4$ is made in a five step reaction process starting from commercially available 4,5-diphenylimidazole and dibromomethane. The synthesis of $[(^{Me,Et}TC^{Ph})Ag]_2Ag_2(PF_6)_4$ was carried out reacting $(^{Me,Et}TC^{Ph})(PF_6)_4$ with NEt_3 and $AgPF_6$ in DMSO as shown in Scheme 2.1 yielding in 90%. The crystal structure (Figure 2.1) reveals a dimeric structure with C-Ag-C bonds orthogonal to each other.

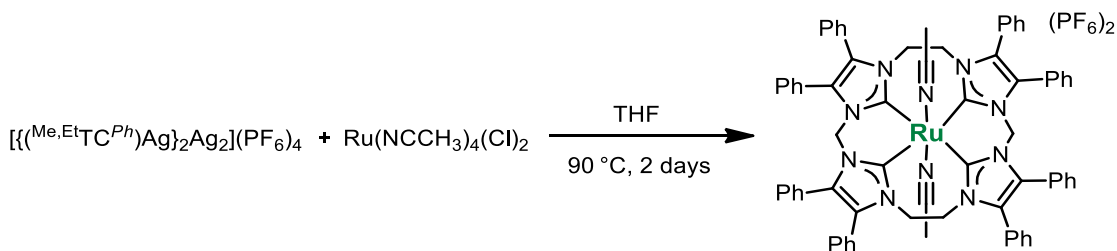
Synthesis and characterization of $[(^{Me,Et}TC^{Ph})Ru(NCCH_3)_2](PF_6)_2$

In the proposed catalytic aziridination cycle the iron(II) catalyst goes through an iron(IV) imide intermediate after reaction with the organic azide. In an attempt to isolate the imide intermediate, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ was reacted with organic azides. Unfortunately, only ESI MS evidence of the proposed imide intermediate was obtained. Therefore, an alternative plan to isolate the imide was to make the ruthenium analog of iron catalyst, $[(^{Me,Et}TC^{Ph})Ru(NCCH_3)_2](PF_6)_2$. Since ruthenium is in the same column of periodic table as iron but on the second row, it should have similar reactivity but better stability for the higher oxidation states of the imide. Initially, silver transmetallating reagent was reacted with commercially available ruthenium halide salts such as RuI_3 , $RuCl_2(DMSO)_4$, and $Ru(C_6H_6)Cl_2$ to get $[(^{Me,Et}TC^{Ph})Ru(NCCH_3)_2](PF_6)_2$. Reactions under various conditions did not yield the product with bound acetonitrile. Therefore, $Ru(NCCH_3)_4Cl_2$ was synthesized

from $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and excess zinc dust in acetonitrile from a literature procedure.²⁹ The reaction of $[\{(\text{Me},\text{EtTC}^{\text{Ph}})\text{Ag}\}_2\text{Ag}_2](\text{PF}_6)_4$ with $\text{Ru}(\text{NCCH}_3)_4\text{Cl}_2$ resulted into $[(\text{Me},\text{EtTC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$ in 11% yield as shown in Scheme 2.2. The ESI MS of the product with expected isotopic distribution is shown in Figure 2.2A. The crystal structure shows the octahedral geometry with the ligand in the equatorial plane and axially bound acetonitrile molecules (Figure 2.2B).

Unfortunately, the Ru complex was catalytically inactive for aziridination or epoxidation. It was also not reactive towards reagents such as organic azides, hypervalent iodine reagents, iodosobenzene, and diazoalkanes. The reason for its decreased reactivity is possibly due to its poor solubility in many solvents. The poor solubility in non-polar organic solvents could be due to the dicationic charge on the complex. Also, the acetonitrile molecules bound to the Ru did not dissociate to have an active site for catalysis. As a result, no further work was continued on this complex.

Scheme 2.2. Synthesis of $[(\text{Me},\text{EtTC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$.



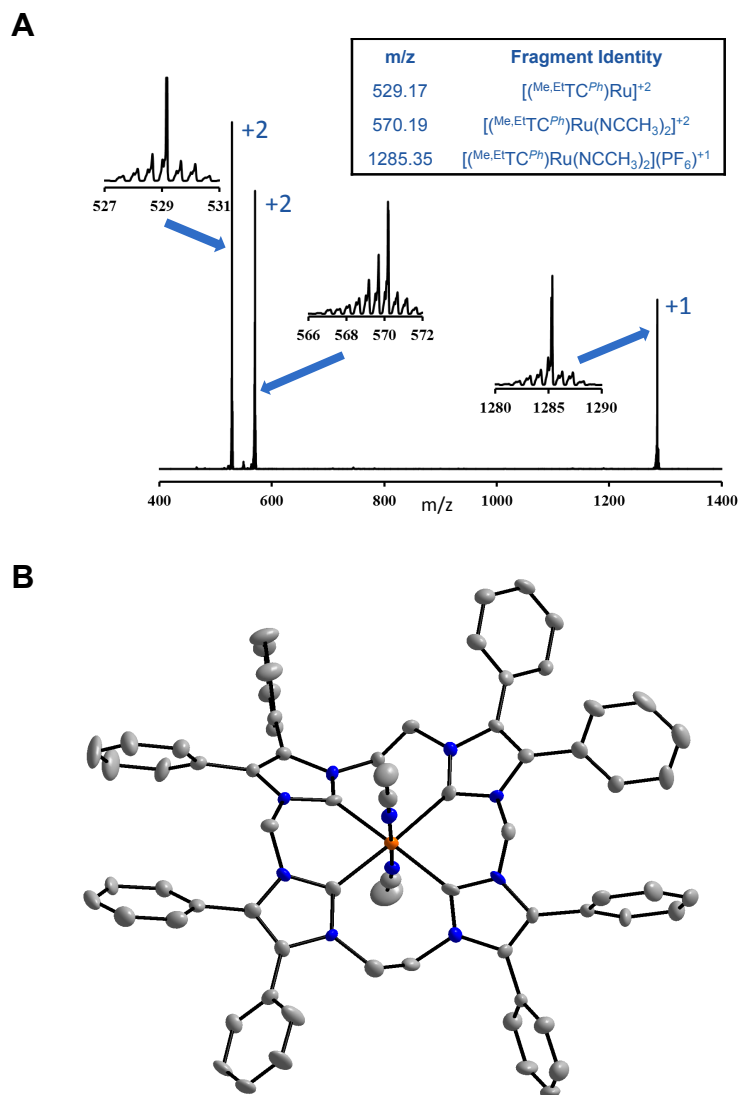


Figure 2.2.A) ESI MS of $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$. B) Crystal structure of $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$. Gray, blue, and orange ellipsoids (50% probability) represent carbon, nitrogen, and ruthenium atoms respectively. Hydrogen atoms, counteranions and solvent molecules are omitted for clarity.

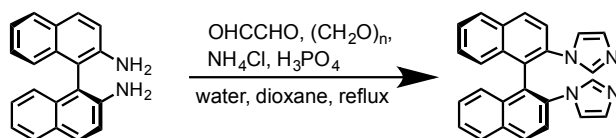
Synthesis of a neural chiral ligand

For aziridination reactions to be useful in organic synthesis to its full capacity enantiopure synthesis of aziridines is crucial. The tetracarbene system developed by the Jenkins group is isostructural to porphyrin. The Che group and Zhang group have developed D_2 symmetric Ru and Co porphyrin derivative catalysts for enantioselective epoxidation^{28b} and cyclopropanation^{28a} respectively. Therefore, a D_2 symmetric tetra-NHC catalyst could perform chiral aziridination.

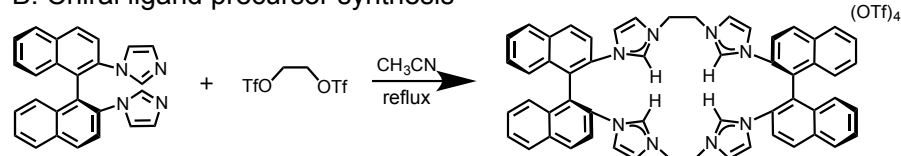
In the first step the chiral diimidazole was synthesized from the enantiopure reagent (S)-(-)-1,1'-Binaphthyl-2,2'-diamine (S-BINAM) (Scheme 2.3A).³⁰ This diimidazole was reacted with 1,2-ditriflateoethane to form a macrocyclic ligand precursor as shown in Scheme 2.3B. The ligand precursor was formed following a two-step procedure and confirmed with ESI MS.

Scheme 2.3. A) Synthesis of chiral diimidazole. B) Synthesis of macrocyclic chiral ligand precursor.

A. Synthesis of diimidazole



B. Chiral ligand precursor synthesis



While the synthesis was in progress, the DFT calculations (functional: B3LYP, basis set: 6-31g**) on iron imide, which is the proposed intermediate in aziridination, were performed using the chiral ligand. The calculated structure showed that the ligand has saddled down as can be seen from Figure 2.3. From this observation it can be deduced that 24-atom is a very large ring size imparting flexibility to the ligand. The change in geometry suggests that it is unlikely that the ligand would sterically favor attack of an alkene in a particular orientation. Therefore, it was concluded that the ring size should be smaller for the rigid geometry. Moreover, the bulky groups should be close to the metal to affect the approach of alkene towards the imide in specific orientation.

Conclusion

An 18-atom tetra-NHC ligand was synthesized from commercially available starting compounds. Development of a silver transmetallating reagent facilitated synthesis of various transition metal complexes supported by this ligand in high yields. Using this silver transmetallating reagent $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$ was synthesized that was catalytically unreactive and therefore future work on this was not continued. In order to be able to do asymmetric aziridination a chiral 24-atom macrocyclic ligand precursor was synthesized. Because of the larger ring size, the ligand is too flexible and unlikely to exhibit expected enantioselectivity.

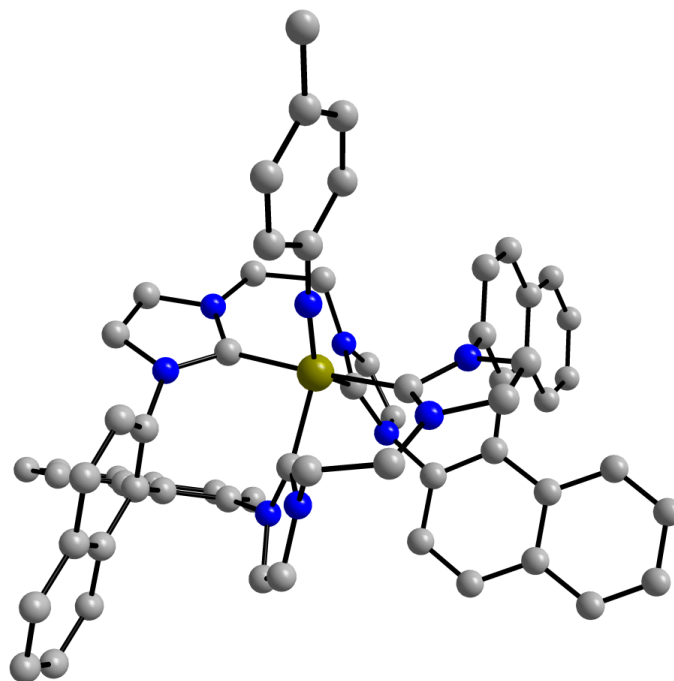


Figure 2.3. DFT calculated structure of the proposed iron imide intermediate supported by the chiral ligand. Gray, blue, and green spheres represent carbon, nitrogen, and iron atoms respectively.

Experimental

All reactions were performed under a dry nitrogen atmosphere with the use of either a dry box or standard Schlenk techniques. 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 O₂ prior to use. Benzene-*d*₆, and chloroform-*d* were degassed by three freeze-pump-thaw cycles prior to drying over activated molecular sieves. These NMR solvents were then stored under N₂ in a glovebox. All other reagents were purchased from commercial vendors and used without purification. ¹H, ¹³C 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 ¹³C NMR chemical shifts were referenced to the residual solvent. DEPT, HSQC, and COSY were performed on a Varian VNMRS 500 MHz narrow-bore 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). The GC/MS analyses were performed using a Hewlett Packard 6890 gas chromatography system with Hewlett Packard 5973 mass spectrometer. Mass spectrometry sample solutions of metal complexes were prepared in tetrahydrofuran. Infrared

spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. UV-vis measurements were taken inside a dry glovebox on an Ocean Optics USB4000 UV-vis system with 1 cm path length quartz crystal cell.

Synthesis and characterization of $[\{({}^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ag}\}_2\text{Ag}_2](\text{PF}_6)_4$.

$({}^{\text{Me,Et}}\text{TC}^{\text{Ph}})(\text{PF}_6)_4$ (1.455 g, 0.944 mmol) and silver(I) hexafluorophosphate (0.477 g, 1.89 mmol) were added to a 20 mL vial wrapped in aluminum foil and dissolved in 15 mL of DMSO while stirring and heating to 90 °C. After 10 min, triethylamine (0.477 g, 4.72 mmol) was added and allowed to stir for 48 h. The reaction mixture was cooled to rt and brought out of the glovebox. The solution was added to a 200 mL beaker and quenched with 150 mL of water to yield a white precipitate. The white powder was collected on a 60 mL fine sintered glass frit. The powder was then purified by dissolving in (40 mL) acetone in the sintered frit, filtering, and triturating with excess water (200 mL). The resulting fine powder was collected on a 60 mL fine sintered glass frit which yielded the pure white powder product (1.238 g, 90% yield). Single crystals suitable for X-ray diffraction can be grown by layering an acetone solution of $[\{({}^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ag}\}_2\text{Ag}_2](\text{PF}_6)_4$ with water to give colorless needles. ^1H NMR (CD_3CN , 499.74 MHz): δ 7.65 (t, J = 7.5 Hz, 4H), 7.58 (t, J = 6.5 Hz, 4H), 7.48 (t, J = 8.0 Hz, 8H), 7.41 (t, J = 7.5 Hz, 4H), 7.36 (t, J = 8.0 Hz, 4H), 7.26 (t, J = 8.0 Hz, 8H), 7.19 (m, 16H), 7.09 (s, 8H), 6.96 (d, J = 7.0 Hz, 8H), 6.79 (s, 8H), 6.62 (d, J = 14.5 Hz, 4H), 6.10 (d, J = 7.5 Hz,

8H), 6.02 (d, $J = 13.5$ Hz, 4H), 5.05 (td, $J_1 = 13.5$ Hz, $J_2 = 3.5$ Hz, 4H), 4.82 (dd, $J_1 = 15.5$ Hz, $J_2 = 2.0$ Hz, 4H), 4.44 (m, 4H), 4.03 (d, $J = 14.0$ Hz, 4H). ^{13}C NMR (CD_3CN , 125.66 MHz): δ 182.83 ($J^{109}_{\text{Ag-C}} = 214.9$ Hz, $J^{107}_{\text{Ag-C}} = 181.0$ Hz), 176.85 ($J^{109}_{\text{Ag-C}} = 218.7$ Hz, $J^{107}_{\text{Ag-C}} = 188.5$ Hz), 137.00 (d, $J_{\text{Ag-C}} = 5.8$ Hz), 135.91 (d, $J_{\text{Ag-C}} = 5.3$ Hz), 135.21 (d, $J_{\text{Ag-C}} = 5.3$ Hz), 133.95 (d, $J_{\text{Ag-C}} = 5.0$ Hz), 132.25, 131.99, 131.81, 131.71, 131.62, 131.47, 131.28, 131.11, 130.55, 130.20, 130.09, 126.91, 126.30, 125.53, 125.48, 61.85, 51.06, 49.16. ^{19}F NMR (CD_3CN , 470.39 MHz): δ -72.81 (d, $J = 705.6$ Hz). IR (neat): 2950, 2917, 2868, 2837, 1709, 1488, 1447, 1376, 1359, 1321, 1261, 1221, 1168, 1074, 1019, 827, 761, 739, 696 cm^{-1} . ESI/MS (m/z): $[\text{M}-2\text{PF}_6]^{2+}$ 1317.70, $[\text{M}-3\text{PF}_6]^{3+}$ 829.82, $[\text{M}-4\text{PF}_6]^{4+}$ 586.37. Electrochemistry (vs. ferrocene in CH_3CN with $(\text{TBA})(\text{PF}_6)$ as supporting electrolyte): -1848 mV (rev.), -2005 mV (rev.). Anal. Calcd for $\text{C}_{132}\text{H}_{104}\text{N}_{16}\text{F}_{24}\text{P}_4\text{Ag}_4$: C, 54.19; H, 3.58; N, 7.66. Found: C, 53.20; H, 3.83; N, 7.59.

Synthesis and characterization of $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2 \cdot [(\text{TC}^{\text{Ph}})\text{Ag}]_2\text{Ag}_2(\text{PF}_6)_4$ (0.506 g, 0.172 mmol) was dissolved in 10 mL THF and stirred for 30 min with heating at 75 °C. To this solution, $\text{RuCl}_2(\text{NCCH}_3)_4$ (0.116 g, 0.345 mmol) was added portionwise and stirred for two days at 70 °C. Filter the reaction mixture through celite and pump off the solvent. To the crude product 5 mL chlorobenzene was added and stirred with heating at 75 °C for an hour. This solution is then filtered and to the filtrate 5 mL dry diethyl ether is

added to crash the product out. The solid was filtered on 15 mL fine sintered glass frit and dried under reduced pressure to collect the (0.054, 11%) product. The crystal structure was obtained by slow evaporation of acetonitrile solution over two days to get colorless crystals suitable for single crystal X-ray diffraction. ^1H NMR (CD_3CN , 499.74 MHz): δ 7.46 – 7.05 (m, 40 H), 5.94 (s, 4H), 4.45 (s, 8H), ^{13}C NMR (CD_3CN , 125.66 MHz): δ 188, 133.93, 132.37, 132.22, 131.84, 131.46, 130.25, 130.12, 129.79, 129.71, 128.98, 128.16. IR: 3056, 2261, 1602, 1488, 1444, 1370, 1296, 1226, 1181, 1075, 1025, 926, 832, 788, 764, 735, 697. ESI/MS (m/z): $[\text{M}-2\text{PF}_6-2\text{CH}_3\text{CN}]^{2+}$ 529.17, $[\text{M}-2\text{PF}_6]^{2+}$ 570.19, $[\text{M}-\text{PF}_6]^{1+}$ 1285.35. Electrochemistry (vs. ferrocene in CH_3CN with $(\text{TBA})(\text{PF}_6)$ as supporting electrolyte): 510(rev.).

Synthesis of chiral ligand precursor. Previously synthesized chiral bis(imidazolyl)-binaphthyl (0.100 g, 0.259 mmol) was dissolved in 15 mL acetonitrile and stirred for 15 min. To this solution, 1,2-ditriflatoethane was added and stirred while heating at 80 °C for two days. After the disappearance of starting material analyzed by TLC, 20 mL water was added to precipitate the impure product and filtered the solid through a 15 mL fine glass sintered frit. The solid was then dissolved in 5 mL methylene chloride and filtered the solution through a 15 mL fine glass sintered frit. Collected the filtrate and concentrated it to take ESI MS of the sample. ESI MS $[\text{M}-4\text{OTf}]^{4+}$ 207.06, $[\text{M}-3\text{OTf}]^{3+}$ 325.74, $[\text{M}-2\text{OTf}]^{2+}$ 563.12, $[\text{M}-\text{OTf}]^{1+}$ 1275.06.

CHAPTER THREE
SYNTHESIS OF DIANIONIC BORATE-BASED NHC METAL
COMPLEXES

A version of this chapter was originally published by Heather M. Bass, S. Alan Cramer, Alexander S. McCullough, Karl J. Bernstein, Christopher R. Murdock, and David M. Jenkins.

Bass, Heather M.; Cramer, S. Alan; McCullough, Alexander S.; Bernstein, Karl J.; Murdock, Christopher R.; Jenkins, David M. "Employing dianionic macrocyclic tetracarbenes to synthesize neutral divalent metal complexes." *Organometallics*, **2013**, 32, 2160–2167.

and by S. Alan Cramer, Forrest L. Sturgill, Preeti P. Chandrachud, David M. Jenkins.

Cramer, S. Alan; Sturgill, Forrest L.; Chandrachud, Preeti P.; and Jenkins, David M. Overcoming NHCs neutrality: installing tetracarbenes on group 13 and 14 metals. *Dalton Trans.*, **2014**, 43, 7687-7690.

and by Preeti P. Chandrachud, Heather M. Bass, and David M. Jenkins.

Chandrachud, Preeti P.; Bass, Heather M.; Jenkins, David M. "Synthesis of fully aliphatic aziridines with a macrocyclic tetracarbene iron catalyst." *Organometallics*, **2016**, 35, 1652-1657.

All work presented in this chapter was altered from the original publications to only include work completed by Preeti P. Chandrachud.

Abstract

A novel borate-based 18-atom macrocyclic NHC ligand was synthesized analogous to its neutral counterpart. This synthesis was achieved by introducing borate bridges, which results in a dianionic ligand. This anionic charge alters the electronic properties of the ligand and resultant metal complexes. The imidazolium protons from the macrocyclic precursor are deprotonated using a strong base to form *N*-heterocyclic carbenes. Various metal complexes are synthesized that are supported by this ligand for potential use as catalysts for aziridination.

Introduction

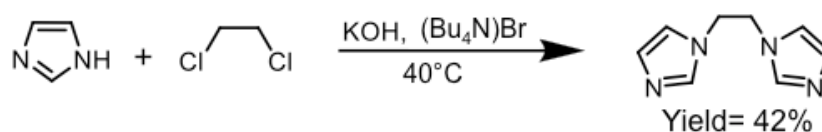
As discussed in Chapter 1, the dicationic iron (II) tetra-NHC complex, $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$, catalyzed the reaction of aliphatic alkenes with aryl azides to form the corresponding aziridines.¹⁶ Although catalytically active, this complex has some limitations such as poor solubility in many organic solvents, poor reactivity towards alkyl azides, and the requirement of excess alkenes. These limit the usefulness of this system for synthesizing variety of aziridines important for organic synthesis.

To overcome these drawbacks a second-generation, borate-based ligand was designed. Borate containing ligands reported in literature often have improved properties over their neutral counterparts.³¹ The presence of borate moiety in the ligand reduces the overall charge on the complex and improves the solubility in some cases.³¹ This subtle change in the design of the ligands has a significant impact on the electronic properties of the complex, such as the ability to stabilize higher oxidation states on the metal.³² In addition, these complexes also exhibit extraordinary reactivity as compared to their carbon analogs.³³

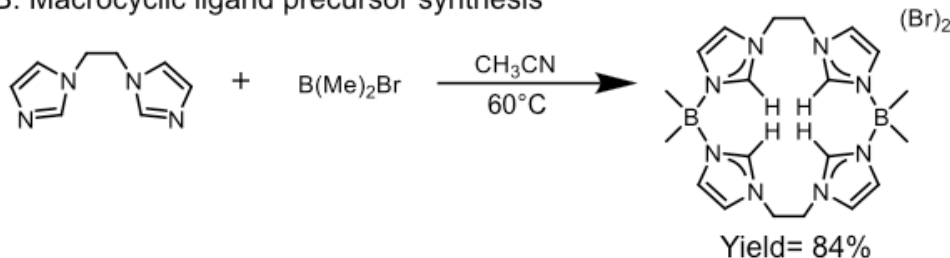
Synthesis and characterization of borate-based macrocyclic ligand precursor

Scheme 3.1. A) Synthesis of diimidazole. B) Synthesis of macrocyclic ligand precursor, (^{BMe₂,Et}TC^H)(Br)₂.

A. Diimidazole synthesis

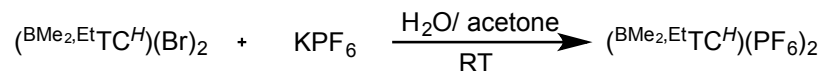


B. Macrocyclic ligand precursor synthesis



The 18-atom macrocyclic imidazolium ring, $(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})(\text{Br})_2$, was synthesized in a two-step reaction from commercially available reagents in multi-gram quantities. In the first step diimidazole was made by reaction of imidazole with 1,2-dichloroethane in a basic solution over two days following a literature procedure (Scheme 3.1A).³⁴ The crystalline diimidazole was then reacted with bromodimethylborane in acetonitrile at 60 °C to complete the macrocyclic precursor incorporating borate bridges as shown in Scheme 3.1B. The second step was carried out in an air-free condition, but once the macrocycle was formed it was stable in the regular atmospheric conditions. This macrocycle precipitated out of acetonitrile solvent as a white powder in approximately 85% yield. This compound has two bromide counteranions to balance the charge. These ions can be converted to hexafluorophosphate (PF_6) by reacting with excess potassium hexafluorophosphate (KPF_6) in water and acetone mixture at room temperature as shown in Scheme 3.2. The PF_6 counteranion is beneficial as it is non-coordinating to the metal center as compared to a halide.

Scheme 3.2. Counteranion conversion of $(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})(\text{Br})_2$



Synthesis and characterization of square planar Co(II) complex, [(^{BMe₂,Et}TC^H)Co]

First, a cobalt complex was prepared using CoI₂ and (^{BMe₂,Et}TC^H)(Br)₂ in presence of lithium diisopropyl amide (LDA) as shown in Scheme 3.3 yielding 11% [(^{BMe₂,Et}TC^H)Co]. The crystal structure of this square planar complex is illustrated in Figure 3.1.

There are a few examples of cobalt complexes with tetracarbene ligands.³⁵ Spicer and Murphy synthesized the first Co(II) tetracarbene complex supported by a flexible crown macrocyclic ligand that is catalytically active for the aryl halide reduction and can be reduced to Co(I) to enhance the catalytic activity.^{35c} Cobalt tetracarbene complexes also perform catalytic oxidative homocoupling of Grignard reagents and the Kumada–Corriu cross-coupling reactions of aryl halides.^{35a} The Jenkins group has synthesized the first-generation square pyramidal Co(II) tetracarbene complex that is catalytically inactive.²³ This second-generation complex, [(^{BMe₂,Et}TC^H)Co], needs further characterization and reactivity tests to investigate its usefulness.

Scheme 3.3. Synthesis of [(^{BMe₂,Et}TC^H)Co]



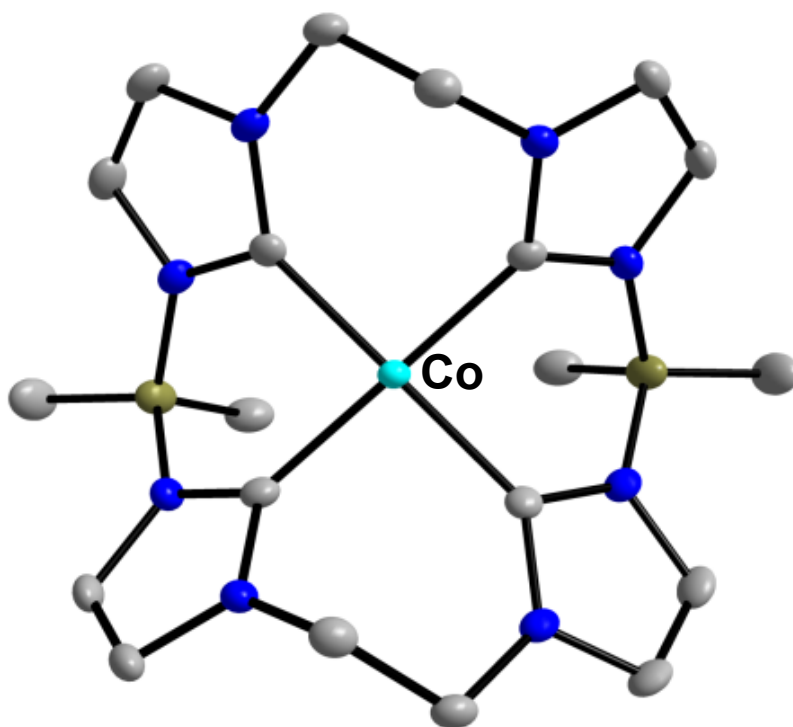


Figure 3.1. Crystal structure of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^{\text{H}})\text{Co}]$. Gray, blue, olive and turquoise ellipsoids (50% probability) represent carbon, nitrogen, boron and cobalt atoms respectively. Hydrogen atoms are omitted for clarity.

Synthesis and characterization of silver transmetallating reagent, $[\{(\text{BMe}_2, \text{Et})\text{TC}^H\}\text{Ag}\}_2\text{Ag}_2]$.

First generation silver transmetallating reagent was valuable in synthesizing a wide variety of metal complexes across the periodic table in high yields.²³ The yield for synthesis of the iron catalyst synthesis was drastically increased from 11% to 90% compared to a previous strong base approach. In order to replicate these results, an attempt was made to synthesize the second-generation silver transmetallating reagent.

The second generation silver transmetallating reagent was synthesized via a weak base approach (Scheme 3.4) similar to the first generation. The crystal structure of this dimeric reagent is shown in Figure 3.2. This reagent successfully made monomeric Fe(III) and Mn(III) complexes using their corresponding commercially available metal salts in higher yields compared to direct deprotonation with a strong base. Unfortunately, the silver transmetallating reagent is extremely air, temperature, and light sensitive even as a solid. After considerable scrutiny of the stability of this reagent, its applicability was investigated to make the complexes. With respect to the yields, it was decided to make iron(III) complex with a strong base approach and Mn(III) complex using silver transmetallating reagent.

Scheme 3.4. Synthesis of $[\{({}^{\text{BMe}_2\text{EtTC}^H})\text{Ag}\}_2\text{Ag}_2]$

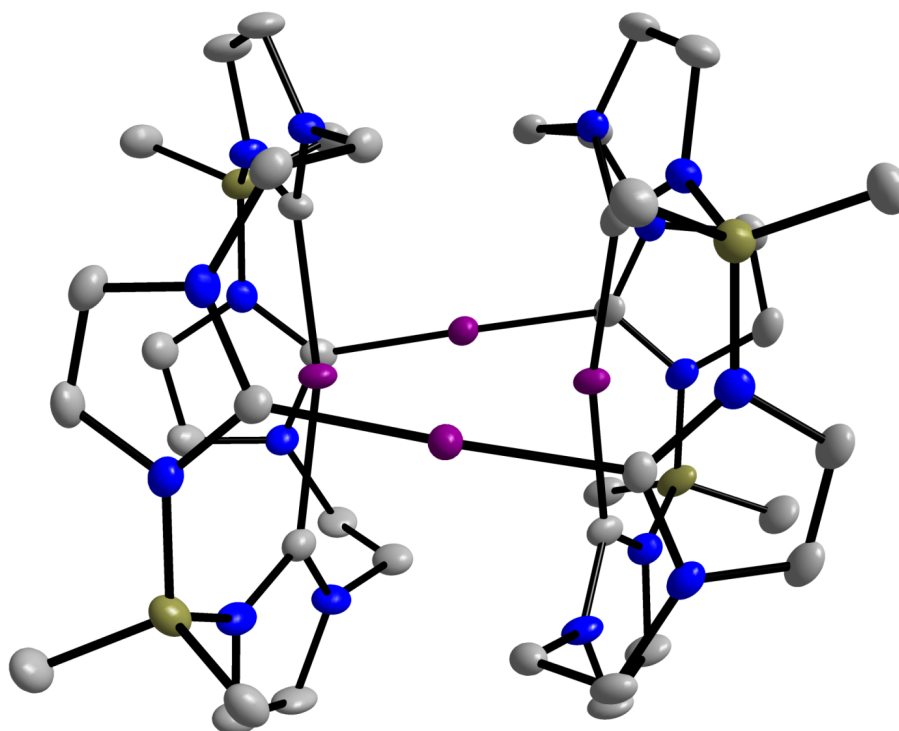
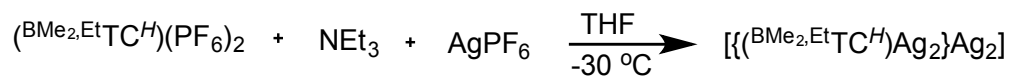


Figure 3.2. Crystal structure of second generation silver transmetallating reagent, $[\{({}^{\text{BMe}_2\text{EtTC}^H})\text{Ag}\}_2\text{Ag}_2]$. Gray, blue, olive and magenta ellipsoids (50% probability) represent carbon, nitrogen, boron and silver atoms respectively. Hydrogen atoms are omitted for clarity.

Synthesis and characterization of Mn(III) complexes, $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnBr}]$ and $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnI}]$

Significant advancement has been achieved in the synthesis of manganese carbene complexes recently,³⁶ most of them with an oxidation state of +1 for manganese.³⁶⁻³⁷ There are only two examples of Mn(III) carbene complexes reported to date.³⁸ Very recently, manganese carbene complexes are found to be catalytically activity for two-electron reduction of CO_2 ,³⁹ cross-coupling of alkyl halides with Gignard reagents,⁴⁰ and selective functionalization of arene C-H bonds for carbene insertion.⁴¹ We synthesized a Mn(III) complex with the borate-based system to investigate its properties. This is the first Mn tetracarbene complex made to our knowledge.

In the beginning, $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Mn}]$, the Mn(II) complex was attempted to synthesize using LDA in presence of $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{Br})_2$ and MnBr_2 . But instead Mn was oxidized to Mn(III) resulting in the $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnBr}]$ complex (Figure 3.3) in 9% yield as shown in Scheme 3.5. To have a more labile ligand, we decided to synthesize $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnI}]$ with the similar strategy using MnI_2 , but this resulted in formation of two complexes with bromide and iodide attached to Mn. To avoid halide confusion, we used $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{PF}_6)_2$ and MnI_2 to obtain $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnI}]$ in 19.5% yield. In order to improve the yield, the silver transmetallating reagent was used and that reaction yielded $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnI}]$ in 75% yield.

Scheme 3.5. Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnBr}]$

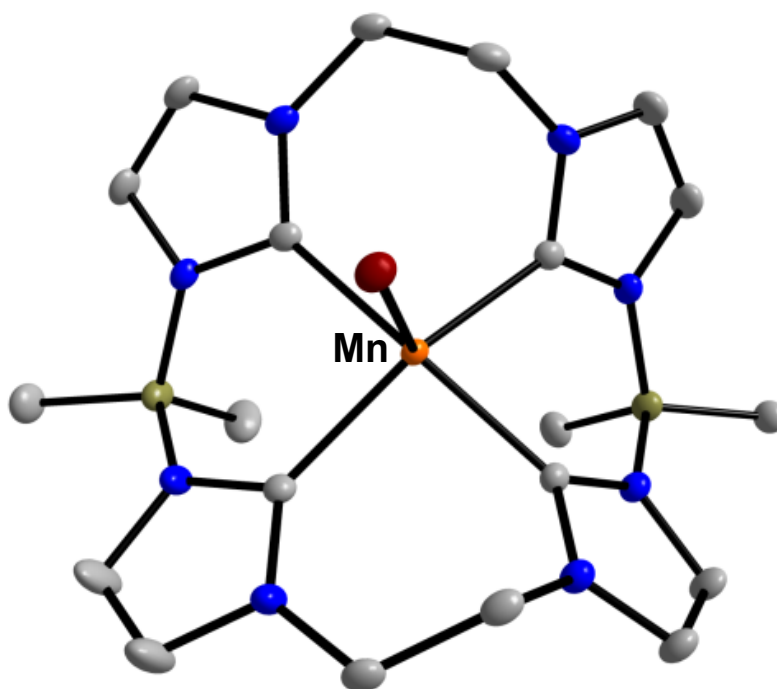
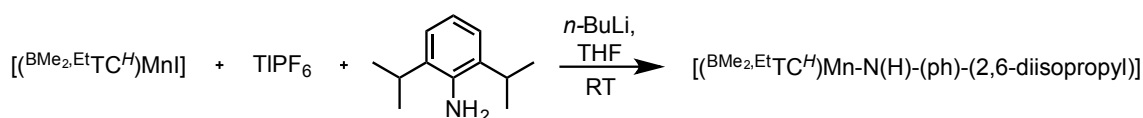


Figure 3.3. Crystal structure of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnBr}]$. Gray, blue, olive, orange, and red ellipsoids (50% probability) represent carbon, nitrogen, boron, manganese, and bromine respectively. Hydrogen atoms are omitted for clarity.

This complex was investigated for the proposed imide intermediate isolation by the reactions with various organic azides. Unfortunately, It did not show any reactivity towards azides, as confirmed by various characterization techniques. Catalytic aziridination with lower equivalents of alkenes was unsuccessful as well. One reason for the low reactivity of this complex could be the bound halide on Mn, which does not allow for an open site. To overcome this problem, the original complex was reacted with TIPF_6 in THF. We expected to get the solvento- complex, $[(^{\text{BMe}_2\text{EtTC}^H})\text{Mn}(\text{THF})](\text{PF}_6)$, in which the more labile ligand allows for an open catalytic site. Despite apparent solid formation in the reaction, no evidence of the desired species was obtained. We then attempted *in-situ* reactions with THF solvento- complex. This Mn(III) complex was and subsequently reacted with *n*-BuLi and 2,6-diisopropylaniline to make the Mn imide (Scheme 3.6). This instead resulted in the Mn amide as shown in Figure 3.4. The long bond distance of 2.068 for the Mn-N(H) bond suggests the formation of amide rather than imide. At this point, we decided to move in other directions for aziridination catalysis.

Scheme 3.6. Synthesis of Mn amide complex



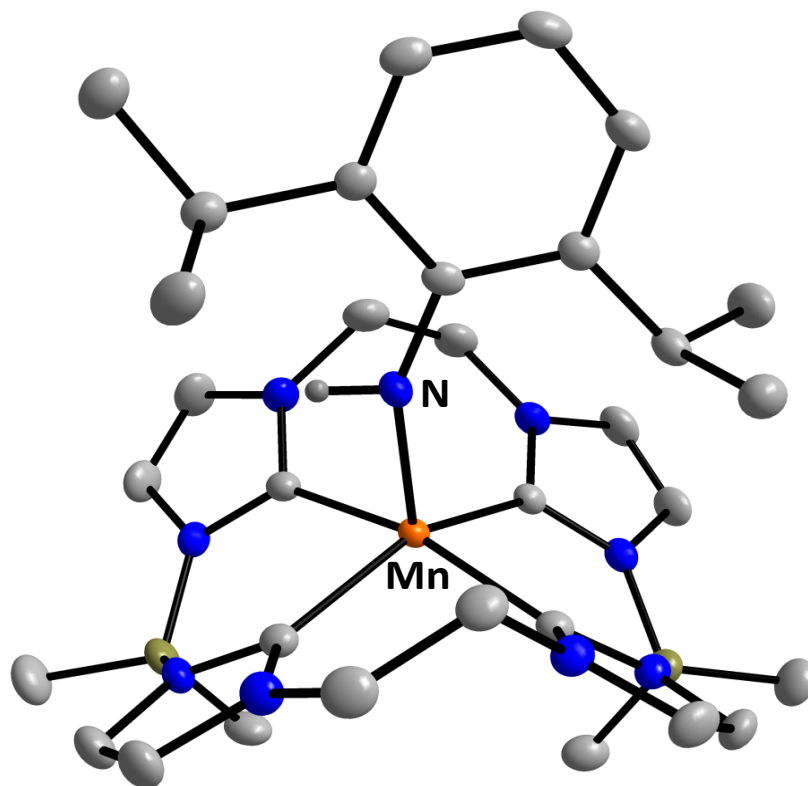


Figure 3.4. Crystal structure of Mn amide. Gray, blue, olive, and orange ellipsoids (50% probability) represent carbon, nitrogen, boron, and manganese respectively. Hydrogen atoms are omitted (except on nitrogen) for clarity.

Synthesis and characterization of Fe(III) complex, [(^{BMe₂,Et}TC^H)FeBr]

Iron complexes with tetra-NHC are very important not only for understanding structure and bonding but also in catalysis.^{16, 42} We made an effort to synthesize an iron complex with FeBr₃ with the end goal of forming an Fe(V) imide from reaction with an azide. Apart from suggesting the mechanism, this would be an enlightening compound to study, as there are very few high oxidation state imide complexes.⁴³ (^{BMe₂,Et}TC^H)(Br)₂ was deprotonated using a strong base, *n*-BuLi, in THF solution and reacted *in-situ* with FeBr₃ overnight to form [(^{BMe₂,Et}TC^H)FeBr] in 25% yield (Scheme 3.7). The single crystal X-ray diffraction (SCXRD) of yellow crystals revealed a square pyramidal geometry (Figure 3.5).

In order to isolate the proposed imide intermediate, various reagents and reaction conditions were tried with this complex. Azides such as *p*-tolyl azide, mesityl azide, and adamantyl azide were reacted with [(^{BMe₂,Et}TC^H)FeBr]. The compound was also examined and found unsuccessful for the catalytic aziridination. We attempted reactions with the solvento- complex, [(^{BMe₂,Et}TC^H)Fe(THF)](PF₆) and the only reactivity that was observed was with hypervalent iodine reagent, PhINTs, in THF solution of [(^{BMe₂,Et}TC^H)Fe(THF)](PF₆). We observed nitrene insertion between Fe and a

carbene as shown in Figure 3.6. After all these efforts it was concluded that for $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{FeBr}]$ to show any reactivity it has to go through Fe(V), which may be unfavorable due to the high oxidation state. Therefore, in the next step we reduced this compound to Fe(II).

Synthesis and characterization of Fe(II) complex, $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{Fe}]$

The first generation iron catalyst was shown to go through oxidation state changes from Fe(II) to Fe (IV) and back to Fe(II).^{16, 44} After all these efforts it was concluded that for $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{FeBr}]$ to show any reactivity it has to go through Fe(V), which may be unfavorable due to the high oxidation state. After we realized that Fe(III) to Fe(V) is probably not a favorable catalytic cycle, $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{FeBr}]$ was reduced using sodium amalgam in THF (Scheme 3.8). A distinct color change from orange-yellow to green-yellow indicates the occurrence of a reaction. Vapor diffusion of pentane to the benzene solution yielded beautiful neon-yellow colored single crystals suitable SCXRD analysis (Figure 3.7A). The iron(II) complex is in a square planar geometry and is soluble in most of the organic solvents. The ligand in this complex is saddled down, which causes the methyl groups on boron block the bottom side of the complex as can be seen from side view of the crystal structure (Figure 3.7B). Vacant axial positions are expected to favor ligand binding ability and therefore catalytic activity of this complex.

Scheme 3.7. Synthesis of $[(^{\text{BMe}_2\text{EtTC}^H})\text{FeBr}]$

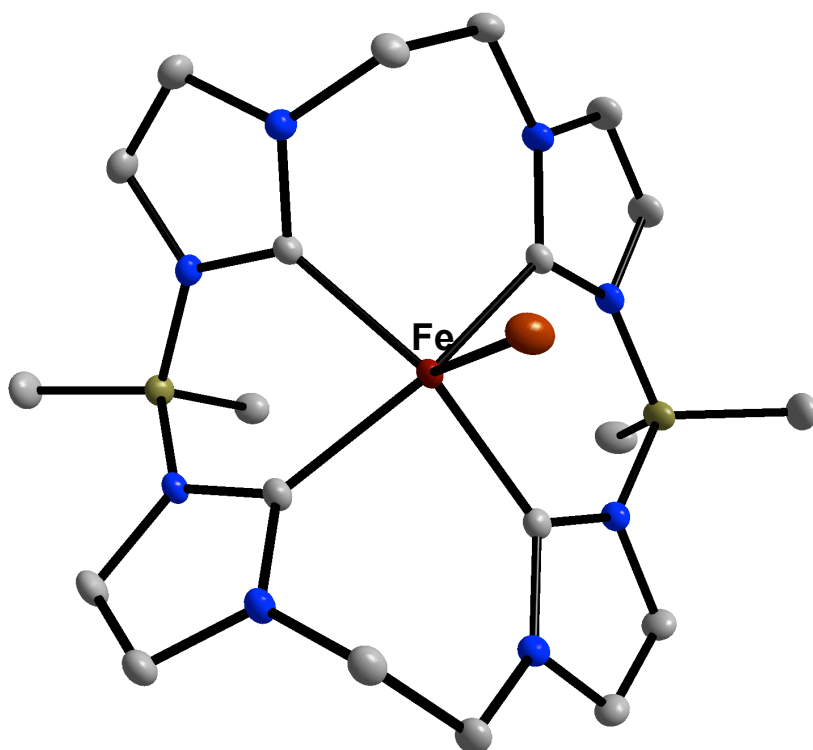


Figure 3.5. Crystal structure of $[(^{\text{BMe}_2\text{EtTC}^H})\text{FeBr}]$. Gray, blue, olive, red and brown ellipsoids represent carbon, nitrogen, boron, iron, and bromine respectively. Hydrogen atoms are omitted for clarity.

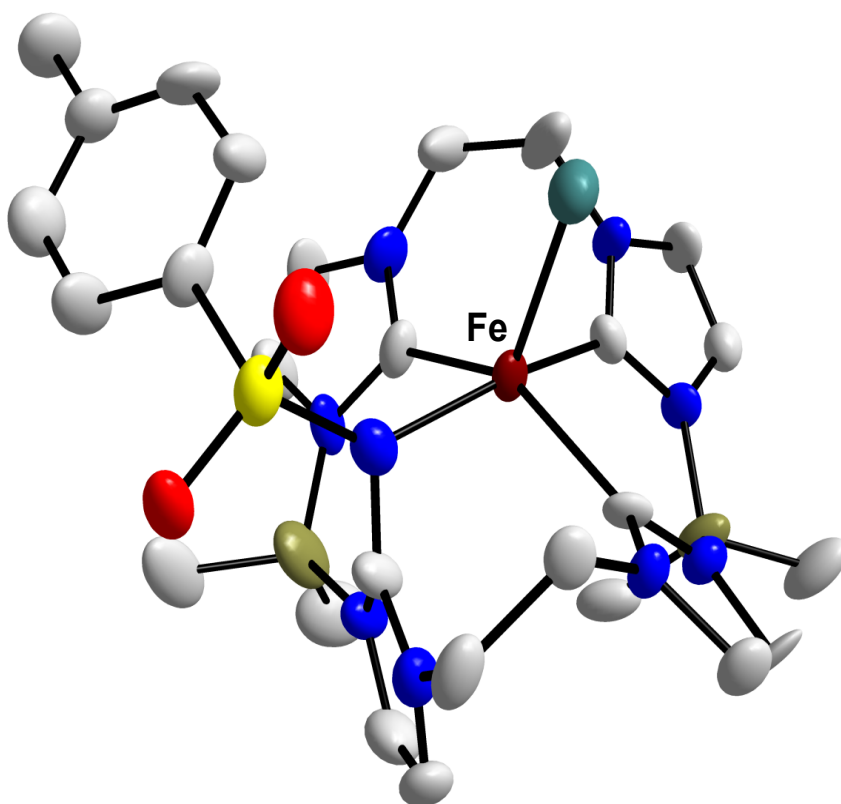


Figure 3.6. Crystal structure of inserted nitrene complex. Gray, blue, olive, yellow, crimson, red and teal ellipsoids represent carbon, nitrogen, boron, sulfur, oxygen, iron, and bromine respectively. Hydrogen atoms and solvent molecules are omitted for clarity.

Scheme 3.8. Synthesis of $[(^{BMe_2,Et}TC^H)Fe]$

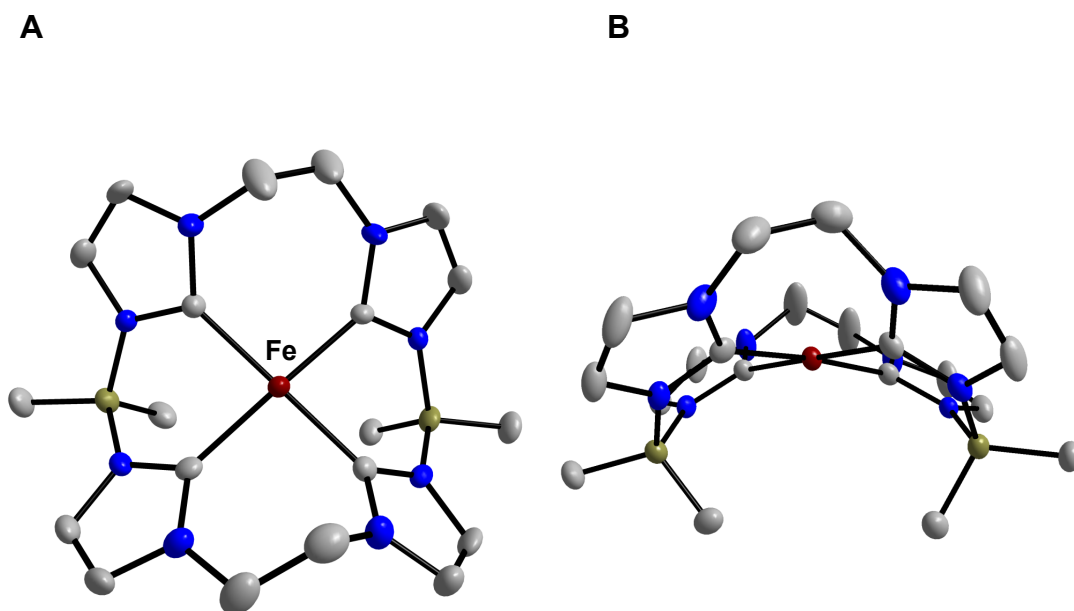
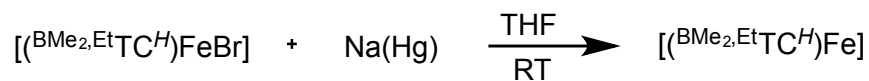


Figure 3.7. A. Crystal structure of $[(^{BMe_2,Et}TC^H)Fe]$ (top view). B. Side view of the crystal structure of $[(^{BMe_2,Et}TC^H)Fe]$. Gray, blue, olive, and red ellipsoids represent carbon, nitrogen, boron, and iron respectively. Hydrogen atoms and solvent molecules are omitted for clarity.

As expected, this complex was found to catalyze aziridination with aliphatic alkenes and alkyl azides along with improved yields for the synthesis of aryl-alkyl aziridines. In addition, bicyclic aziridines can be formed with greater yields for six-membered bicyclic aziridines rather than five-membered one. While attempting to isolate the aziridination intermediates, we were able to isolate some addition products. All these results regarding this catalyst are described in next chapters.

Synthesis and characterization of a main group complex, $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{InBr}]$

A plethora of main group metal complexes are synthesized supported by anionic auxiliary ligands such as porphyrin and salen.⁴⁵ For example, an aluminum porphyrin complex is reported to perform catalytic ring opening polymerization^{45a} and an aluminum salen complex is found to be phospho-transfer catalyst.⁴⁶ Similarly, gallium, tin and indium salen complexes are used for ring opening polymerization.⁴⁷ Despite being novel auxiliary ligand, there are very few examples of polydentate NHCs on the main group metals.⁴⁸ The reason behind this is the resulting complexes are cationic. One way to overcome this problem is to install anionic ligands; therefore, the second-generation borate-based ligand is a good candidate. Using this ligand the Jenkins group synthesized Al, Sn, and In complexes via a strong base approach.⁴⁹

The synthesis of $[(^{\text{BMe}_2\text{Et}}\text{TC}^H)\text{InBr}]$ is shown in Scheme 3.9, and the colorless crystalline product yielded the crystal structure in Figure 3.8. Unfortunately, this compound degrades in most of the solvents and therefore, its complete characterization was not possible.

Conclusion

In conclusion, we used a borate-based macrocyclic NHC ligand precursor for the synthesis of various monomeric metal complexes. This approach involves synthesis of first-row late transition metals, Mn, Co, and Fe. Out of these Mn and Fe form trivalent five coordinate metal complexes with a halide attached along with the macrocyclic tetracarbene ligand. Alternatively, Co forms a divalent square planar complex. The Fe(III) complex can be reduced to Fe(II) to form a square planar complex. In an effort to make a suitable Mn complex, we also synthesized a borate-based, second generation silver transmetallating reagent analogous to a previously reported transmetallating reagent. Out of these metal complexes, $[(^{\text{BMe}_2\text{Et}}\text{TC}^H)\text{Fe}]$ was found to be catalytically active which is discussed in later chapters.

In addition to these we also synthesized main group In(III) complex. Unfortunately, this compound was found to degrade in most solvents and therefore could not be characterized completely or used for catalysis.

Scheme 3.9. Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{InBr}]$

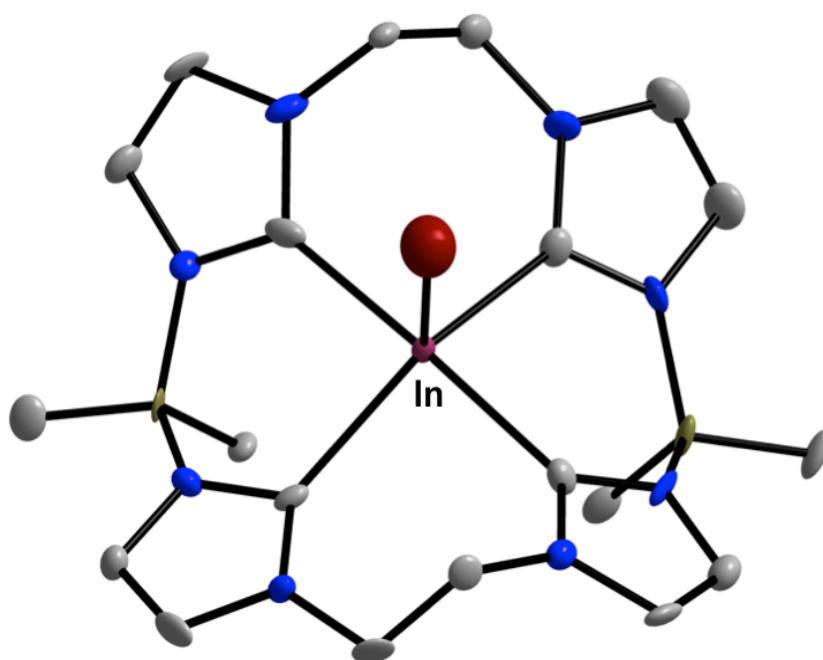
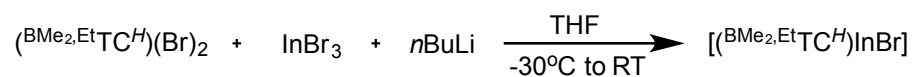


Figure 3.8. Crystal structure of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{InBr}]$. Gray, blue, olive, and pink, and red ellipsoids (50% probability) represent carbon, nitrogen, boron, and indium, and bromine respectively. Hydrogen atoms and solvent molecules are omitted for clarity.

Experimental

All reactions were performed under a dry nitrogen atmosphere with the use of either a dry box or standard Schlenk techniques. 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 O₂ prior to use. Benzene-*d*₆, and chloroform-*d* were degassed by three freeze-pump-thaw cycles prior to drying over activated molecular sieves. These NMR solvents were then stored under N₂ in a glovebox. All other reagents were purchased from commercial vendors and used without purification. ¹H, ¹³C 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 ¹³C NMR chemical shifts were referenced to the residual solvent. DEPT, HSQC, and COSY were performed on a Varian VNMRS 500 MHz narrow-bore 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). The GC/MS analyses were performed using a Hewlett Packard 6890 gas chromatography system with Hewlett Packard 5973 mass spectrometer. Mass spectrometry sample solutions of metal complexes were prepared in tetrahydrofuran. Infrared

spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. UV-vis measurements were taken inside a dry glovebox on an Ocean Optics USB4000 UV-vis system with 1 cm path length quartz crystal cell.

Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Co}]$. $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{PF}_6)_2$ (0.2088g, 0.299 mmol) was added to tetrahydrofuran (10 mL) in a 20 mL vial and stirred for 10 min. LDA (0.1318g, 1.23 mmol) was added in to the stirring $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{Br})_2$ mixture. After 20 min, CoI_2 (0.1002g, 0.320 mmol), which had been previously dissolved in tetrahydrofuran (10 mL), was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h. The slurry was filtered to collect the filtrate. All volatiles were removed under reduced pressure. Benzene (3 mL) was added to the crude solid and stirred for 20min. The slurry was then filtered and the collected filtrate was set for crystallization. The pure product was crystallized via vapor diffusion of pentane into the benzene solution and the bright red crystals were collected after 2 days (0.0158g, 11% yield).

Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Ag}]_2\text{Ag}_2$. $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{PF}_6)_2$ (0.3169g, 0.455 mmol) was added to tetrahydrofuran (10 mL) in a 20 mL vial and stirred for 5 min. This solution was then cooled down to -30°C . *n*-BuLi (0.1951g, 1.821 mmol) was pipetted in to the stirring $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{PF}_6)_2$ mixture, stirred for 20 min and again cooled down to -30°C for 30 min. AgPF_6 (0.2302 g, 0.910mmol), was added to the vial containing the reaction mixture covered with aluminum foil. The reaction

mixture was allowed to stir for 4 h still covered with aluminum foil. The slurry was filtered quickly to collect the filtrate. All volatiles were removed under reduced pressure to get a white powder. Benzene (50 mL) was added to the crude solid and stirred for 5 min. The slurry was then filtered and the collected filtrate was dried under reduced pressure. Single crystals were obtained via vapor diffusion of pentane into the benzene solution to get colorless crystals after 1 day (0.2263g, 80% yield).

Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnBr}]$ using the strong base approach.

$(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{Br})_2$ (0.2163g, 0.382 mmol) was added to tetrahydrofuran (5 mL) in a 20 mL vial and stirred for 10 min. LDA (0.1655g, 1.545 mmol) was added to the stirring $(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{Br})_2$ mixture. After 20 min, manganese(II) bromide (0.1662g, 0.774 mmol), which had been previously dissolved in warm tetrahydrofuran (10 mL), was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h. The slurry was filtered to collect the filtrate. All volatiles were removed under reduced pressure. Benzene (3 mL) was added to the crude solid and stirred for 20min. The slurry was then filtered and the collected filtrate was set for vapor diffusion crystallization with benzene and pentane. The pure product as bright red crystals were collected after 2 days (0.020g, 9.7% yield).

Synthesis of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{MnI}]$ using silver transmetallating reagent.

$[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Ag}]_2\text{Ag}_2$ (0.1837g, 0.149 mmol) was added to tetrahydrofuran (5 mL) in a aluminum foil covered 20 mL vial and stirred for 10 min. Manganese(II)

iodide (0.0918 g, 0.297 mmol), which had been previously dissolved in warm tetrahydrofuran (10 mL), was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h. The slurry was filtered to collect the filtrate. All volatiles were removed under reduced pressure. Benzene (3 mL) was added to the crude solid and stirred for 20 min. The slurry was then filtered and the collected filtrate was set for crystallization. The pure product was crystallized via vapor diffusion of pentane into the benzene solution as bright red crystals were collected after 2 days (0.1307 g, 75% yield).

Synthesis and characterization of $[(^{\text{BMe}_2\text{EtTC}^H})\text{FeBr}]$. $(^{\text{BMe}_2\text{EtTC}^H})(\text{Br})_2$ (1) (1.492 g, 2.636 mmol) was added to tetrahydrofuran (30 mL) in a 100 mL round bottom flask and stirred for 10 min. *n*-BuLi (1.129 g, 10.54 mmol) was pipetted in to the stirring $(^{\text{BMe}_2\text{EtTC}^H})(\text{Br})_2$ mixture. After 20 min, iron(III) bromide (0.779 g, 2.64 mmol), which had been previously dissolved in tetrahydrofuran (10 mL), was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h. The slurry was filtered to collect the filtrate. All volatiles were removed under reduced pressure. Benzene (50 mL) was added to the crude solid and stirred for 2 h. The slurry was then filtered and the collected filtrate was concentrated to 15 mL. The pure product was crystallized via vapor diffusion of pentane into the benzene solution and the bright red crystals were collected after 2 days (0.355 g, 25% yield). ^1H NMR (benzene- d_6 , 499.74 MHz): δ 29.4, -5.8, -14.4, -18.7. Evans' method (benzene- d_6): 1.7 μB . UV-vis (THF) λ_{max} , nm (ϵ): 363 (430), 426

(220). DART/MS (m/z): $[M+H]^+$ 538.12286 (found), 538.12452 (calcd), $[M-Br]^+$ 458.19515 (found) 458.19725 (calcd). Electrochemistry (vs ferrocene in CH_3CN with $(TBA)(PF_6)$ as supporting electrolyte): Fe^{III}/Fe^{II} , -950 mV. Anal. Calcd for $C_{20}H_{28}B_2BrFeN_8$: C, 44.66; H, 5.25; N, 20.83. Found: C, 45.41; H, 5.34; N, 20.30.

Synthesis and characterization of $[(^{BMe_2,Et}TC^H)FeBr]$ using silver transmetallating reagent. $[(^{BMe_2,Et}TC^H)Ag]_2Ag_2$ (0.0659g, 0.053 mmol) was added to tetrahydrofuran (5 mL) in a aluminum foil covered 20 mL vial and stirred for 10 min. $FeBr_3$ (0.0315 g, 0.107 mmol), which had been previously dissolved in warm tetrahydrofuran (10 mL), was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h. The slurry was filtered to collect the filtrate. All volatiles were removed under reduced pressure. Benzene (3 mL) was added to the crude solid and stirred for 20min. The slurry was then filtered and the collected filtrate was set for crystallization. The pure product was crystallized via vapor diffusion of pentane into the benzene solution and the bright red crystals were collected after 2 days (0.0332g, 58% yield).

Synthesis and characterization of $[(^{BMe_2,Et}TC^H)Fe]$. In a 20 mL vial, sodium metal (0.020 g, 0.88 mmol) was added followed by 10 drops of mercury and allowed to stir for 30 min. 2 mL of tetrahydrofuran was added to the sodium amalgam and stirred for another 10 min. To this mixture, $[(^{BMe_2,Et}TC^H)FeBr]$ (0.355 g, 0.660 mmol) solution in 15 mL tetrahydrofuran was added. This

reaction was allowed to stir for 18 h. The slurry was filtered over Celite without mercury then the filtrate was dried under reduced pressure. The crude product was extracted with 10 mL of benzene. The benzene solution was filtered over Celite and the pure product was obtained by vapor diffusion of pentane yielding neon yellow crystals after 3 days (0.185 g, 52% yield). ^1H NMR (benzene- d_6 , 499.74 MHz): δ 34.1, 17.6, 15.0, -33.9, -70.1. Evans' method (benzene- d_6): 2.8 μB . UV-vis (THF) λ_{max} , nm (ϵ): 363 (1400), 448 (930). DART/MS (m/z): $[\text{M}+\text{H}]^+$ 459.20399 (found) 459.20452 (calcd). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{B}_2\text{FeN}_8$: C, 52.45; H, 6.16; N, 24.47. Found: C, 50.33; H, 6.12; N, 21.99.

Synthesis and characterization of $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{InBr}]$. $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)(\text{Br})_2]$ (214 mg, 0.377 mmol) was added to a 20 mL vial with tetrahydrofuran (10 mL) and stirred at room temperature (450 rpm) for 5 min. The resulting slurry was cooled to $-30\text{ }^\circ\text{C}$. $n\text{-BuLi}$ (2.50 M, 0.604 mL, 1.5 mmol) was added to the slurry and allowed to stir until the white slurry became an orange-yellow solution (~ 15 min.). Indium(III) bromide (134 mg, 0.377 mmol) was then added to the resulting solution and allowed to stir at room temperature overnight. The reaction mixture was then filtered over Celite and the resulting solution was concentrated to 3 mL under reduced pressure. The colorless product was isolated by vapor diffusion of pentane into this solution (21.5 mg, 10% yield). Due to decomposition of the product in most solvents, full characterization was not possible within the time constraints of it degrading. A single crystal suitable for X-ray diffraction can be

obtained by vapor diffusion of pentane into a benzene solution containing the product. ^1H NMR (C_6D_6 , 499.74 MHz): δ 7.14 (d, J = 1.6 Hz, 4H), 5.96 (d, J = 1.6 Hz, 4H), 4.66-4.59 (m, 4H), 3.13-3.07 (m, 4H), 0.82 (s, 6H), 0.59 (s, 6H). IR (neat): 3390, 3115, 2929, 1630, 1546, 1455, 1415, 1394, 1371, 1291, 1260, 1217, 1150, 1109, 1078, 1038, 1019, 966, 946, 839, 797, 750, 736, 727, 697, 670, 635 cm^{-1} . ESI/MS (m/z): $[\text{M}-\text{Br}]^+$ 517.11.

CHAPTER FOUR
FIRST FULLY ALKYL CATALYTIC AZIRIDINATION UTILIZING
BORATE-BASED FE(II) COMPLEX

A version of this chapter was originally published by Preeti P. Chandrachud, Heather M. Bass, and David M. Jenkins.

Chandrachud Preeti P.; Bass Heather M.; Jenkins David M. "Synthesis of fully aliphatic aziridines with a macrocyclic tetracarbene iron catalyst." *Organometallics*, **2016**, 35, 1652-1657.

Abstract

The new macrocyclic tetracarbene iron(II) complex, $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ (**1**) catalyzed the aziridination of alkyl azides and aliphatic alkenes showcasing the first fully aliphatic version of this $\text{C}_2 + \text{N}_1$ reaction. High isolated yields were obtained when no functional groups were present on the organic azides and alkenes, while modest yields were achieved when non-protic functional groups were included. Even multiple functional groups can be added to the azide and alkene fragments to produce the most complex aziridines yet synthesized by this $\text{C}_2 + \text{N}_1$ catalytic reaction. The catalyst generated higher yields for aziridination with aryl azides and alkenes than the previously reported catalyst, $[(^{\text{Me}, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$. The contrast is particularly apparent with functionalized aryl azides where the second generation catalyst now provides practical yields for synthetic chemistry. Finally, catalytic intramolecular aziridination was investigated since many natural products with aziridines feature

bicyclic tertiary aziridines. For five- and six-membered rings, the bicyclic aziridines were formed catalytically, in contrast to previously studied catalyzed and uncatalyzed reactions.

Introduction

Novel catalytic systems are often initially designed for conjugated or aryl systems prior to the development of their alkyl variants since the C-X bonds on conjugated systems are more facile towards activation.⁵⁰ For example, C-H bond activation and functionalization reactions were developed primarily with aryl systems and only later shifted to alkyl cases.^{50a, 51} A well-documented catalytic reaction that follows this trend is Suzuki coupling. Initially reported on aryl systems in 1981,⁵² the all alkyl variant was not discovered until 1991 by Suzuki and later expanded by Fu and coworkers.⁵³ The development of the catalytic aziridination reaction follows a similar trend.

Although there are a multitude of approaches to preparing aziridines,^{1b, 54} a catalytic $C_2 + N_1$ reaction, analogous to Jacobsen epoxidation, that conjoins an alkene (C_2) and an organic azide (N_1) is considered highly desirable from the standpoint of atom economy.^{1a, 12, 55} Since there is a substituent on the aziridine nitrogen, the azide fragment transfers a hydrogen, aryl, or alkyl group to the newly formed three-membered ring. Despite considerable improvements in the last few years in catalytic primary aziridination⁵⁶ and aziridination with aryl

substituents on the nitrogen,^{12, 49, 55a} almost no examples produce aliphatic moieties off the nitrogen ring.⁵⁷ Since many examples of natural products or drugs that feature aziridines contain aliphatic carbons on the aziridine nitrogen,^{2c, 58} the development of a C₂ + N₁ catalytic system that features both aliphatic azides and alkenes would greatly benefit the synthesis of these strained rings.

The lack of alkyl aziridines formed through a C₂ + N₁ reaction is primarily due to the ineffectiveness of alkyl azides as a nitrene source.⁵⁹ Aryl and benzylic azides are widely employed for aza-Wittig reactions,⁶⁰ Staudinger ligations,⁶¹ and rearrangements of aryl nitrene reactions,⁶² while alkyl azides are less reactive and mostly employed for intramolecular [3+2] cycloadditions or Click chemistry.⁶³ Betley and coworkers have reported the only example of a catalytic aziridination with an alkyl azide, but their reaction was limited to styrene as the alkene source.⁵⁷

We have previously reported a borate-based dianionic carbene macrocycle with increased σ -donor strength versus our initial neutral macrocyclic tetracarbene.^{31a} This increased donor strength improves the susceptibility of alkyl azides to react with a catalyst to form the key metal imide intermediate.^{16, 44, 64} This metal imide can then react with alkenes to form aziridines. A catalyst system that overcomes this limitation will drastically expand the scope of C₂ + N₁ aziridination reactions.

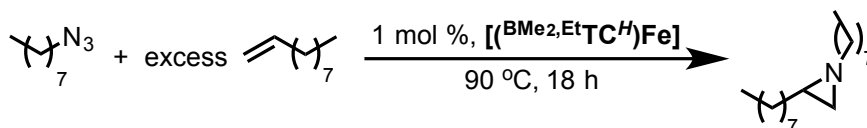
A new second generation tetracarbene iron catalyst, $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ (**1**), performs the first aziridination with alkyl azides and aliphatic alkenes. In addition, the catalyst is tolerant towards a variety of functional groups on both the alkenes and azides leading to more complex aziridination products than what have been reported previously. The catalyst achieves higher yields on reactions between aryl azides and aliphatic alkenes compared to our first generation catalyst system. In particular, the second generation catalyst has higher yields for aziridines with functionalized aryl azides. Finally, since many aziridines in natural products, drugs or their synthetic intermediates feature a bicyclic tertiary aziridine,^{58a, 65} we tested intramolecular aziridination reactions. In the case of five- and six-membered ring systems, the catalyst formed the anticipated aziridine in contrast to previous studies with olefinic azides.

Optimized reaction conditions for catalytic reactions

To determine the optimal conditions for catalytic aziridination a series of reactions were performed with *n*-octyl azide, 1-decene and **1**. The best results were obtained with 1% catalyst loading with 50-fold excess of alkene and no additional solvent (Scheme 4.1). After 18 h at 90° C, the catalytic reaction reached completion (all organic azide was consumed). The reaction was cooled to room temperature and the product, 1,2-dioctylaziridine (**2**), was purified by column chromatography on silica gel using a gradient elution of a mixture of ethyl

acetate and hexanes. The corresponding excess alkene can be recovered from the column as it comes out with hexanes as eluent. The isolated yield of 1,2-dioctylaziridine was 82%. The identity of the product was confirmed by ^1H and ^{13}C NMR spectroscopy (including 2D NMR), and DART high resolution MS.

Scheme 4.1. General reaction scheme for catalytic reaction.



Non-functionalized catalytic alkyl alkyl aziridination

To determine the efficacy of the catalytic system, additional aliphatic azides and alkenes were tested. Each test was conducted with the same reaction time (18 h) and temperature (90°C) and each aziridine was isolated in the same manner after column chromatography. The reported yields are all isolated yields.

Additional reactions with no functional groups on the azide or alkene were generally successful with **1** as the catalyst (Table 4.1). Primary azides yielded greater than 80% isolated yield when combined with an unencumbered alkene. Aziridine, 9-(octyl)-9-azabicyclo[6.1.0]nonane (**3**), was isolated in an 80% yield from *n*-octyl azide and *cis*-cyclooctene at 1% catalyst loading. Increasing the catalyst loading to 5% improved the yield to 92%; however, removing the catalyst entirely (i.e. a control reaction) gave only a 6% yield of **3**.

Table 4.1. Alkyl aziridination reactions without functional groups with $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ as the catalyst.

Entry	Alkene	Azide	Catalyst loading (mol %)	Aziridine	Yield
1			1%		80%
2			1% / 5%		82% / 90%
3			1%		49%
4			1%		47%
5			1%		60%

The sterically encumbered *t*-butyl azide reacted with 1-decene and **1** (1% loading) to form 1-(*t*-butyl)-2-octylaziridine (**4**) in a 49% yield, while cyclohexyl azide reacted under the same conditions to produce its respective aziridine, **5**, in 47% yield. Reducing the steric encumbrance by placing one extra carbon in the chain improves the yield modestly. (2-azidoethyl)benzene reacted with 1-decene and **1** (1% loading) to form 1-(2-phenylethane)-2-octylaziridine (**6**) in 60% yield.

Functionalized catalytic alkyl alkyl aziridination

Since most aziridines that are employed as intermediates in the synthesis of pharmaceuticals or natural products have multiple functional groups, we believed that it was critical to test the effectiveness of catalyst **1** with both alkenes and azides adorned with additional functionalities. With regard to functional groups on the organic azide our results were partially successful (Table 4.2). Methyl-6-azidohexanoate reacted with 1-decene and **1** (1% loading) to form methyl-6-(2-octylaziridin-1-yl)hexanoate (**7**) in a 40% yield (50% yield if the catalyst loading was increased to 5%). A similar reaction with 5-chloro-1-azidopentane, 1-decene, and **1** did form the desired aziridine, 1-(5-chloropentyl)-2-octylaziridine (**8**), but a small impurity remained even after column chromatography. As a counterpoint, we also tested aziridination reactions with functionalized alkenes. Our test reactions were generally successful, albeit with modest isolated yields (Table 4.2). The reaction of *n*-octyl azide with ethyl-hept-6-

enoate and **1** generated ethyl-5-(1-octylaziridin-2-yl)pentanoate (**9**) in a 36% yield. Finally, we attempted an aziridination reaction with functional groups on both the azide and alkene substituents. Methyl-6-azidohexanoate reacted with 6-chlorohex-1-ene and **1** (5% catalyst loading) to give methyl-6-(2-(4-chlorobutyl)aziridin-1-yl)hexanoate (**10**) in a 33% yield. We believe that no example of this complexity has yet been reported for catalytic aziridination from any organic azide and alkene in a $C_2 + N_1$ reaction.

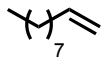
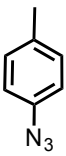
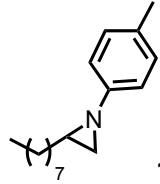
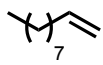
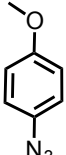
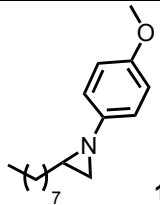
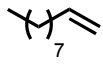
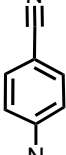
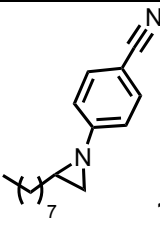
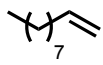
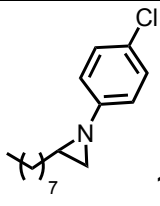
Catalytic aryl alkyl aziridination

As part of our goal for developing a catalyst that works with all manner of alkenes and organic azides, we tested **1** with aryl azides. A test reaction with 1-decene, *p*-tolyl azide and **1** (1% loading) formed 2-octyl-1-(*p*-tolyl)aziridine, (**11**) in nearly quantitative yield (95%) after 18 h. The original catalyst, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$, yielded 82% of **11** under the same reaction conditions.¹⁶ Reactions with 1-decene and **1** plus the following organic azides, 1-azido-4-methoxybenzene, 4-azidobenzonitrile, 1-azido-4-chlorobenzene, yielded the expected aziridines in 80%, 68%, and 58% isolated yields (Table 4.3). Matching reactions with the 1-azido-4-methoxybenzene or 4-azidobenzonitrile, 1-decene and $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ as the catalyst yielded only 65% and 38% of the respective aziridines.

Table 4.2. Alkyl aziridination reactions with functional groups with $[(^{\text{BMe}_2,\text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ as the catalyst.

Entry	Alkene	Azide	Catalyst loading (mol %)	Aziridine	Yield
6			1%/ 5%		40%/ 50%
7			5%		32%
8			10%		36%
9			5%		33%

Table 4.3. Aryl aziridination reactions with $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ as the catalyst.

Entry	Alkene	Azide	Catalyst loading (mol %)	Aziridine	Yield
10			1%	 11	95%
11			5%	 12	80%
12			1%	 13	68%
13			1%	 14	58%

We have previously proposed that the mechanism for these iron catalyzed $C_2 + N_1$ aziridination reactions goes through an iron(IV) imide intermediate.^{16, 49} We believe that the increased electron density at the metal center due to the borate-based macrocycle^{31a} lowers the energy necessary to form the iron imide, which explains why weaker nitrene sources, such as alkyl azides, are effective with this second generation catalyst. Similarly, the higher yields with the aryl azides is due to increased reactivity in the first step of the catalytic cycle, the formation of the iron(IV) imide.

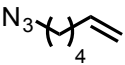
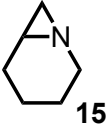
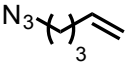
Alkyl intramolecular aziridination

Our final test for the catalyst **1** was intramolecular $C_2 + N_1$ aziridination, since a $C_2 + N_1$ reaction where both the alkene and azides are on the same molecule would lead to a tertiary bicyclic aziridine in a single step with no need for excess alkene. Since tertiary bicyclic aziridines are found in natural products, the formation of these ring systems is critical for synthetic medicinal chemistry.⁶⁶ Surprisingly few reactions of this type have been demonstrated and the most common synthetic approach for forming this class of bicyclic aziridines is through a ring closing of a cyclic halo-amine, such as 2-(bromomethyl)-pyrrolidine.⁶⁷

We tested the intramolecular catalytic aziridination reactions with short chain alkene azides that would lead to products desirable for natural products and pharmaceuticals.^{66a, 68} The reaction of 6-azidohex-1-ene with **1** (0.1%

loading) as catalyst in C₆D₆ at 80 °C led to an 83% yield of the aziridine, 1-azabicyclo[4.1.0]heptane (**15**) (Table 4.4). This result is particularly extraordinary since 6-azidohex-1-ene has not been demonstrated to form the bicyclic aziridination product in either catalyzed or uncatalyzed reactions. Fifty years ago, Logothetis reported that thermal decomposition of 6-azidohex-1-ene, did not yield the aziridine, but in fact the imine, 2-methyl-3,4,5,6-tetrahydropyridine.⁶⁹ More recently Betley employed an iron(II)-dipyrinato catalyst to yield the pyrrolidine via C-H bond activation, leaving the alkene functionality intact.⁷⁰

Table 4.4. Intramolecular aziridination reactions with 1 as the catalyst.

Entry	Reagent	Catalyst loading (mol %)	Aziridine	Yield
14		0.1%	 15	83%
15		0.1%	 16	30%

Based on the success of this initial result for intramolecular aziridination, we wondered whether additional bicyclic ringed systems could be synthesized in this manner. A similar reaction with 5-azidopent-1-ene and **1** in C₆D₆ yielded the expected aziridine, 1-azabicyclo[3.1.0]hexane (**16**), albeit in only 30% yield. A test catalytic reaction with 8-azidooct-1-ene and **1** did not yield aziridine but crystallization of the reaction mixture with pentane yielded red crystals. Single crystal X-ray diffraction revealed that an iron tetrazone, **17**, had been formed during the reaction. These combine results suggest that the formation of the six-membered ring is critical to a high yield of aziridine.

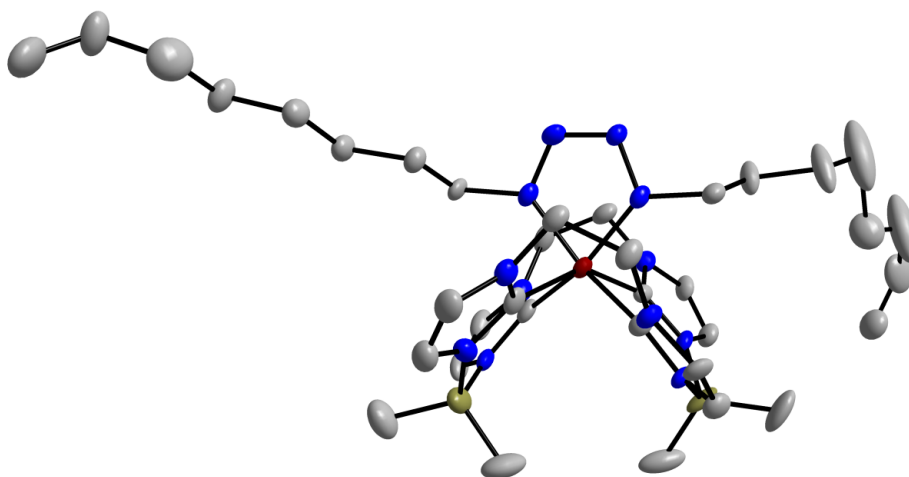


Figure 4.1. Crystal structure of $[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}((n\text{-oct-1-ene})\text{N}_4(n\text{-oct-1-enel}))]$, **17**. The gray, blue, olive, and red ellipsoids (30% probability) represent carbon, nitrogen, boron, and iron atoms respectively. Hydrogen atoms are omitted for clarity.

Conclusion

In conclusion, we have synthesized a second generation iron aziridination catalyst that is supported by a macrocyclic tetracarbene. The iron complexes were characterized by NMR, mass spectrometry, and single crystal X-ray diffraction. $[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}]$ reacts with a wide variety of alkyl azides and aliphatic alkenes in the first general aziridination reaction to form fully aliphatic aziridines. We believe that the enhanced reactivity for the catalyst in the $\text{C}_2 + \text{N}_1$ aziridination reaction is due to the increased electron donor strength of the borate containing macrocycle which activates the alkyl azides to form a reactive imide intermediate.

Aliphatic aziridines are a critical, but underexplored, subset of this functional group since they are potential intermediates in pharmaceuticals or natural product syntheses. We formed linear and cyclic aziridines in high isolated yields in reasonable reaction times with low catalyst loading. In addition, we demonstrated that the catalyst has reasonable functional group tolerance and even multiple functional groups can be employed to make the most complex aziridine yet by a $\text{C}_2 + \text{N}_1$ approach. $[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}]$ is more effective at aziridination with aryl azides and aliphatic alkenes than our previous system, particularly with functional groups on the azide. Finally, we succeeded in intramolecular aziridination reaction that formed the first examples of tertiary bicyclic aziridines in a $\text{C}_2 + \text{N}_1$ reaction. This combination of effectiveness for

alkyl and aryl azides with aliphatic alkenes makes $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ the best $\text{C}_2 + \text{N}_1$ aziridination catalyst for organic azides and alkenes to date. This catalyst makes great progress towards our goal of atom economical formation of aziridines through direct synthesis from organic azides and alkenes. Future work will be directed at more complex bicyclic systems for biologically active intermediates.

Experimental

All reactions were performed under a dry nitrogen atmosphere with the use of either a dry box or standard Schlenk techniques. 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 O_2 prior to use. Benzene- d_6 , and chloroform- d were degassed by three freeze-pump-thaw cycles prior to drying over activated molecular sieves. These NMR solvents were then stored under N_2 in a glovebox. All other reagents were purchased from commercial vendors and used without purification. ^1H , ^{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. DEPT, HSQC, and COSY were performed on a Varian VNMRS 500 MHz narrow-bore 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). The GC/MS analyses were performed using a Hewlett Packard 6890 gas chromatography system with Hewlett Packard 5973 mass spectrometer. Mass spectrometry sample solutions of metal complexes were prepared in tetrahydrofuran. Mass spectrometry sample solutions of organic compounds from catalysis reactions were prepared in ethyl acetate or hexanes. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. UV-vis measurements were taken inside a dry glovebox on an Ocean Optics USB4000 UV-vis system with 1 cm path length quartz crystal cell. Carbon, hydrogen, and nitrogen analyses were obtained from Atlantic Microlab, Norcross, GA for complex **2** and Galbraith laboratories Inc. Knoxville, TN for complex **3** under N₂.

General Catalytic Reaction. [(^{BMe₂,Et}TC^H)Fe], (**1**) was added to a 20 mL vial followed by the addition of the alkene. The reaction mixture was heated and stirred for 10 min. The organic azide was then added to the reaction and allowed to stir at the designated temperature. Once organic azide was no longer present after 18 h (as determined by GC/MS) the mixture was removed from heat and the product was purified by column chromatography on silica gel using a gradient

elution of a mixture of ethyl acetate and hexanes unless otherwise mentioned. The corresponding excess alkene can be recovered from the column as it comes out with hexanes as eluent. The recovered alkene can be reused after removing the hexanes.

Synthesis of 1,2-dioctylaziridine, 2. *1% catalyst loading:* *n*-octyl azide (0.101 g, 0.651 mmol), 1-decene (5.023 g, 35.81 mmol), and **1** (0.003 g, 0.007 mmol) were used in the General Catalytic Reaction described above yielding 0.142 g, 82%. ¹H NMR (CDCl₃, 499.74 MHz): d 2.26 (m, 1H), 2.07 (m, 1H), 1.52 (m, 2H), 1.47 (d, *J* = 3.4 Hz, 1H), 1.46-1.13 (m, 25H), 1.16 (d, *J* = 6.3 Hz, 1H), 0.87 (m, 6H). ¹³C NMR (CDCl₃, 125.66 MHz): d 61.68, 39.52, 33.82, 33.20, 31.86, 31.82, 29.90, 29.60, 29.58, 29.48, 29.25, 29.23, 27.60, 27.44, 22.64, 22.63, 14.06, 14.06. IR: 2953, 2921, 2853, 1458, 1376, 1243, 1165, 1082, 998, 973, 808, 722 cm⁻¹. DART HR MS (*m/z*): [M+H]⁺ 268.29854 (found); [C₁₈H₃₈N]⁺ 268.29988 (calcd).

Synthesis of 9-(octyl)-9-azabicyclo[6.1.0]nonane, 3. *1% catalyst loading:* *n*-octyl azide (0.101 g, 0.651 mmol) and *cis*-cyclooctene (4.500 g, 40.83 mmol), and **1** (0.003 g, 0.007 mmol) were used in the General Catalytic Reaction described above yielding 0.124 g, 80%. *5% catalyst loading:* *n*-octyl azide (0.091 g, 0.59 mmol), and *cis*-cyclooctene (4.342 g, 39.40 mmol), and **1** (0.013 g, 0.029 mmol) were used in the General Catalytic Reaction described above yielding 0.128 g, 92%. ¹H NMR (CDCl₃, 499.74 MHz): d 2.30 (t, *J* = 7.5 Hz, 2H), 2.09 (d, *J*

= 13.0 Hz, 2H), 1.61-1.45 (m, 6H), 1.43-1.34 (m, 4H), 1.33-1.12 (m, 14H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): d 60.35, 43.65, 31.80, 29.63, 29.54, 29.19, 27.32, 27.11, 26.45, 26.22, 22.62, 14.07. IR: 2951, 2920, 2852, 1455, 1376, 1358, 1114, 809, 722 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 238.25300 (found); $[\text{C}_{16}\text{H}_{32}\text{N}]^+$ 238.25293 (calcd).

Synthesis of 1-(*tert*-butyl)-2-octylaziridine, 4. 1% catalyst loading: *tert*-butyl azide (0.0630 g, 0.63 mmol), 1-decene (3.575 g, 25.5 mmol), and **1** (0.0029 g, 0.0063 mmol) were used in the General Catalytic Reaction described above yielding 0.0660 g, 49%. ^1H NMR (CDCl_3 , 499.74 MHz): d 1.54 (m, 1H), 1.45 (d, $J = 6.4$ Hz, 2H), 1.41-1.22 (m, 14H), 0.95 (s, 9H), 0.86 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 52.38, 33.72, 32.19, 31.84, 29.58, 29.52, 29.25, 27.98, 26.70, 26.61, 22.63, 14.05. IR: 2957, 2921, 2866, 1457, 1376, 1361, 1249, 1231, 1207, 997, 973, 898, 841, 810, 734, 683 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 212.23741 (found); $[\text{C}_{14}\text{H}_{30}\text{N}]^+$ 212.23728 (calcd).

Synthesis of 1-cyclohexyl-2-octylaziridine, 5. 1% catalyst loading: cyclohexyl azide (0.0600 g, 0.48 mmol), 1-decene (3.671g, 26.2 mmol) and **1** (0.0022 g, 0.0048 mmol) were used in the General Catalytic Reaction described above yielding 0.0538 g, 47.2%. ^1H NMR (CDCl_3 , 499.74 MHz): d 1.80 (m, 2H), 1.72 (m, 3H), 1.58 (m, 1H), 1.45 (d, $J = 4.0$ Hz, 1H), 1.44-1.23 (m, 16 H), 1.21 (d, $J = 6.0$ Hz, 1H), 1.15 (m, 3H), 1.00 (m, 1H), 0.87 (t, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 69.20, 38.58, 33.59, 33.22, 32.63, 32.60, 32.03, 29.76, 29.72,

29.44, 28.02, 26.29, 25.21, 25.19, 22.82, 14.25. IR: 2950, 2921, 2853, 1451, 1376, 1171, 1074, 868, 733 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 238.25196 (found); $[\text{C}_{16}\text{H}_{32}\text{N}]^+$ 238.25293 (calcd).

Synthesis of 1-(2-phenylethane)-2-octylaziridine, 6. *1% catalyst loading:* (2-azidoethyl)benzene (0.1382 g, 0.94 mmol), 1-decene (4.0052g, 28.5 mmol) and **1** (0.0043 g, 0.0094 mmol) were used in the General Catalytic Reaction described above yielding 0.145 g, 60%. ^1H NMR (CDCl_3 , 499.74 MHz): d 7.26 (m, 2H), 7.20 (m, 3H), 2.88 (m, 2H), 2.54 (m, 1H), 2.40 (m, 1H), 1.51(d, $J = 3$ Hz, 1H), 1.37-1.21 (m, 15H), 1.19 (d, $J = 5$ Hz, 1H), 0.88 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 140.08, 128.69, 128.30, 125.98, 63.19, 39.83, 36.52, 33.88, 33.10, 31.86, 29.57, 29.48, 29.26, 27.52, 22.65, 14.09. IR: 3028, 2955, 2922, 2853, 1496, 1454, 1403, 1376, 1358, 1259, 1159, 1084, 1013, 863, 794, 746, 698 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 260.23715 (found); $[\text{C}_{18}\text{H}_{30}\text{N}]^+$ 260.23728 (calcd).

Synthesis of methyl-6-(2-octylaziridin-1-yl)hexanoate, 7. *1% catalyst loading:* Methyl-6-azidohexanoate (0.292 g, 1.71 mmol), 1-decene (5.705 g, 40.67 mmol), and **1** (0.008 g, 0.017 mmol) were used in the General Catalytic Reaction described above yielding 0.195 g, 40%. *5% catalyst loading:* Methyl-6-azidohexanoate (0.088 g, 0.51 mmol), 1-decene (3.619 g, 25.80 mmol), and **1** (0.011 g, 0.025 mmol) were used in the General Catalytic Reaction described above yielding 0.074 g, 50%. ^1H NMR (CDCl_3 , 300.1 MHz): d 3.65 (s, 3H), 2.27

(m, 3H), 2.10 (m, 1H), 1.63-1.54 (m, 4H), 1.48 (d, $J = 3.3$ Hz, 1H), 1.44-1.16 (m, 17H), 1.17 (d, $J = 6.2$ Hz, 1H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 75.0 MHz): d 174.14, 61.30, 51.43, 39.57, 33.99, 33.84, 33.15, 31.85, 29.57, 29.53, 29.48, 29.26, 27.59, 26.97, 24.92, 22.64, 14.08. IR: 2950, 2922, 1733, 1458, 1375, 1245, 1168, 1046, 907, 731, 649 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 284.25804 (found); $[\text{C}_{17}\text{H}_{34}\text{NO}_2]^+$ 284.25841 (calcd).

Synthesis of 1-(5-chloropentyl)-2-octylaziridine, 8. 5% catalyst loading: 5-chloro-1-azidopentane (0.090 g, 0.61 mmol), 1-decene (3.773g, 26.89 mmol), and **1** (0.014 g, 0.031 mmol) were used in the General Catalytic Reaction described above yielding 0.050 g, 32%. ^1H NMR (CDCl_3 , 499.74 MHz): d 3.53 (t, $J = 6.7$ Hz, 2H), 2.27 (m, 1H), 2.12 (m, 1H), 1.78 (p, $J = 3.5$ Hz, 2H), 1.66 (m, 2H), 1.56 (m, 3H), 1.49 (d, $J = 3.5$ Hz, 1H), 1.35-1.23 (m, 14H), 1.18 (d, $J = 6.3$ Hz, 1H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): d 61.26, 44.93, 39.61, 33.87, 33.14, 32.62, 31.85, 29.57, 29.47, 29.25, 29.18, 27.58, 24.75, 22.64, 14.07. IR: 2949, 2917, 2838, 1451, 1374, 1239, 1167, 1098, 1045, 973, 913, 846, 731, 648, 634 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 260.21444 (found); $[\text{C}_{15}\text{H}_{31}\text{ClN}]^+$ 260.21395 (calcd).

Synthesis of ethyl-5-(1-octylaziridin-2-yl)pentanoate, 9. 10% catalyst loading: *n*-octyl azide (0.138 g, 0.889 mmol), ethyl-hept-6-enoate (1.392 g, 8.910 mmol), and **1** (0.041 g, 0.089 mmol) were used in the General Catalytic Reaction described above yielding 0.090 g, 36%. ^1H NMR (CDCl_3 , 300.1 MHz): d 4.10 (q,

$J = 7.0$ Hz, 2H), 2.29 (m, 3H), 2.10 (m, 1H), 1.66 (m, 2H), 1.49 (d, $J = 3.3$ Hz, 1H), 1.45-1.19 (m, 20H), 1.17 (d, $J = 1.5$ Hz, 1H), 0.87 (t, 3H). ^{13}C NMR (CDCl_3 , 75.0 MHz): d 173.69, 61.63, 60.17, 39.19, 34.30, 33.78, 32.81, 31.82, 29.88, 29.58, 29.23, 27.43, 27.12, 24.78, 22.64, 14.23, 14.08. IR: 2951, 2920, 2866, 1736, 1457, 1356, 1237, 1166, 1099, 1034, 998, 973, 899, 841, 808, 723 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 284.25907 (found); $[\text{C}_{17}\text{H}_{34}\text{NO}_2]^+$ 284.25841 (calcd).

Synthesis of methyl-6-(2-(4-chlorobutyl)aziridin-1-yl)hexanoate, 10. 5% catalyst loading: Methyl-6-azidohexanoate (0.098 g, 0.57 mmol), 6-chlorohex-1-ene (1.357 g, 11.44 mmol), and **1** (0.013 g, 0.029 mmol) were used in the General Catalytic Reaction described above yielding 0.049 g, 33%. ^1H NMR (CDCl_3 , 300.1 MHz): d 3.65 (s, 3H), 3.59 (m, 2H), 2.80 (m, 1H), 2.61-2.41 (m, 3H), 2.30 (m, 3H), 1.66-1.47 (m, 10H), 1.29 (m, 2H). ^{13}C NMR (CDCl_3 , 75.0 MHz): d 174.10, 60.66, 53.64, 51.46, 51.42, 45.46, 33.99, 28.97, 27.11, 25.41, 25.35, 24.86, 22.87. IR: 2948, 2920, 2866, 2838, 1735, 1452, 1436, 1375, 1200, 1168, 1124, 1053, 998, 973, 913, 841, 731, 677, 647 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 262.15737 (found); $[\text{C}_{13}\text{H}_{25}\text{ClNO}_2]^+$ 262.15683 (calcd).

Synthesis of 2-octyl-1-(*p*-tolyl)aziridine, 11. 1% catalyst loading: *p*-tolyl azide (0.294 g, 2.21 mmol), 1-decene (4.510 g, 32.15 mmol), and **1** (0.010 g, 0.022 mmol) were used in the General Catalytic Reaction described above yielding 0.513 g, 95%. The characterization (^1H and ^{13}C NMR) matched the literature data.¹⁶

Synthesis of 1-(4-methoxyphenyl)-2-octylaziridine, 12. 5% catalyst loading: 1-azido-4-methoxybenzene (0.0684 g, 0.46 mmol), 1-decene (4.004 g, 28.54 mmol), and **1** (0.011 g, 0.024 mmol) were used in the General Catalytic Reaction described above yielding 0.0962 g, 80%. ^1H NMR (CDCl_3 , 499.74 MHz): d 6.91 (d, $J = 9$ Hz, 2H), 6.76 (d, $J = 9$ Hz, 2H), 3.75 (s, 3H), 2.03-1.97 (m, 3H), 1.62-1.48 (m, 4H), 1.42-1.24 (m, 10H), 0.89 (t, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): d 154.85, 121.39, 114.17, 55.51, 40.39, 34.22, 33.25, 31.86, 29.59, 29.54, 29.26, 27.72, 22.66, 14.09. IR: 2950, 2918, 2837, 1507, 1460, 1376, 1241, 905, 833, 729, 650 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 262. 21725 (found); $[\text{C}_{17}\text{H}_{21}\text{NO}]^+$ 262.21654 (calcd).

Synthesis of 4-(2-octylaziridin-1-yl)benzonitrile, 13. 1% catalyst loading: 4-azidobenzonitrile (0.0881 g, 0.61 mmol), 1-decene (2.550 g, 18.18 mmol), and **1** (0.003 g, 0.006 mmol) were used in the General Catalytic Reaction described above yielding 0.107 g, 68%. ^1H NMR (CDCl_3 , 300.1 MHz): d 7.48 (d, $J = 8$ Hz, 2H), 7.01 (d, $J = 8$ Hz, 2H), 2.19-2.08 (m, 3H), 1.62-1.50 (m, 4H), 1.39-1.24 (m, 10H), 0.88 (t, 3H). ^{13}C NMR (CDCl_3 , 75.0 MHz): d 159.20, 133.16, 121.21, 119.36, 104.93, 40.60, 34.20, 32.87, 31.83, 29.53, 29.46, 29.23, 27.55, 22.64, 14.09. IR: 2950, 2920, 2854, 2222, 1602, 1500, 1462, 1406, 1358, 1376, 1312, 1201, 1169, 1100, 998, 972, 892, 841, 725, 642 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 257.20107 (found); $[\text{C}_{17}\text{H}_{25}\text{N}_2]^+$ 257.20122 (calcd).

Synthesis of 1-(4-chlorophenyl)-2-octylaziridine, 14. *1% catalyst loading:* 1-azido-4-chlorobenzene (0.0751 g, 0.49 mmol), 1-decene (3.721g, 26.53 mmol), and **1** (0.002 g, 0.004 mmol) were used in the General Catalytic Reaction described above yielding 0.075 g, 58%. For purification, a silica gel column was run in gradient hexanes/DCM combinations as eluent. ^1H NMR (CDCl_3 , 499.75 MHz): d 7.15 (d, $J = 9$ Hz, 2H), 6.90 (d, $J = 9$ Hz, 2H), 2.09-2.00 (m, 3H), 1.61-1.49 (m, 4H), 1.42-1.22 (m, 10H), 0.89 (t, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): d 153.86, 128.97, 126.96, 121.92, 40.47, 34.20, 33.08, 31.85, 29.56, 29.51, 29.25, 27.63, 22.65, 14.09. IR: 2952, 2921, 2853, 1594, 1488, 1460, 1408, 1376, 1299, 1197, 1167, 1091, 1009, 972, 890, 829, 749, 722, 709 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 266.16663 (found); $[\text{C}_{16}\text{H}_{25}\text{ClN}]^+$ 266.16700 (calcd).

Synthesis of 1-azabicyclo[4.1.0]heptane, 15. *0.1% catalyst loading:* Complex **1** (0.0005 g, 0.0011 mmol) was dissolved in 1 mL benzene- d_6 and mesitylene (0.0672 g, 0.00059 mmol) was added to the reaction mixture as an internal standard. Addition of 6-azidohex-1-ene (0.1367 g, 1.092 mmol) changed the color to orange from yellow. The reaction was stirred at 80° C for 18 h. The reaction progress was followed by ^1H NMR. The yield for the reaction was 83% (0.078 g) based on integration versus the internal standard. The isolation of this compound was not possible due to its low boiling point and degradation under vacuum. ^1H NMR (C_6D_6 , 499.75 MHz): d 4.17 (m, 1H), 3.61 (dd, $J = 4$ Hz, $J = 12$ Hz, 1H), 3.51 (dd, $J = 9$ Hz, $J = 6$ Hz, 1H), 2.84 (m, 1H), 2.63 (m, 1H), 1.17 (m,

1H), 1.07 (m, 2H), 0.78 (m, 1H), 0.64 (m, 2H). ^{13}C NMR (C_6D_6 , 125.66 MHz): δ 70.40, 54.56, 46.53, 27.51, 25.54, 22.38. DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 98.09654 (found); $[\text{C}_6\text{H}_{12}\text{N}]^+$ 98.09643 (calcd).

Synthesis of 1-azabicyclo[3.1.0]hexane, 16. *0.1% catalyst loading:* Complex **1** (0.0016 g, 0.0035 mmol) was dissolved in 1 mL benzene- d_6 and mesitylene (0.210 g, 1.74 mmol) was added to the reaction mixture as an internal standard. Addition of 5-azidopent-1-ene (0.388 g, 3.3908 mmol) changed the color to orange from yellow. The reaction was stirred at 80° C for 18 h. The reaction progress was followed by ^1H NMR. The yield for the reaction was 30% (0.088 g) based on integration versus the internal standard. The compound was characterized as per the literature.¹⁷

Synthesis of 1-azabicyclo[6.1.0]nonane. Complex **1** (0.005g, 0.011 mmol) was dissolved in 1 mL benzene- d_6 and 8-azidooct-1-ene (0.017g, 0.11 mmol) was added to the reaction mixture. The reaction was run for 18h at 80° C and the progress was followed by ^1H NMR. The corresponding aziridine was not formed according to ^1H NMR, DART MS and GC/MS analysis. Single crystals were obtained from vapor diffusion of pentane into the reaction mixture directly over two days.

Synthesis of 5-chloro-1-azidopentane. 1-chloro-5-iodopentane (1.295 g, 5.570 mmol) was dissolved in 50 mL acetonitrile in a 250 ml round bottom flask. Thallium azide (2.190 g, 8.888 mmol) was added in the above stirring mixture.

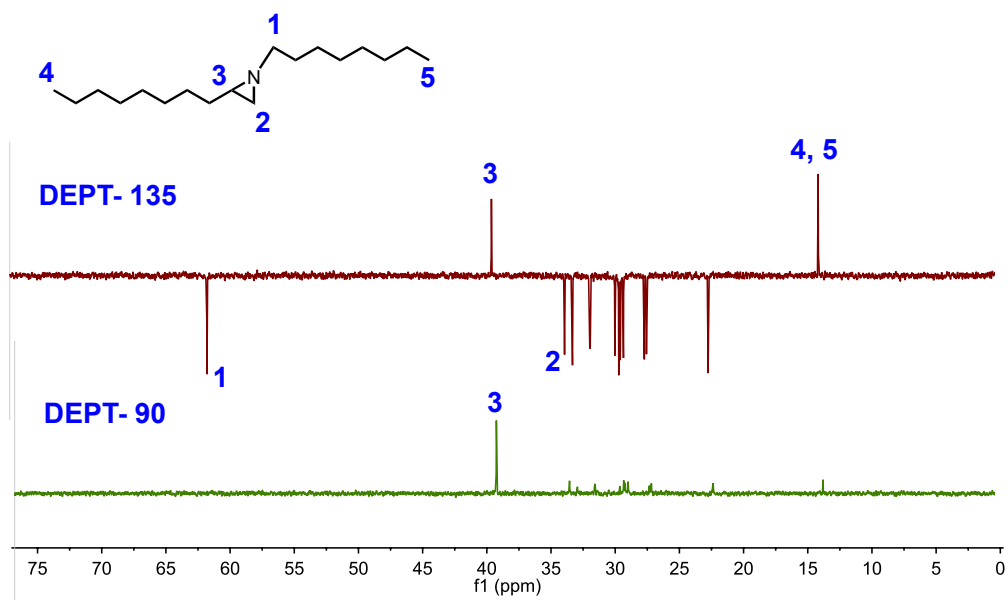
The reaction was refluxed at 65°C for 3 days. The yellow solid crashed out from solution was filtered over Celite on a 60 mL C frit to collect the filtrate. The solvent was evaporated under reduced pressure to collect the pure product, yielding 0.718 g, 87%. ¹H NMR (CDCl₃, 300.1 MHz): d 3.54 (t, *J* = 6.6 Hz, 2H), 3.29 (t, *J* = 6.5 Hz, 2H), 1.80 (m, 2H), 1.57 (m, 4H). ¹³C NMR (CDCl₃, 75.0 MHz): d 51.35, 44.80, 32.17, 28.31, 24.20. DART HR MS (*m/z*): [M+H]⁺ 148.06516 (found); C₅H₁₀CIN₃ 148.06360 (calcd).

Control Reaction. Control reaction following the method of the General Catalytic Reaction was attempted but without **1**. Synthesis of 9-(octyl)-9-azabicyclo[6.1.0]nonane, **3**. *n*-octyl azide (0.101 g, 0.651 mmol) and *cis*-cyclooctene (4.500 g, 40.83 mmol) were used in the General Catalytic Reaction described above yielding 0.009 g, 6% yield.

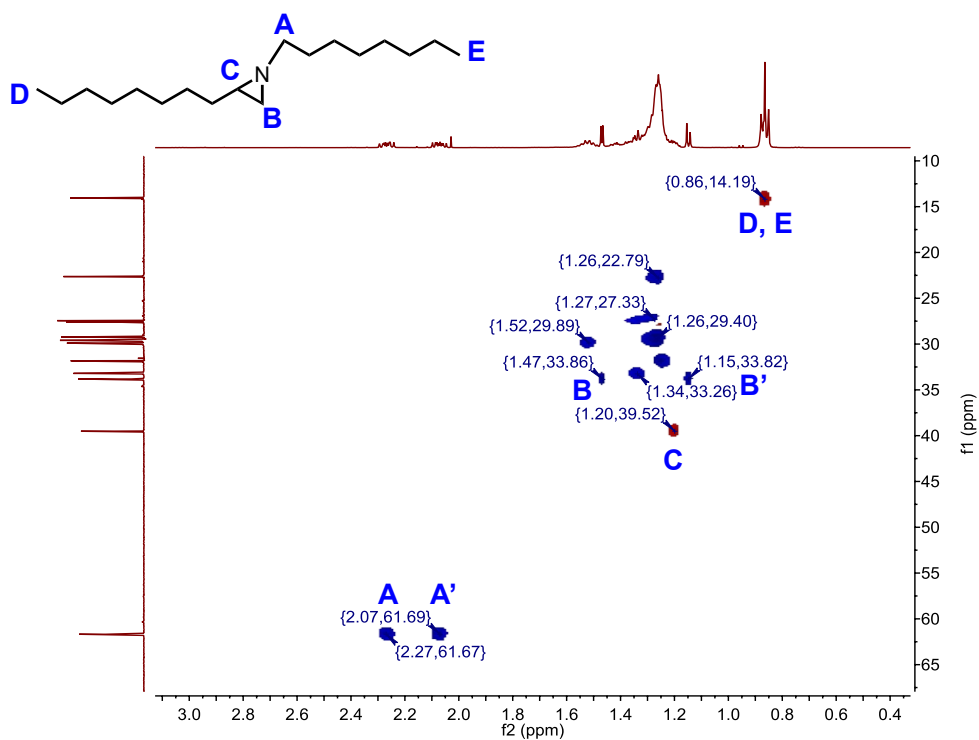
Spectrum 4.1. ^1H NMR of 1,2-dioctylaziridine (2)



Spectrum 4.3. DEPT of 1,2-dioctylaziridine (**2**)

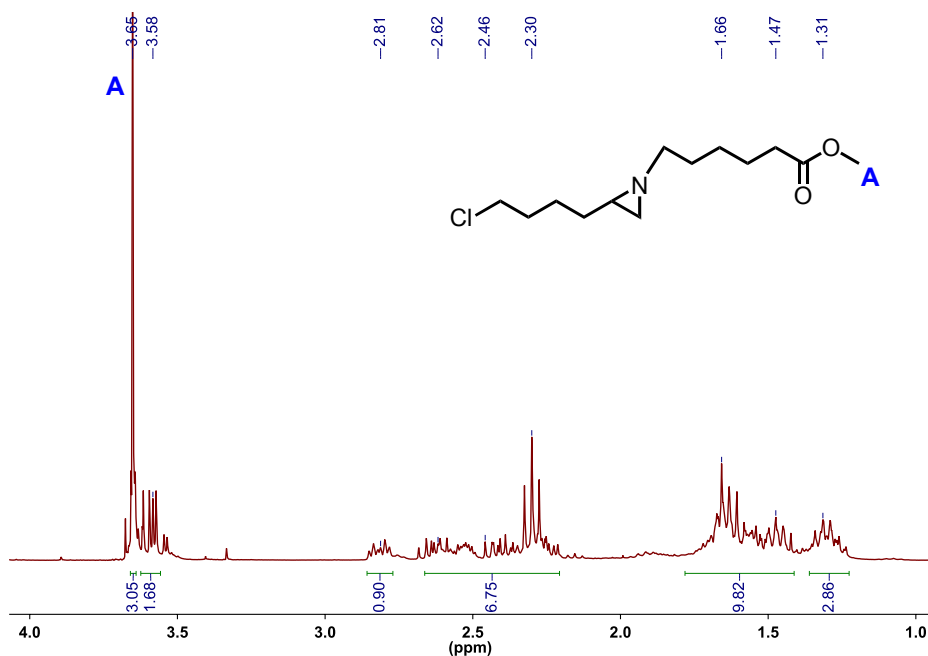


Spectrum 4.4. HSQC of 1,2-dioctylaziridine (**2**)

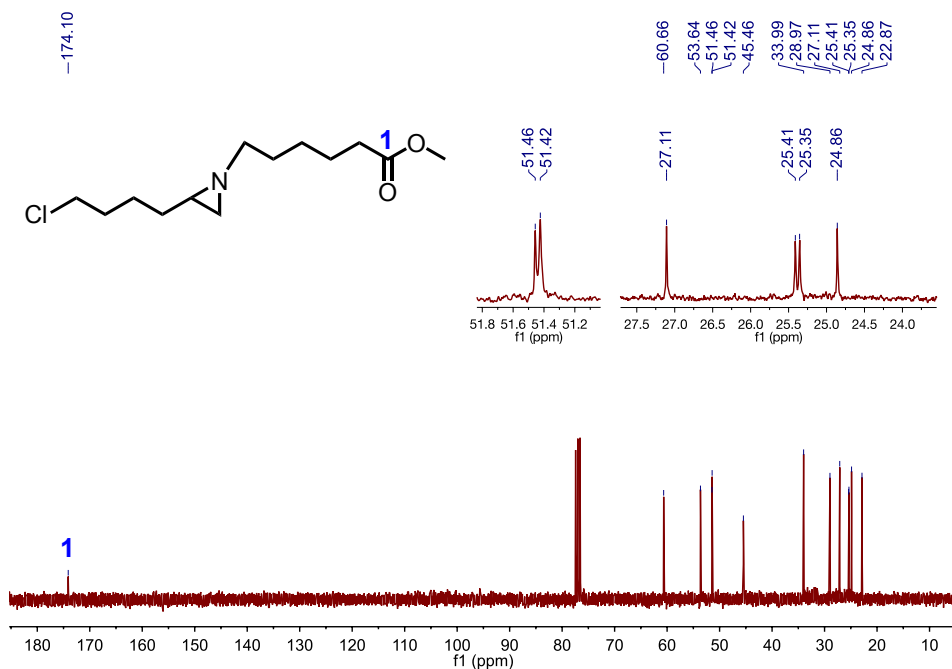


NMR of methyl-6-(2-(4-chlorobutyl)aziridin-1-yl)hexanoate (10)

Spectrum 4.5. ^1H NMR of methyl-6-(2-(4-chlorobutyl)aziridin-1-yl)hexanoate (10)

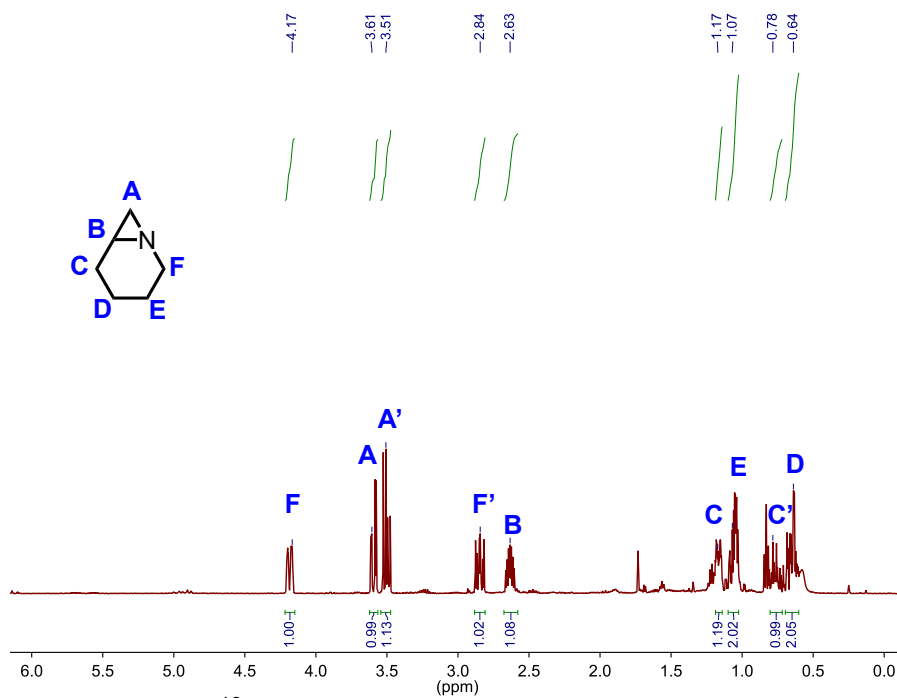


Spectrum 4.6. ^{13}C NMR of methyl-6-(2-(4-chlorobutyl)aziridin-1-yl)hexanoate (10)

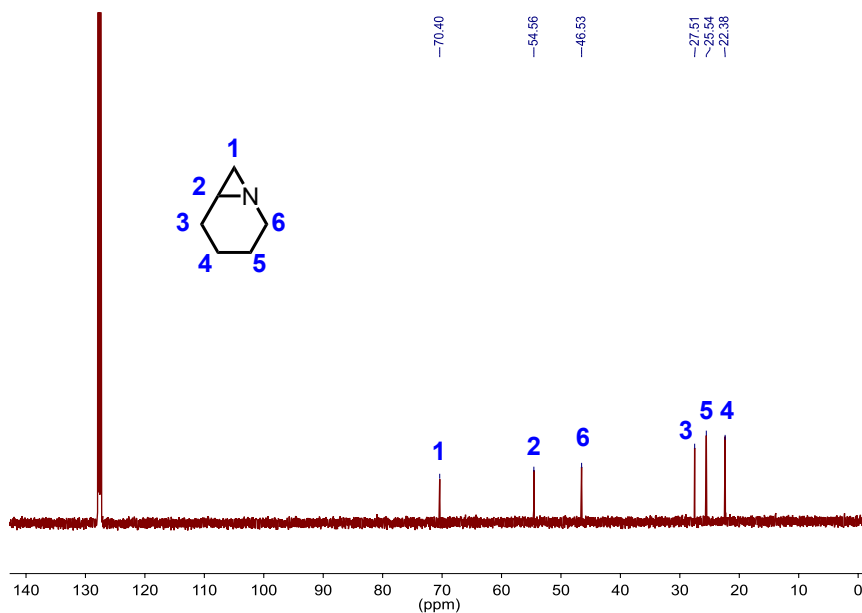


NMR of 1-azabicyclo[4,1,0]heptane, (15)

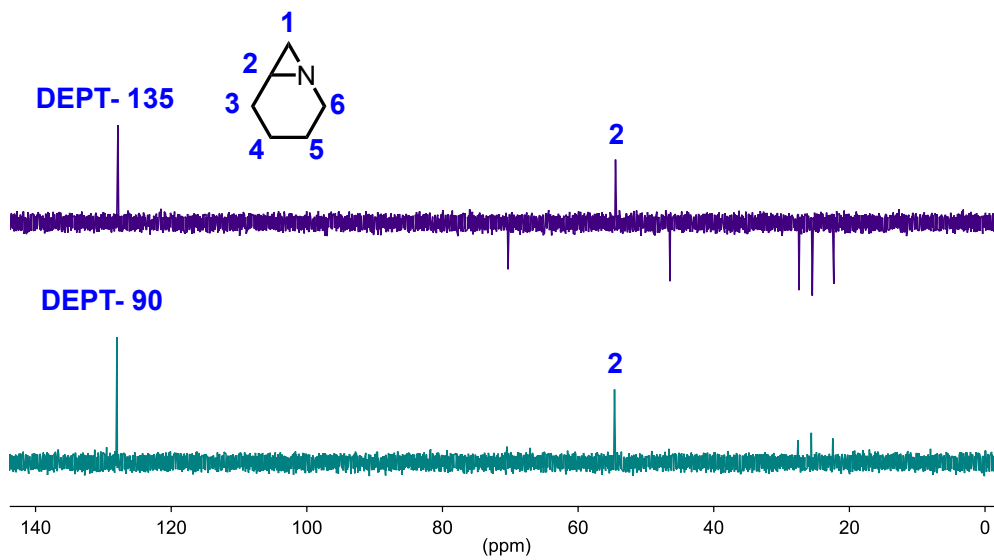
Spectrum 4.7. ^1H NMR of 1-azabicyclo[4.1.0]heptane (15)



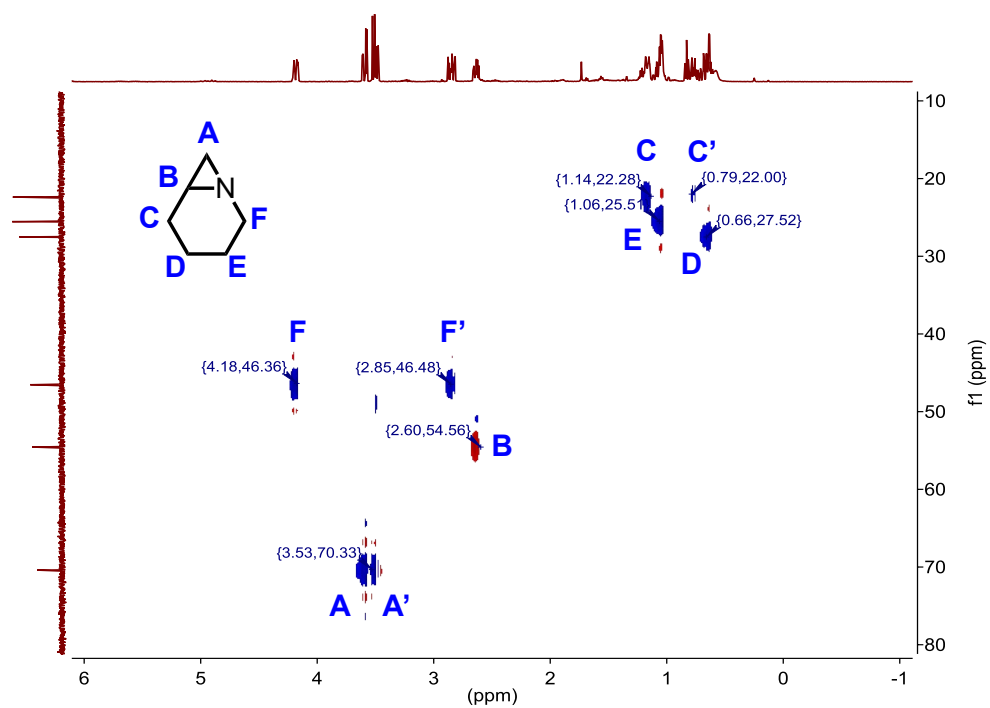
Spectrum 4.8. ^{13}C NMR of 1-azabicyclo[4.1.0]heptane (15)



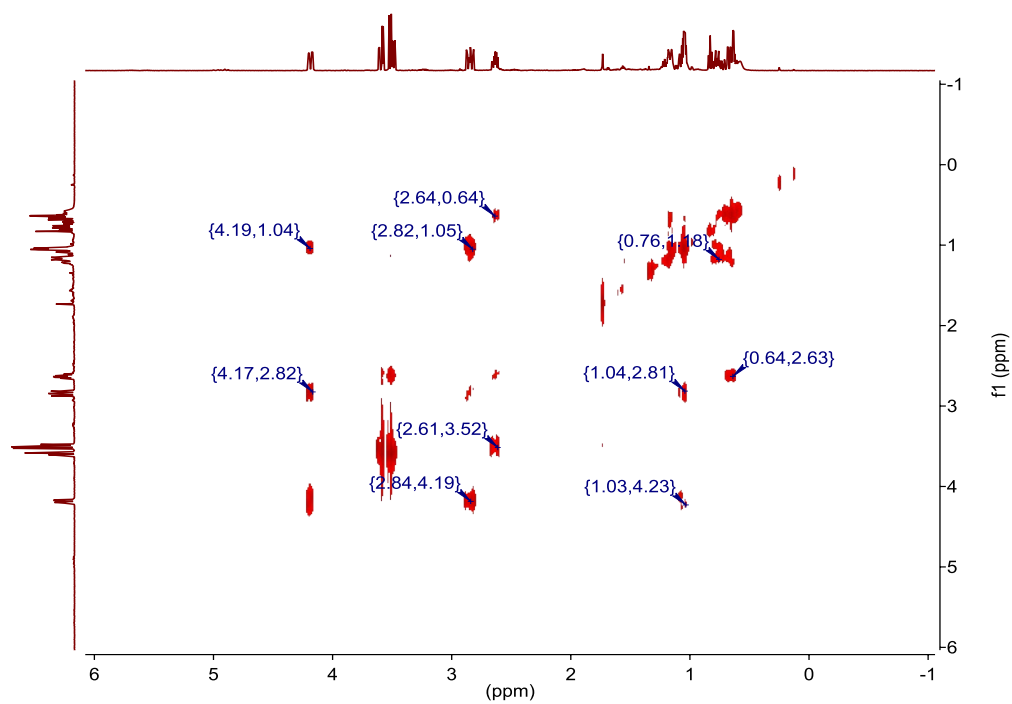
Spectrum 4.9. DEPT of 1-azabicyclo[4.1.0]heptane (**15**)



Spectrum 4.10. HSQC of 1-azabicyclo[4.1.0]heptane (**15**)



Spectrum 4.11. COSY of 1-azabicyclo[4.1.0]heptane (**15**)



CHAPTER FIVE
STUDY OF THE CATALYTIC CYCLE FOR THE AZIRIDINATION
REACTION

A version of this chapter is being included in a manuscript by Jesse L. Kern, Preeti P. Chandrachud, Sharani Roy and David M. Jenkins. Jesse L. Kern from Roy group has done all the theoretical calculations and I did the experimental work of the manuscript.

Kern, Jesse L.; Chandrachud, Preeti P.; Roy S., Jenkins, David M. "Elucidation of the disparate mechanisms of $C_2 + N_1$ aziridination from tetracarbene iron catalysts." (*Manuscript in process*)

Abstract

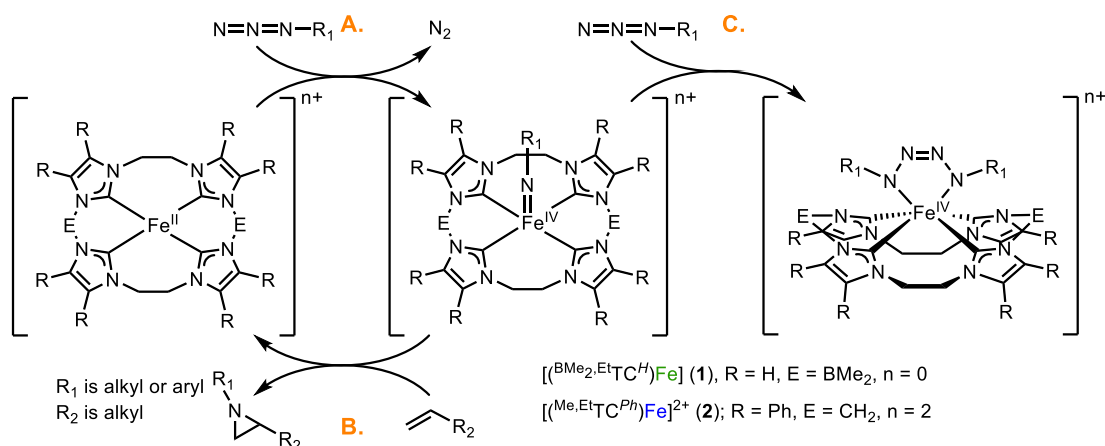
Study of the mechanism of catalytic aziridination is important to develop a more effective system to overcome current limitations. To investigate the details of each mechanistic step in catalytic aziridination by $[(^{BMe_2,Et}TC^H)Fe]$ (2st generation catalyst), **1**, and, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ (1st generation catalyst), **2**, DFT calculations were carried out. In addition, the calculations were supported by experimental evidence for the formation of aziridine and tetrazene from the proposed iron imide intermediate. In addition, various addition products were obtained in an attempt to isolate the active intermediate with $[(^{BMe_2,Et}TC^H)Fe]$. This study has given a great insight into our system that will help to eliminate some of the existing limitations in aziridination.

Introduction

Elucidating the mechanism will allow for the development of more effective aziridination catalysts supported by strong σ -donors such as *N*-heterocyclic carbenes (NHC). We recently reported two iron NHC-based catalysts for aziridine synthesis using organic aryl as well as alkyl azides on aliphatic alkenes.^{16, 71} Due to increased interest in non-porphyrin catalytic aziridination, its mechanism investigation is important.

While the basics of a proposed catalytic cycle have been considered previously (Scheme 5.1),⁴⁴ the individual elementary steps (shown as A, B, and C) within each portion of the cycle have not been described. These individual steps have implications for the effectiveness of the aziridination reaction, and understanding them can answer several key questions about the catalysis.

Scheme 5.1. Reaction scheme for the formation of aziridines from tetracarbene iron catalysts 1 and 2.



The questions to be answered are why do alkyl azides work with 2nd generation system (**1**) but not the 1st generation system (**2**)? How does the alkene react with the purported iron imide intermediate? Does it go through a box-like intermediate (concerted reaction) or a series of one electron reductions (radical reaction)? This question is particularly critical because of the implications for stereochemical control. Finally, what is the role of the metallotetrazene during catalysis? Does prevention of metallotetrazene allow for lower alkene loading?

In this mechanistic study, we pair DFT calculations for the entire proposed catalytic cycle for both the first and second generation tetracarbene iron catalysts with new experimental evidence for both systems. These results show that formation of iron imide is favorable for both aliphatic and aryl azides for the second generation system, but only for aryl azides for the first generation system. For the second generation system, the iron imide reaction goes through a radical mechanism to form the aziridine leading to a mixture of stereochemical products. Conversely, the first generation system yields only a single stereochemical product for shorter reaction time, which is consistent with predicted concerted mechanism. Finally, the prevention of metallotetrazene formation allows for lower alkene loadings to be employed by preventing the competition reaction that occurs from the iron imide intermediate.

Theoretical studies for the formation of imide – Step A

When aziridines are formed catalytically from organic azides and alkenes, metal imides are widely believed to be the key intermediates. Gallo⁷² and Ghosh⁷³ have employed DFT to investigate the mechanisms of imide formation and subsequent aziridination of porphyrin catalysts on Ru, and Co, respectively. Similar to many catalytically active systems, we were unable to isolate the proposed imide intermediate on first and second generation catalysts.^{12, 64a, 74} Therefore, DFT calculations were valuable to illustrate the pathways from starting Fe(II) to Fe(IV) imide intermediate for which TPSSh/cc-pVTZ model system was employed.

We compared the formation of imide with catalysts **1** and **2** with *p*-tolyl azide and *n*-octyl azide, resulting in four distinct reactions. The first test case was between *p*-tolyl azide and **1** (Figure 5.1A). In this system, all intermediates and transition states were lowest in energy for *S* = 1. The calculated transition state was only +8.7 kcal/mol higher than the intermediate suggesting that the formation of imide via this route is highly facile (no intermediates or transition states were found for the γ -bound case). The calculated imide intermediate is -41.7 kcal/mol lower than **1** and *p*-tolyl azide.

Switching to the reaction of *n*-octyl azide with **1** yielded similar results (Figure 5.1B). All species were in the lowest energy in the *S* = 1 state. The α -

bound azide intermediate was lower in energy than the γ -bound position. The transition state was somewhat higher than the *p*-tolyl azide case, +13.2 kcal/mol.

The differences between the catalysts **1** and **2** become apparent when comparing the energy diagrams for the reactions with *p*-tolyl azides. The reaction of *p*-tolyl azide with **2** offered a more complex picture than the same reaction with **1** (Figure 5.2A). Both α - and γ -bound azides were favorable intermediates. Notably, there are two possible routes at this point, a bent azide intermediate, which has been proposed by Bercaw,⁷⁵ and the direct loss of dinitrogen, which is seen for **1**. Although the bent azide intermediate is stable, the energy is considerably higher (+17 kcal/mol) than the transition state for the direct loss of dinitrogen. The total energy required to reach the transition state is +17.3 kcal/mol.

Unlike the case with **1**, the differences between the alkyl and aryl azide for a reaction with **2** are quite stark (Figure 5.2B). Only a single bound azide state (α) was found to be stable. More critically, the transition state for direct loss of dinitrogen is +20.2 kcal/mol higher than the intermediate. This supports the experimental observation that the alkyl azide will not react with the catalyst **2** at 90 °C to form an imide.

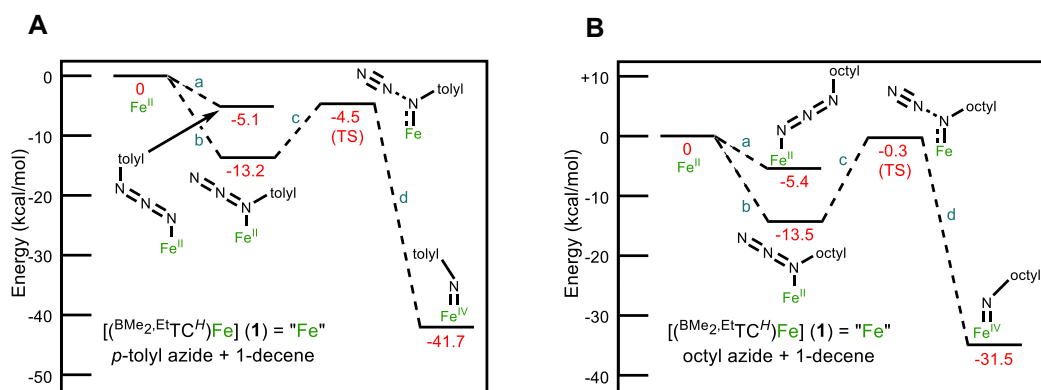


Figure 5.1. Energy diagram for the formation of imide from 1. **A.** Imide formation from the reaction of 1 with *p*-tolyl azide. **B.** Imide formation from the reaction of 1 with *n*-octyl azide.

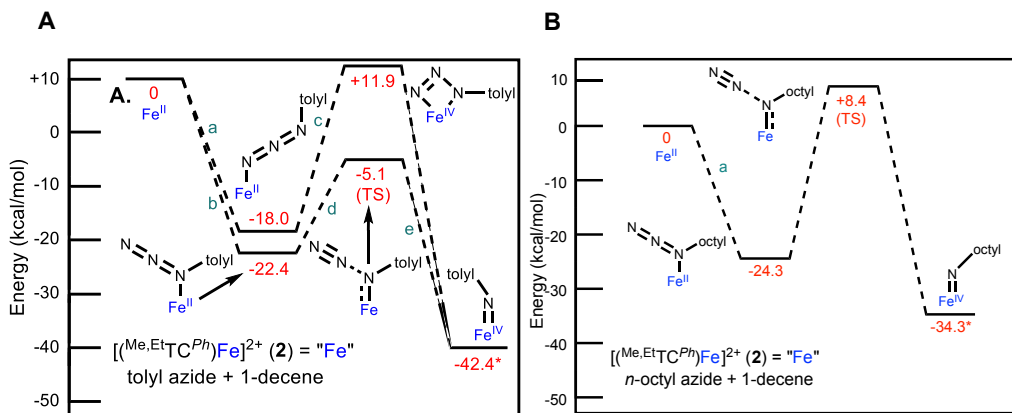


Figure 5.2. Energy diagram for the formation of imide from 2. **A.** Imide formation from 2 and *p*-tolyl azide. **B.** Imide formation from 2 and *n*-octyl azide.

Theoretical studies for the formation of aziridine from imide –

Step B

While a metal imide is generally thought to be a key intermediate in $C_2 + N_1$ aziridination with organic azides, the individual steps that occur to form the aziridine are less well-documented. The two leading candidates are a concerted reaction that goes through a box intermediate and radical pathway that goes through a pair of single electron transfers. While the research is limited, Ghosh and Gallo groups have supported radical pathways for the Co porphyrin and Ru porphyrin system respectively for aziridination.⁷²⁻⁷³ We have evaluated the two distinct pathways for the three combinations of azide and alkene that form aziridines with our catalysts from theoretical and experimental perspective.

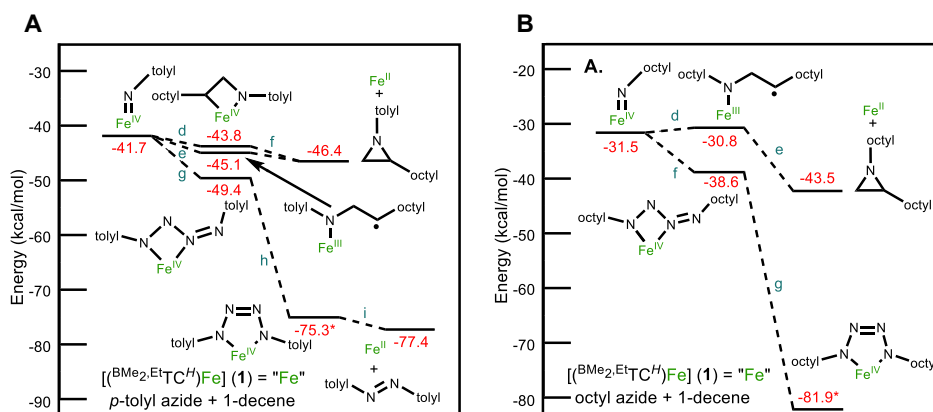


Figure 5.3. Energy diagram for the formation of aziridine from imide of catalyst 1. **A.** Reaction from *p*-tolyl imide of 1 to aziridine. **B.** Reaction from *n*-octyl imide of 1 to aziridine.

The first theoretical test reaction was between the *p*-tolyl imide of **1** and 1-decene (Figure 5.3A). This combination was chosen because we have previously reported that this permutation of azide and alkene yielded the expected aziridine, 2-octyl-1-(*p*-tolyl)aziridine, in 95% yield.^{43e} The formation of aziridine can proceed through two intermediates that are close in energy, a box intermediate and an open-chain radical intermediate. The box intermediate has two possible regioisomers depending on the position of alkyl chain. But in this case, only the lower energy version is shown where the alkyl chain is opposite of the nitrogen. From this intermediate, a reductive elimination would give the iron(II) catalyst and the resulting aziridine. This pathway would retain stereochemistry of the starting alkene. Alternatively, the radical intermediate is just over 1 kcal/mol lower in energy. The spin density map for this intermediate is more complex. A β electron is on the carbon to atoms removed from the nitrogen and the iron has three α electrons. This implies that the iron has been reduced by one electron and the aziridine is formed by a second one electron reduction. Since a radical intermediate is formed, the species could lose the starting stereochemistry if the radical “snap-back” reaction is not fast enough. Notably, previous DFT studies with organic azides have only forecast the radical mechanism and not a potential concerted type mechanism.⁷²⁻⁷³ Overall, the energy difference is too small to ascertain solely based on calculations which is the preferred mechanism.

Since very few studies have incorporated alkyl azides for aziridination and, to our knowledge, no calculations on mechanism have been reported, we were particularly interested in the fully alkyl case. DFT calculation showed that there was only one stable intermediate, the radical case, for the addition of alkene to the imide (Figure 5.3B). The energy for this intermediate is less than 1 kcal/mol above the imide species. Notably, the spin density map for this reaction is distinct from the aryl azide version. In this case, one α electron reside on the second carbon and one α electron on the iron. The iron center has only one unpaired electron whereas in the previous example it had three unpaired electrons. As before, this would suggest that stereochemistry could be lost due to the diradical intermediate. Finally, the higher energy intermediate leads to a larger energy drop to the final aziridine product.

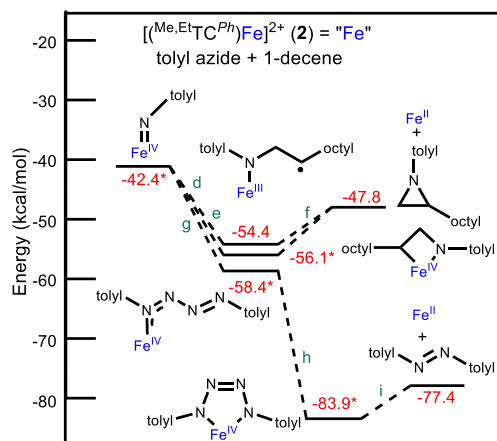


Figure 5.4. Energy diagram for the formation of aziridine from *p*-tolyl imide of 2.

The aziridination formation from the first generation system follows a different trajectory than the second generation catalyst (Figure 5.4). In this case, the same two intermediates are found, but the box intermediate is lower in energy than the open-chain radical intermediate. Furthermore, the box intermediate is an $S = 0$ spin state which is the same spin state as the iron imide intermediate. This path suggests that the stereochemistry of the starting alkene would be retained for the first generation system. The energy difference is small enough that the both possibilities cannot be ruled out, although the higher energy and spin transition disfavor the radical mechanism. The spin density map is similar to the result with *p*-tolyl azide and the second generation system. A final note is that the energy of the released aziridine plus catalyst is considerably higher than the intermediate. This result is due to the different resting states of the catalysts. Unlike **1**, the first generation system has a six coordinate resting state.¹³ Thus, it is likely that the aziridine is only released when an additional ligand, such as an azide or alkene, binds in a *trans* position to the aziridine. And in fact, the energy for azide binding to catalyst is considerably greater for **2** than **1**.

Scheme 5.2 General reaction scheme.

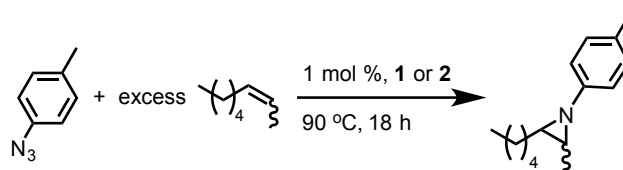
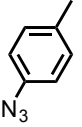
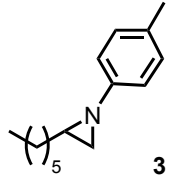
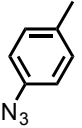
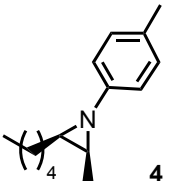
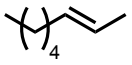
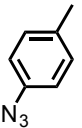
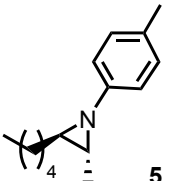
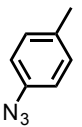
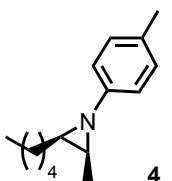
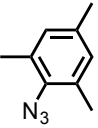
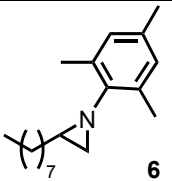


Table 5.1. Aziridination reactions with 1 and 2.

Entry	Alkene	Azide	Catalyst	Aziridine	Yield
1			1		91%
2			1		4: 67% 5: 28%
3			1		4: 12% 5: 58%
4			2		4: 24% 5: 0% 4: 44% ^a 5: 7% ^a
5			1		45% 44% ^b

a = reaction run over 6 days; b = reaction run with 5 equivalent of alkene

To corroborate the detailed DFT studies, we ran a series of reactions that yielded distinct stereoisomers. A general reaction is shown in Scheme 5.2. Depending on the concerted box intermediate or open-chain radical intermediate mechanism of the aziridination, we would expect the stereochemistry to be fully retained or partially (or even fully) lost, respectively. Test reactions included a series of octene derivatives, including 1-octene, *cis*-2-octene and *trans*-2-octene with both catalysts **1** and **2**. To our knowledge, no one has experimentally confirmed these mechanisms extensively through product distribution with organic azides and *cis* and *trans* alkenes.⁷⁰

Initial testing focused on reactions of **1** with the family of octenes: 1-octene, *cis*-2-octene, and *trans*-2-octene. A catalytic reaction of neat 1-octene, *p*-tolyl azide and 1% loading of **1** (versus azide) yielded the expected aziridine, 2-hexyl-1-(*p*-tolyl)aziridine (**3**), in 91% isolated yields after purification with column chromatography (Table 5.1, Entry 1). This high yield for primary alkene is consistent with our previous research.⁷¹

The reaction of neat *cis*-2-octene, *p*-tolyl azide and 1% **1** as catalyst yielded two recoverable products, which were only able to be separated by careful gradient elution of ethyl acetate and hexanes over silica gel. ¹H and ¹³C NMR showed only modest differences between the two species with the primary distinctions between 1.5-2.2 ppm in the ¹H NMR (See NMR in experimental). COSY and HSQC confirmed that the two peaks for the major product at 2.03 and

2.16 ppm in the ^1H NMR were the expected single protons off the aziridine ring (See NMR in experimental). In a similar manner, the minor product's peaks at 1.91 and 2.15 correspond to the protons on an aziridine ring, which would be the alternate stereoisomer. To distinguish between the *syn* and *anti* aziridines, we employed the homonuclear decoupling NMR experiment to measure the coupling for the two protons on the aziridine ring versus each other. The major product showed coupling constants of $J = 6.6$ and 6.5 Hz, which the minor product showed coupling constants of $J = 2.3$ and 2.0 Hz (See NMR in experimental). The larger coupling constants are consistent with a *syn* aziridines, while the smaller values are consistent with an *anti* stereochemistry.⁷⁶ We thus assigned the major product as *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine (**4**) and the minor product as *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine (**5**). The isolated yields for **4** and **5** were 67% and 28%, respectively which gives a total yield of 95% (Table 1, Entry 2) and a diastomeric ratio (d.r.) of 2.4:1.

The reaction of neat *trans*-2-octene, *p*-tolyl azide and 1% **1** as catalyst yielded the same two products, albeit in lower yield. In this case, **4** was formed in 12% yield, while **5** was formed in 58% yield, giving a total yield of 70% (Table 1, Entry 3) with a d.r. of 4.8:1.

In both cases, the expected diastereomer was the major product, but a considerable amount of the opposite diastereomer was produced. Since the stereochemistry would be retained with a box intermediate, these results

corroborate with the calculations that show the reaction is proceeding through a non-concerted radical mechanism. As expected for this mechanism, the *trans* case leads to higher retention of stereochemistry since there is less steric repulsion during the radical intermediate.

Since the DFT calculations showed a different intermediate for the first generation catalyst, we tested this reaction with *cis*-2-octene, *p*-tolyl azide and 1% of **2** as catalyst. After 18 hours, which was the complete reaction time for catalyst **1**, the reaction was not complete (by following consumption of organic azide), but only one aziridine product was detected. Aziridine **4** was isolated in 24% yield showing complete retention of stereochemistry (Table 1, Entry 4). A second reaction was run for six days to ensure that all organic azide reacted. In this case, both **4** and **5** were produced in 44% and 7% yields, respectively (d.r. ratio of 6.3:1).

This result is a stark contrast to the reaction with catalyst **1**. Given that some background reaction will occur between the azide and alkene without catalyst and that this would lead to a mixture of *syn* and *anti* products, it seems feasible that the catalysis is retaining stereochemistry by proceeding through a concerted mechanism as shown in the calculations. The formation of both stereoisomers was also observed in the control reactions performed with *cis* and *trans* octene. Of course, it is not possible to rule out a radical mechanism for **2**, which could have a faster ring closing final step than **1**. Regrettably, test

reactions with *trans*-2-octene did not yield sufficient aziridine for analysis of products. Since **2** is a less reactive catalyst than **1**, this is not surprising. Overall, the combination of DFT and experimental results suggest that the structurally similar catalysts are proceeding through disparate mechanisms of aziridination.

Isolation of the addition products with [(^BMe₂,EtTC^H)Fe] and organic azides – Step C

In order to isolate the reactive imide intermediate catalyst **1** was reacted with *p*-tolyl azide at room temperature. The immediate effervescence and color change from light yellow to blue and to dark yellow indicated a reaction was occurring. The crystal structure (Figure 5.5) revealed it to be the iron tetrazene, **7**, similar to the one isolated with the first generation catalyst.⁴⁴

This product suggested the formation of the reactive imide intermediate, which then reacted with a second equivalent of *p*-tolyl azide in [2+3] fashion to form the tetrazene. DFT calculations on the first generation systems, *p*-tolyl imide on **1** (Figure 5.3A) showed that the energy for the corresponding tetrazene is lower than the imide by 33.6 kcal/mol. This pathway then continues to form diazene which was seen as a byproduct experimentally. On the similar lines, theoretical calculation on the system with *n*-octyl imide on **1** (Figure 5.3B) showed the energy for the tetrazene lower by 50.4 kcal/mol than the imide.

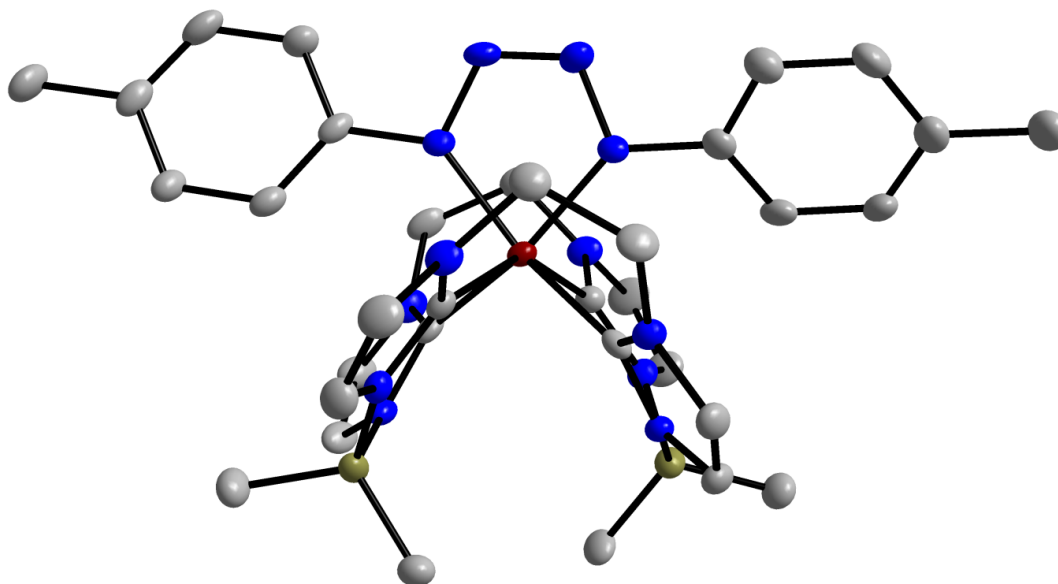


Figure 5.5. Crystal structure of tetrazene $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Fe}((p\text{-tolyl})\text{N}_4(p\text{-tolyl}))]$, 7. The gray, blue, olive, and red ellipsoids (50% probability) represent carbon, nitrogen, boron, and iron atoms respectively. Hydrogen atoms are omitted for clarity.

In case of second generation system, *p*-tolyl imide on **2**, the tetrazene formation was found to be lower by 41.5 kcal/mol than the respective imide (Figure 5.4). Similar to the second generation aryl system, this pathway continued to the formation of diazene as well which is uphill in energy due to lower energy of tetrazene.

From these results, we deduced that there is a competition reaction occurring after the formation of imide to react either with alkene to form the aziridine or with azide to form the tetrazene. To drive the reaction to aziridine excess alkene is needed in the reaction. Therefore, these systems need excess alkene to form aziridine over tetrazene. But the reason as to why the aziridine is formed, tetrazene being the thermodynamically favored product, is small energy difference between the transition states.

In order to hinder the approach of second equivalent of azide we tried the reaction with bulky mesityl azide and catalyst **1**. Unfortunately, we were not able to isolate the imide in this case due to the resulting complex degrading to the bridging nitride complex, **8** (Figure 5.6). But it is important to note that tetrazene formation is not observed with mesityl azide. Therefore, the hypothesis for the required overload of alkene is tested by the reaction of mesityl azide with excess and the five equivalents of 1-decene. It was observed that the yield of resulting aziridine, **6**, is almost the same for both the conditions although less than that of *p*-tolyl azide (Table 5.1, entry 5).

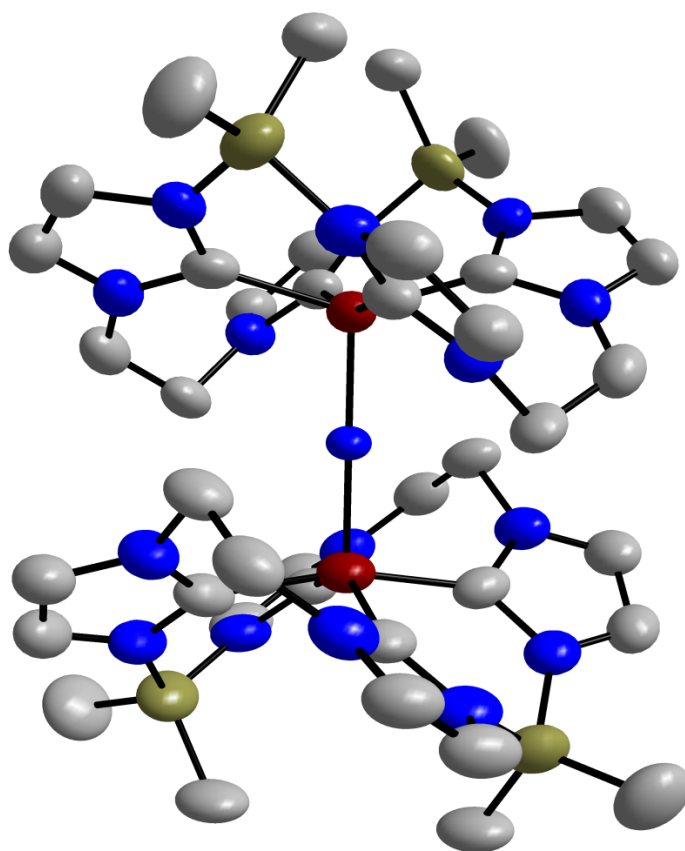


Figure 5.6. Crystal structure of bridging nitride, **8**. The gray, blue, olive, and red ellipsoids (30% probability) represent carbon, nitrogen, boron, and iron atoms respectively. Hydrogen atoms are omitted for clarity.

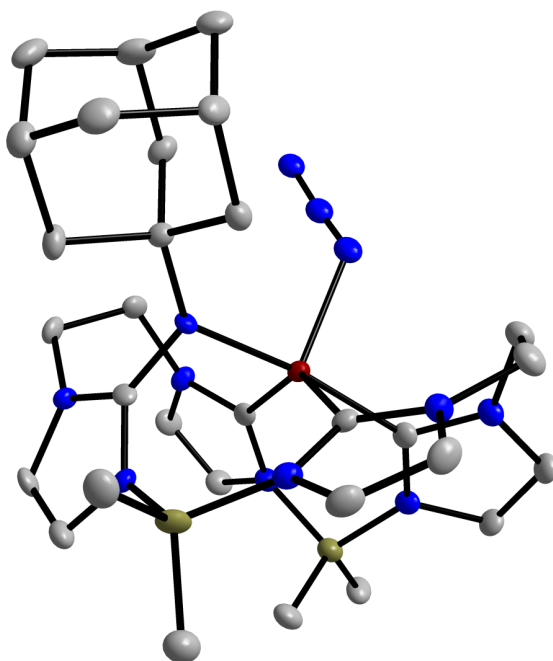


Figure 5.7. Crystal structure of inserted nitrene product with adamantyl azide. The gray, blue, olive, and red ellipsoids (50% probability) represent C, N, B, and Fe atoms respectively. Hydrogen atoms are omitted for clarity.

Since the catalyst **1** reacts with alkyl reagents, we tried the reaction with another bulky adamantyl azide. In this case, an interesting addition product, **9**, was formed as illustrated by SCXRD, where the nitrene was inserted between iron and one of the carbene bonds (Figure 5.7).

Finally, a reaction was tried with **1** and *n*-octyl azide to isolate the intermediate in the fully alkyl aziridine synthesis. The catalyst formed metallotetrazene [$(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}((n\text{-octyl})\text{N}_4(n\text{-octyl}))$], **10**, as shown in Figure 5.8.

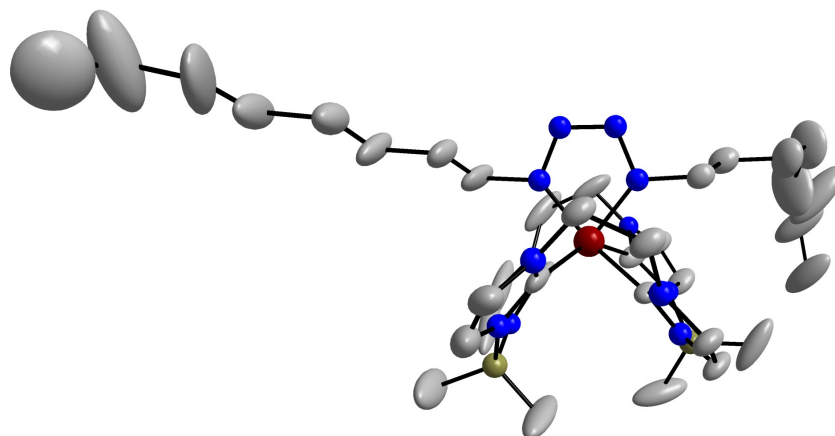


Figure 5.8. Crystal structure of $[(^{\text{BMe}_2, \text{EtTC}^{\text{H}}})\text{Fe}((n\text{-octyl})\text{N}_4(n\text{-octyl}))]$, **10**. The gray, blue, olive, and red ellipsoids (30% probability) represent carbon, nitrogen, boron, and iron atoms respectively. Hydrogen atoms are omitted for clarity.

Conclusion

We studied the mechanism for catalytic aziridination by first and second generation iron catalysts using DFT calculations and experiments. DFT calculations showed that the imide is the intermediate in all the processes with aryl and alkyl azide with alkene but the first generation catalyst does not activate alkyl azides due to a very high energy gap between the transition states. Experimental evidence suggests the radical intermediate to form aziridine from the imide in case of second generation catalyst but the possibility of either box-

type or radical intermediate in case of first generation catalyst. These results are supported by the DFT calculations as well. Finally the metallotetrazene is isolated in all the three cases, which is formed from the competition reaction between azide and alkene with the imide. Therefore, the formation of tetrazene should be eliminated to improve the catalytic system.

Experimental

All reactions were performed under a dry nitrogen atmosphere with the use of either a dry box or standard Schlenk techniques. 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 O₂ prior to use. Benzene-*d*₆, and chloroform-*d* were degassed by three freeze-pump-thaw cycles prior to drying over activated molecular sieves. These NMR solvents were then stored under N₂ in a glovebox. All other reagents were purchased from commercial vendors and used without purification. ¹H, ¹³C 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 ¹³C NMR chemical shifts were referenced to the residual solvent. COSY, HSQC, and HOMOCOP experiments were performed on a Varian VNMRS 600 MHz narrow-bore 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 ethyl acetate. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance. UV-vis measurements were taken inside a dry glovebox on an Ocean Optics USB4000 UV-vis system with 1 cm path length quartz crystal cell. Carbon, hydrogen, and nitrogen analyses were obtained from Atlantic Microlab, Norcross, GA for metal tetrazene complexes.

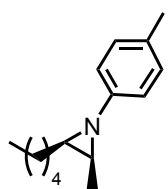
General Catalytic Reaction.

$[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}]$, (**1**) was added to a 20 mL vial followed by the addition of the alkene. The reaction mixture was heated and stirred for 10 min. The *p*-tolyl azide was then added to the reaction and allowed to stir at 90°C. Once azide was no longer present after 18 h (as determined by TLC) the mixture was removed from heat and the products were purified by column chromatography on silica gel using a gradient elution of a mixture of ethyl acetate and hexanes.

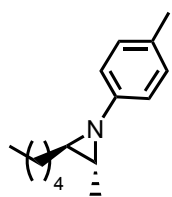
Synthesis of 2-hexyl-1-(*p*-tolyl)aziridine, 3. 1% catalyst **1** loading: *p*-tolyl azide (0.154g, 1.157 mmol), 1-octene (3.602g, 31.37 mmol), and **1** (0.005 g, 0.011 mmol) were used in the General Catalytic Reaction described above yielding 0.230 g, 91% of 2-hexyl-1-(*p*-tolyl)aziridine, **6**. ^1H NMR (CDCl_3 , 499.74 MHz):

7.02 (d, $J = 8.5\text{Hz}$, 2H), 6.89 (d, $J = 8.5\text{Hz}$, 2H), 2.27 (s, 3H), 2.04 (m, 3H), 1.59 (m, 4H), 1.33 (m, 6H), 0.91 (t, $J = 7\text{Hz}$, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 152.79, 131.49, 129.54, 120.68, 40.37, 34.22, 33.34, 32.01, 29.37, 27.84, 22.77, 20.82, 14.24. IR: 2915, 2848, 1613, 1509, 1472, 1462, 1405, 1293, 1197, 1173, 1111, 895, 820, 730, 719, 678 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 218.19088 (found); $[\text{C}_{15}\text{H}_{24}\text{N}]^+$ 218.19033 (calcd).

Synthesis of *syn*- and *anti*- 2-methyl-3-hexyl-1-(*p*-tolyl)aziridine. 1% catalyst **1 loading:** *p*-tolyl azide (0.142 g, 1.066 mmol), *cis*-2-octene (3.602g, 32.10 mmol), and **1** (0.005 g, 0.011 mmol) were used in the General Catalytic Reaction described above yielding 0.155 g, 67% of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**, and 0.0673 g, 29% and *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.



***syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.** ^1H NMR (CDCl_3 , 499.74 MHz): 7.01 (d, $J = 8.5\text{Hz}$, 2H), 6.88 (d, $J = 8.5\text{Hz}$, 2H), 2.27 (s, 3H), 2.16 (p, $J = 6.5\text{Hz}$, 1H), 2.03 (q, $J = 6.5\text{Hz}$, 1H), 1.61 (m, 2H), 1.56 (m, 2H), 1.40 (m, 4H), 1.35 (d, $J = 5.5\text{Hz}$, 3H), 0.94 (t, $J = 7.0\text{Hz}$, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 153.36, 131.34, 129.50, 120.16, 44.79, 39.57, 32.03, 28.46, 27.89, 22.82, 20.82, 14.22, 13.99. IR: 2915, 2848, 1613, 1509, 1472, 1462, 1425, 1387, 1284, 1220, 1174, 1147, 1109, 946, 821, 730, 719, 688 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 218.19012 (found); $[\text{C}_{15}\text{H}_{24}\text{N}]^+$ 218.19033 (calcd).



***anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, 5.** ^1H NMR (CDCl_3 , 499.74 MHz): 7.02 (d, $J = 8.0\text{Hz}$, 2H), 6.89 (d, $J = 8.0\text{Hz}$, 2H), 2.28 (s, 3H), 2.15 (m, 1H), 1.91 (m, 1H), 1.54 (m, 2H), 1.34 (m, 6H), 1.10 (d, $J = 5.0\text{Hz}$, 3H), 0.90 (t, $J = 7.0\text{ Hz}$, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 147.80, 130.97, 129.39, 121.06, 46.13, 39.89, 31.91, 27.60, 22.80, 20.83, 15.44, 14.19. IR: 2915, 2848, 1613, 1508, 1472, 1462, 1379, 1294, 1194, 1173, 1111, 821, 730, 719 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 218.19055 (found); $[\text{C}_{15}\text{H}_{24}\text{N}]^+$ 218.19033 (calcd).

Synthesis of 4 and 5 using catalyst 1. 1% catalyst 1 loading: *p*-tolyl azide (0.186 g, 1.397 mmol), *trans*-2-octene (4.704g, 41.92 mmol), and **1** (0.006 g, 0.014 mmol) were used in the General Catalytic Reaction described above yielding 0.035 g, 12% of compound **4** and 0.176 g, 58% compound **5**.

Synthesis of 4 and 5 using catalyst 2. 1% catalyst 2 loading: *p*-tolyl azide (0.108 g, 0.809 mmol), *cis*-2-octene (3.904 g, 34.79 mmol), and **2** (0.011 g, 0.008 mmol) were used in the General Catalytic Reaction described above yielding 0.077 g, 44% of compound **4** and 0.013 g, 7% compound **5**.

Synthesis of 2-hexyl-1-mesitylaziridine, 6. 1% catalyst 1 loading and excess 1-decene: mesityl azide (0.109 g, 0.676 mmol), 1-decene (3.602 g, 26.18 mmol), and **1** (0.003 g, 0.007 mmol) were used in the General Catalytic Reaction described above yielding 0.0835 g, 45% of 2-hexyl-1-mesitylaziridine, **7**. 1% catalyst 1 loading and five equivalents of 1-decene: mesityl azide (0.197 g, 1.222

mmol), 1-decene (0.858 g, 6.117 mmol), and **1** (0.006 g, 0.012 mmol) were used in the General Catalytic Reaction described above yielding 0.148 g, 44% of 2-hexyl-1-mesitylaziridine, **7**. ^1H NMR (CDCl_3 , 499.74 MHz): 6.75 (s, 2H), 2.31 (s, 6H), 2.21 (s, 3H), 2.10 (m, 1H), 1.43 (m, 2H), 1.29 (m, 12H), 0.89 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): 149.02, 130.82, 129.69, 129.07, 44.28, 37.04, 32.85, 32.02, 29.73, 29.71, 29.42, 26.72, 22.82, 20.55, 19.24, 14.25. IR: 2916, 2848, 1689, 1472, 1462, 1376, 1303, 1268, 1205, 1015, 908, 853, 731, 719 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 274.25265 (found); $[\text{C}_{15}\text{H}_{24}\text{N}]^+$ 274.25293 (calcd).

Synthesis of 4 and 5 using catalyst 2. 1% catalyst **2** loading: *p*-tolyl azide (0.155 g, 1.164 mmol), *trans*-2-octene (4.621 g, 41.18 mmol), and **2** (0.016 g, 0.012 mmol) were used in the General Catalytic Reaction described above. No aziridine was formed according to the ^1H , ^{13}C NMR and DART MS analysis.

Control Reactions. Control reaction following the method of the General Catalytic Reaction was attempted but without **1** or **2**. The reaction with *p*-tolyl azide (0.160g, 1.202 mmol) and *cis*-2-octene (4.500 g, 40.10 mmol) following the General Catalytic Reaction described above yielding 0.871g, 33% *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**, and 0.025g, 9% *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**. The reaction with *p*-tolyl azide (0.166g, 1.247 mmol) and *trans*-2-octene (4.300 g, 38.32 mmol) following the General Catalytic Reaction

described above yielding 0.033g, 12% *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**, and 0.078g, 29% *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.

Synthesis of $[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}((p\text{-tolyl})\text{N}_4(p\text{-tolyl}))]$, **7.**

$[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}]$ (**1**) (0.180 g, 0.392 mmol) was added to tetrahydrofuran (10 mL) in a 20 mL vial and stirred for 10 min. *p*-tolyl azide (1.129 g, 10.54 mmol) was pipetted in to the stirring $[(^{\text{BMe}_2, \text{Et}}\text{TC}^H)\text{Fe}]$ mixture. The reaction mixture changes color from yellow to blue and then to dark yellow. The reaction mixture was allowed to stir for 1 h. All volatiles were removed under reduced pressure. Benzene (20 mL) was added to the crude solid and stirred for 1 h. The slurry was then filtered over celite and the collected filtrate was concentrated to 15 mL. The pure product was crystallized via vapor diffusion of pentane into the benzene solution and the yellow crystals were collected after 2 days (0.038 g, 14% yield). The product can also be purified from a short silica gel pipette column using benzene or THF. ^1H NMR (CD_3CN , 499.74 MHz): δ 7.39 (d, $J = 8\text{Hz}$, 4H), 6.94 (s, 4H), 6.90 (d, $J = 8\text{Hz}$, 4H), 6.78 (s, 4H), 3.59 (dd, $J_1 = 15\text{Hz}$, $J_2 = 6\text{Hz}$, 4H), 2.15 (s, 6H), 2.08 (dd, $J_1 = 15\text{Hz}$, $J_2 = 6\text{Hz}$, 4H), 0.16 (s, 6H), 0.53 (s, 6H). ^{13}C NMR (CD_3CN , 125.66 MHz): δ 168.20, 156.61, 135.94, 129.79, 125.68, 124.73, 124.50, 68.26, 45.92, 26.22, 20.94. UV-vis (THF) λ_{max} , nm (ϵ): 439 (1090). IR: 3134, 2924, 1499, 1426, 1377, 1360, 1287, 1199, 1148, 1063, 1038, 956, 944, 820, 799, 706, 687.

Synthesis of bridging nitride, 8. $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ (**1**) (0.050 g, 0.109 mmol) was added to tetrahydrofuran (5 mL) in a 20 mL vial and stirred for 5 min. Mesityl azide (0.018 g, 0.109 mmol) was pipetted in to the stirring $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ mixture. The reaction mixture changes color from yellow to blue and then immediately to dark brown. Multiple crystallization techniques were tried to obtain single crystals. The dark blue product never produced good quality single crystals. Brown crystals were produced via vapor diffusion of pentane into the benzene extract of the above reaction mixture.

Synthesis of inserted nitrene with adamantyl azide, 9. $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ (**1**) (0.026 g, 0.055 mmol) was added to tetrahydrofuran (5 mL) in a 20 mL vial and stirred for 5 min. adamantyl azide (0.010 g, 0.055 mmol) was pipetted in to the stirring $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ mixture. The color of the reaction mixture changes from yellow to red. The reaction mixture was allowed to stir overnight. All volatiles were removed under reduced pressure. Benzene (5 mL) was added to the crude solid and stirred for 1 h. The slurry was then filtered over celite and bright red crystals were obtained from the collected filtrate by vapor diffusion of pentane into the benzene solution after 30 days.

Synthesis of $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}((n\text{-octyl})\text{N}_4(n\text{-octyl}))]$, 10. $[(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}]$ (**1**) (0.055 g, 0.120 mmol) was added to tetrahydrofuran (8 mL) in a 20 mL vial and stirred for 5 min. *n*-octyl azide (0.186 g, 1.200 mmol) was pipetted in to the

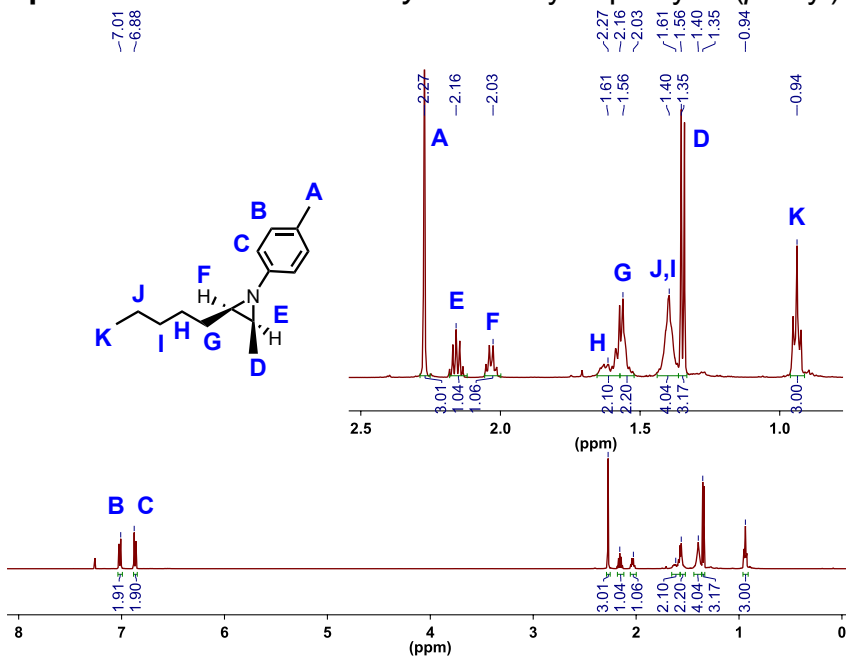
stirring [$(^{\text{BMe}_2\text{Et}}\text{TC}^{\text{H}})\text{Fe}$] mixture. The color of the reaction mixture changes from yellow to red. The reaction mixture was allowed to stir overnight. All volatiles were removed under reduced pressure. Benzene (5 mL) was added to the crude solid and stirred for 20 min. The slurry was then filtered over celite and crystals were obtained from the collected filtrate by vapor diffusion of pentane into the benzene solution after 3 days (0.75 g, 85%).

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 N_2 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 Lorentz 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 intrinsic phasing method and were refined using SHELXTL 5.0 software package.

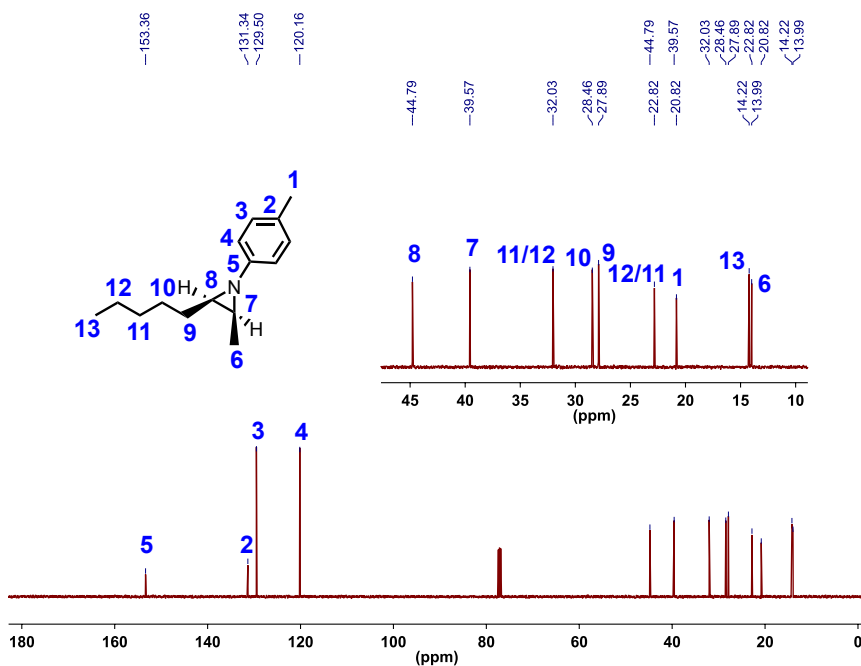
NMR of selected aziridines

NMRs of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.

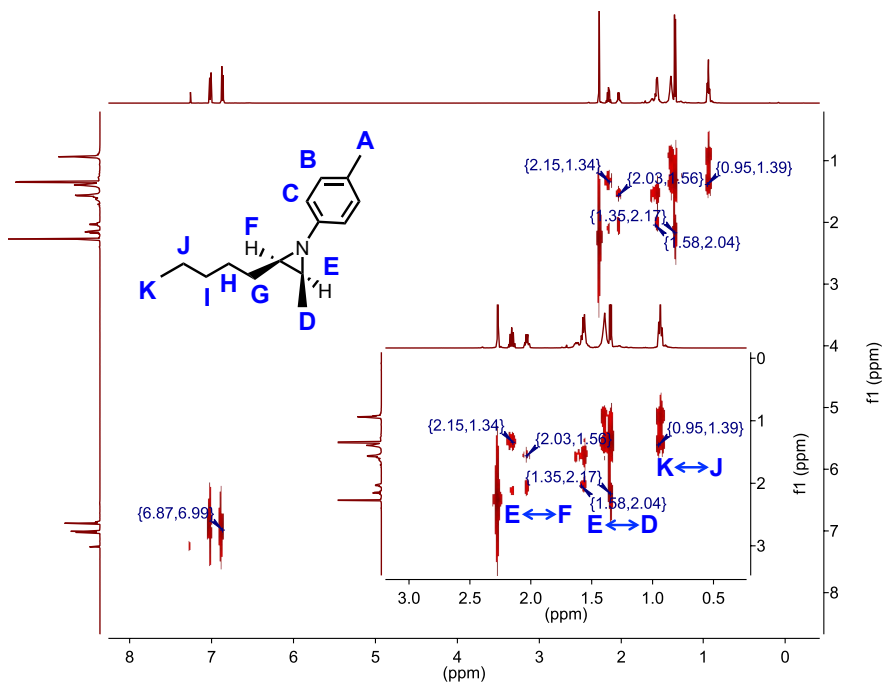
Spectrum 5.1. ^1H NMR of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.



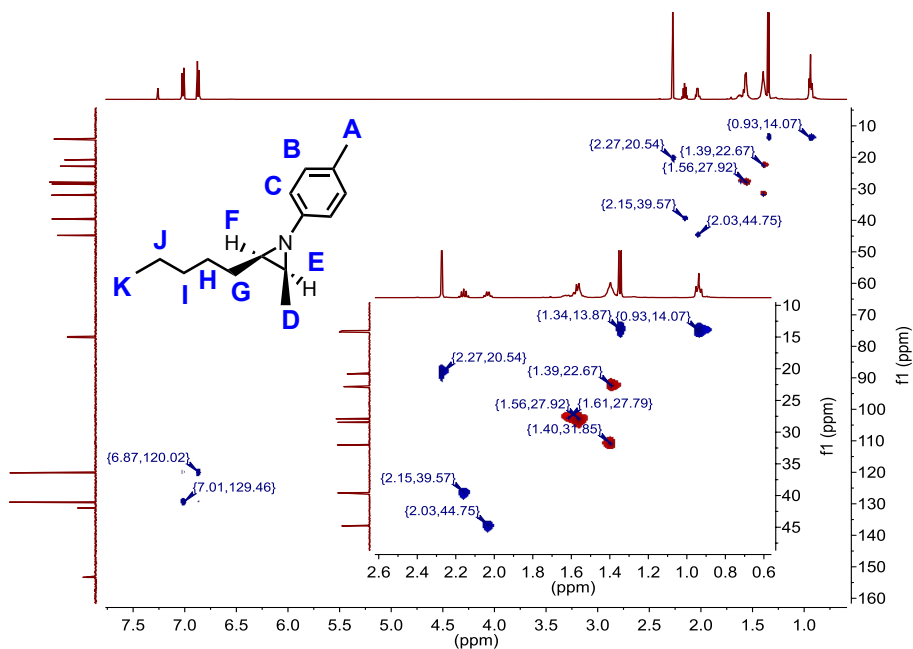
Spectrum 5.2. ^{13}C NMR of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.



Spectrum 5.3. COSY of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.

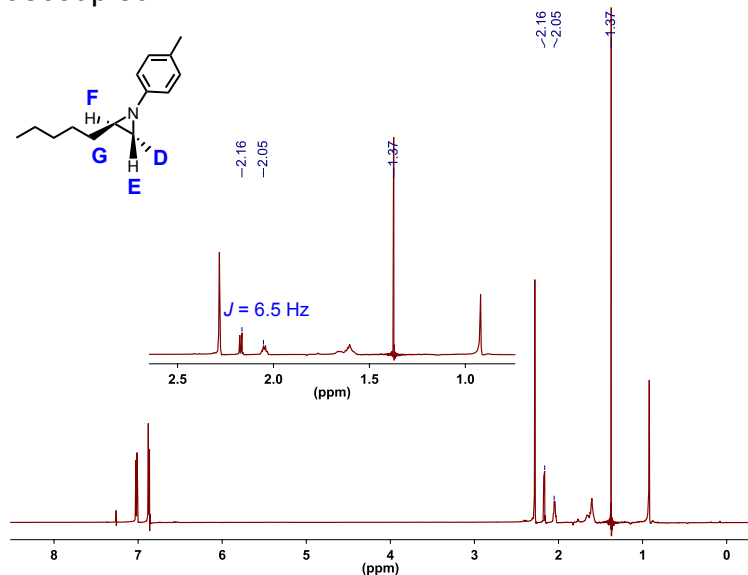


Spectrum 5.4. HSQC of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.



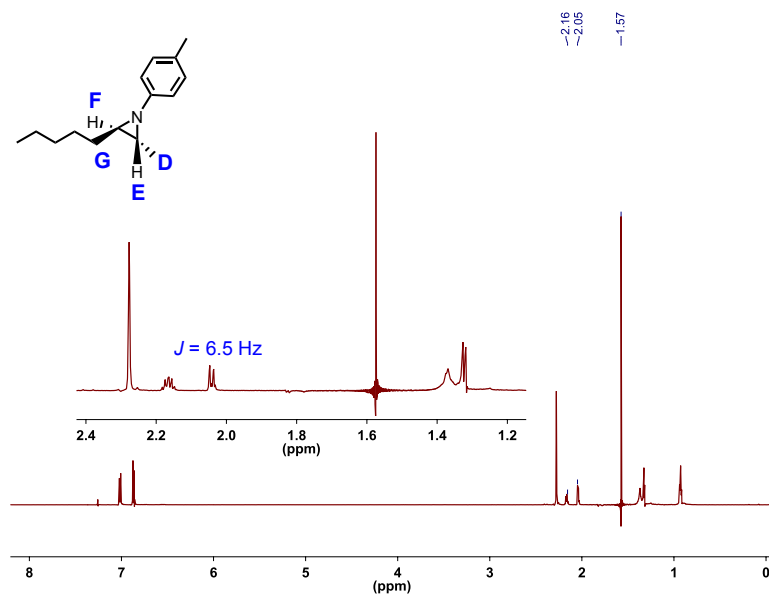
Spectrum 5.5. Homonuclear decoupling of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.

Signal for E proton (2.16 ppm) results into a doublet with $J = 6.6$ Hz due to the coupling with F proton solely as D set of protons 1.35 (d, $J = 5.5$ Hz, 3H) are decoupled.



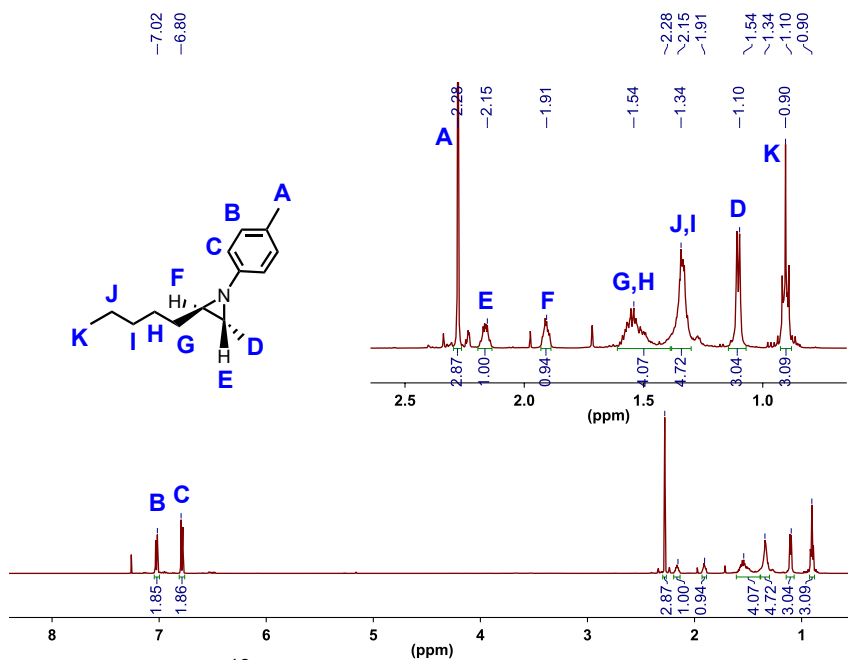
Spectrum 5.6. Homonuclear decoupling of *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **4**.

Signal for F proton (ppm) results into a doublet with $J = 6.5$ Hz due to coupling with E proton solely as G set of protons 1.56 (m, 2H) are decoupled.

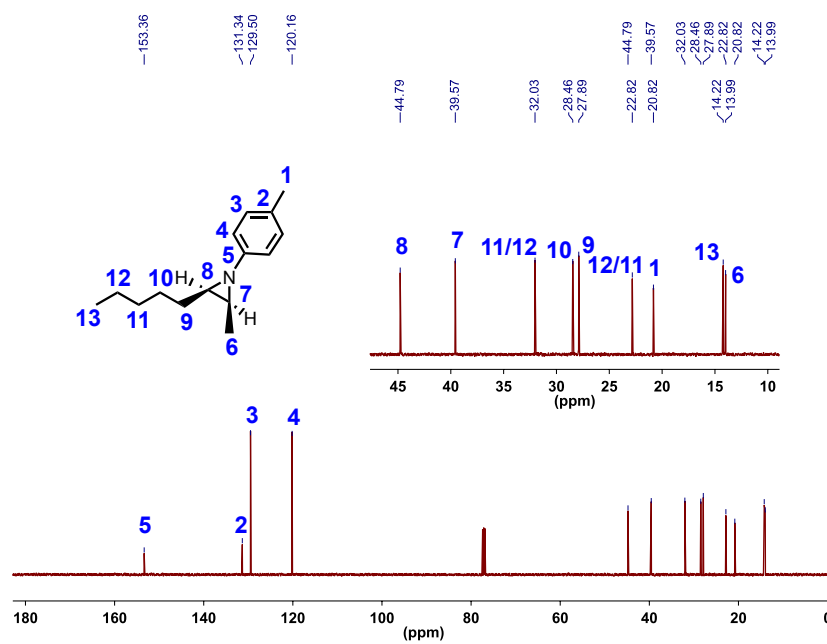


NMR of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, 5.

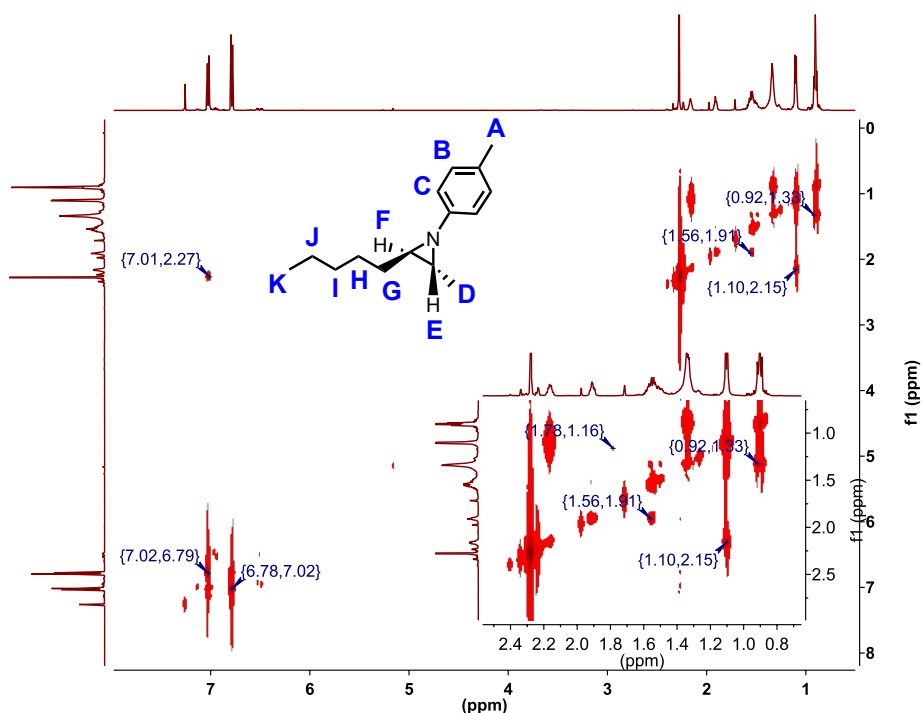
Spectrum 5.7. ^1H NMR of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, 5.



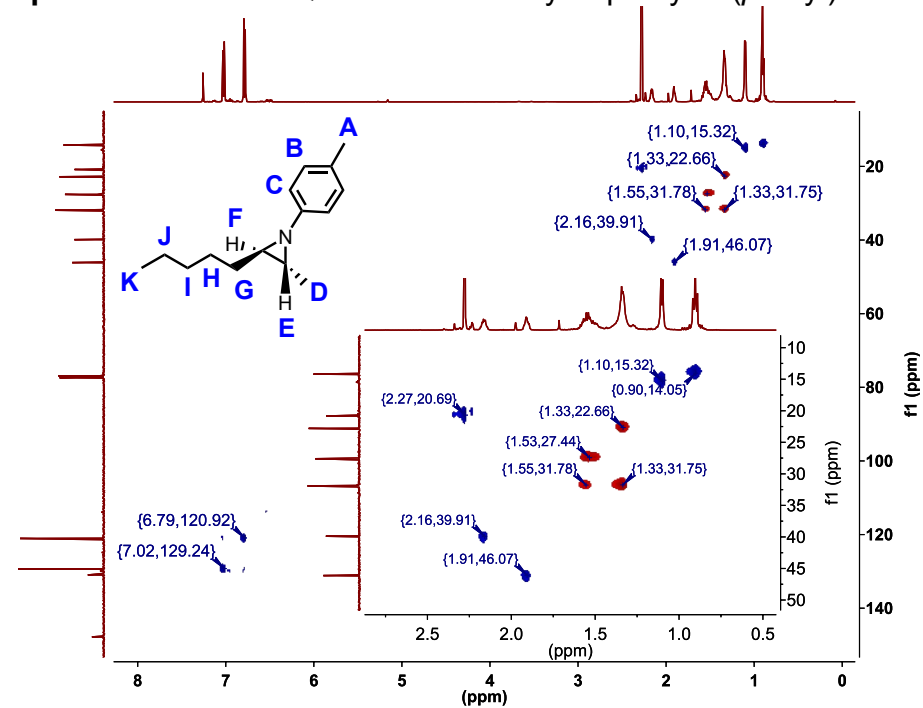
Spectrum 5.8. ^{13}C NMR of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, 5.



Spectrum 5.9. COSY of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.

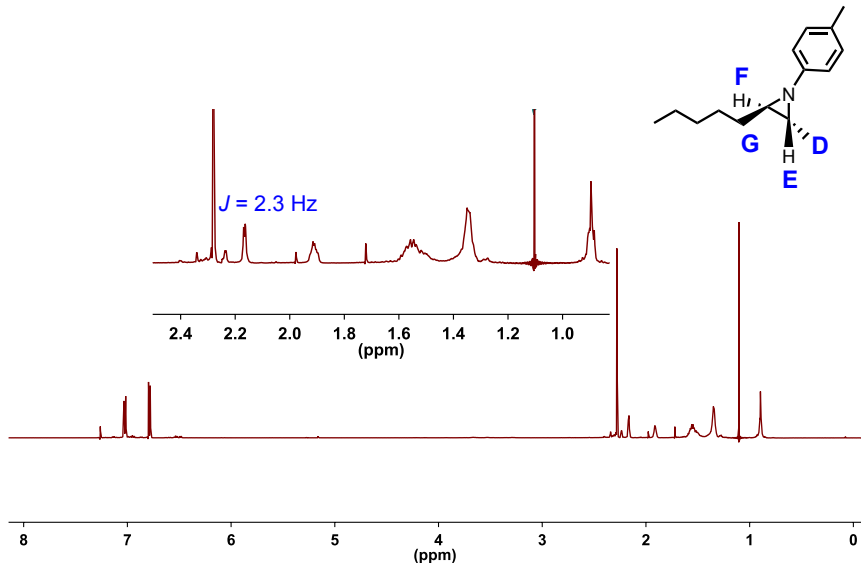


Spectrum 5.10. HSQC of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.



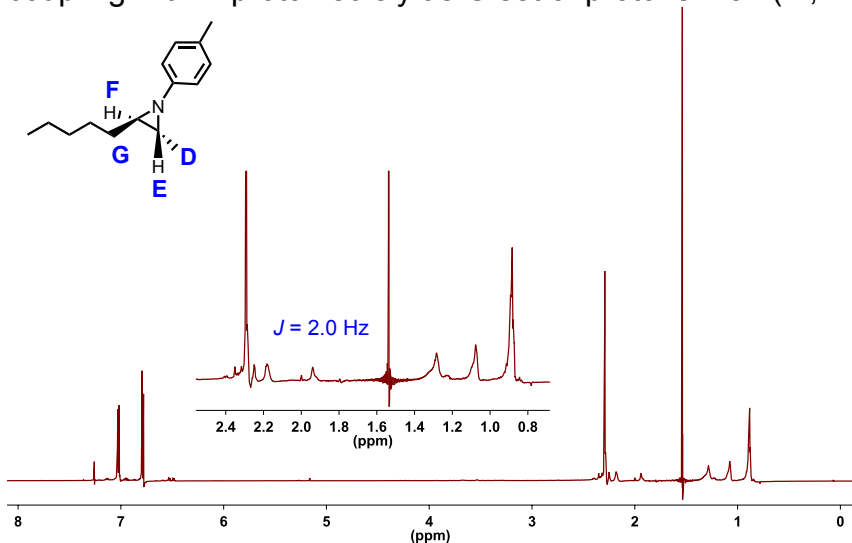
Spectrum 5.11. Homonuclear decoupling of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.

Signal for E proton (2.15 ppm) results into a doublet with $J = 2.3$ Hz due to the coupling with F proton solely as D set of protons 1.10 (d, $J = 5.0$ Hz, 3H) are decoupled.



Spectrum 5.12. Homonuclear decoupling of *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine, **5**.

Signal for F proton (1.91 ppm) results into a doublet with $J = 2.0$ Hz due to coupling with E proton solely as G set of protons 1.54 (m, 2H) are decoupled.



CHAPTER SIX
SYNTHESIS OF N-CARBAMATE PROTECTED AZIRIDINES
USING SECOND GENERATION IRON CATALYST

Abstract

Protection and deprotection of various functional groups is an integral part of organic synthesis. Carbamate protecting groups are commonly used for protection of amines. We synthesized *N*-carbamate aziridines with boc- (*t*-butoxycarbonyl), fmoc- (fluorenylmethyloxycarbonyl), and cbz- (carboxybenzyl or benzyloxycarbonyl) groups. The deprotection of these aziridines to form primary aziridines and nucleophilic ring opening reactions will be attempted. We isolated vinylic *N*-carbamate amines as side products from these reactions.

Introduction

Aziridines are key intermediates useful for establishing stereogenic centers containing nitrogen atoms.⁷⁷ Therefore, they are used in the synthesis of many natural products and pharmaceuticals such as Tamiflu.⁷⁷ Having *N*-protected aziridines is useful for making primary aziridines and functional group transformations such as aziridine to an amine^{56b, 78} or ring closing reaction.⁷⁹ *N*-protected aziridines are not new mainly due to the tosyl-derived nitrene sources such as iodoimine reagent (PhI=NTs, Ts = tosyl),⁸⁰ chloramine-T,⁸¹ or tosyl azide.^{55c, 82} The major drawback of using these reagents is that there is a possibility of aziridine ring degradation while deprotecting tosyl group due to the required harsh conditions.¹¹

The carbamate protecting group, consisting of boc-, fmoc-, and cbz-

derivatives, is a good alternative due to their orthogonal stability towards reagents and milder deprotection conditions compared to tosyl group. Boc-carbamates can be deprotected using trifluoroacetic acid at room temperature.⁸³ Fmoc-carbamates, on the other hand, can be deprotected using a weak base such as morpholine.⁸⁴ Finally, cbz- carbamates can be deprotected by catalytic hydrogenation.⁸⁵ Therefore, synthesis of the *N*-carbamate protected aziridines from variety of alkenes will be vital for a broader and desirable method. There are very few examples of *N*-boc aziridine syntheses from boc-azide by photolysis.⁸⁶ Fewer examples are reported with fmoc- and cbz- protected aziridines using corresponding azides. Recently, Yoon group reported photocatalytic synthesis of aziridines using azidoformates and aliphatic as well as conjugated alkenes in presence of Ru and Ir catalysts.⁸⁷ However their system is limited to only using 2,2,2-trichloroethyl azidoformate (TrocN₃).

In order to design a generalizable approach we performed aziridination with carbamate azides and aliphatic alkenes. Along with corresponding aziridines, the reaction produces various side-products that were characterized.

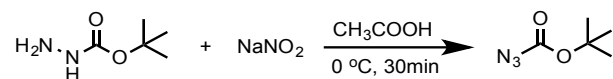
Results and discussion

The first step was to synthesize carbamate azides from the commercially available starting compounds. We synthesized boc- azide starting from *t*-butyl carbazate and sodium nitrite following a literature procedure (Scheme 6.1A).⁸⁸

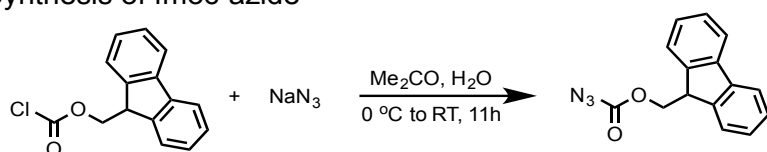
Fmoc- and cbz- azides were synthesized from 9-fluorenylmethyl chloroformate (Scheme 6.1B) and benzyl chloroformate (Scheme 6.1C) respectively.⁸⁹

Scheme 6.1. Syntheses of carbamate azides

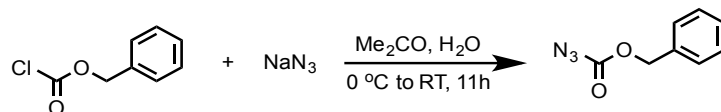
A. Synthesis of boc-azide



B. Synthesis of fmoc-azide



C. Synthesis of cbz-azide



Initially, cyclohexene and 1-decene were selected as alkenes to test the reactivity with strained and non-strained alkenes for catalytic aziridination with carbamate azides in presence of $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$ as a catalyst. The general reaction followed is depicted in Scheme 6.2.

Scheme 6.2. General synthesis scheme for *N*-carbamate aziridines.

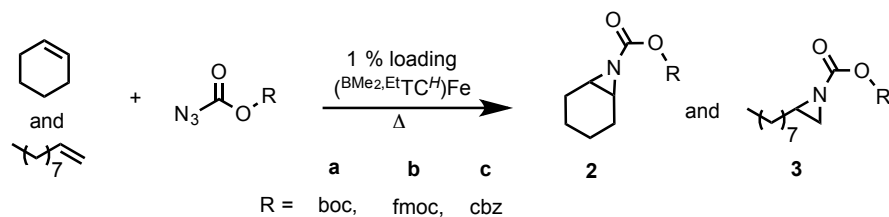
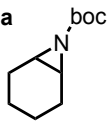
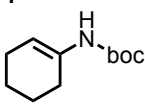
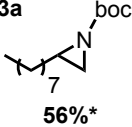
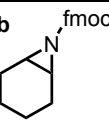
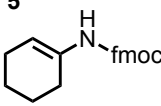
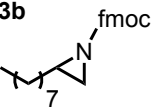
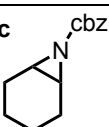


Table 6.1. Results of *N*-carbamate aziridination.

Entry	Alkene	Azide	Temp./ Time	Aziridine	Vinyllic amine
1		Boc-N ₃	80 °C/ 18h	2a  65%	4  9%
2		Boc-N ₃	90 °C/ 18h	3a  56%*	-
3		Fmoc-N ₃	80 °C/ 46h	2b  30%	5  13%
4		Fmoc-N ₃	90 °C/ 46h	3b  	-
5		Cbz-N ₃	80 °C/ 18h	2c  60%	-

* Aziridine is not completely pure.

The first attempted reaction was boc-azide and *neat* cyclohexene at 80 °C for 18h to yield the corresponding aziridine, *t*-butyl-7-azabicyclo[4.1.0]heptane-7-carboxylate (**2a**) in 65% yield (Table 6.1, entry 1). Unexpectedly, after working up the reaction two separate products were isolated with same mass detected by DART MS. With the help of ^1H and ^{13}C NMR, IR and single crystal XRD the other product was identified as *t*-butylcyclohex-1-en-1-ylcarbamate, **4**, (enamine) in 9% yield as shown in Figure 6.1A. The amine product is a solid likely due to the hydrogen bonding while resulting aziridine is a liquid.

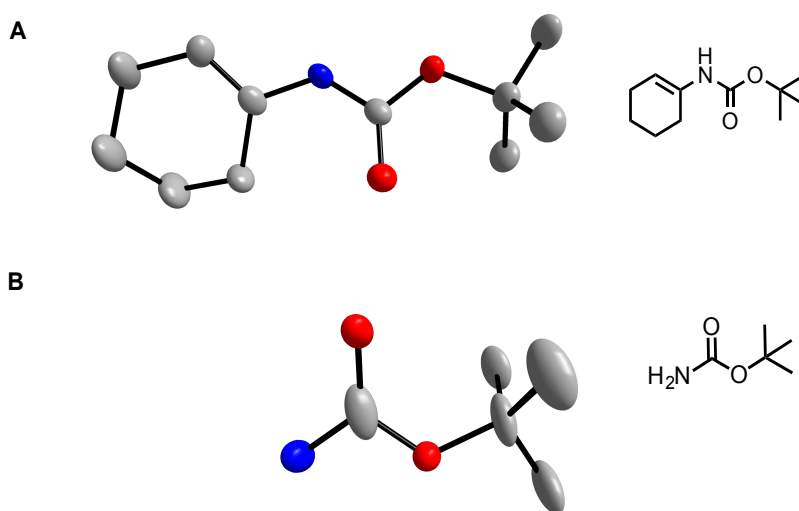


Figure 6.1. A) Crystal structure of *t*-butylcyclohex-1-en-1-ylcarbamate. B) Crystal structure of *t*-butyl carbamate. Gray, blue, and red ellipsoids (50% probability) represent carbon, nitrogen, and oxygen atoms respectively. Hydrogen atoms are omitted for clarity.

The presence of the enamine can be attributed to either ring opening of the aziridine or due to vinylic C-H bond activation. Kwart and Khan reported this side product formation during aziridination with cyclohexene and benzenesulfonyl azide in copper catalyzed system. Another side product is *t*-butylcarbamate as identified from crystal structure (Figure 6.1B).

The reaction with boc-azide and 1-decene at 90 °C in presence of **1** produced aziridine **3a** in 56% yield (Table 6.1, entry 2). Not surprisingly, the enamine product is not isolated from the same reaction due to the absence of ring strain. Unfortunately, after much effort this product was not purified completely.

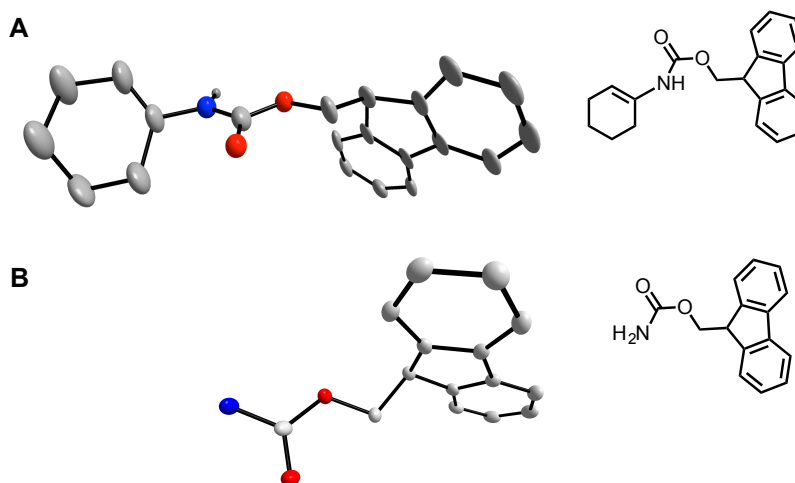


Figure 6.2. A) Crystal structure of (9*H*-fluoren-9-yl)methylcyclohex-1-en-1-ylcarbamate. B) Crystal structure of (9*H*-fluoren-9-yl)methyl carbamate. Gray, blue, and red ellipsoids (50% probability) represent C, N, and O atoms respectively. Hydrogen atoms are partially omitted for clarity.

The reaction of fmoc-azide with cyclohexene was heated for two days at 80 °C for the complete consumption of azide. After the reaction was complete a carefully performed column helped to isolate aziridine, (9*H*-fluoren-9-yl)methyl-7-azabicyclo[4.1.0]heptane-7-carboxylate, **2b**, in 30% yield (Table 6.1, entry 3). Similar to the reaction with boc-azide, (9*H*-fluoren-9-yl)methylcyclohex-1-en-1-ylcarbamate, enamine (**5**) (Figure 6.2 A) was isolated as a side product in 13% yield along with fmoc-amine (Figure 6.2 B). Both the side products being solid, single crystals were grown by slow evaporation of ethyl acetate to identify the compound (Figure 6.2).

The reaction of fmoc-azide and 1-decene was performed at 90 °C for two days which resulted in aziridine (**3b**) in 30% yield (Table 6.1, entry 4). As expected, the enamine is not isolated in this case as well.

Finally the reaction of cbz-azide with cyclohexene was attempted to form aziridine **2c** in 60% yield (Table 6.1, entry 5). The isolation of side products and the reaction with 1-decene is still under progress.

Conclusion

Carbamate groups are an attractive choice as protecting group for amines and aziridines due to their variability in stability under reaction conditions. Therefore, *N*-carbamate protected aziridines using boc-, fmoc-, and cbz- azides

and aliphatic alkenes were synthesized in moderate yield. Vinylic amines were separated as byproducts from the reaction with strained alkenes.

Experimental

All reactions were performed under a dry nitrogen atmosphere with the use of either a dry box or standard Schlenk techniques. 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 O₂ prior to use. Benzene-*d*₆, and chloroform-*d* were degassed by three freeze-pump-thaw cycles prior to drying over activated molecular sieves. These NMR solvents were then stored under N₂ in a glovebox. All other reagents were purchased from commercial vendors and used without further purification. ¹H, ¹³C 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 ¹³C 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 ethyl acetate or hexanes. Infrared spectra were collected on a Thermo Scientific Nicolet iS10 with a Smart iTR accessory for attenuated total reflectance.

General catalytic reaction

$[(^{\text{BMe}_2\text{Et}}\text{TC}^H)\text{Fe}]$, **1**, was added to a 20 mL vial followed by the addition of the alkene. The reaction mixture was heated and stirred for 10 min. The organic azide was then added to the reaction and allowed to stir at the designated temperature. Once organic azide was no longer present after 18 h (as determined by TLC) the mixture was removed from heat and the product was purified by column chromatography on silica gel using a gradient elution of a mixture of diethyl ether and pentane. The corresponding excess alkene can be recovered from the column as it comes out with pentane as eluent. The recovered alkene can be reused after removing the pentane.

Synthesis of *t*-butyl-7-azabicyclo[4.1.0]heptane-7-carboxylate, 2a: 1% catalyst loading: boc-azide (0.169 g, 1.181 mmol), cyclohexene (4.521 g, 55.04 mmol), and **3** (0.005 g, 0.012 mmol) were used in the General Catalytic Reaction described above yielding 0.150 g, 65%. ^1H NMR (CDCl_3 , 499.74 MHz): δ 2.54 (d, 2H), 1.90 (m, 2H), 1.76 (m, 2H), 1.43 (s, 9H), 1.39 (m, 2H), 1.21 (m, 2H). ^{13}C NMR (CDCl_3 , 125.66 MHz): δ 163.30, 80.48, 36.84, 27.94, 23.71, 19.83. DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 198.14890 (found); $[\text{C}_{11}\text{H}_{20}\text{NO}_2]^+$ 198.14886 (calcd).

Characterization of *t*-butylcyclohex-1-en-1-ylcarbamate, 4. From the above reaction, *t*-butylcyclohex-1-en-1-ylcarbamate was isolated yielding 0.020 g, 9%. ¹H NMR (CDCl₃, 499.74 MHz): δ 5.81 (s, 1H), 5.52 (s, 1H), 2.07 (m, 4H), 1.66 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H). ¹³C NMR (CDCl₃, 125.66 MHz): δ 153.00, 132.22, 109.28, 79.64, 28.33, 28.05, 23.85, 22.58, 22.10. IR: 3325, 2978, 2929, 2857, 1694, 1667, 1516, 1447, 1380, 1366, 1348, 1306, 1244, 1088, 1042, 1020, 974, 932, 916, 883, 858, 842, 806, 772, 749, 671 cm⁻¹. DART HR MS (*m/z*): [M+H]⁺ 198.14881 (found); [C₁₁H₂₀NO₂]⁺ 198.14886 (calcd).

Synthesis of *t*-butyl 2-octylaziridine-1-carboxylate, 3a: 1% catalyst loading: boc-azide (0.113 g, 0.789 mmol), 1-decene (3.785 g, 27.00 mmol), and **3** (0.004 g, 0.008 mmol) were used in the General Catalytic Reaction described above yielding 0.113 g, 56%. ¹H NMR (CDCl₃, 499.74 MHz): δ 1.55 (m, 1H), 1.44 (s, 9H), 1.35 (m, 2H), 1.26 (m, 12H), 0.86 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃, 125.66 MHz): δ 162.66, 80.75, 43.78, 38.21, 32.22, 31.63, 29.50, 29.21, 27.89, 26.90, 23.84, 22.62, 14.05. DART HR MS (*m/z*): [M+H]⁺ 256.22700 (found); [C₁₅H₃₀NO₂]⁺ 256.22711 (calcd).

Synthesis of (9*H*-fluoren-9-yl)methyl-7-azabicyclo[4.1.0]heptane-7-carboxylate, 2b: 1% catalyst loading: fmoc-azide (0.209 g, 0.786 mmol), cyclohexene (6.233 g, 75.88 mmol), and **3** (0.004 g, 0.008 mmol) were used in the General Catalytic Reaction described above yielding 0.075 g, 30%. ¹H NMR (CDCl₃, 499.74 MHz): δ 7.76 (d, *J* = 7 Hz, 2H), 7.62 (d, *J* = 7 Hz, 2H), 7.40 (t, *J* =

7Hz, 2H), 7.32 (t, J = 7Hz, 2H), 4.36 (d, J = 7Hz, 2H), 4.25 (t, J = 7 Hz, 1H), 2.61 (m, 2H), 1.96 (m, 2H), 1.84 (m, 2H), 1.45 (m, 2H), 1.27 (m, 2H). ^{13}C NMR (CDCl_3 , 125.66 MHz): δ 163.84, 143.76, 141.31, 127.73, 127.04, 125.17, 119.94, 67.94, 46.99, 37.05, 23.68, 19.77. DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 320.16439 (found); $[\text{C}_{21}\text{H}_{22}\text{NO}_2]^+$ 320.16451 (calcd).

Characterization of (9H-fluoren-9-yl)methylcyclohex-1-en-1-ylcarbamate, 5.

From the above reaction, (9H-fluoren-9-yl)methylcyclohex-1-en-1-ylcarbamate was isolated yielding 0.033 g, 13%. ^1H NMR (CDCl_3 , 499.74 MHz): δ 7.76 (d, J = 7.9Hz 2H), 7.61 (d, J = 7.6Hz, 2H), 7.41 (t, J = 7.9Hz, 2H), 7.32 (t, J = 7.6Hz, 2H), 5.82 (s, 1H), 5.77 (s, 1H), 4.44 (d, J = 7.0Hz, 2H), 4.23 (t, J = 7.0 Hz, 1H), 2.09 (m, 4H), 1.68 (m, 2H), 1.58 (m, 2H). ^{13}C NMR (CDCl_3 , 125.66 MHz): δ 171.29, 144.08, 141.46, 127.82, 127.19, 125.11, 120.11, 66.64, 60.53, 47.34, 28.08, 24.04, 22.69, 22.15. IR: 3324, 3017, 2935, 1697, 1674, 1509, 1462, 1450, 1376, 1346, 1301, 1226, 1198, 1139, 1106, 1086, 1057, 1034, 984, 936, 916, 859, 838, 772, 794, 756, 735, 642 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 320.16345 (found); $[\text{C}_{21}\text{H}_{22}\text{NO}_2]^+$ 320.16451 (calcd).

Synthesis of (9H-fluoren-9-yl)methyl 2-octylaziridine-1-carboxylate, 3b: 1% catalyst loading: fmoc-azide (0.156 g, 0.588 mmol), 1-decene (5.045 g, 35.98 mmol), and **3** (0.003 g, 0.006 mmol) were used in the General Catalytic Reaction described above yielding 0.067 g, 30%. ^1H NMR (CDCl_3 , 499.74 MHz): δ 7.78 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.32 (t, J =

7.4 Hz, 2H), 4.45 (d, $J = 7.4$ Hz, 2H), 4.24 (t, $J = 7.2$ Hz, 1H), 1.45 (m, 3H), 1.28 (m, 16H), 0.89 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125.66 MHz): δ 163.58, 143.65, 141.31, 127.74, 127.05, 125.05, 120.01, 67.90, 47.06, 43.82, 38.54, 32.24, 31.87, 31.58, 29.50, 29.24, 26.91, 22.66, 14.10. IR: 2915, 2848, 1721, 1472, 1463, 1450, 1413, 1374, 1239, 1207, 1075, 910, 758, 739, 730, 719 cm^{-1} . DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 378.24250 (found); $[\text{C}_{25}\text{H}_{32}\text{NO}_2]^+$ 378.24276 (calcd).

Synthesis of benzyl 7-azabicyclo[4.1.0]heptane-7-carboxylate, 2c: 1% catalyst loading: Cbz-azide (0.116 g, 0.655 mmol), cyclohexene (4.673 g, 56.89 mmol), and **3** (0.003 g, 0.007 mmol) were used in the General Catalytic Reaction described above yielding 0.091 g, 60%. ^1H NMR (CDCl_3 , 499.74 MHz): δ 7.36 (s, 5H), 5.11 (s, 2H), 2.66 (d, 2H), 1.94 (m, 2H), 1.81 (m, 2H), 1.40 (m, 2H), 1.22 (m, 2H). ^{13}C NMR (CDCl_3 , 125.66 MHz): δ 163.96, 136.07, 128.48, 128.15, 128.15, 67.82, 37.11, 23.66, 19.75. DART HR MS (m/z): $[\text{M}+\text{H}]^+$ 232.13390 (found); $[\text{C}_{14}\text{H}_{18}\text{NO}_2]^+$ 232.13321 (calcd).

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 N_2 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 Lorentz 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 intrinsic phasing method and were refined using SHELXTL 5.0 software package.

CHAPTER SEVEN

CONCLUSION

Two types of macrocyclic *N*-heterocyclic carbene (NHC) ligands were designed for catalytic aziridination. The first generation ligand was an 18-atom neutral macrocyclic tetra-NHC ligand. Development of a silver transmetallating reagent facilitated the synthesis of various transition metal complexes supported by this ligand in high yields. This silver transmetallating reagent was used to synthesize $[(^{\text{Me,Et}}\text{TC}^{\text{Ph}})\text{Ru}(\text{NCCH}_3)_2](\text{PF}_6)_2$ analogous to the first generation iron catalyst. Despite efforts to isolate the proposed intermediates and conduct catalytic reactions, the Ru complex was found to be unreactive. To be able to do asymmetric aziridination, a chiral 24-atom macrocyclic neutral ligand precursor was synthesized. Because of the larger ring size, the ligand is flexible enough to saddle down and was unlikely to exhibit the expected enantioselectivity. Although being robust, the metal complexes supported by this ligand have limited reactivity.

To overcome these limitations, the second generation borate-based macrocyclic tetra-NHC ligand was synthesized. Due to the presence of borate moieties the ligand is dianionic and the resulting divalent metal complexes are neutral. Co, Mn, and Fe monomeric complexes were synthesized using this second generation ligand. Out of these, Mn(III) and Fe(III) form metal complexes with a halide axially bound along with the ligand. Alternatively, Co forms a

divalent square planar complex. The Fe(III) complex can be reduced to Fe(II) to form a square planar complex. Out of these metal complexes, $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Fe}]$ was found to be catalytically active.

$[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Fe}]$ is reactive towards alkyl azides along with aryl azides which lead us to the synthesis of fully alkyl aziridines. Catalytic $\text{C}_2 + \text{N}_1$ aziridination for fully alkyl aziridines synthesis is not reported. Aliphatic aziridines are critical functional groups since they are potential intermediates in pharmaceuticals or natural product syntheses. We isolated number of non-functionalized fully alkyl aziridines in high yields. In addition, we demonstrated reasonable functional group tolerance for the catalyst to form one of the most complex aziridines ever reported by a $\text{C}_2 + \text{N}_1$ approach. In case of aziridines with aryl azide and aliphatic alkenes, $[(^{\text{BMe}_2,\text{Et}}\text{TC}^H)\text{Fe}]$ is more effective than our previous system even with functional groups on aryl azides. Finally, we succeeded in intramolecular aziridination reaction that formed the first examples of five- and six- membered tertiary bicyclic aziridines in a $\text{C}_2 + \text{N}_1$ reaction.

To understand the aziridination mechanism, DFT calculations and experiments were carried out on both the iron-based catalysts. The calculations matched very well with the experimental results for the formation of aziridines from imide intermediates. The mixture of stereochemical products suggested the radical intermediate for the second generation catalyst whereas in the first generation catalyst, retention of stereochemistry for the shorter reaction and

mixture for longer suggest either radical or box-type intermediate. Finally, various addition products were synthesized in the attempts to isolate the imide intermediate with $[(^{\text{BMe}_2, \text{Et}}\text{TC}^{\text{Ph}})\text{Fe}]$, including the metallotetrazene.

Towards our goal of making new classes of aziridines, we synthesized *N*-carbamate protected aziridines using boc-, fmoc-, and cbz- azides and aliphatic alkenes. Carbamate groups are an attractive choice as protecting group for amines and aziridines since each one can be deprotected under distinct reaction conditions. In the future, deprotection to form primary aziridines and nucleophilic ring opening reactions will be tried with *N*-carbamate amines.

This catalyst has made a great progress towards our goal of atom economical formation of aziridines through direct synthesis from organic azides and alkenes. With this experience and knowledge about aziridination using NHC complexes, a better system can be designed for biologically significant molecules. The borate-containing second generation ligand shows greatly improved reactivity as compared to the first generation neutral version. The formation of tetrazene intermediate should be avoided in the reaction pathway as this will allow lower alkene loading. Finally, chiral ligands should be 18-atom or 16-atom in ring size with functional groups near the metal center to impart enantioselectivity upon aziridination. I believe that this work will have an impact towards improving aziridination in modern organic synthesis.

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VITA

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For her Ph.D. she decided to come to University of Tennessee, Knoxville, on the opposite side of the world. Having masters in organic chemistry she joined the group working in organometallic chemistry in order to expand the experience. In graduate school, Preeti always put forth great effort in pursuit of scientific research as she enjoys working in the lab. She contributed to peer-reviewed publications, review article, and presented at national meetings.