# The Synthesis of Indolizidine and Quinolizidine Derivatives using the Electron-rich Dearomatization Agent, {WTp(NO)($PMe_3$)}

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## Abstract

Chapter 1 introduces the reader to aromaticity and the activation of aromatic molecules through coordination to electron deficient and electron-rich metal fragments. Coordination of aromatics to electron-deficient metals in an $\eta^6$ fashion activates them towards nucleophilic additions. Conversely, coordination to an electron-rich metal fragment through $\eta^2$ (dihapto) coordination renders aromatic molecules *dearomatized* and makes them susceptible to electrophilic addition.

Chapter 2 gives an overview of alkaloid chemistry and the syntheses of several alkaloid analogs using electron-rich dearomatization techniques. Through dihapto-coordination, several inexpensive aromatics can be chemically transformed to alkaloid analogs. The chapter ends with the introduction of the synthetic challenges of converting pyrroles and pyridines to indolizidines and quinolizidines, respectively.

Chapter 3 focuses on the reactivity of pyrrole and its activation through electron-rich dearomatization. Upon coordination of 2-methylpyrrole to a tungsten(0) dearomatization agent followed by protonation, a dihapto-coordinated 2H-2-methylpyrrolium complex is isolated. After a Michael addition of MVK or EVK to the 2-methylpyrrolium complex, an intramolecular cyclization takes place to form an indolizidinium core.

Chapter 4 explores the formation and reactivity of a coordinated indolizidinium complex. The indolizidinium core has an α,β-unsaturated iminium where the alkene portion can be dihydroxylated or hydrogenated. Following hydride reduction of the hydrogenated indolizidinium complex, a fully saturated coordinated-indolizidine can be

isolated. Subsequent oxidation leads to a dehydroindolizidine that can be dihydroxylated to form a dihydroxylated indolizidine.

Chapter 5 introduces the reader to the reactivity of pyridine and its activation when coordinated to a tungsten(0) dearomatization agent. A dihapto-coordinated 2-picolinium complex may be formed and a Michael addition with acrolein, MVK or EVK can occur at the nitrogen. Upon formation of the dearomatized 2,6-lutidinium complex a Michael addition with MVK followed by an aldol condensation leads to a cyclized quinolizidinium core.

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Writing these acknowledgements I understand that no matter what I put in these next few pages I will never be able to adequately express my gratitude for the people who helped make this dissertation possible.

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More specifically I am very grateful for my family's support through my graduate school experience. Interestingly, I think >99% of my conversations with any of you were *not* about science and yet they influenced my scientific career so greatly that they might as well have been. To my sisters (and husbands) I am so lucky to have you in my life. I would not have survived graduate school without you to talk to and complain about life and work. Aaron and Chip you are brothers to me, not just in-law. To my mother, you have been such wonderful emotional support during my time in graduate school and that is hard to put into words exactly how grateful I am. To my father, every Friday morning I would get an email from you that contained the news from Brooklyn. I loved every single one and was disappointed the few Fridays without emails because you were away or I was on my way home. I look forward to getting them for as long as you are willing to

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My research advisor and mentor Dr. W. Dean Harman, where to begin? I worked for a student of Dean's at Muhlenberg, Dr. Joseph M. Keane (who will be mentioned a little later in these acknowledgements) and when I visited UVA I told Dean that I wanted to work for him and he said okay. I still don't quite understand how that happened. All I know is that I am so grateful that he let me into his lab and I cannot put into words how much that has changed the course of my scientific career and my life.

When I first started in Dean's lab I was scared out of my wits. To use a phrase common amongst graduate students (of all ages and generations, apparently), I was "waiting to be found out." I felt unprepared and inexperienced to be in the company of such amazing chemists, when would they realize I did not belong? Even the students who entered in my year seemed to *know* what was going on. I could not see how an inexperienced college graduate becomes a real *graduate student* like the ones I saw presenting at Harman Lab group meetings.

I am not nor have I ever been an excellent student. For a long time at the beginning of graduate school my chemistry knowledge consisted of whatever facts seemed familiar from class that I could recite on cue. But Dean did not accept that and he spent time with me and other lab members and taught us how to work and think like chemists. He was able to build a bridge between the chemistry knowledge I learned in

class and how to apply it in my lab work and tackle synthetic challenges. Moreover, Dean wanted all of us to learn the fundamentals of chemistry that are usually brushed over in our chemistry classes. We spent weeks doing *Thinkwell* group meetings where we got to discuss, in depth, general chemistry topics. I am not sure I will ever love chemistry discussions as much as I love our discussions about entropy. Those were awesome. But I forget, are we in a vacuum?

It is important to note that the thesis you hold before you was not the project I started on when I entered graduate school. I was first put on a tungsten product with the goal of coordination of a steroid. I worked hard on that project but I reached a frustrating point where nothing was working. I was very fortunate that Dean, Dr. Bill Myers (to be discussed shortly) and I had a sit-down about my chemistry future. All I will say about that meeting is that Dean and Bill both wanted me to understand that I did not *have* to continue the pursuit of my PhD for the sake of getting a PhD. For some reason they both believed in me and thought that I could succeed if I wanted to but I needed to become more focused in my research efforts. I remember being very scared and upset that day but for some reason I knew it was going to be okay. I had Dean on my side, fighting for me, what couldn't I do? He was an *incredible* mentor and he would not stop trying to help me become a better chemist. So I came back to Dean and Bill and said that I wanted to continue with my PhD and here I am today.

In addition to Dean being an *incredible* mentor, there was another professor who was instrumental in my graduate career. Dr. Bill Myers, from the University of Richmond, came to our lab every summer for years bringing students, stories and a wealth of chemistry knowledge. Our lab was already lucky to have Dean for a mentor but

over the summers (and through email during the year) we had a second mentor. Bill was one of the most kind and influential people that I have ever known. I have never seen him angry or upset about anything, quite the contrary, he was always happy and looking forward to the day. I was so lucky to have gotten to talk and work with Bill for so many years. Not only did he teach me about High Res Mass Spectrometry and NMR spectroscopy but he also was an excellent storyteller and listener. The pyrrole sections of my thesis (chapter 3 and 4) started from research that Bill and his students had been working on and I am so grateful that he let me continue their research. When he was at UVA over the summer he would sit in the conference room where I could pop in any time of day and ask science questions or tell him about life etc. He was truly a remarkable man. Sadly, Bill passed away in the Fall of 2016. The Harman Lab lost a good friend and mentor that day. I am sad that I did not have the chance to present this research to him; I hope he would have approved. I am eternally grateful for his help and support.

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# Chapter One

# An Introduction to Dearomatization Chemistry

## 1.1 Introduction to aromaticity and the reactivity of aromatic molecules

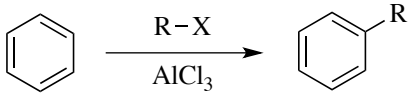
Aromatic molecules are known for their stability. This stability stems from an uninterrupted cyclic array of π-electrons across several *p*-orbitals that conform to Huckel's rule of 4n + 2 π electrons, a feature known as *aromaticity*.[1] This circular arrangement of alternating single and double bonds enables delocalization of the π electrons across the entire molecule. One result of this delocalization can be observed when looking at the bond lengths of an aromatic molecule versus a non-aromatic conjugated system. The simplest aromatic, benzene, has six carbons with a uniform carbon-carbon bond length of 1.397 Å, while butadiene has two distinct bond lengths of 1.34 Å for the double bonds and 1.48 Å for the single bond.[2] Because of this delocalized π system, aromatic molecules are stable and show very limited reactivity. An addition reaction performed on an aromatic would disrupt the cyclic π-system leading to an unstable non-aromatic product. Because of this property, aromatic molecules are most known for their ability to perform substitution reactions, where the final product remains aromatic.

An aromatic's inability to perform addition reactions limits its utility as a building block for more chemically complex structures. An individual unsaturated bond can be modified in a variety of ways providing a site of saturation as well up to two new asymmetric centers. Benzene, a typical aromatic molecule, has three unsaturated bonds that theoretically could be converted to six sites of chemical elaboration. However, because of aromatic stabilization the unsaturated bonds cannot be exploited as readily as an isolated double bond. It is for this reason that aromatic molecules, despite their low

cost and availability in a wide variety of derivatives remain an underutilized feedstock of organic starting materials.

Friedel-Crafts type reactivity (alkylation and acylation) is a famous example of a substitution reaction that aromatic molecules are known to perform (Scheme 1.1). Beginning with an aromatic molecule, an alkyl or acyl group can be incorporated into the ring system with the final product remaining aromatic. An issue with Friedel-Crafts alkylation is the difficulty in controlling the number of alkyl groups that are incorporated into the aromatic, limiting the usefulness of the reaction. Despite this drawback, Friedel-Crafts alkylation and acylation remain a common method of chemical elaboration for aromatic molecules.

**Scheme 1.1** Friedel-Crafts Alkylation and Acylation.

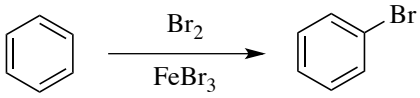



R = secondary or tertiary alkyl or acyl group
X = halogen

The Friedel-Crafts reaction is a specific example of electrophilic aromatic substitution (EAS), where a hydrogen on an aromatic is substituted by an electrophile. Common examples of EAS reactions include: bromination, nitration and sulfonation (Scheme 1.2 shows a bromination example).[2] Despite the variety of electrophiles capable of reacting with an aromatic, like the Fridel-Crafts reaction, controlling the number of substitutions is difficult and therefore more than a single product is often isolated. There are additional constraints on EAS such as substituent effects on the benzene. A deactivating group on the aromatic will quell the molecule's ability to perform EAS. While this reaction pathway is a highly regarded method of chemically elaborating an aromatic molecule, the results of EAS reactions are always substitution products that

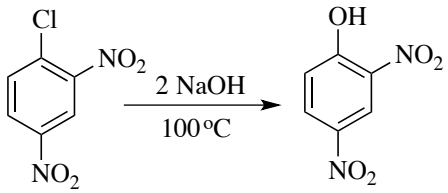
leave aromaticity intact. A chemist performing EAS can create a substituted aromatic but cannot take full advantage of the unsaturated bonds present in the aromatic.

**Scheme 1.2** Electrophilic Aromatic Substitution of benzene: bromination.




Nucleophilic aromatic substitution (NAS) is another way to chemically modify arenes (though it is not as common as EAS) provided that the aromatic has a good leaving group. Aromatic molecules are electron rich and therefore more reactive (at least to some degree) towards electrophiles than nucleophiles. The incorporation of an electron-withdrawing group facilitates the reaction of an aromatic and a nucleophile. An example of NAS can be seen in the reaction of 2,4-dinitrochlorobenzene with sodium hydroxide (Scheme 1.3).[2] The nitro groups are electron withdrawing and activate the aromatic towards NAS. The resulting product has a chlorine group substituted with a hydroxyl group. Despite the limited scope of NAS, it is still a useful method for chemical elaboration of aromatic molecules. Like EAS, NAS is a substitution reaction and the final product remains aromatic.

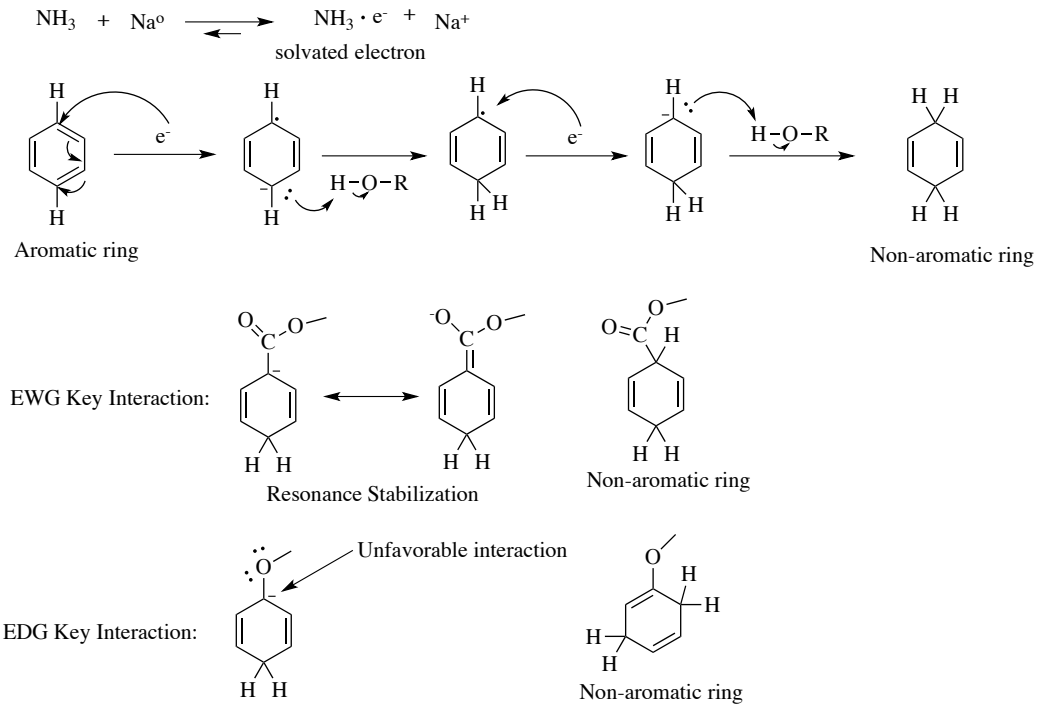
**Scheme 1.3** Nucleophilic Aromatic Substitution of 2,4-dinitrochlorobenzene.




An alternative method for chemical modification of aromatic molecules is through the Birch Reduction. In contrast to the substitution reactions mentioned previously (EAS and NAS), the Birch Reduction is capable of disrupting aromaticity, leaving a non-aromatic, cyclic diene (Scheme 1.4 for example with benzene). The reagents required to

achieve the Birch Reduction are sodium or lithium, liquid ammonia and an alcohol. Under these conditions, the aromatic is capable of receiving solvated electrons that enable the addition of two protons, thereby providing the desired diene. An interesting feature of the Birch Reduction is the alternative products that form based on the substituents of the aromatic ring. In the case of an electron-withdrawing group (EWG), in the final product the carbon with the EWG is reduced because the anion that forms at that position is stabilized through resonance with the withdrawing-substituent (Scheme 1.4). If instead benzene is substituted with an electron-donating group (EDG), a different mechanism is observed and the reduction takes place at the ortho and meta positions (Scheme 1.4). If the reaction were to occur in a similar manner to the EWG then there would be an anion adjacent to a donor pair of electrons, which is an unfavorable interaction. Unlike EAS and NAS, the Birch Reduction is able to perform an *addition* reaction to an aromatic molecule disrupting its aromaticity.

**Scheme 1.4** Mechanism of the Birch Reduction.



With the exception of the Birch Reduction, aromatic molecules are most commonly expected to undergo substitution reactions where aromaticity remains in the final product. While substitution reactions are useful in creating substituted aromatics, they do not take full advantage of the unsaturated bonds that could be used to create saturated systems. A field of metal-dearomatization chemistry was created to overcome the obstacle of aromaticity enabling the use of aromatic molecules as starting materials for more complex, saturated, cyclic molecules. Metal-dearomatization chemistry involves the coordination of an aromatic substrate to a metal fragment that interacts with the arene's π-system rendering the aromatic susceptible to unexpected reactivity. Enzymes are also capable of performing dearomatization chemistry. However, because the enzyme-dearomatization mechanism is a biological mechanism it will not be discussed in this dissertation.[3] The two types of metal dearomatization systems that will be discussed presently are electron-deficient and electron-rich metal complexes.

## 1.2 Electron-deficient Dearomatization agents

Electron-deficient dearomatization agents are able to withdraw electron density from coordinated aromatic molecules. Most notably these dearomatization agents coordinate in an $\eta^6$ fashion with aromatics binding in a facial interaction, in which the metal can accept electron density from the aromatic's π-system. It is important to note that while an aromatic is $\eta^6$-coordinated it is not technically *dearomatized* meaning the

molecule is still aromatic although its reactivity is greatly increased due to the influence of the metal. The reactivity of these $\eta^6$-coordinated aromatics will be discussed presently.

### 1.2.1 The $Cr(CO)_3(\eta^6$-arene) dearomatization agent

Chromium hexacarbonyl in the presence of an arene in a high-boiling solvent under an inert atmosphere gives the $Cr(CO)_3(\eta^6$-arene) complex (Figure 1.1 shown with coordinated benzene).[4] It is also observed that $\eta^6$-naphthalene can be replaced with alternative aromatic molecules to vary the aromatic that can be coordinated.[5] The ability for naphthalene to be displaced more readily than benzene is likely due to the fact that when naphthalene goes through an $\eta^4$ transition state where the uncoordinated ring of naphthalene rearomatizes, providing added stability. This ability has led to the coordination of other aromatics such as: benzene, styrene and other substituted benzenes and naphthalenes.[5]

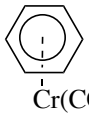
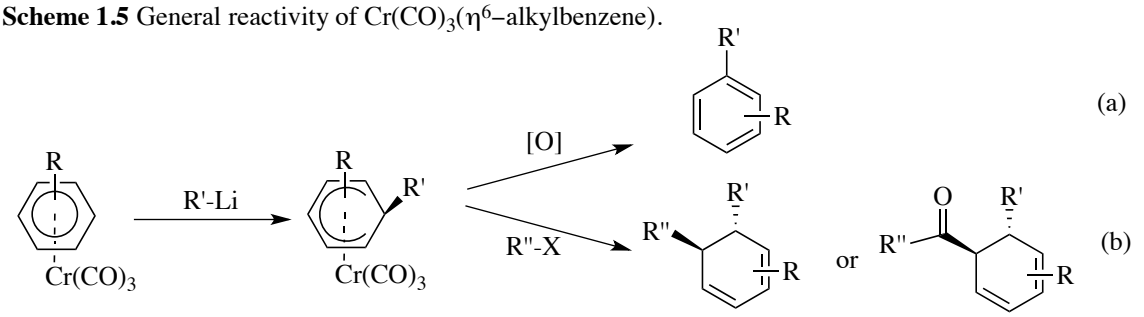



**Figure 1.1** $Cr(CO)_3(\eta^6$–benzene).

In order to understand the increased reactivity afforded by coordination to the chromium fragment, we must first understand the properties of the metal complex. Because of the electron-withdrawing ability of the chromium fragment (due to the $\pi$ - acidity of the carbonyl ligands), electron density is heavily removed from the coordinated aromatic molecule. Being coordinated to an electron-deficient metal makes the protons of the aromatic much more acidic and susceptible to deprotonation.[6]

Because of the electron-deficiency of the {$Cr(CO)_3$} fragment, the aromatic in turn becomes electron-deficient and is activated towards nucleophilic addition. The addition reactions happen stereoselectively *anti* to the metal, largely due to the steric bulk of the metal center. Regioselectivity of the added nucleophile is often dictated by the rings substituents though this is not always consistent.[6-11] Scheme 1.5 (a) shows the *dearomatization* of an alkyl-benzene and the successful addition of a nucleophilic 'R' group. The metal and organic can be oxidized to isolate a substituted aromatic molecule. While this reaction is a substitution reaction like those discussed in Section 1.1, it is a nucleophilic substitution, which is a much more limited reaction type for an aromatic. Alternatively, instead of employing oxidation conditions to liberate the aromatic, after a nucleophilic addition takes place the coordinated cyclohexadienyl becomes activated towards electrophilic addition (Scheme 1.5(b)). The proposed mechanism for the electrophilic addition supposes the electrophile adds to the metal first, a CO migration occurs inserting itself between the metal and the electrophile, until finally a reductive elimination places the acyl group on the same side of the aromatic where it is coordinated. Once the organic is liberated from the metal, a trans 1,2-addition product can be isolated.[12]

**Scheme 1.5** General reactivity of $Cr(CO)_3(\eta^6$–alkylbenzene).




Dearomatization using the {$Cr(CO)_3$} fragment is a useful tool for performing addition reactions on aromatic molecules and forming new carbon-carbon bonds. Using

this methodology a plethora of organic molecules were created that could be further elaborated to create more complex organic frameworks. The reactivity of aromatic molecules is dramatically increased via the coordination to the electron-deficient $\{Cr(CO)_3\}$ fragment. Despite these benefits, a drawback to this method is the achirality of the metal fragment. As a result the organic molecules isolated using the $\{Cr(CO)_3\}$ fragment are racemic mixtures. Several methods can be used to surpass this issue and isolate chiral organic products including: chiral auxiliaries[13], chiral aromatic molecules[14], formation of planar chiral arenes[15] and chiral ligands on chromium.[16] It is worth noting that incorporating an arene with a chiral ligand into the $\{Cr(CO)_3\}$ fragment did not affect the metal's ability to dearomatize and activate the aromatic molecule.

The dearomatization ability of the $\{Cr(CO)_3\}$ fragment is a uniquely powerful synthetic tool that activates aromatic molecules to reactivity not observed for uncoordinated arenes. Because of the success of the chromium dearomatization agent other dearomatization agents were explored.

### 1.2.2 The $[Mn(CO)_3(\eta^6\text{-arene})]^+$ dearomatization agent

The cationic $[Mn(CO)_3(\eta^6\text{-arene})]^+$ (Figure 1.2 seen with benzene) complex can be isolated beginning with $Mn(CO)_5Br$. After reacting with $AgBF_4$ in dichloromethane followed by addition of an arene under reflux, $[Mn(CO)_3(\eta^6\text{-arene})][BF_4]$ is formed.[17] Like the $\{Cr(CO)_3\}$ fragment, the $\{Mn(CO)_3\}^+$ fragment is electron-withdrawing and therefore activates arenes toward nucleophilic addition. Because the manganese complex

is cationic and in a +1 oxidation state it is more electron deficient than the chromium system. As a consequence, a wider range of nucleophiles can be added to the coordinated aromatic. While the chromium dearomatization agent only shows reactivity with organolithium reagents, the $[Mn(CO)_3(\eta^6\text{-arene})]^+$ complex reacts with Grignard reagents, ketone enolates, malonates and hydrides.[4] A similarity between the manganese and chromium dearomatization agents is the stereoselectivity and regioselectivity of the nucleophile added. Again the initial nucleophilic addition takes place on the face of the aromatic *anti* to the metal and the specific location can be influenced by substituents on the ring.

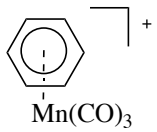
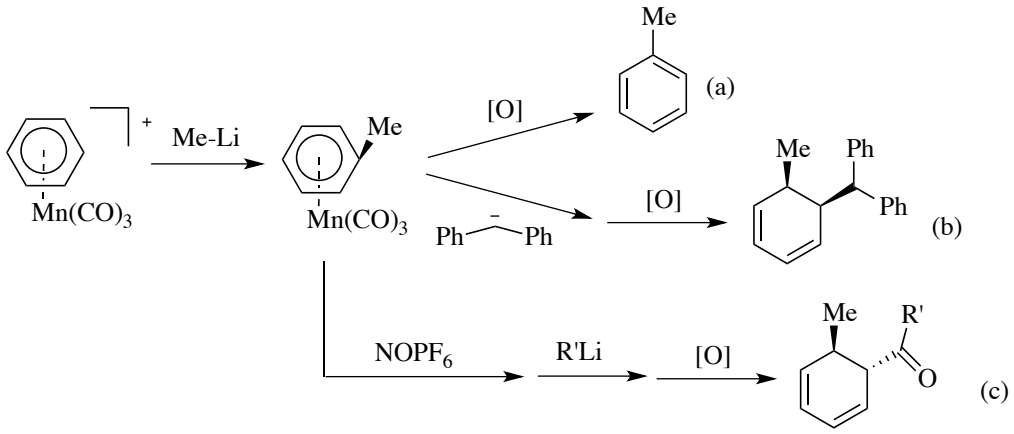



**Figure 1.2** $[Mn(CO)_3(\eta^6\text{–benzene})]^+$.

The $\{Mn(CO)_3\}^+$ fragment distinguishes itself from its chromium analog in its ability to perform a *second* nucleophilic addition reaction on the aromatic ligand. After initial nucleophilic addition the chromium fragment allows the addition of an electrophile as the fragment has become more electron-rich (see Scheme 1.5). In contrast, after initial nucleophilic addition, the $\{Mn(CO)_3\}^+$ fragment allows a *second* nucleophile to add instead of an electrophile as seen in Scheme 1.6.[4] This is a direct result of the increased electron deficiency of the $\{Mn(CO)_3\}^+$ fragment compared to the chromium fragment discussed earlier. The second nucleophile must be very reactive (i.e., an anionic carbon source) in order to successfully add to the aromatic (Scheme 1.6 B).[4] The double nucleophilic addition afforded by $\{Mn(CO)_3\}^+$ is an impressive example of the influence the metal has on the aromatic. As observed in Scheme 1.6 B both nucleophiles add on the *anti* face of the aromatic, away from the steric bulk of the metal. After the initial

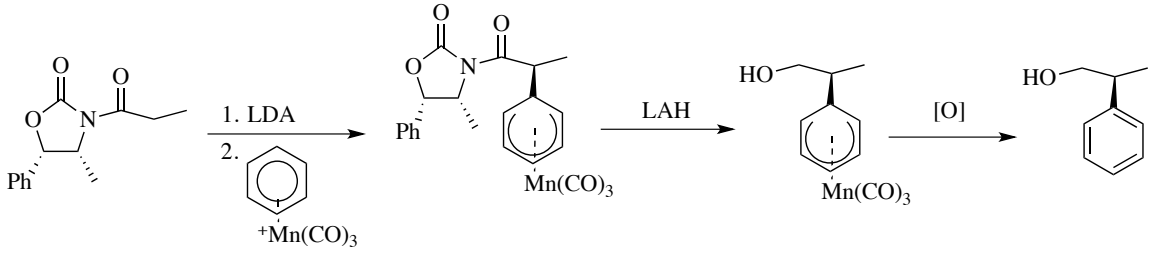
nucleophilic addition if $NOPF_6$ is put in solution, a CO will be replaced by $NO^+$, a better π-acid. A second nucleophilic addition can then occur attacking the metal before undergoing CO insertion and reductive elimination. The result of this reactivity yields the *trans* addition product. The $NO^+$ ligand also allows weaker nucleophiles to add as the metal has become more electron-deficient (Scheme 1.6 C).[18,19]

**Scheme 1.6** Example of a reaction scheme for double nucleophilic addition of **[**$Mn(CO)_3(\eta^6-benzene)]^+$.




Despite its versatility in forming *cis* and *trans* cyclohexadienes starting from an aromatic molecule, like the chromium system, the $\{Mn(CO)_3\}^+$ fragment is achiral and needs assistance isolating enantiopure organic products. One attempt to isolate an enantiopure organic involved the incorporation of a chiral auxillary via the use of a chiral nucleophile (Scheme 1.7).[4] Other approaches include the implementation of a $C_2$-symmetric substituent on the aromatic that encouraged nucleophilic addition at one spot over another solely based on steric interactions.[20,21] The $\{Mn(CO)_3\}^+$ dearomatization agent is a powerful tool for activating aromatic molecules to nucleophilic addition. The$\{Mn(CO)_3\}^+$ has led to complex, non-aromatic cyclic structures using aromatic molecules as starting materials.

**Scheme 1.7** Use of a chiral nucleophile to create enantiopure organic molecules.

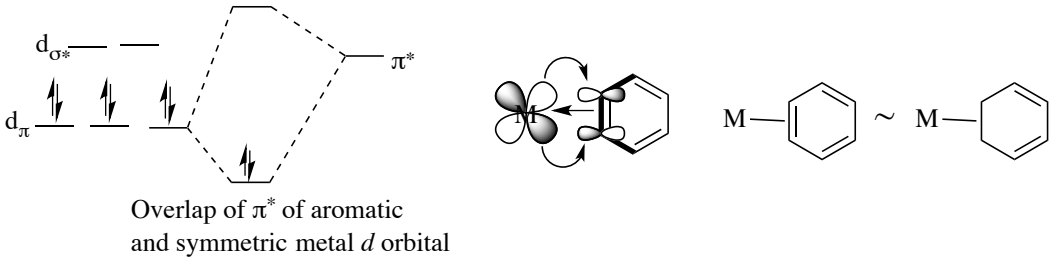



## 1.3 Electron-rich Dearomatization agents

The electron-deficient dearomatization agents that were discussed in section 1.2 have been around for several decades. While they continue to be an interesting source of chemical transformations using aromatic molecules, an alternative method for the dearomatization of aromatics was discovered. Harman et al. found that an electron-rich metal fragment could coordinate an aromatic and activate it towards increased reactivity.[22] This method of dearomatization differs from those discussed previously by coordinating to an aromatic across two carbons, or through 'dihapto' ($\eta^2$) coordination rather than through all six carbons ($\eta^6$). In addition to a small amount of electron-density donated from the aromatic to the metal via σ donation, dihapto-coordination is achieved by donation of electron-density from a *dπ* orbital of an electron-rich metal into the $\pi^*$-antibonding orbital of an aromatic (Figure 1.3). When electron-density is placed in an anti-bonding orbital the overall strength of the bonding interactions for the carbon-carbon bonds are decreased and in the case of an arene, aromaticity is disrupted. Evidence for this disruption can be seen in the alteration of bond lengths for benzene. Benzene has uniform a bond length as discussed earlier, but when benzene is fully dearomatized its

bond lengths become distorted.[23] When an aromatic is coordinated across two carbons, electron-density from the metal and the aromatic are focused on the two remaining unsaturated bonds, which become more diene-like in appearance and reactivity. Though it is important to note that the dihapto-coordinated aromatic is more reactive than a diene as the arene complex is more electron-rich.

**Figure 1.3** Orbital diagram of dearomatization via dihapto-coordination to an electron-rich metal fragment.



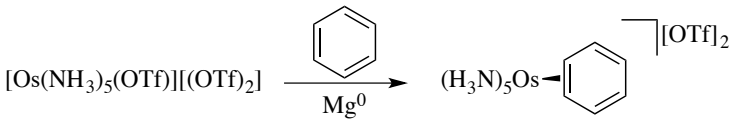

Overlap of $\pi^*$ of aromatic
and symmetric metal *d* orbital

### 1.3.1 The $\{Os(NH_3)_5\}^{2+}$ Dearomatization Agent

The initial discovery of electron-rich dearomatization occurred with a pentaammineosmium(II) fragment. After the reduction of $[Os(NH_3)_5(OTf)][(OTf)_2]$, using $Mg^0$ in the presence of the desired arene, the dihapto coordinated species is isolated (Scheme 1.8 seen with benzene).[23] In opposition to the dearomatization agents mentioned in Section 1.2, the pentaammineosmium(II) fragment is electron-rich and is able to donate electron density into an aromatic, activating it towards electrophilic addition followed by addition of a nucleophile. Despite being in the +2 oxidation state, osmium is a third row transition metal with a $d^6$ electron count making it electron-rich. Additionally the five ammine ligands each donate electron-density to the metal. Through dihapto-

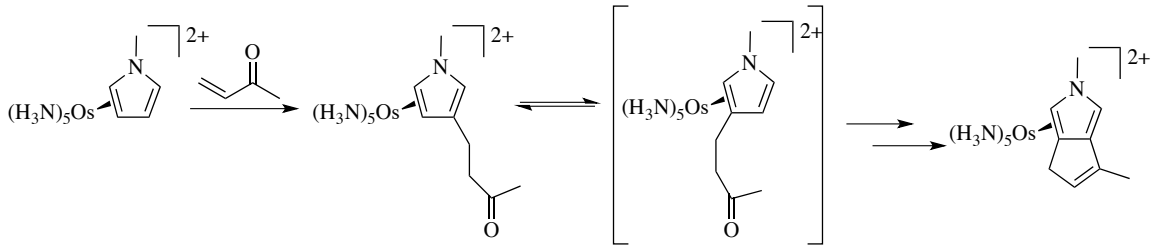
coordination the osmium fragment is able to donate electron density from its *d*π-orbital to a symmetric $\pi^*$ orbital (see Figure 1.3). This method of dearomatization also extends to heteroaromatics such as furan, pyrrole, and thiophene, which are inaccessible to the previous dearomatization agents.[23,24] A limitation of electron-rich dearomatization is the ability of the metal to coordinate any molecule with a π-bond. For example, if a ketone is in solution with an arene, the pentaammineosmium(II) fragment will preferentially insert itself into the π-system of the ketone, as it forms a more stable dihapto-coordinated product than with an aromatic as aromaticity is not breached when coordinating a carbonyl.

**Scheme 1.8** Synthesis of the dihapto-coordination of benzene by the pentaamineosmium(II) dearomatization agent.




While there are many examples of successful activation of aromatics using the pentaammineosmium(II) system, this electron-rich fragment distinguishes itself from the previous dearomatization agents by its ability to increase the reactivity of hetero-aromatics like pyrrole. One interesting example of the dearomatization of *N*-methylpyrrole involves a Michael addition of methyl vinyl ketone (MVK) that eventually ring-closes to form a pyrrolizidine derivative (Scheme 1.9).[23] Other examples of pyrrole's dearomatization will be discussed in later chapters of this dissertation. Like the previous dearomatization agents discussed, the pentaammineosmium(II) fragment provides stereo and regio-control of the additions but is achiral and requires the use of chiral auxiliaries to isolate chiral organic structures. Numerous papers were published on the successful activation of a range of aromatic molecules using the pentaammineosmium(II) fragment.[23]

**Scheme 1.9** Synthesis of pyrrolidizine analog from the electron-rich dearomatization of *N*-methylpyrrole.



Because of the success and novelty of the electron-rich pentaammineosmium(II) dearomatization system, further research was conducted to create other electron-rich dearomatization agents that were not as costly or toxic as osmium but also chiral. Several other dearomatization agents were developed.

### 1.3.2 The {ReTp(L)(CO)} Dearomatization agent

In the attempt to maintain a $d^6$ electron count on a different metal, a rhenium(I) fragment was explored. To achieve the proper electronics for electron-rich dearomatization, the rhenium(I) complex features a Tp (hydridotris(pyrazolyl)borate) ligand, a variable electron-donating ancillary ligand (L = trimethylphosphine [$PMe_3$], methylimidazole [MeIm], 4-dimethylaminopyrodine [DMAP] or pyridine), and a carbonyl for a π-acid (Figure 1.4 shown with $PMe_3$ and MeIm). Unlike the osmium fragment, the rhenium(I) dearomatization agent is, advantageously, a stereogenic center enabling the potential for isolating enantiopure activated aromatic molecules.

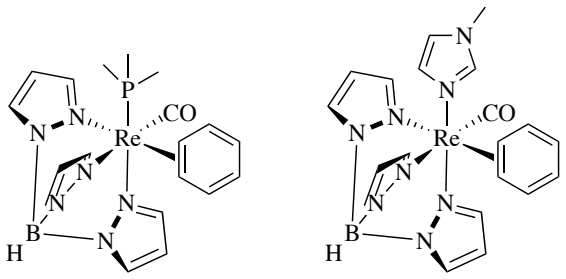
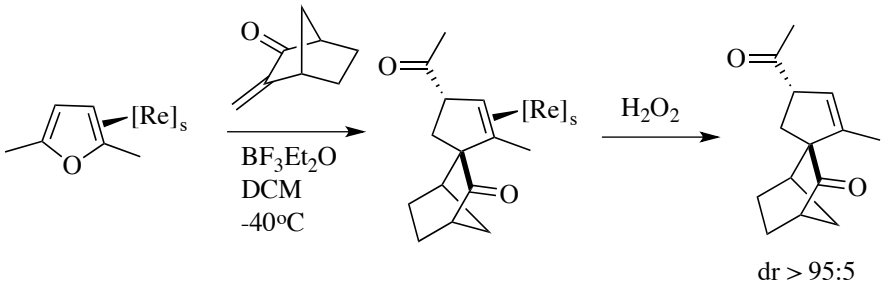


**Figure 1.4** Rhenium(I) dearomatization agents, ReTp($PMe_3$)(CO)($\eta^2$-benzene) and ReTp(MeIm)(CO)($\eta^2$-benzene).

The rhenium(I) system is able to successfully coordinate and activate benzene, naphthalene, anthracene, lutidine, pyrroles, thiohphene, furans, and phenol. The novel reactivity accessed by the coordination of aromatics to the Re(I) fragment has been published in a series of articles.[25]

In addition to its ability to dearomatize and activate aromatics, the rhenium(I) complex is able to be enantioenriched. When the Re(I) dearomatization fragment is formed, it exists in a racemic mixture. By using a bulky, chiral organic ligand to dihapto-coordinate to the rhenium(I) fragment, two diastereomeric metal complexes form that can be separated based on stability. Unfortunately this method of enantioenrichment requires the stable diastereomer formed to be sacrificed. A notable example can be observed through the dearomatization of 2,5-dimethylfuran, which is activated towards a cyclization product with high enantiopurity (Scheme 1.10).[26] Despite its versatility in converting aromatics into novel alicyclic molecules, the Re(I) fragment is still costly and has limited scalability. The need for a more economical and scalable dearomatization agent led to the development of two additional dearomatization agents using molybdenum(0) and tungsten(0).

**Scheme 1.10** Synthesis of a tricyclic dione from enantioenriched 2,5-dimehtyl furan.




### 1.3.3 The {MoTp(L)(NO)} Dearomatization agent

The molybdenum(0) dearomatization agent has the formula {MoTp(L)(NO)} (L = MeIm or DMAP) (Figure 1.5). This is a similar ligand set to the previous Re(I) dearomatization agent except for the replacement of a carbonyl with an $NO^+$ ligand. The reason for the more powerful π-acid is because of the increased electron density of the Mo(0) as compared to the Re(I). Because molybdenum is more electron-rich, it needs a stronger π-acid to temper the electron-density and allow dihapto-coordination.

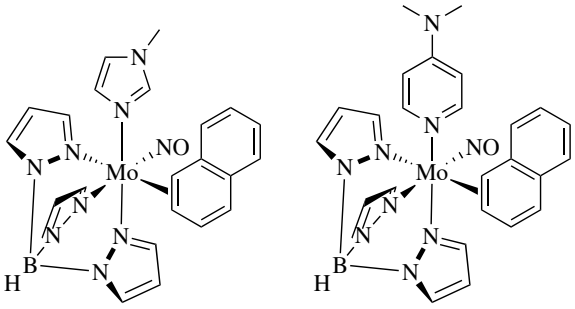


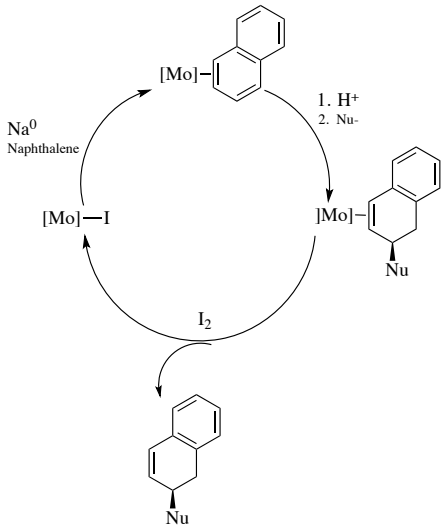

**Figure 1.5** Molybdenum(0) dearomatization agents, MoTp(MeIm)(NO)($\eta^2$-naphthalene) and MoTp(4-DMAP)(NO)($\eta^2$-naphthalene).

Aside from the low cost of molybdenum when compared to the previous dearomatization agents, the molybdenum(0) complex shows great versatility in the ligands required to invoke dihapto-coordination. The pentaammineosmium(II) metal fragment had five ammine ligands donating the precise amount of electron-density to

allow dearomatization chemistry to occur. Any alteration of those ammines results in the loss of the metal's ability to dihapto-coordinate aromatics. The rhenium(I) fragment showed greater versatility than osmium(II) in the ancillary ligand as does the current molybdenum(0) fragment. When the molybdenum(0) system has a MeIm as its ancillary ligand it can coordinate a variety of aromatic molecules and activate them towards interesting reactivity. However, the scope of reactivity is limited because the molybdenum(0) fragment is easily oxidized and has the potential to be oxidized by strong electrophiles. However, if the ancillary ligand is switched to DMAP, the scope of reactivity increases greatly. In the presence of acid, the amino group of the ancillary ligand becomes protonated and makes the metal fragment more difficult to oxidize.[27] This subtle change in electronic character of the metal allows for stronger electrophiles to be used broadening the limits of reactivity for the molybdenum(0) dearomatization agent.

The other notable feature of the Mo(0) fragment is its ability to activate an arene, release the modified organic and have the oxidized metal complex be converted back into an active dearomatization agent. An example of this recycling reactivity can be seen with MoTp(NO)(MeIm)($\eta^2$-naphthalene). After modification of the naphthalene the organic is isolated after metal oxidation. The metal is oxidized to a Mo(I) species that can be isolated and then re-reduced to create the Mo(0) complex once more (Scheme 1.11).[28]

**Scheme 1.11** Recycling ability of the Mo(0) dearomatization agent.




These advantageous features of the molybdenum(0) dearomatization agent have brought molybdenum to the forefront of dearomatization chemistry. Alternative aromatics and new reaction pathways are currently being explored.

### 1.3.3 The {WTp(PMe$_3$)(NO)} Dearomatization agent

The most prominent electron-rich dearomatization agent over the past decade has been the tungsten(0) dearomatization agent, {WTp(PMe$_3$)(NO)} (Figure 1.6 seen with benzene). Unlike the rhenium(I) and molybdenum(0) fragments, the ancillary ligand (PMe$_3$) cannot be changed. The electron donation of the PMe$_3$ ligand into the metal is the precise amount required for dihapto-coordination of aromatic molecules.

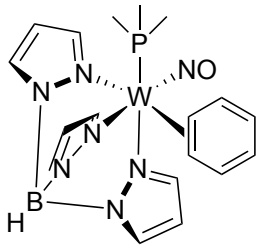
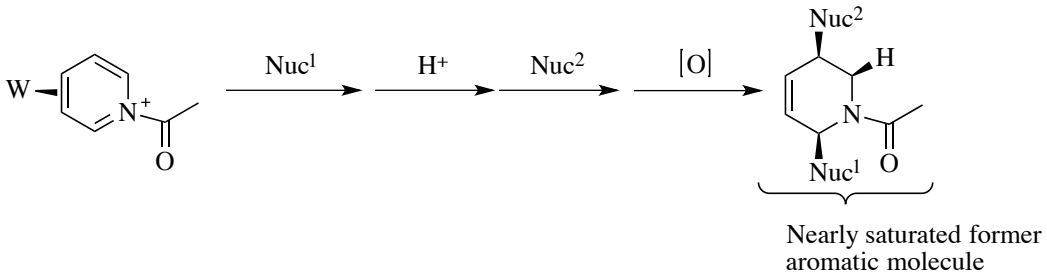



**Figure 1.6** WTp(NO)($PMe_3$)($\eta^2$-benzene).

The coordinated benzene complex, WTp($PMe_3$)(NO)($\eta^2$-benzene) has a $t_{1/2}$ = 1.1 hr at 22°C in acetone-$d_6$.[29] By putting W($\eta^2$-benzene) in solution with another aromatic, benzene will fall off leaving an open coordination site that can be occupied by that other aromatic molecule. Presently, in addition to benzene, naphthalene and anthracene, aromatic heterocycles have been coordinated and activated by {WTp($PMe_3$)(NO)}. These examples include: pyrroles,[30-32] furans,[33] and pyridines.[34-42] Additionally, several classes of arenes have been successfully activated by the electron-rich tungsten fragment including: phenols,[43-47] anisole,[48,49] anilines,[47,50,51] and indolines.[52,53] For many of these aromatic molecules complete or nearly complete saturation of the uncoordinated double bonds has been achieved. After the activated aromatic is released from the metal the lone unsaturated bond that remains could potentially be elaborated further, creating a fully saturated ring system. A cyclohexene can be formed beginning with benzene. An example of this reactivity can be seen with dihapto-coordinated acetylated pyridine in Scheme 1.12.[41]

**Scheme 1.12** Activation of acyl-protected pyridine by the tungsten(0) dearomatization agent.



Recently conditions were found for isolating the tungsten(0) dearomatization agent in enantiopure form. The method used for this enantioenrichment exploits tungsten's ability to coordinate aromatics that can be protonated by weak acids to increase the basicity of uncoordinated arenes. For the purposes of isolating an enantiopure tungsten(0) fragment, 1,3-dimethyoxybenzene is used as it can be protonated and deprotonated easily. By forming the W($\eta^2$-1,3-dimethoxybenzene) complex and then protonating the complex with the chiral acid, L-dibenzoyl tartaric acid (*L*-$DBTH_2$) two different diastereomeric salts are formed and can be separated based on solubility. After deprotonation, neutral, enantioenriched W($\eta^2$-1,3-dimethoxybenzene) is isolated and dimethoxybenzene can be substituted for other aromatics that can be subsequently activated yielding enantiopure organic molecules. With the use of *D*-$DBTH_2$, the alternative diastereomeric salt of W($\eta^2$-1,3-dimethoxybenzene) can be isolated and carried through to the alternative enantiopure organic molecule.[54]

Aside from the successful activation of the aforementioned aromatics and the enantioenrichment feature, tungsten has shown unusual and fascinating activation of select pyrroles and pyridines. Both will be discussed later in this dissertation.

## 1.4 Conclusion

Through the use of electron-deficient and electron-rich dearomatization agents the scope of reactivity for aromatic molecules is greatly increased. EAS, NAS and the Birch Reduction remain staples in organic synthesis as classical methods for performing reactions on aromatic molecules. The use of metal dearomatization agents has been a

useful way to expand the scope of reactivity of aromatic molecules beyond substitution reactions and the Birch Reduction. Research is still underway to find new reaction pathways that an aromatic is capable of under dearomatization conditions.

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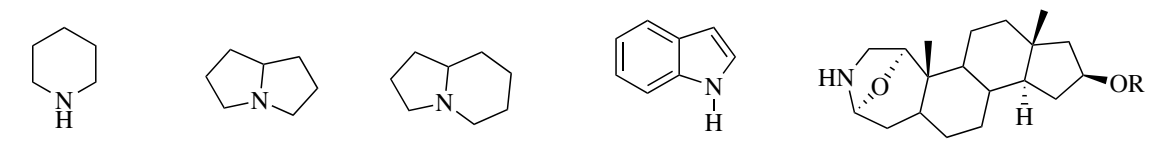
# Chapter Two

## Synthesis of Biologically Active Alkaloids via Electron-rich Dearomatization

## 2.1. Introduction to Alkaloids

In a 2002 book by Alfred Hesse entitled "Alkaloids: Nature's curse or blessing?" alkaloids are presented as "nitrogen-containing organic substances of natural origin."[1,2] Alkaloids have been studied for many years and continue to be of interest today. A great scientific effort has been put forth to isolate and identify a variety of alkaloids because of their biological activity and potential for medicinal purposes. A 2005 review by Daly et al. detailed the findings of alkaloids discovered in amphibian skin.[3] Over 300 new alkaloids were added to the 500 that had already been discovered previously in 1999 by Daly et al.[3,4] In essence, the discovery of small nitrogen-containing molecules isolated from nature continues to expand exponentially even after many years of study. The alkaloids discovered range in size from small six membered rings, like a piperidine to the large steroid-like Samandarines. Several common alkaloid cores are shown in Figure 2.1. Because of the diversity of alkaloids found in nature and their potential therapeutic properties the synthesis of alkaloids in all forms is a significant research interest.




Piperidine Pyrrolizidine Indolizidine Indole-based alkaloid (+)-Samandarine

**Figure 2.1** Examples of nitrogen based alkaloid-cores found in amphibian skin.

## 2.2 Epibatidine and 7-Azanorbornanes

Epibatidine is a specific example of a biologically active nitrogen-containing alkaloid isolated from amphibian skin (Figure 2.2). This azabicyclic ring is isolated from the frog *Epipedobates tricolor* (Phantasmal Poison Frog) and is found to have unusual pharmacological properties.[5] Epibatidine shows potential as an analgesic as it is 200 times more potent than morphine but it is not an opioid reducing the risk of addiction.[3] Unfortunately epibatidine has not been used as a pharmaceutical because it was found to have toxic properties. However, because of the biological implications of a non-opioid analgesic, epibatidine was an important synthetic target. Notably, in 1993 Corey et al. successfully synthesized epibatidine after a nine step synthesis.[6] While the Corey Group, and many others successfully prepared epibatidine, their laborious efforts revealed the synthetic challenge in creating such a complex alkaloid.

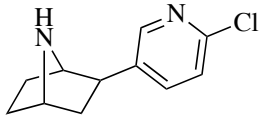
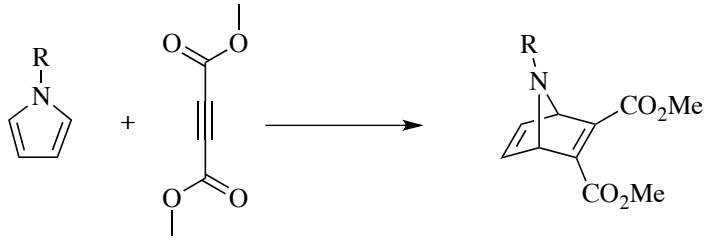



**Figure 2.2** Epibatidine

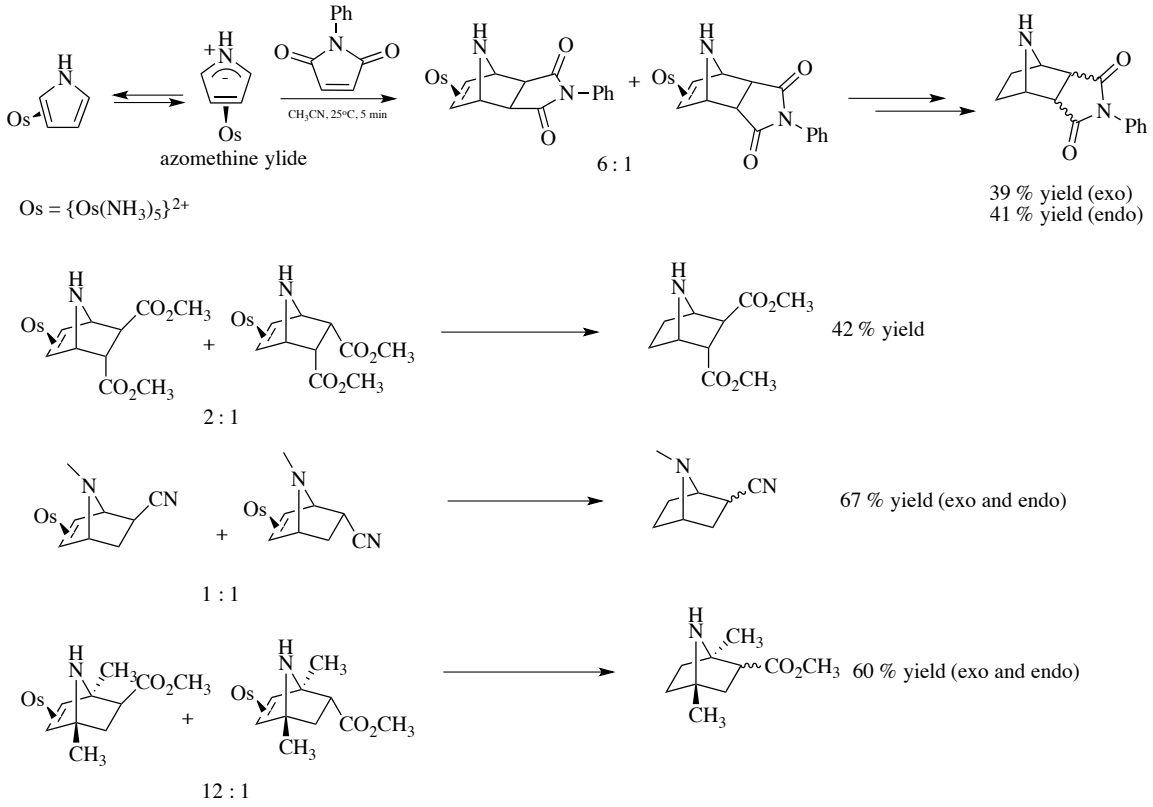
A general route used for the synthesis of 7-azanorbornanes (like epibatidine) is through Diels-Alder cycloadditions with electron-deficient pyrroles and alkynes (Scheme 2.1).[7] These reactions are very limited in scope, requiring an electron withdrawing group on the nitrogen of pyrrole; unsubstituted pyrrole will not perform these reactions.[7] A central issue with Diels-Alder reactivity of pyrroles is the instability of the cycloadduct product and its likelihood to decompose.[7-11] Advantageously, similar cycloaddition reactions can take place under ambient conditions, using an electron-rich pentaammineosmium(II) dearomatization system.

**Scheme 2.1** Diels-Alder reaction to form 7-azanorbornene core.




As discussed in Chapter 1, electron-rich dearomatization is a powerful synthetic tool that can activate aromatics to perform reactions that would not be possible otherwise. Using the pentaammineosmium(II) system, pyrrole is dihapto-coordinated across carbons 2 and 3. However, this coordination mode exists in equilibrium with the metal binding across carbons 3 and 4. When bound across C3 and C4 the pyrrole becomes an azomethine ylide, a very reactive species which readily undergoes 1,3-dipolar cycloadditions (Scheme 2.2).[12] The pentaammineosmium(II) pyrrole complex is able to perform cycloadditions with various dipolarophiles such as: *N*-methylmaleimide, dimethyl maleate, dimethyl fumurate, methyl acrylate, acrylonitrile, methylene-γ-butyrolactone, and others (Scheme 2.2).[13] This type of reaction is possible because of metal stabilization and could not be achieved under ambient conditions without the metal. The reactivity of pyrroles activated through dihapto-coordination to the pentaammineosmium(II) system was explored and the results published in a series of articles from 1989-1995.[14]

**Scheme 2.2** Cycloaddition of *N*-phenylmaleimide and Os($\eta^2$-pyrrole) and other examples of successful cyclo additions




Using the pentaammineosmium(II) dearomatization agent to activate pyrrole, several epibatidine analogs can be synthesized and isolated.[13] Although epibatidine itself could not be created using this method, the utility of the electron-rich dearomatization method is clearly demonstrated. Beginning with an unreactive aromatic molecule, a valued natural product analog can be isolated under ambient conditions solely because of the electron-donating ability of the osmium(II) fragment. The increased reactivity of pyrrole, afforded by the osmium(II) fragment, began the pursuit of nitrogen containing, biologically active species made from dearomatized nitrogen-containing aromatic molecules.

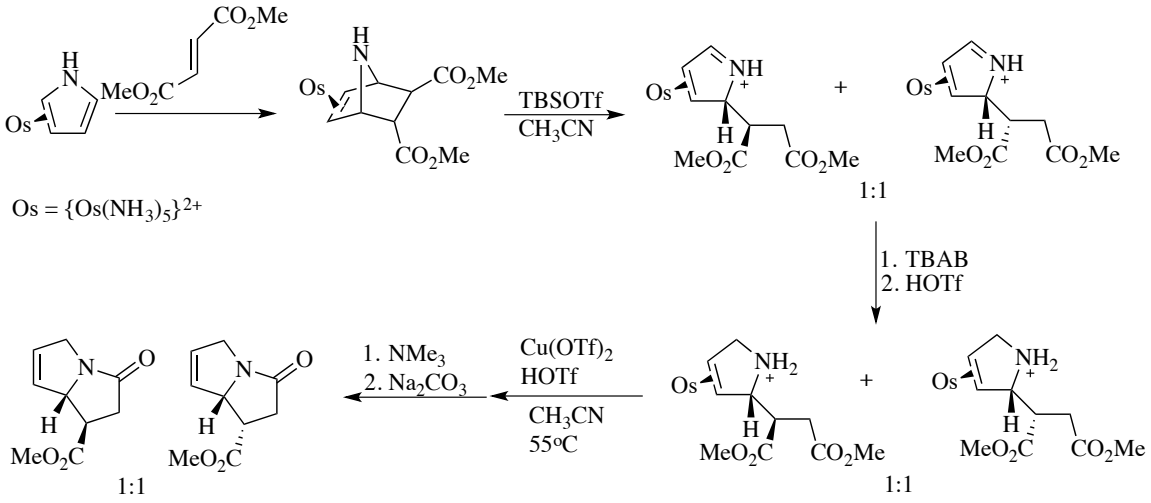
## 2.3 Synthesis of Pyrrolizidines Cores Using the Pentaammineosmium(II) System

In the 2005 Daly review, the authors identify pyrrolizidines as a prominent alkaloid in amphibian skin, reporting over two dozen.[3] Pyrrolizidines are characterized by two five-membered rings with a bridgehead nitrogen as seen in Figure 2.1. Presently, the biological activity of pyrrolizidines is under investigation. It has been reported that pyrrolizidines are successful β-galactosidase and β-mannosidase inhibitors.[15] One study has been published detailing the use of pyrrolizidne-rich tree bark and other leaves for the treatment of ailments from bacterial infections to breast cancer.[16] Because they are found in nature and show interesting biological activity, pyrrolizidines are important targets for synthetic chemists.

In one study by Donohoe et al, a pyrrolizidine core was isolated beginning with *N*-boc protected pyrrole.[17] Two enantiopure, hydroxylated pyrrolizidines are isolated, one after 12 and the other after 16 synthetic steps. As observed with epibatidine, the syntheses of these biologically active alkaloids are typically very labor intensive. It would be useful to have a synthetic route that can reach pyrrolizidines in fewer synthetic steps.

In addition to epibatidine analogs, the pentaammineosmium(II) dearomatization agent is able to encourage the chemical transformation of pyrroles to pyrrolizidines. In the pursuit of reaction conditions to isolate the 7-azanorbornene described earlier, a retro-Mannich ring opening can occur to form α-substituted-2H-pyrrolium compounds which can ring close to form a pyrrolizidine core (Scheme 2.3).[18] Although some success has been observed in isolating pyrrolizidines from pyrrole precursors using this method, the overall reaction scheme is limited in scope.[19]

**Scheme 2.3** Synthesis of pyrrolizidine core from Os($\eta^2$-pyrrole).



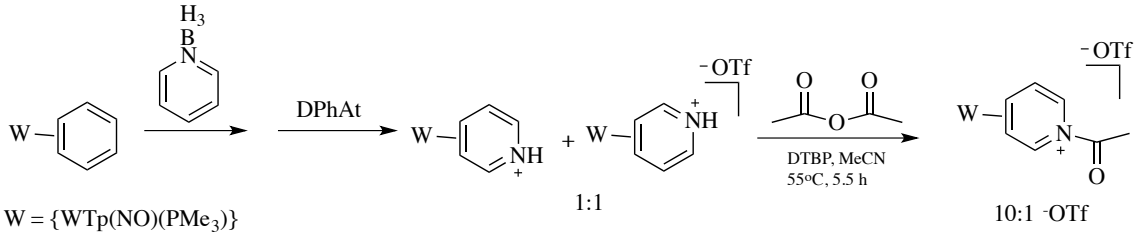

## 2.4 Synthesis of Piperidine Analogs Using a Tungsten(0) Dearomatization Agent

Piperidines are saturated, six-membered rings that contain one nitrogen heteroatom as seen in Figure 2.1. They can be found in amphibian skin and they exist in a wide variety of substitution patterns.[3] Piperidine analogs can be synthesized from pyridine using the electron-rich dearomatization agent, {WTp(NO)($PMe_3$)}. In the 2005 Daly review, over 30 piperidines were discovered and characterized with a wide range of substituents including: alkyl chains, ethers and hydroxyl groups.[3] Using the tungsten(0) dearomatization agent pyridine is dihapto-coordinated and activated towards addition reactions to form piperidine analogs.

It is with some difficulty that pyridine is dihapto-coordinated to the tungsten(0) fragment because of its preference to bind $\kappa^1$ to the metal through nitrogen's lone pair.[20] However, when pyridine-borane is in solution with W($\eta^2$-benzne) followed by

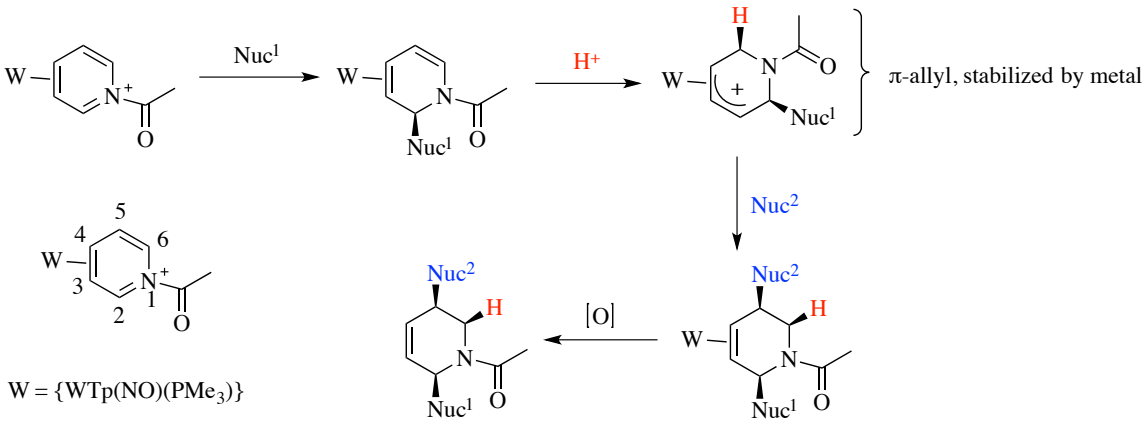
protonation and the addition of an acyl protecting group, the W($\eta^2$-acylpyridinium) complex can be isolated (Scheme 2.4).[20-25]

**Scheme 2.4** Synthesis of W($\eta^2$–acylpyridinium).




Dihapto-coordinated pyridine undergoes nucleophilic addition exclusively at the C2 position, with the nucleophile adding anti to the metal. A variety of dihydropyridine complexes can be isolated (Scheme 2.5**)**.[25] The dihapto-dihydropyridine complex resembles the structure of an enamide but shows an umpolung of reactivity. Because of the metal's influence, the α carbon of the enamide shows remarkable nucleophilicity and can be protonated easily.[24] The complex formed after protonation is a π-allyl and it is susceptible to a second nucleophilic addition at C5. The resulting addition takes place *anti* to the metal (Scheme 2.5).[24] The coordinated-tetrahydropyridines formed using dihapto-coordinated pyridine can be removed from the metal using various oxidation agents (CAN, DDQ, $O_2$, and $I_2$).[24] The isolated tetrahydropyridines have a single unsaturated bond remaining with the potential for further chemical modification (Scheme 2.5). If one exploits this unsaturated bond and removes the acyl-protecting group piperidine alkaloids can be formed beginning with pyridine.

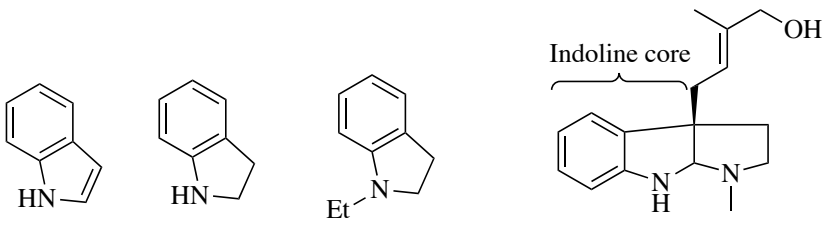
**Scheme 2.5** Synthesis of tetrahydropyridines via activation of W($\eta^2$-acylpyridinium).




Although a fully saturated piperidine was never synthesized in our lab, piperidine analogs were created with the potential for further chemical elaboration. In addition to the two nucleophiles adding regio- and stereoselectively to the pyridine, the unsaturated bond available after metal oxidation represents yet another site for modification at a chemist's discretion. Through dihapto-coordination to the electron-rich tungsten(0) fragment, pyridine is activated towards addition reactions that can lead to the creation of tetrahydropyridines, which are analogs of the biologically active piperidine.[20-26]

## 2.5 Synthesis of Indole Analogs Using a Tungsten(0) Dearomatization Agent

Another example of a biologically active, nitrogen-containing alkaloid is indole (Figure 2.3). One example of these indole-based molecules is pseudophrynaminol which is found to be a potent noncompetitive blocker of nicotine receptors (Figure 2.3).[4] It is believed that other indole-analogs might have similar biological activity and therefore are important synthetic targets with the potential for pharmaceutical utility.

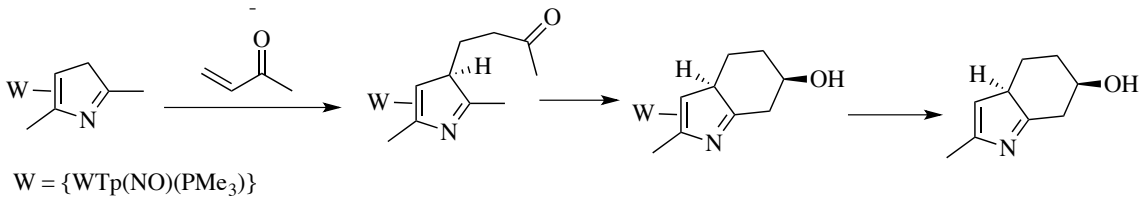



Indole Indoline *N*-ethylindoline pseudophrynaminol

**Figure 2.3** Examples of indole, indole analogs and the biologically active pseudophraynaminol.

The first instance of an indole-core being formed using a tungsten(0) dearomatization agent is through the dihapto-coordination of 2,5-dimethylpyrrole. $\eta^2$-coordination of 2,5-dimethylpyrrole across carbons 4 and 5 in the presence of a Michael acceptor encourages an addition at C3. After several hours an intramolecular cyclization takes place yielding an indole-core (Scheme 2.6). Oxidation of the metal liberated several of the organic tetrahydroindoles but most oxidation attempts do not yield clean organic products. Despite the successful formation of a tetrahydroindole core from 2,5-dimethylpyrrole, the overall reaction scheme did not yield a great number of organic products. The reactivity of dihapto-coordinated pyrrole complexes will be discussed in greater detail in the following chapter.

**Scheme 2.6** Synthesis of a tetrahydroindole from 2,5-dimethylpyrrole.

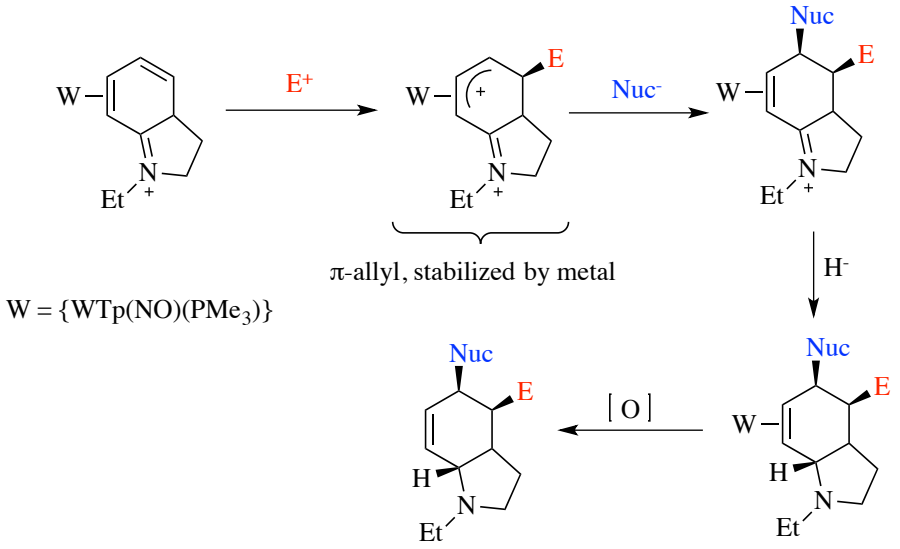



W = {WTp(NO)($PMe_3$)}

In the pursuit of a variety of substituted indole-based analogs, we explored the dearomatization of the indole derivative *N*-ethylindoline. The dihapto-coordinated conjugate acid of *N*-ethylindoline, W($\eta^2$-*N*-ethylindolinium), can be isolated. The coordination mode of this indolinium complex resembles the structure of the dihapto-

coordinated *N,N*,-dimethylanilium complex, which shows remarkable proclivity for chemical modification.[27] Once $\eta^2$-coordinated, the tungsten *N*-ethylindolinium complex is able to undergo electrophilic addition with a range of electrophiles (proton, fluorine, and oxygen) to form a π-allyl complex similar to that observed with dihapto-coordinated pyridine (Scheme 2.7). Once the π-allyl complex forms, a myriad of nucleophiles can be added, creating a variety of addition products that could not have formed with uncoordinated indoline. Following reduction of the iminium and metal oxidation, a series of hexahydroindoles were isolated and submitted for biological screening (Scheme 2.7).[28] As seen with the tetrahydropyridines discussed earlier, following oxidation of the metal, there is one remaining alkene on the isolated organic that can be further exploited if desired.

**Scheme 2.7** Synthesis of hexahydroindoles via activation of W($\eta^2$-*N*-ethylindolinium).




Using electron-rich dearomatization techniques, a collection of nitrogen-containing alkaloids has been synthesized. Each isolated organic is an analog of a biologically active molecule (Figure 2.4). Many of the organic molecules made using the

electron-rich dearomatization techniques have been submitted for biological screening.[13,18,24,28]

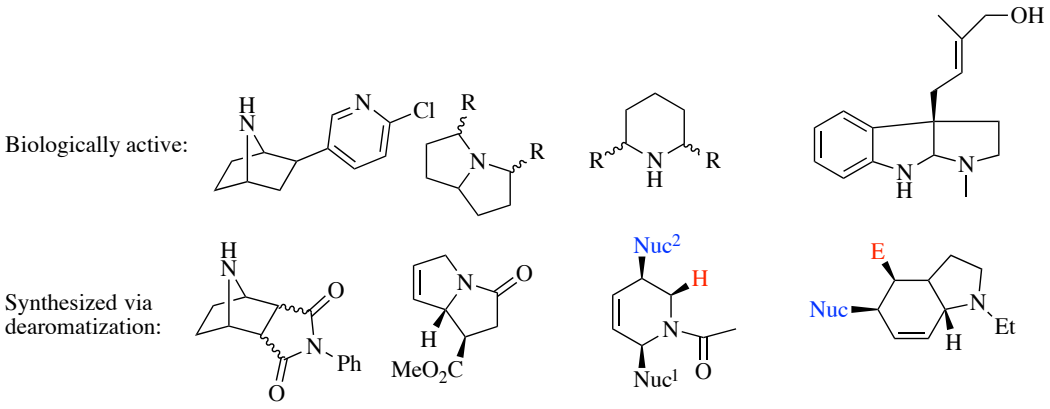


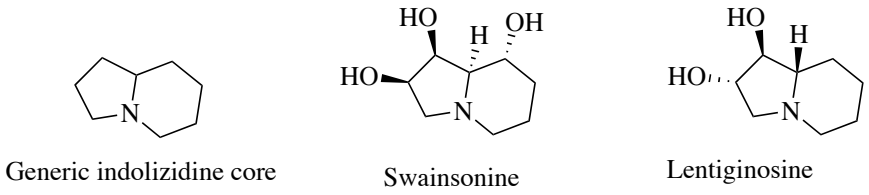

**Figure 2.4** Comparision of biologically active molecules and those synthesized through electron-rich dearomatization.

## 2.6 Synthesis of Indolizidine and Quinolizidine cores Using a Tungsten(0) Dearomatization Agent

### 2.6.1 Indolizidines

One of the most prolific nitrogen-containing alkaloids discussed by Daly et al is the indolizidine.[3] An indolizidine is a fused five and six membered ring with a bridgehead nitrogen (Figure 2.5). Indolizidines exist in innumerable substitution patterns. In the 2005 *Natural Products Review* over 200 different indolizidines were identified from the poison dart frogs under investigation.[3] Although there are countless indolizidines with interesting biological activity, two that are of particular interest to the

biological and synthetic community are swainsonine, a trihydroxylated-indolizidine with hydroxyl groups at the 1, 2 and 8 positions and lentiginosine with hydroxyl groups at the 1 and 2 positions (Figure 2.5).




Generic indolizidine core Swainsonine Lentiginosine

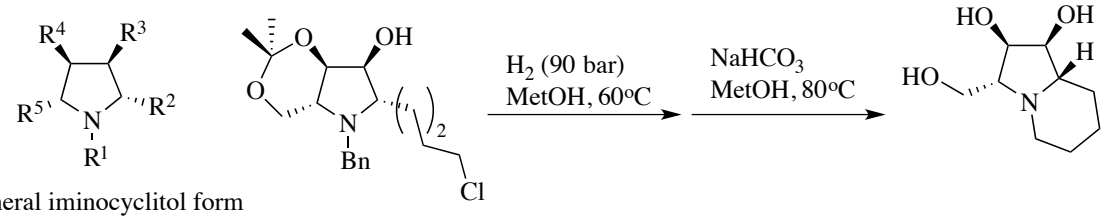
**Figure 2.5** Generic indolizidine, swainsonine and lentiginosine.

The biological activity of swainsonine was first apparent when livestock feeding off certain plants developed a neurological disorder. These plants were aptly named "locoweeds" for the issues they caused in the livestock that fed on them.[29] Years later experiments found that swainsonine is the biologically active molecule that caused the neurological disease.[29] Swainsonine is a potent α-mannosidase inhibitor, which interferes with the breakdown of sugars in the body causing mannosidosis.[16,30,31] Despite the detrimental biological effects of swainsonine in livestock, the biological activity of the indolizidine was further explored. Future research would find use for swainsonine in clinical trials for its ability to potentially treat cancer, HIV, and several immunological disorders.[32]

Swainsonine is just one example of a biologically active indolizidine under investigation for therapeutic properties. In 2016, Dr. Joseph P. Michael published an extensive chapter entitled "Simple Indolizidines and Quinolizidine alkaloids" detailing many recent syntheses for dozens of indolizidines and quinolizidines.[33] Nearly all of the syntheses described are labor-intensive, multi-step processes. To our knowledge, there are no simple syntheses to isolate individual indolizidines or a simple methodology that could lead to a variety of indolizidines. In 2015, Bergeron-Brlek et al. synthesized a

series of iminocyclitols using a single reaction, which they then converted to several indolizidines (Scheme 2.8).[34] Although this method somewhat represents a general motif with the potential for indolizidine variability, the scope presented by the authors is still fairly narrow, and does not achieve the goal of a simple indolizidine synthesis with the potential for varying substituents. A synthetic methodology enabling the isolation of indolizidines with the potential for derivation would be useful to the synthetic community as these molecules are of great interest due to their potential biological activity.

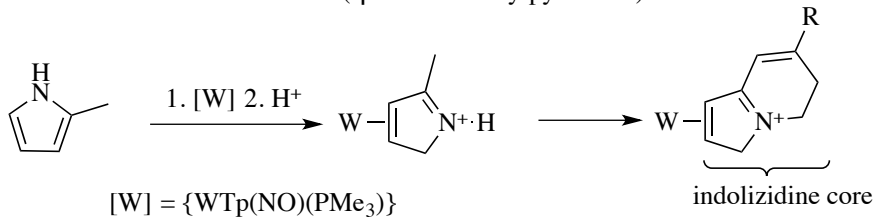
**Scheme 2.8** General iminocyclitol form; example of indolizidine synthesis from an iminocyclitol isolated.




General iminocyclitol form

The tungsten dearomatization agent {WTp(NO)($PMe_3$)} is able to dihapto-coordinate pyrroles and activate them toward addition reactions. It was later discovered that tungsten(0) can coordinate the conjugate acid of 2-methylpyrrole forming a W($\eta^2$-2H-2-methylpyrrolium) complex. After dihapto-coordination, a Michael addition can take place followed by an intramolecular cyclization that forms an indolizidine core (Scheme 2.9).[35] It is important to note that the Michael addition and cyclization take place in a single-pot reaction. It was hypothesized that this reaction sequence could be incorporated into a general synthetic scheme to prepare novel indolizidines. This will be discussed in chapters 3 and 4.

**Scheme 2.9** General route for W(η²–2H-2-methylpyrrolium) to an indolizidine core.

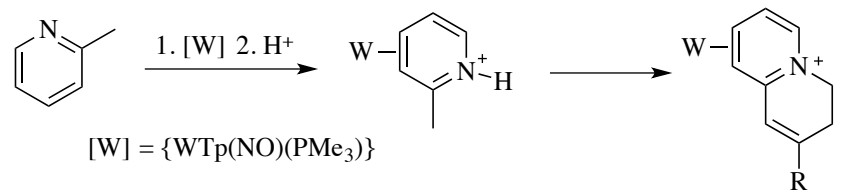



## 2.6.2. Quinolizidines

Though not as prolific as indolizidines, quinolizidines are a similar class of nitrogen-based alkaloid that can be isolated from amphibian skin.[3] A quinolizidine is composed of two fused six-membered rings with a bridgehead nitrogen. Like indolizidines, their syntheses are often multi-step and specifically tailored towards each quinolizidine (many examples can be found in the chapter by Dr. Michael).[33] However, because they show biological activity as glucosidase inhibitors, they remain important synthetic targets in the hope that their biological activity could prove therapeutic.[36]

Because an indolizidine core is able to be prepared from a 2-methylpyrrole precursor using the tungsten dearomatization agent, it was hypothesized that a similar cyclization could take place using a pyridine analog to form quinolizidine cores (Scheme 2.10). The results of this pursuit will be discussed in Chapter 5.

**Scheme 2.10** Proposed route for W(η²–2-picolinium) to a quinolizidine core.



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# Chapter Three

## Formation and Reactivity of the 2H-tautomer of Dihapto-Coordinated 2-methylpyrrole

## 3.1 A General Introduction to Pyrrole

Pyrrole is a five-membered-aromatic ring with a nitrogen heteroatom. The aromatic π-system of pyrrole is made up of two unsaturated bonds as well as a lone pair on the nitrogen. The lone pair on nitrogen is part of the aromatic system because it sits in a *p*-orbital that is symmetric with the overall cyclic array of π-electrons in the ring. The presence of a lone pair affords pyrrole several resonance structures (Figure 3.1).

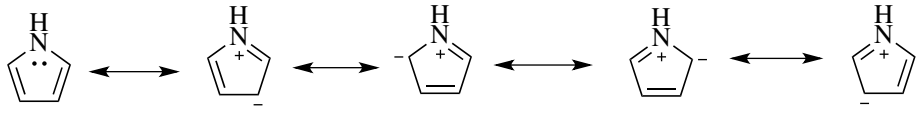
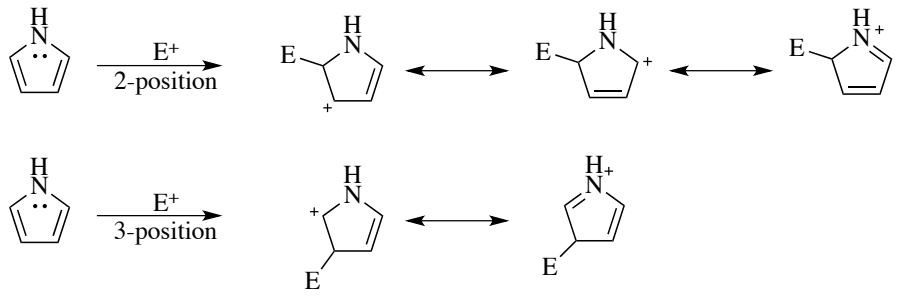


**Figure 3.1** Resonance structures of pyrrole.

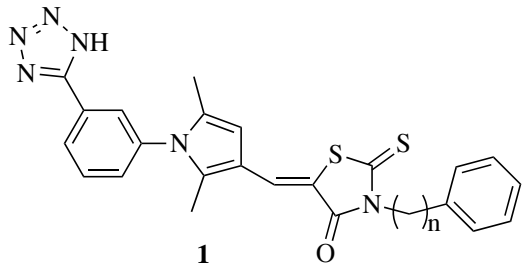
Because pyrrole is an aromatic molecule it is more susceptible to substitution reactions than addition reactions that disrupt aromaticity. The most common substitution reaction known to pyrrole is electrophilic aromatic substitution (EAS). Compared to benzene, pyrrole is much more electron-rich and therefore better prepared to react with electrophiles.[1] For unsubstituted pyrrole, there are two carbons where an electrophile can add, α or β to the nitrogen. The usual result for electrophilic substitution is at the α-carbon because of the added resonance stabilization as can be seen in Scheme 3.1.

**Scheme 3.1** Electrophilic Aromatic Substitution of pyrrole.



EAS of pyrroles has led to a variety of important biological molecules. Such substituted pyrroles have shown potential biological activity for: antimicrobial, anti-viral,

anti-malarial, anti-convulsant, anti-inflammatory, anti-cancer, anti-psychotic and anti-hypertensive.[2] One example of a pyrrole-based molecule that shows HIV inhibitory properties is **1** and it can be seen in Figure 3.2.




**1**

**Figure 3.2** Pyrrole ring in biologically active species.

Because of their likelihood to undergo substitution reactions, Mal et al. wrote in a 2011 book chapter about heterocycles that 'pyrrole-containing small molecules' are rarely encountered in natural sources because of the exceptional reactivity of the pyrrole moieties to electrophilic substitution.[3] In this light, pyrrole is very reactive and can be used to create many useful pyrrole-based molecules, some of which have therapeutic potential.

Considering an alternative method for pyrrole reactivity, if pyrrole were susceptible to addition-type reactions, it could be used in the synthesis of a class of pyrrolenes and pyrrolidines. Notably, 2,5-disubstituted pyrrolidines have been isolated from natural sources and have shown to have some biological activity.[4] With the goal of increasing the reactivity of pyrrole, a great scientific effort has been put forth to dihapto-coordinate pyrrole to an electron-rich metal fragment and activate it towards unexpected reactivity.

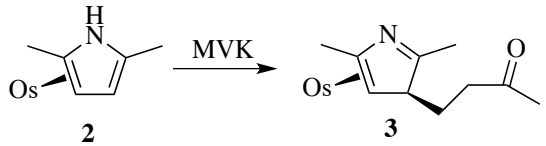
### 3.2 Previous work on the Electron-rich Dearomatization of Pyrroles

Because of the aromaticity of pyrrole, the chemical elaborations allowed by the heterocycle are limited; substitution reactions are most normally observed. A method of encouraging unexpected reactivity with pyrrole is through dihapto-coordination to an electron-rich metal fragment. Once $\eta^2$-coordianted, pyrrole becomes susceptible to increased reactivity broadening the scope of chemical modifications possible. Pyrrole has been dihapto-coordinated by the osmium(II), rhenium(I), and tungsten(0) dearomatization agents and their results will be discussed presently.

The pentaammineosmium(II) dearomatization agent is able to coordinate pyrrole and form a stable dihapto-complex. Once coordinated, the electron-density of the metal disrupts pyrrole's aromaticity and activates the aromatic to electrophilic addition. The metal binds to pyrrole across carbons 2 and 3 but is in rapid equilibrium with its alternative coordination form across carbons 4 and 5. Evidence for this equilibrium, is observed in the broadening of shifts in the $^1$H NMR spectrum at ambient temperatures.[5] Because of the increased electron-density of the dihapto-coordinated pyrrole, it develops enamine characteristics as evidenced by soft electrophiles adding to the β-carbon. An example can be seen with methyl vinyl ketone (MVK) and dihapto-coordinated 2,5-dimethylpyrrole (**2**) to form (**3**, scheme 3.2). These reactions take place regio- and stereoselectively due to influence by the metal.[6-10] While this is a small modification to the pyrrole ring it represents the ability of the osmium(II) system to activate dihapto-coordinated pyrrole to reactivity that would not be possible otherwise. The other noted reactivity of dihapto-coordinated pyrrole is that of the azomethine ylide that enables

cycloaddition reactions to occur. These cycloadditions form 7-azanorbornene cores, which were discussed in the previous chapter (see section 2.2).[11] Despite the pentaammineosmium(II) fragment's ability to activate pyrrole and other aromatics towards increased reactivity, the cost, toxicity and achirality of the metal center led us to design other dearomatization agents.

**Scheme 3.2** Michael addition of MVK to Os($\eta^2$-2,5dimethylpyrrole).

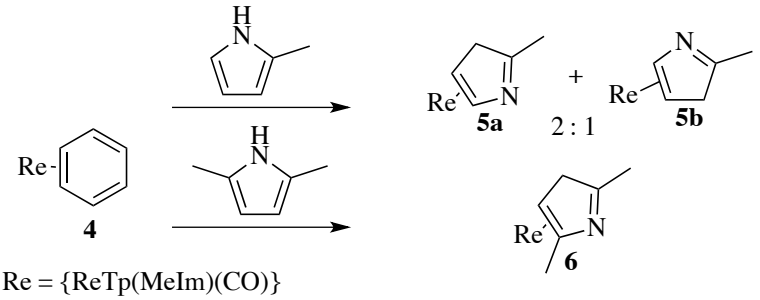



**2** **3**

Os = $[Os(NH_3)_5]^{2+}$

When pyrrole is in the presence of the rhenium(I) dearomatization agent, {ReTp(MeIm)(CO)}, a paramagnetic $\kappa^1$ pyrrolyl product forms. To circumvent this issue *N*-methylpyrrole, 2-methylpyrrole and 2,5-dimethylpyrrole were used instead. It was found that this simple steric alteration is enough to prevent N-H insertion. However, upon dihapto-coordination of 2-methylpyrrole and 2,5-dimethylpyrrole, the 3H tautomer forms (**5** and **6**, Scheme 3.3). For 2-methylpyrrole two coordination diastereomers are observed: nitrogen down (**5a**) and nitrogen up (**5b**) in a 2:1 ratio. 2,5-dimethylpyrole (**6**) forms with nitrogen down only (Scheme 3.3).[12]

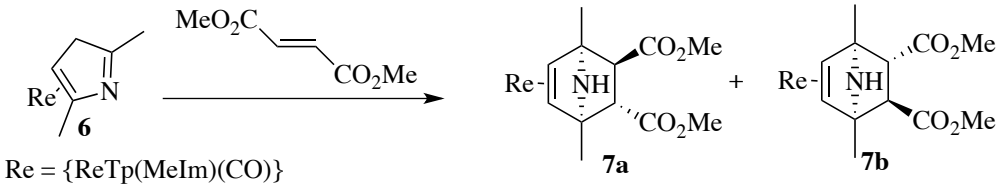
**Scheme 3.3** Rhenium(I) dihapto-coordination of 2-methyl and 2,5-dimethylpyrrole.




Re = {ReTp(MeIm)(CO)}

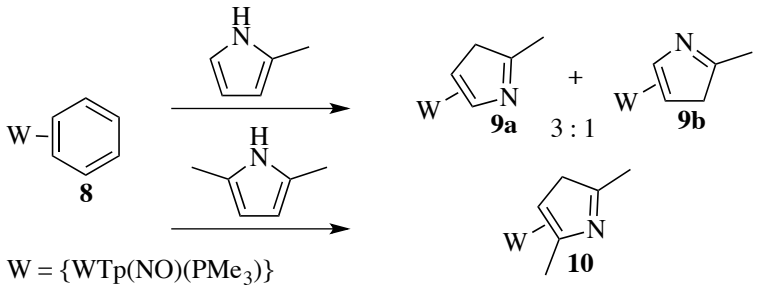
Because of the cycloaddition reactivity observed with the Os($\eta^2$-pyrrole) system, research was conducted to see if the rhenium(I) dearomatized pyrrole was capable of similar transformations.[13] Pleasantly it was found that the rhenium(I) complex of 2,5-dimethylpyrrole (**6**) undergoes cycloaddition with dimethyl fumarate to yield the respective diastereomeric cycloadducts (**7a** and **7b**, Scheme 3.4).[13] Unfortunately attempts to isolate these organic products resulted in their decomposition. Because of cost and practical scalability issues with the rhenium(I) system, a tungsten(0) dearomatization agent was implemented and its reactivity with pyrrole explored.

**Scheme 3.4** Cycloaddition of *trans*-dimethyl fumurate with Re($\eta^2$-2,5-dimethylpyrrole).



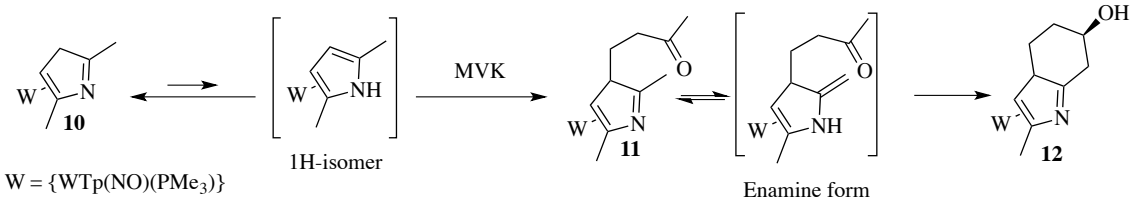

When pyrrole is in solution with W($\eta^2$-benzene) (**8**) the dihapto-coordinated product of pyrrole is not observed. Instead a tungsten-hydride complex forms as evidenced by the $J_{PW} \sim 125$ Hz in the $^{31}$P NMR spectrum.[12] Coordination of a pyrrolyl ligand does not increase the reactivity of the ligand as if pyrrole had been dihapto-coordinated. As observed with rhenium, a simple increase in steric bulk enables the successful $\eta^2$-dearomatization of pyrroles. 2-methylpyrrole forms its 3H tautomer of nitrogen down (**9a**) and nitrogen up (**9b**) in a 3:1 ratio and 2,5-dimethylpyrrole forms solely nitrogen down (**10**, Scheme 3.5).[12]

**Scheme 3.5** Tungsten(0) dihapto-coordination of 2-methyl and 2,5-dimethylpyrrole.




In reactivity similar to that observed with the rhenium(I) dearomatization agent, cycloaddition reactions were able to be performed on W($\eta^2$-2,5-dimethylpyrrole) (**10**).[13] Further exploration was conducted to explore the tungsten(0) dihapto-coordinated 2,5-dimethylpyrrole's increased reactivity.[13] When W($\eta^2$-2,5-dimethylpyrrole) (**10**) is put in THF with a Lewis acid (LiOTf) in the presence of a Michael acceptor, the resulting product shows addition to C3 of pyrrole (**11**, Scheme 3.6).[14] This reactivity suggests the existence of dihapto-coordinated-1H isomer of pyrrole (Scheme 3.6). Pleasantly, it was found that several of these Michael addition products continue through an intramolecular cyclization to form an indole core (**12**).[14] This cyclization likely happens through the formation of an enamine external to the ring.

**Scheme 3.6** Formation of an indole-like core from W($\eta^2$-2,5-dimethylpyrrole).



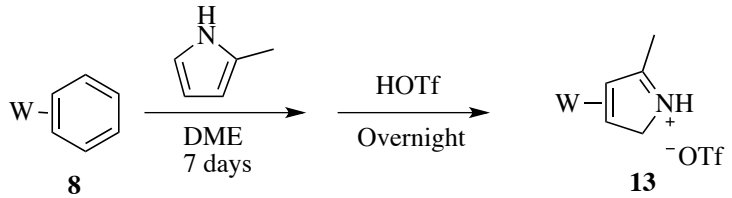

While the dearomatization of pyrroles using the tungsten(0) dearomatization agent, {WTpNO(PMe$_3$)}, has been quite thoroughly explored, there is one coordination mode of pyrrole that had not been investigated in depth. The research that will be discussed presently examines the dearomatized 2H-pyrrolium configuration, which

shows distinct reactivity from the neutral, 3H-pyrrole complexes that were discussed previously.

### 3.3 Isolating the Tungsten(0) Coordinated 2H-pyrrolium Complex

The tungsten(0) dearomatization agent, {WTp(NO)($PMe_3$)} is able to form dihapto-coordinated products with 2-methylpyrrole (**9a** & **9b**) and 2,5-dimethylpyrrole (**10**) though both are observed in their 3H tautomers (see Scheme 3.5). However, a different isomer was discovered using 2-methylpyrrole. A former researcher in our lab, Diana A. Iovan discovered that combining 2-methylpyrrole and the W($\eta^2$-benzene) complex (**8**) for seven days, followed by the addition of triflic acid leveled in DME (pKa ~ - 2) overnight leads to the formation of the dihapto coordinated 2H-pyrrolium species (**13**, Scheme 3.7). This 2H-pyrrolium species (**13**) shows different reactivity than its neutral 3H-pyrrole analogs (**9a** & **9b**). Its reactivity will be discussed presently.

**Scheme 3.7** Reaction scheme for formation of W($\eta^2$-2H-2-methylpyrrolium).




**8** **13**

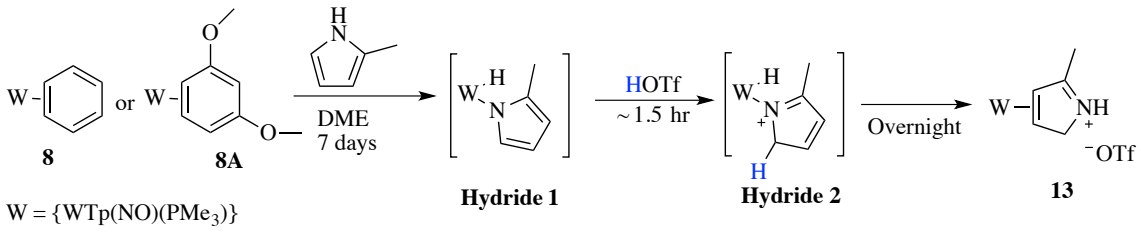
W = {WTp(NO)($PMe_3$)}

### 3.4 Results and discussion

When the benzene complex (**8**) or (as it was later discovered) W($\eta^2$-1,3-dimethoxybenzene) (**8A**) is put in solution with 2-methylpyrrole (synthesized via a

modified Wolff-Kischner reduction of 2-formylpyrrole)[15] the tungsten fragment activates the aromatic in two ways. The immediate result is the formation of two dihapto-coordinated pyrroles (**9a** & **9b**) but a secondary result is activation of the N-H bond of the pyrrole ligand and the resulting product is a 7-coordinate tungsten hydride (**Hydride 1**) as confirmed in $^{31}$P NMR spectroscopy by a $J_{WP}$ = ~ 125 Hz (Scheme 3.8).[16] At room temperature, after 7 days the dihapto-coordinated products (**9a** & **9b**) convert to the tungsten hydride (**Hydride 1**). After the addition of triflic acid leveled in DME (pKa ~ -2) a new hydride species forms (**Hydride 2**) that likely represents α-protonation of the pyrrolyl ligand. Overnight the new tungsten hydride (**Hydride 2**) converts to the desired 2H-pyrrolium complex (**13**, Scheme 3.8). No other compounds were observed in the $^{31}$P NMR spectra.[17] It was found that **8** or **8a** requires 7 days to achieve 100% conversion at ambient temperature. However, complete conversion of **8** or **8A** to **Hydride 1** can also be achieved in two days at 40 °C or 24 hours at 50 °C.

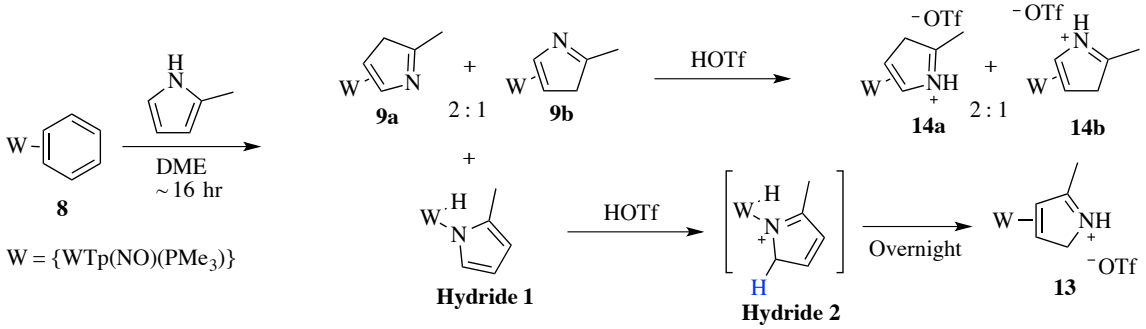
**Scheme 3.8** Formation of two *distinct* hydrides before conversion to W(η$^2$-2H-2-methylpyrrolium).




To better understand the formation of **13**, experiments were conducted to test a reaction intermediate. As mentioned in section 3.2, the neutral 3H-2-methylpyrrole (**9a** & **9b**) species can be isolated. The normal procedure for isolating these two neutral dihapto-complexes (**9a** & **9b**) is nearly the same as for the formation of **13** except for a shorter reaction time and without acid. When **8** or **8A** is put in solution with 2-methylpyrrole three products form initially: **Hydride 1** and the two 3H-neutral species (**9a** & **9b**,

Scheme 3.10).[12] If acid is added at this stage, two dihapto-coordinated products are observed in the $^{31}$P NMR that are *distinct* from the desired **13** and are most likely the protonated 3H-pyrrolium species (**14a** & **14b**, Scheme 3.9). Without isolating **14a** and **14b** they each show distinct $J_{WP}$ values compared the desired **13**. In addition to **14a** and **14b**, a small amount of a third product is observed with the proper chemical shift for **13**, though it is observed in small quantities making $J_{WP}$ determination difficult. If **13** forms, it likely comes from the small amount of **Hydride 1** in solution at the time of acid addition. After acid addition **Hydride 1** converts to **Hydride 2** and then to the desired **13**. From this experiment it was gleaned that in order to form **13**, all of **9a** and **9b** that are initially formed in solution must convert over to **Hydride 1** before protonation can carry **Hydride 1** through the proper reaction pathway to create **13**.

**Scheme 3.9** Formation of dihapto 3H pyrrolium products.




Although the established procedure calls for triflic acid, several alternative acids were tested with varying results. The weak acid Diisopropylammonium triflate (DiPAt, pKa ~ 11.1) is not strong enough to protonate the 7-coordinate species (**Hydride 1**) and carry it to **13**. However, the slightly stronger diphenylammounium triflate (DPhAt, pKa ~ 0.78) and anilinium triflate (pKa ~ 5) are able to convert the 7-coordinate hydride complex (**Hydride 1**) into the desired 2H-pyrrolium complex (**13**) but the resulting products had residual acid impurities. Because triflic acid leveled in DME (pKa ~ - 2) did

not leave any acid remaining in the final product. Triflic acid remains the method of protonation to isolate **13**. After the addition of any of the acids mentioned above, the resulting precipitate of **13** is still impure and requires purification.

The two main methods of purification implemented were trituration and column chromatography. Several alternative routes including extraction with aqueous solvents such as water or sodium bicarbonate were attempted but these methods did not yield a cleaner product. To determine proper trituration conditions, full solubility tests were explored, the results of which can be seen in Table 3.1. Unfortunately a great many of these solvents as well as several combinations did not lead to a cleaner product. The remaining purification technique was column chromatography.

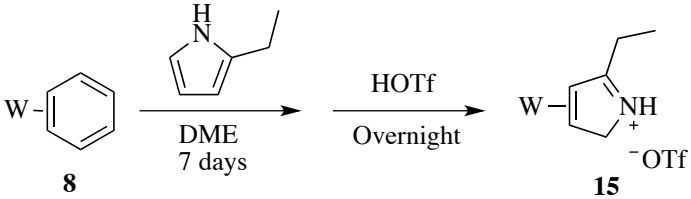
**Table 3.1** Solubility test results of complex **13**.

| Solvent | Result | Solvent | Result |
|---|---|---|---|
| Acetone | Soluble | Toluene | Insoluble |
| Acetonitrile | Soluble | *o*-xylene | Insoluble |
| Benzene | Insoluble | Water | Insoluble |
| Chloroform | Soluble | 2-butanone | Soluble |
| *p*-dioxane | Soluble | Methanol | Soluble |
| DME | Soluble | Ethanol | Soluble |
| DMF | Soluble | *n*-propanol | Soluble |
| DMSO | Soluble | *iso*-propanol | Mostly insoluble |
| Ethyl Acetate | Mostly Soluble | *n*-butanol | Soluble |
| THF | Soluble | *tert*-butanol | Mostly insoluble |

A great effort was put forth to test different column conditions to purify **13**. When choosing the proper solid phase for chromatography it was necessary to consider the acidic proton on the nitrogen. During chromatography the solid phase and mobile phase could be basic enough to deprotonate the nitrogen which would likely lead to decomposition. In keeping with a more acidic solid phase, silica, acidic alumina, deactivated basic alumina and florosil® were attempted. Several column conditions included trace formic acid in the mobile phase to further aid preventing deprotonation. The most successful attempt observed was with deactivated basic alumina but the resulting product was only somewhat cleaner and isolated with low recovery and not consistently. Because of the difficulty in purification, the reactivity of **13** was explored with the expectation that purification will be achieved at a later stage.

Because of the success of the formation of the 2H-pyrrolium complex (**13**), experiments were conducted to test the reactivity of 2-ethylpyrrole (synthesized under modified Wolff-Kischner conditions from 2-acetylpyrrole)[15]. The 2H-ethylpyrrolium complex (**15**) is formed easily, although the isolated product contains impurities in the same manner as **13**. Purification attempts were unsuccessful (Scheme 3.10**)**.

**Scheme 3.10** Reaction scheme for formation of W($\eta^2$-2H-2-ethylpyrrolium) (**15**).



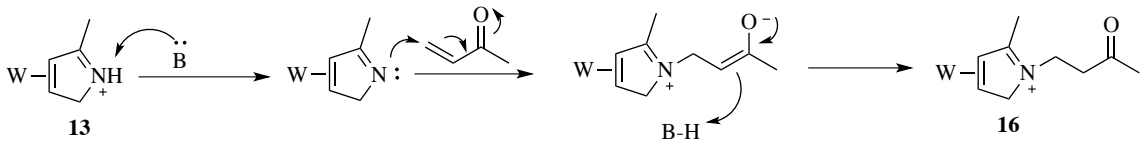

**8** **15**

W = {WTp(NO)($PMe_3$)}

To explore the reactivity of **13**, Michael addition reaction conditions were tested. When **13** is put in solution with methyl vinyl ketone (MVK) and the weak base triethylamine, the Michael adduct (**16**) forms (Scheme 3.11).[17] While the initial procedure

called for 7 hours of reaction time, under more concentrated conditions the reaction time has been reduced to about 4 hours.

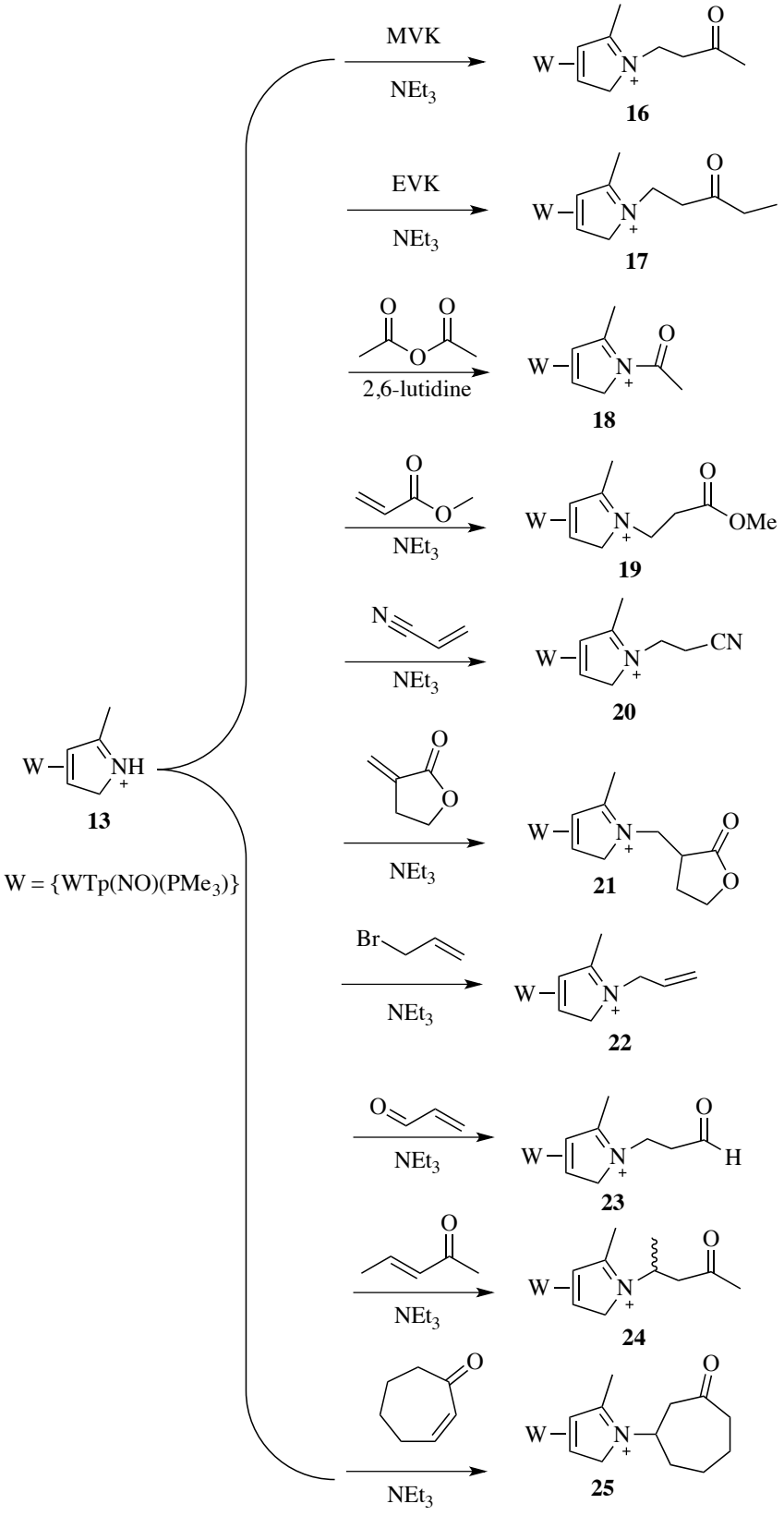
**Scheme 3.11** Reaction mechanism of Michael Addition of MVK to **16**.




W = {WTp(NO)($PMe_3$)}

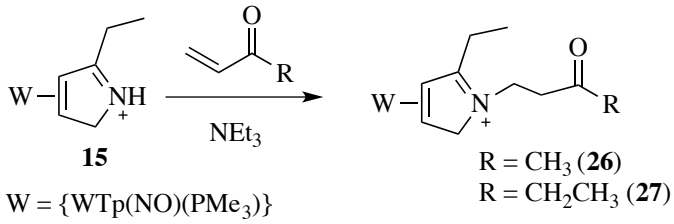
Successful Michael additions include: methyl vinyl ketone (MVK, **16**)[17], ethyl vinyl ketone (EVK, **17**)[17], acetic anhydride (**18**)[17], methyl acrylate (**19**)[17], acrylonitrile (**20**)[17], α-methylene-γ-butyrolactone (**21**),[17] allyl bromide (**22**),[17] acrolein (**23**), 3-penten-2-one (**24**) and 2-cyclohepten-1-one (**25**, see scheme 3.12). Several other Michael acceptors including: 4-hexen-3-one, trans-cinnamonaldehyde, trans-crotonaldehyde and 3-methyl-2-butenal were attempted but clean products were unable to be isolated. 1-acetyl-cyclohexene and mesityl oxide were attempted but neither reaction showed progress, even with the aid of Lewis acids and various solvent/base combinations.

**Scheme 3.12** Current scope of Michael additions to **13**.



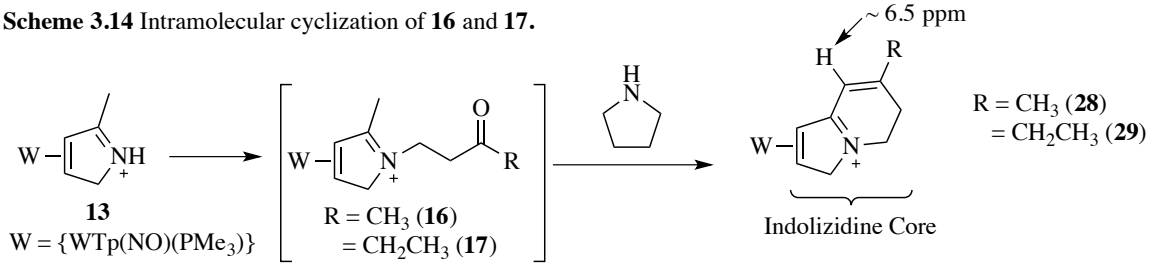
The 2H-ethylpyrrolium complex (**15**) showed reactivity with MVK (**26**) and EVK (**27,** see scheme 3.13). The complexes formed were isolated and fully characterized. Additional exploration of the reactivity of **15** was not conducted as will be explained later in this section.

**Scheme 3.13** Michael addition of MVK and EVK to **15**.




Interestingly, it was observed that after converting **13** to the Michael addition product (**16**) if it is left in solution with pyrrolidine, **16** undergoes an intramolecular cyclization. The resulting product is a dihapto-coordinated indolizidinium core with an α,β-unsaturated iminium (**28**, Scheme 3.14).[17] Similar results were seen with the ethyl vinyl ketone Michael adduct (**17**) which forms the cyclized product **29** (scheme 3.15). The indicator that **28** and **29** form is the presence of an alkene peak around 6.5 ppm in the $^1$H NMR spectrum representing the hydrogen on the α-proton of the unsaturated iminium.

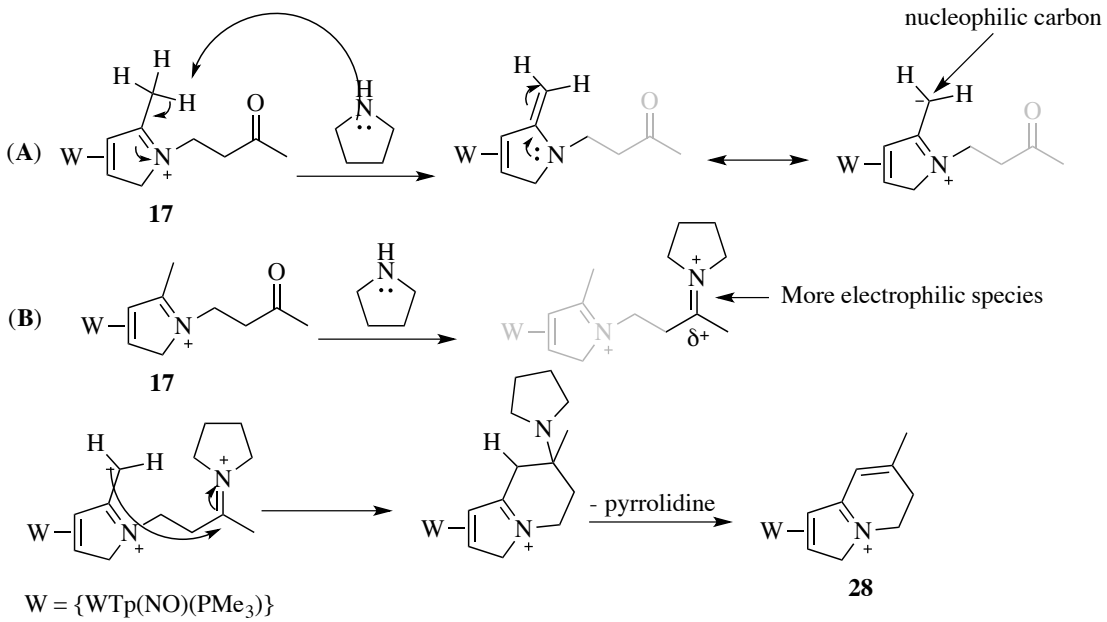
**Scheme 3.14** Intramolecular cyclization of **16** and **17.**




The subtleties of the intramolecular cyclization must be considered in two parts. For explanation purposes, the MVK adduct (**16**) will be discussed. First, the dihapto-coordinated pyrrole ring shows extraordinary reactivity, as the methyl group must be deprotonated in order to react with the Michael adduct in the cyclization. Deprotonation

of the methyl is likely permissible because of the added stabilization the anion receives being in conjugation with the iminium (A, Scheme 3.15). The next feature of consequence is the electrophilic carbon of the Michael Adduct. In the case of the MVK adduct (**16**) the carbon of the ketone is the electrophilic position where the cyclization takes place. The intramolecular cyclization does not occur solely in the presence of triethylamine, pyrrolidine must be present for the cyclization to proceed. Despite triethylamine and pyrrolidine's similar basicity, the notable difference is that triethylamine is a tertiary base while pyrrolidine is secondary, which can help lead to an iminium intermediate (B, Scheme 3.15). There is precedent for a secondary amine catalyzing reactions by forming an *in situ* iminium making the carbon of the original ketone much more electrophilic.[18] The overall reaction can be seen in scheme 3.15.

**Scheme 3.15** Activation of the exocyclic methyl group and the carbonyl to encourage intramolecular cyclization.




Once the intramolecular cyclization takes place, pyrrolidine is lost and the $\eta^2$-indolizidnium complex (**28**) is formed. While monitoring the progress of this reaction by $^{31}$P NMR spectroscopy, it was observed that the cyclized product could ring-open and

revert back to the Michael adduct (**16**), which can also revert back to the 2H-pyrrolium complex (**13**). It was believed that water could be attributed to these retro-reactions. To drive the equilibrium forward, the reaction is performed using chloroform that has been dried through activated basic alumina and the pyrrole complex is kept under very dilute conditions to minimize the effect of the water byproduct. After column chromatography on deactivated basic alumina, clean **28** can be isolated.

The intramolecular cyclization of the 2H-2-methylpyrrolium MVK adduct (**28**) forms easily from **16**, as does cyclization of the EVK adduct (**17**) to form the relative dihapto-coordinated indolizidinium, **29**. Unfortunately, similar results are not observed for the 2H-ethylpyrrolium complexes, **26** or **27**. This result could stem from a change in deprotonation ability of the methyl of **13** versus the methylene of **15**. The 2H-2-ethylpyrrolium complex (**15**) was set aside to explore in more depth the intramolecular cyclization that led to **28** and **29**.

### 3.5 Conclusion

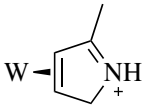
It was discovered that allowing W($\eta^2$-benzene) or W($\eta^2$-1,3-dimethoxybenzene) to react with 2-methylpyrrole for 7 days followed by the addition of acid, the dihapto-coordinated 2H-2-methylpyrrolium isomer can be isolated. The 2H-2-methylpyrrolium tautomer showed the ability to perform a Michael addition at the nitrogen. It was found that the Michael additions of methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) were able to undergo an intramolecular cyclization to form a dihapto-coordinated indolizidinium core. This indolizidinium core is analogous to the biologically active

indolizidine class of molecule and it was formed in two steps beginning with 2-methylpyrrole.

### 3.6 Experimental Procedures

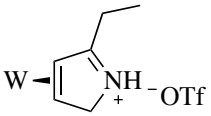
**General Methods**. NMR spectra were obtained on a 300, 500, 600 or 800 MHz spectrometer. All chemical shifts are reported in ppm, and proton and carbon shifts are referenced to tetramethylsilane (TMS) utilizing residual $^{1}H$ or $^{13}C$ signals of the deuterated solvents as an internal standard. Phosphorous NMR signals are referenced to 85% $H_3PO_4$ (δ 0.00) using a triphenyl phosphate external standard (δ -16.58). Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra (IR) were recorded as a glaze on a spectrometer fitted with a horizontal attenuated total reflectance (HATR) accessory or an FT-IR spectrometer equipped with a diamond anvil ATR assembly. Electrochemical experiments were performed under a dinitrogen atmosphere using a potentiostat. Cyclic voltammetry data were taken at ambient temperature (~25 °C) at 100 mV/s in a standard three-electrode cell with a glassy-carbon working electron, *N*,*N*-dimethylacetamide (DMA) or acetonitrile (MeCN) solvent (unless otherwise specified), and tetrabutylammonium hexafluorophosphate (TBAH) electrolyte (approx. 0.5 M). All potentials are reported verses the NHE (normal hydrogen electron) using cobaltocenium hexafluorophosphate ($E_{1/2}$ = -0.78 V), ferrocene ($E_{1/2}$ = +0.55 V), or decamethylferrocene ($E_{1/2}$ = +0.04 V) as internal standard. The peak-to-peak separation was less than 100 mV for all reversible couples. Unless otherwise noted, all synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere. Dimethoxyethane (DME) and chloroform was purified through a column packed with activated basic alumina. Other solvents and liquid reagents were thoroughly purged with dry nitrogen prior to use. Triflate salts of amines were synthesized by addition of a diethyl-ether solution of trifilic acid to the

appropriate conjugate base dissolved in diethyl-ether. Deuterated chloroform was purified through a column packed with activated basic alumina. Other deuterated solvents were used as received from Cambridge Isotopes. Deactivated basic alumina was made by stirring basic alumina with water (15% by mass) in ethyl acetate. Pyrazole (Pz) protons of the tris(pyrazolyl)borate (Tp) ligand were uniquely assigned whenever possible (e.g., "PzA3") using a combination of two-dimensional NMR data and phosphorous-proton NOE interactions. BH peaks (around 4-5 ppm) are not identified due to their quadrupole broadening. All phosphrous NMR spectra are phosphorous-proton decoupled. IR data are used to confirm the presence of a BH group (around 2500 $cm^{-1}$). OH and NH peaks are not always identified due to exchange with water in the solvent. Compounds: **8**, **8A**, **13**, **14**, **16** – **22**, **28** and **29** were previously reported.[16,17]



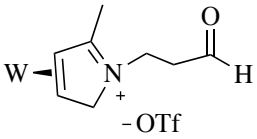

**13**: Alternative procedure for the synthesis of [WTp(NO)($PMe_3$)($\eta^2$-2H-2-methylpyrrolium)][OTf]: **8A** (2.2383 g, 3.49 mmol) was put in a flame-dried test-tube charged with stir-bar. 2-methylpyrrole (1.3647 g, 16.8 mmol) in DME (~ 10 g) was then added. The reaction stirred at room temperature for 25 hours. The reaction was then put in an oil bath at 40 °C for 48 hours. Once the dark brown reaction solution cooled to room temperature triflic acid (.6476 g, 4.3 mmol) was added in DME (~ .5 g). The reaction stirred at room temperature for ~ 14 hours. The reaction solution was then precipitated in stirring ether (1.8 L). The precipitate was collected on a 150 mL medium

porosity fritted funnel. The brown precipitate was dried on the frit for 5 minutes. The precipitate was collected in a vial and dissolved in minimal methanol and reprecipitated in stirring ether (1.8 L). The precipitate was collected on a 150 mL medium porosity fritted funnel. The precipitate dried under vacuum for ~ 30 minutes. A brown precipitate was collected (1.4212 g, 1.94 mmol, 56% yield). Note: the solid was not completely pure and the 2nd methanol precipitation may have made the product slightly cleaner but not substantially. Characterization details have been previously reported.[17]



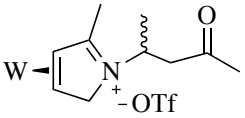

**15**: [WTp(NO)($PMe_3$)($\eta^2$-2H-2-ethylpyrrolium)][OTf]: Under a dinitrogen atmosphere, **8** (0.5007 g, 0.862 mmol), was put in an oven-dried vial charged with a stirbar. Added 2-ethyl pyrrole (0.8224 g, 8.6 mmol) in DME (4 mL) to vial and stirred for 7 days. Triflic acid (0.1640 g, 1.1 mmol) dissolved in DME (~ 0.5 mL) was added to thee stirring solution. Reaction stirred overnight. Precipitated reaction solution in stirring ether (~ 300 mL), and collected precipitate on 30 mL medium porosity fritted funnel. The precipitate (**15**) was dried under vacuum (0.3864 g, 0.5166 mmol, 60.0% yield). $^1$H NMR ($CDCl_3$, 600 MHz, δ): 10.2 (s, 1H, NH), 8.06 (d, *J* = 1.9, 1H, Pz3B), 7.99 (d, *J* = 1.9, 1H, Pz3A), 7.83 (d, *J* = 2.4, 1H, Pz5B), 7.79 (d, *J* = 2.2, 1H, Pz5C), 7.66 (d, *J* = 2.3, 1H, Pz5A), 7.33 (d, *J* = 1.9, 1H, Pz3C), 6.41 (t, *J* = 2.2, 1H, Pz4B), 6.31 (t, *J* = 2.3, 1H, Pz4C), 6.24 (t, *J* = 2.2, 1H, Pz4A), 5.55 (dd, *J* = 17.8, 5.4, 1H, H2-Anti), 5.12 (d, *J* = 17.0, 1H, H2-syn), 3.83 (ddd, *J* = 10.0, 6.3, 2.9, 1H, H4), 2.88 (q, *J* = 7.4, 2H, H6), 2.42

(t, $J$ = 6.7, 1H, H3), 1.50 (t, $J$ = 7.6, 3H, H7), 1.17 (d, $J$ = 8.5, 9H, $PMe_3$). $^{13}C$ NMR ($CDCl_3$, 800 MHz, δ): 197.2 (iminium), 144.0 (Pz3B), 141.0 (Pz3C), 140.4 (Pz3A), 137.5 (Pz5B or Pz5C), 137.2 (Pz5B or Pz5C), 136.4 (Pz5A), 107.7 (Pz4B), 107.2 (Pz4C), 106.4 (Pz4A), 61.2 (d, $J$ = 8.4, C4), 59.8 (C2), 59.1 (C3), 25.7 (C6), 13.7 (d, $J$ = 29.8, $PMe_3$), 10.4 (C7). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -14.81, $J_{WP}$ = 270. CV (DMA) V, $E_{p,a}$ = 1.12 V. IR: $\nu_{BH}$ = 2515 $cm^{-1}$, $\nu_{NO}$ = 1577 or 1620 $cm^{-1}$ and $\nu_{CN}$ = 1577 or 1620 $cm^{-1}$.




**23**: [WTp(NO)($PMe_3$)($\eta^2$-5-methyl-(1-acrolein)-2H-methylpyrrolium)][OTf]: **13** (0.1049 g, 0.1429 mmol) was placed in a 4-dram vial. Non-base treated chloroform (1.0 mL) was added and a homogeneous solution formed. Acrolein (0.0823 g, 1.467 mmol) was added followed by triethylamine (0.0283 g, 0.2797 mmol). The reaction was allowed to sit for 15 minutes. The reaction solution was then chromatographed on deactivated basic alumina (~ 1 inch in 15 mL course porosity fritted funnel). Eluted column with 10:90 acetonitrile: ethyl acetate (~ 100 mL) followed by 15:85 acetonitrile: ethyl acetate (~ 50 mL) until gray-yellow band was removed. Finally eluted with 50:50 acetonitrile: ethyl acetate (~ 75 mL) to elute a brown band. The brown band was concentrated *in vacuo* to yield an oil **23** (0.0304 g, 0.0385 mmol, 27% yield). $^1H$ NMR ($CDCl_3$, 600 MHz, δ): 9.66 (s, 1H, H8), 8.02 (d, $J$ = 2.0, 1H, Pz3A), 8.00 (d, $J$ = 1.9, 1H, Pz3B), 7.82 (d, $J$ = 2.4, 1H, Pz5B), 7.76 (d, $J$ = 2.2, 1H, Pz5C), 7.66 (d, $J$ = 2.3, 1H, Pz5A), 7.48 (d, $J$ = 2.2, 1H, Pz3C), 6.40 (t, $J$ = 2.3, 1H, Pz4B), 6.31 (t, $J$ = 2.3, 1H, Pz4C), 6.29 (t, $J$ = 2.3, 1H,

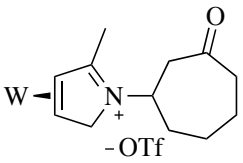
Pz4A), 5.72 (dd, $J$ = 16.3, 6.0, 1H, H3 anti), 5.31 (d, $J$ = 16.3, 1H, H3 syn), 4.23 (m, 1H, H6 either syn or anti), 4.16 (ddd, $J$ = 10.3, 6.8, 3.3, 1H, H1), 3.97 (m, 1H, H6 either syn or anti), 3.13 (m, 1H, H7 either syn or anti), 3.12 (m, 1H, H7 either syn or anti), 2.70 (s, 3H, H5), 2.45 (t, $J$ = 6.6, 1H, 2H), 1.21 (d, $J$ = 8.5, 9H, $PMe_3$). $^{13}C$ NMR ($CDCl_3$, 800 MHz, δ): 198.7 (C=O, aldehyde), 193.7 (C≡N), 143.5 (Pz3A), 141.8 (Pz3C), 140.4 (Pz3B), 137.4 (Pz5C), 137.0 (Pz5B), 136.3 (Pz5A), 107.5 (Pz4B), 107.3 (Pz4C), 106.3 (Pz4A), 66.6 (C3), 64.5 (C1), 57.9 (C2), 43.0 (C7), 40.5 (C6), 17.9 (C5), 13.8 (d, $J$ = 29.7, $PMe_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -14.55, $J_{WP}$ = 270. CV ($CH_3CN$) $E_{p,c}$ = -1.77 V, $E_{p,a}$ = 1.07 V. IR: $\nu_{BH}$ = 2507 $cm^{-1}$, $\nu_{NO}$ = 1573 or ~1600 $cm^{-1}$, and $\nu_{CN}$ = 1573 or ~1600.0 $cm^{-1}$, $\nu_{CO}$ = 1717 $cm^{-1}$.




**24**: [WTp(NO)($PMe_3$)($\eta^2$-5-methyl-(1-3-pentan-2-one)-2H-methylpyrrolium)][OTf]: **13** (0.0506 g, 0.0689 mmol), was put in a 4-dram vial. To the vial added non-dried chloroform (0.5 mL), triethylamine (0.0213 g, 0.2105 mmol), and finally 3-penten-2-one (0.0748 g, 0.7621 mmol). The reaction was allowed to sit for 64 hours. The reaction solution was then chromatographed on deactivated basic alumina (~ 1 inch in 15 mL course porosity fritted funnel). Eluted with 15:85 acetonitrile: ethyl acetate (~ 100 mL) until gray-yellow band was removed. Then eluted with 50:50 acetonitrile: ethyl acetate (~ 150 mL) and acetonitrile (~ 100 mL) to elute a brown band. The brown band was concentrated *in vacuo* to yield **24** (0.0149 g, 0.0182 mmol, 26% yield). $^1H$ NMR ($CDCl_3$,

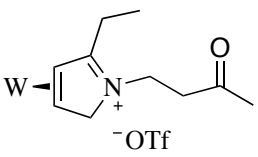
600 MHz, δ): Major isomer: 8.03 (d, *J* = 2.0, 1H, Pz3B), 7.99 (d, *J* = 1.9, 1H, Pz3A), 7.83 (d, *J* = 2.0, 1H, Pz5B), 7.76 (d, *J* = 2.2, 1H, Pz5C), 7.67 (d, *J* = 2.3, 1H, Pz5A), 7.44 (d, *J* = 2.2, 1H, Pz3C), 6.40 (t, *J* = 2.3, 1H, Pz4B), 6.31 (t, *J* = 2.3, 1H ,Pz4C), 6.29 (t, *J* = 2.3, 1H, Pz4A), 5.59 (dd, *J* = 16.3, 6.0, 1H, H3 anti), 5.18 (d, *J* = 16.3, 1H, H3 syn), 4.75 (m, 1H, H6 either syn or anti), 4.18 (ddd, *J* = 10.3, 6.8, 3.3, 1H, H1), 3.30 (dd, *J* = 18.5, 5.7, 1H, H7 either syn or anti), 2.90 (dd, *J* = 18.5, 5.7, 1H, H7 either syn or anti), 2.65 (s, 3H, H5), 2.41 (t, *J* = 6.6, 1H, 2H), 2.25 (s, 3H, H8), 1.21 (d, *J* = 8.5, 9H, $PMe_3$). Minor isomer: 8.06 (d, *J* = 2.0, 1H, Pz3B), 8.00 (d, *J* = 1.9, 1H, Pz3A), 7.83 (d, *J* = 2.0, 1H, Pz5B), 7.74 (d, *J* = 2.2, 1H, Pz5C), 7.67 (d, *J* = 2.3, 1H, Pz3C), 7.66 (d, *J* = 2.4, 1H, Pz5A), 6.39 (t, *J* = 2.3, 1H, Pz4B), 6.33 (t, *J* = 2.3, 1H, Pz4C), 6.29 (t, *J* = 2.3, 1H, Pz4A), 5.66 (dd, *J* = 16.3, 6.0, 1H, H3 anti), 5.15 (d, *J* = 16.3, 1H, H3 syn), 4.82 (m, 1H, H6 either syn or anti), 4.29 (ddd, *J* = 10.3, 6.8, 3.3, 1H, H1), 3.36 (dd, *J* = 18.2, 6.0, 1H, H7 either syn or anti), 2.77 (dd, *J* = 18.2, 6.0, 1H, H7 either syn or anti), 2.79 (s, 3H, H5), 2.58 (t, *J* = 6.6, 1H, 2H), 2.01 (s, 3H, H8), 1.24 (d, *J* = 8.5, 9H, $PMe_3$). $^{13}C$ NMR ($CDCl_3$, 800 MHz, δ): Major isomer: 205.3 (C=O), 194.0 (C≡N), 143.3 (Pz3A), 141.7 (Pz3C), 140.3 (Pz3B), 137.3 (Pz5C), 137.0 (Pz5B), 136.3 (Pz5A), 107.5 (Pz4B), 107.3 (Pz4C), 106.3 (Pz4A), 64.4 (C1), 60.6 (C3), 56.9 (C2), 49.9 (C6), 47.7 (C7), 30.4 (C8), 20.7 (C9), 17.9 (C5), 13.6 (d, *J* = 29.3, $PMe_3$). Minor isomer: 204.6 (C=O), 192.1 (C≡N), 143.4 (Pz3A), 142.6 (Pz3C), 140.4 (Pz3B), 137.3 (Pz5C), 137.0 (Pz5B), 136.1 (Pz5A), 107.4 (Pz4B), 107.4 (Pz4C), 106.2 (Pz4A), 65.3 (C1), 60.9 (C3), 58.1 (C2), 49.7 (C7), 49.1 (C6), 29.7 (C8), 19.2 (C9), 18.4 (C5), 14.1 (d, *J* = 29.3, $PMe_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): Major isomer: -14.57 ppm, $J_{WP}$ = 270. Minor isomer -14.44 ppm, $J_{WP}$ = 270.

CV ($CH_3CN$) $E_{p,c}$= -1.75 V, $E_{p,a}$ = 1.06 V. IR: $\nu_{BH}$ = 2506 $cm^{-1}$, $\nu_{NO}$ = 1572 or ~1600 $cm^{-1}$, and $\nu_{CN}$ = 1572 or ~1600 $cm^{-1}$, $\nu_{CO}$ = 1714 $cm^{-1}$.

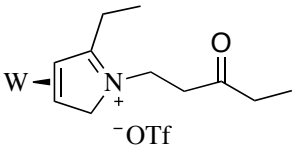



**25**: [WTp(NO)($PMe_3$)($\eta^2$—(3-cyclohepta-1-one)-2H-methylpyrrolium)][OTf]: **13** (0.0503 g, 0.0685 mmol) was placed in a vial. Chloroform (not-dried, ~ 1 mL), triethylamine (0.014 g, .1384 mmol) and 2-cyclohepten-1-one (0.0966 g, 0.8770 mmol) were added. The reaction sat for 46 hours. The reaction solution was then chromatographed on deactivated basic alumina (~ 1 inch in 15 mL course porosity fritted funnel). Eluted with 15:85 acetonitrile: ethyl acetate (~ 200 mL) until gray-yellow band was removed. Then eluted with 20:80 acetonitrile: ethyl acetate (~ 300 mL) and 50:50 acetonitrile: ethyl acetate (~ 200 mL) to elute a brown band. The brown band was concentrated *in vacuo* to yield **25** (0.0151 g, 0.0179 mmol, 26% yield). $^1H$ NMR ($CDCl_3$, 600 MHz, δ): 8.02 (d, *J* = 1.8, 1H, Pz3B), 7.98 (d, *J* =1.8, 1H, Pz3A), 7.83 (d, *J* = 2.2, 1H, Pz5B), 7.76 (d, *J* = 2.5, 1H, Pz5C), 7.67 (d, *J* = 2.3, 1H, Pz5A), 7.52 (d, *J* = 2.3, 1H, Pz3C), 6.41 (t, *J* = 2.3, 1H, Pz4B), 6.32 (t, *J* = 2.3, 1H ,Pz4C), 6.28 (t, *J* = 2.3, 1H, Pz4A), 5.63 (dd, *J* = 17.0, 6.3, 1H, H3 anti), 5.20 (d, *J* = 16.0, 1H, H3 syn), 4.36 (m, 1H, H6), 4.26 (ddd, *J* = 10.3, 6.7, 3.0, 1H, H1), 3.17 (dd, *J* = 14.0, 11.4, 1H, H12 either syn or anti), 2.88 (dd, *J* = 14.0, 11.4, 1H, H12 either syn or anti), 2.83 (m, 1H, H10), 2.68 (s, 3H, H5), 2.58 (m, 1H, H7), 2.52 (m, 1H, H10), 2.45 (t, *J* = 6.6, 1H, 2H), 2.05 (m, 1H, H9), 2.04 (m, 1H, H8), 1.98 (m, 1H, H7), 1.69 (m, 1H, H8), 1.52 (m, 1H, H9), 1.22 (d, *J*

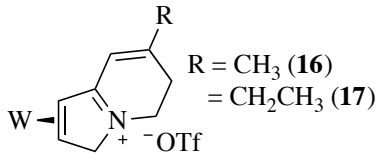
= 8.5, 9H, $PMe_3$). Minor isomer: 8.00 (d, *J* = 1.8, 1H, Pz3B), 7.82 (d, *J* = 2.2, 1H, Pz3A), 7.76 (d, *J* = 3.0, 1H, Pz5B), 7.75 (d, *J* = 2.5, 1H, Pz5C), 7.67 (d, *J* = 2.3, 1H, Pz5A), 7.53 (d, *J* = 2.1, 1H, Pz3C), 6.40 (t, *J* = 2.4, 1H, Pz4B), 6.32 (t, *J* = 2.8, 1H, Pz4C), 6.28 (t, *J* = 2.3, 1H, Pz4A), 5.66 (dd, *J* = 17.0, 6.2, 1H, H3 anti), 5.15 (d, *J* = 16.0, 1H, H3 syn), 4.34 (m, 1H, H6), 4.31 (ddd, *J* = 10.1, 6.7, 3.0, 1H, H1), 3.17 (dd, *J* = 14.0, 10.7, 1H, H12 either syn or anti), 2.74 (m, 1H, H10), 2.67 (s, 3H, H5), 2.66 (dd, *J* = 14.05, 10.7, 1H, H12 either syn or anti), 2.47 (m, 1H, H10), 2.43 (m, 1H, H2), 2.31 (m, 1H, H7), 2.14 (m, 1H, H9), 2.03 (m, 1H, H8), 2.00 (m, 1H, H7), 1.60 (m, 1H, H9), 1.52 (m, 1H, H8), 1.21 (d, *J* = 8.5, 9H, $PMe_3$). $^{13}C$ NMR ($CDCl_3$, 800 MHz, δ): Major isomer: 209.0 (C=O), 192.2 (C≡N), 143.3 (Pz3A), 141.9 (Pz3C), 140.1 (Pz3B), 137.3 (Pz5C), 137.1 (Pz5B), 136.3 (Pz5A), 107.5 (Pz4B), 107.3 (Pz4C), 106.2 (Pz4A), 64.4 (C1), 60.9 (C3), 57.3 (C2), 55.9 (C6), 48.1 (C12), 42.7 (C10), 36.6 (C7), 26.7 (C8 or C9), 23.7 (C8 or C9), 17.9 (C5), 13.7 (d, *J* = 29.3, $PMe_3$). Minor isomer: 209.1 (C=O), 192.2 (C≡N), 143.4 (Pz3A), 141.9 (Pz3C), 140.2 (Pz3B), 137.3 (Pz5C), 137.0 (Pz5B), 136.3 (Pz5A), 107.6 (Pz4B), 107.3 (Pz4C), 106.3 (Pz4A), 64.4 (C1), 60.9 (C3), 57.1 (C2), 55.7 (C6), 49.0 (C12), 41.4 (C10), 35.5 (C7), 26.4 (C8 or C9), 24.2 (C8 or C9), 17.8 (C5), 13.8 (d, *J* = 29.5, $PMe_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): Major isomer: -14.52 ppm, $J_{WP}$ = 270. Minor isomer -14.44 ppm, $J_{WP}$=270. CV ($CH_3CN$) $E_{p,c}$ = -1.71 V, $E_{p,a}$ = 1.06 V. IR: $\nu_{BH}$ = 2502 $cm^{-1}$, $\nu_{NO}$ = 1592 or ~1568 $cm^{-1}$, and $\nu_{CN}$ = 1592 or ~1568 $cm^{-1}$, $\nu_{CO}$ = 1698 $cm^{-1}$.



**26**: [WTp(NO)($PMe_3$)($\eta^2$-1-(butan-2-one)-2H-ethylpyrrolium)][OTf]: Under a nitrogen atmosphere **15** (0.0791 g, 0.1057 mmol), was placed in an oven-dried vial. Triethylamine (0.0175 g, 0.1729 mmol) in chloroform (0.3 mL) was added. Methyl vinyl ketone (0.0508 g, 0.7248 mmol), in chloroform (0.4 mL) was also added. The reaction solution was brown and homogeneous. The reaction solution sat for 4 hours. The solution was precipitated in stirring ether (100 mL) and the precipitate was collected on 15 mL fine porosity fritted funnel. A light brown precipitate was collected (**26**, 0.0530 g, 0.0648 mmol, 61.3% yield). $^1$H NMR ($CDCl_3$, 600 MHz, δ): 8.02 (d, *J* = 1.8, 1H, Pz3A), 8.01 (d, *J* = 1.9, 1H, Pz3B), 7.82 (d, *J* = 2.3, 1H, Pz5B), 7.76 (d, *J* = 2.2, 1H, Pz5C), 7.66 (d, *J* = 2.4, 1H, Pz5A), 7.53 (d, *J* = 2.0, 1H, Pz3C), 6.39 (t, *J* = 2.2, 1H, Pz4B), 6.33 (t, *J* = 2.3, 1H, Pz4C), 6.29 (t, *J* = 2.2, 1H, Pz4A), 5.70 (dd, *J* = 16.2, 6.5, 2.6, 1H, H2-Anti), 5.32 (d, *J* = 16.5, H2-Syn), 4.18 (dt, *J* = 14.4, 5.7, 1H, H8), 4.11 (m, 1H, H4), 3.96 (m, 1H, H8), 3.14 (m, 1H, H6), 3.10 (t, *J* = 5.6, 2H, H9), 2.77 (m, 1H, H6), 2.48 (t, *J* = 6.6, 1H, H3), 2.12 (s, 3H, H11), 1.57 (d, *J* = 7.7, 3H, H7), 1.21 (d, *J* = 8.5, 9H, $PMe_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 205.8 (Iminium or CO), 197.6 (Iminium or CO), 143.7 (Pz3A or Pz3B), 142.1 (Pz3C), 140.4 (Pz3A or Pz3B), 137.5 (Pz5B), 137.2 (Pz5C), 136.4 (Pz5A), 107.6 (Pz4B), 107.4 (Pz4C), 106.4 (Pz4A), 66.9 (C2), 63.2 (d, *J* = 8.2, C4), 58.3 (C3), 43.2 (C9), 41.9 (C8), 29.9 (C11), 23.7 (C6), 13.9 (d, *J* = 28.2, $PMe_3$), 11.7 (C7). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -14.6, $J_{WP}$ = 270. CV (DMA) V, $E_{p,a}$ = 1.13 V. IR: $\nu_{BH}$ = 2511 cm$^{-1}$, $\nu_{NO}$ = 1577 or 1604 cm$^{-1}$, $\nu_{CN}$ = 1577 or 1604 cm$^{-1}$, and $\nu_{CO}$ = 1716 cm$^{-1}$ .




**27**: WTp(NO)($PMe_3$)($\eta^2$-1-(pentan-3-one)-2H-ethylpyrrolium)][OTf]: Under a nitrogen atmosphere, **15** (0.0528 g, 0.0706 mmol), was placed in an oven-dried vial and dissolved in chloroform (0.4 mL). Triethylamine (0.0121 g, 0.1196 mmol) and ethyl vinyl ketone (0.0369 g, 0.4393 mmol) were added to the vial. The solution was brown and homogeneous. The reaction sat for 4 hours. The solution was precipitated in stirring ether (50 mL) and a precipitate was collected on a 15 mL fine porosity fritted funnel. A light brown precipitate was collected (**27**, 0.0316 g, 0.0380 mmol, 53.8% yield). $^1$H NMR ($CDCl_3$, 600 MHz, δ): 8.01 (d, *J* = 1.9, 1H, Pz3A), 7.99 (d, *J* = 1.9, 1H, Pz3B), 7.82 (d, *J* = 2.3, 1H, Pz5B), 7.76 (d, *J* = 2.3, 1H, Pz5C), 7.66 (d, *J* = 2.3, 1H, Pz5A), 7.49 (d, *J* = Pz3C), 6.39 (t, *J* = 2.2, 1H, Pz4B), 6.31 (t, *J* = 2.2, 1H, Pz4C), 6.27 (t, *J* = 2.2, 1H, Pz4A), 5.88 (ddd, *J* = 16.3, 6.9, 2.9, 1H, H2-anti), 5.30 (d, *J* = 15.8, 1H, H2-syn), 4.19 (dt, *J* = 14.4, 5.6, 1H, H8), 4.05 (m, 1H, H4), 3.97 (dt, *J* = 14.2, 6.4, 1H, H8), 3.15 (m, 1H, H6), 3.07 (m, 2H, H9), 2.46 (m, 1H, H3), 2.41 (q, *J* = 7.1, 2H, H11), 1.55 (t, *J* = 7.7, 3H, H7), 1.20 (d, *J* = 8.5, 9H, $PMe_3$), 1.02 (t, *J* = 7.3, 3H, H12 $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 208.6 (Iminim or CO), 197.4 (iminium or CO), 143.7 (Pz3B), 141.9 (Pz3C), 140.4 (Pz3A), 137.5 (Pz5C), 137.2 (Pz5A), 136.4 (Pz5A), 107.6 (Pz4B), 107.4 (Pz4C), 106.4 (Pz4A), 66.7 (C2), 63.1 (d, *J* = 8.3, C4), 58.1 (C3), 42.0 (C8), 41.8 (C9), 35.8 (C11), 23.7 (C6), 13.8 (d, *J* = 30.1, $PMe_3$), 11.7 (C7), 7.7 (C12). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -14.6, $J_{WP}$ = 270. CV (DMA): $E_{p,a}$ = 1.15 V. IR: $\nu_{BH}$ = 2503 cm$^{-1}$, $\nu_{NO}$ =1562 or 1601 cm$^{-1}$ and $\nu_{CN}$ = 1562 or 1601 cm$^{-1}$, $\nu_{CO}$=1712 cm$^{-1}$.




An alternative procedure and work up for **28** and **29**.

**28**: In an oven dried vial put **13** (2.0833 g, 2.838 mmol), triethylamine (0.2865 g, 2.831 mmol) in chloroform (2 mL), and methyl vinyl ketone (0.9718 g, 13.87 mmol) in chloform (8 mL). After 5 hours the reaction solution was transferred to a flame-dried 250 mL round bottom flask with stirbar. Rinsed reaction solution in with chloroform (42 mL). Added pyrrolidine (0.9259 g, 13.0 mmol). The reaction stirred for 17 hours. The reaction solution was then brought outside of the box and dry loaded on deactivated alumina. The dried alumina was then added onto a column of deactivated alumina (~ 2 cm in a 350 mL medium porosity fritted funnel). A pale reddish-brown band was eluted with ethyl acetate. A yellow band was then eluted off the column with 35 – 45 % acetonitrile in ethyl acetate (~ 300 mL). The collected yellow band was concentrated to dryness *in vacuo.* The resulting oil was picked up in minimal DCM and placed in a 1L round-bottom flask. Added ethyl acetate (~ 500 mL) and began concentrating until a precipitate began to form. Transferred to smaller round bottoms as volume lessened. Repeated DCM/ ethyl acetate step and re-concentrated to about 50 mL. Once precipitate began to form on the walls of the round bottom stopped evaporating and put in the freezer at -15 °C for four days (though overnight gives similar yield). A brown precipitate was collected **16** (0.4710 g, 0.5991 mmol, 21.1% yield). Characterization details have been previously reported.[17]

**29**: general procedure same as **28** except use ethyl vinyl ketone instead of methyl vinyl ketone. Characterization details have been previously reported.[17]

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# Chapter Four

## The Synthesis and Reactivity of the Indolizidinium Core Formed via the Dearomatization of 2-methylpyrrole

## 4.1 The Formation of the Indolizidine Core

As discussed in Section 2.5, indolizidines are an important biologically active alkaloid and synthetic target.[1,2] A great number of indolizidines have been isolated from natural sources and their biological activities tested. Indolizidines that are not isolated from natural sources are normally created using complex, multi-step syntheses that often require intricate starting materials. A reaction pathway that can create an indolizidine and allow for variation of substituents would be a powerful tool for a synthetic chemist especially if those syntheses began with inexpensive starting materials.

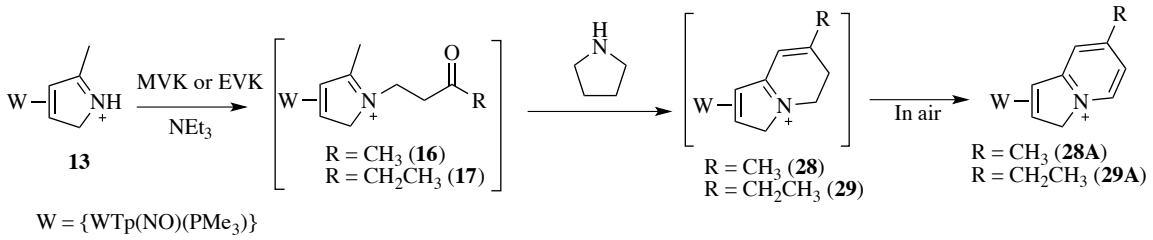
The formation of a dihapto-coordinated indolizidinium core after the electron-rich dearomatization and protonation of 2-methylpyrrole is a striking observation as a metal-coordinated indolizidine analog can be isolated in two simple steps beginning with 2-methylpyrrole.[3] Moreover, upon formation of the indolizidinium complex, an α,β-unsaturated iminium forms with the possibility for chemical modification. The potential chemical elaboration afforded by the α,β-unsaturated iminium in the indolizidinium core could lead to a method for creating a variety of indolizidines. The reactivity of the dihapto-coordinated indolizidinium complex will be discussed presently.

## 4.2 Results and Discussion

Because of the successful formation of the cyclized MVK adduct (**28**) and EVK adduct (**29**), other Michael addition products were tested for their ability to undergo intramolecular cyclization. Of the Michael adducts formed earlier, the acrolein adduct (**23**) and the 3-penten-2-one adduct (**24**) showed some evidence of cyclization as observed by the formation of an alkene resonance in the 6 – 7 ppm region in each of their $^{1}$H NMR spectra. Unfortunately clean cyclized products for **23** and **24** were not isolated. None of the other Michael adducts were able to form cyclized products.[3]

An interesting alternative cyclized product is isolated from the MVK adduct (**16**) when the cyclization takes place in air. Under normal reaction conditions **28** forms easily overnight under a nitrogen atmosphere. Open to air the cyclization seemed to take place more slowly (monitoring via $^{31}$P NMR). Due to the slower reaction time, more pyrrolidine and MVK were added in the hopes of increasing the speed of the reaction. After letting the reaction sit for 8 days (much longer than originally intended), a new product had formed. Following chromatography a clean product was isolated that was identified as the *re-aromatized* indolizinium product (**28A**, Scheme 4.1). The cyclized product, **28**, likely forms and is then oxidized in air to the aromatized product **28A**. A similar reaction occurs with the EVK adduct (**17**) though the reaction proceeds more slowly taking 27 days to form **29A** (Scheme 4.1). Similar conditions with acrolein were unable to yield an indolizinium or even a cyclized complex.

**Scheme 4.1** Cyclizaiton of **16** and **17** in ambient atmosphere to form **28A** and **29A**.




**13**

W = {WTp(NO)(PMe$_3$)}

Preliminary investigation of the reactivity of the indolizidinium core focused on the MVK cyclized product (**28**). With the goal of this cyclization process being the isolation of an indolizidine core, studies were conducted to find conditions that would isolate the organic indolizidine. In order to find these conditions it is necessary to explore the reduction potentials of the complexes in question.

An analytical tool used to monitor the progress of the reaction, in addition to $^{31}$P NMR spectroscopy, is cyclic voltammetry. This analytical technique measures the redox potentials of metal complexes (all measured at 100 mV/s). The W($\eta^2$-benzene) complex (**8**) has an anodic wave with an $E_{p,a}$ = -0.13 V.[4] This observation implies **8** undergoes a one-electron oxidation at a fairly low potential. The neutral 3H-2-methylpyrrole complexes (**9a** & **9b,** Scheme 3.5) have a more positive anodic wave, $E_{p,a}$ = +0.40 V implying that it requires a stronger oxidant than **8** for a one-electron oxidation.[5] The 2H-pyrrolium complex (**13**), the Michael adduct (**16**) and the cyclized indolizidinium complex (**28**) each have anodic waves around $E_{p,a}$ = +1.3 V.[3] This substantial positive shift implies the increasing difficulty of a one-electron oxidation when compared to the neutral 3H complexes (**9a** & **9b**) or the initial W($\eta^2$-benzene) complex (**8**). The presence of an iminium in **13**, **16** and **28** causes the reduction potential to increase dramatically. An iminium functional group is electron-withdrawing and in **13**, **16** and **28** the iminium is in conjugation with the $\pi$-system, and by extension, the metal itself. The metal in

conjugation with an electron-withdrawing functional group augments the metal-organic back-bonding interaction raising the reduction potential of the W(I)/W(0) half-reaction.

While dihapto-coordination to an electron-rich tungsten(0) fragment activates 2-methylpyrrole and enables the formation of an indolizidinium core (**28**), the goal of the project is to isolate a novel indolizidine necessitating the removal of the metal before the novel organic can be isolated. With such a high purported reduction potential (i.e., **28** has an $E_{p,a}$ = +1.3 V), oxidizing the metal requires a powerful oxidizing agent. Unfortunately, with a more powerful oxidizing agent the risk of destroying the organic molecule is greatly increased. As discussed earlier, the high reduction potential is directly related to the presence of the iminium. To overcome this oxidation obstacle, experiments were conducted to reduce the iminium. With the iminium reduced to a tertiary amine the reduction potential should be lowered to the point where a successful oxidation can take place, liberating a novel indolizidine without destroying the organic.

An interesting way to consider the reactivity of the α,β-unsaturated iminium (eniminium) in **28** is by comparing it to an enone. This comparison can be made because both are defined by an alkene in conjugation with an electron-withdrawing group. Because of this conjugation, both an eniminium and an enone have two sites for potential reduction: 1,2 reduction that reduces solely the iminium or 1,4 reduction which will reduce the alkene and leave the iminium or ketone. Carbons C8a and C7 are the sites of reduction because they are both electron deficient due to their proximity to the iminium. When comparing the two sites for reduction it is useful to use the terminology, 'hard' and 'soft.' When a site or reagent is described as 'hard' it is characterized by a "compact electron distribution," while 'soft' is characterized as a "small effective charge."[6]

Because ‘hard’ nucleophiles add to the carbonyl carbon (1,2-reduction, Figure 4.1 A for example with **28**) that site is considered ‘hard.’[7] Another way to describe this reactivity is to say there is a larger buildup of positive charge at the carbonyl carbon (or iminium carbon) compared to the rest of the olefin. Likewise, when a site is considered ‘soft’ it is thought to have less of a direct charge. ‘Soft’ nucleophiles often react in a 1,4-reduction pathway leading to the notion that there is less charge focused on that carbon than the carbon of the carbonyl or iminium (Figure 4.1 B for example with **28**).[7]

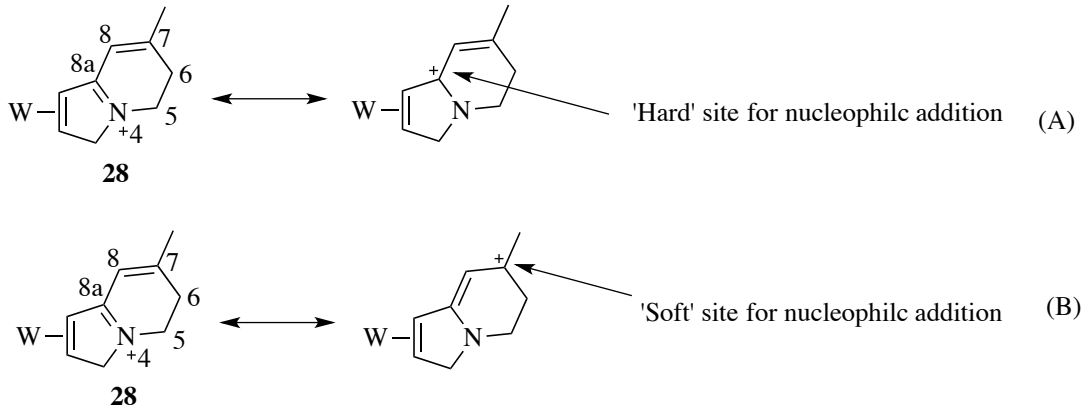
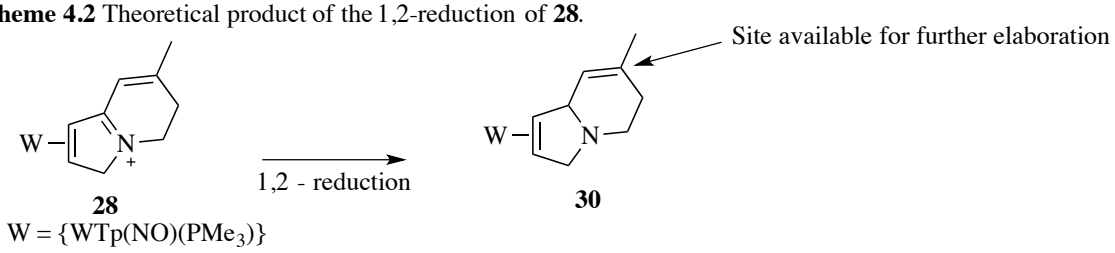



**Figure 4.1** resonace structures of **28** highlighting sites of electron-deficiency.

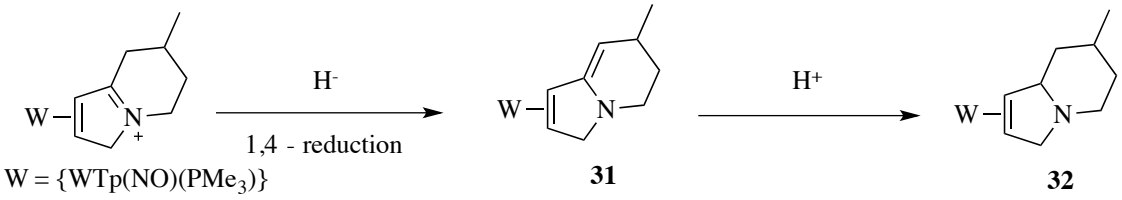
If a hydride ($H^-$) is used as the reducing agent and a 1,2-reduction is successful, the resulting product would be a dihapto-coordinated indolizidine with an unsaturated bond (**30**, Scheme 4.2). If **30** could be successfully synthesized it would be an advantageous precursor for a variety of indolizidines because an unsaturated bond is susceptible to a multitude of chemical transformations. Therefore, **30** could be used to create a diverse range of dihapto-coordinated indolizidines. Additionally, with the reduction of the iminium, the $d^5/d^6$ reduction potential would decrease allowing for a weaker oxidizing agent to be used to isolate the organic indolizidine.

**Scheme 4.2** Theoretical product of the 1,2-reduction of **28**.




Conversely, if a hydride reducing agent initiated a 1,4-reduction, the resulting product would be a dihapto-coordinated indolizidine with an enamine (**31**, Scheme 4.3). An enamine is a reactive species that could theoretically be used for chemical elaboration when formed in **31**. However, because enamines are very electron-rich they react easily with electrophiles.[8] It is not difficult to imagine that under hydride reduction conditions **31** (once formed) is able to find a spurious proton and be reduced again to form the fully saturated dihapto-coordinated indolizidine (**32**, Scheme 4.3). The formation of **32** is less advantageous than **30** because the latter is prepared for further chemical modification while **32** is completely saturated.

**Scheme 4.3** Theoretical product of the 1,4-reduction of **28** creating **31** that can subsequently form **32**.

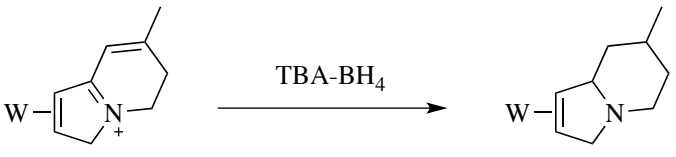



Various hydride reducing agents were explored in order to find the right 'hard' reagent that is capable of performing a 1,2-reduction on the α,β-unsaturated iminium forming **30**. Under normal circumstances sodium cyanoborhydride ($NaCNBH_4$) is strong enough to reduce an iminium bond.[9] However, sodium cyanoborohydride did not react with **28**. The results of this reaction show that the iminium in **28** is likely less reactive because of its coordination to the metal fragment. The electron-donation from the metal

fragment stabilizes the iminium making it less reactive. A stronger hydride reducing agent is needed.

Sodium borohydride ($NaBH_4$) was next explored because it is known to reduce iminiums and is a more powerful reducing agent than $NaCNBH_4$.[10] When sodium borohydride is put in solution with the cyclized complex **28**, a mixture of products is observed in the $^{31}P$ NMR spectrum. Varying conditions were explored including changing solvent and temperature but none yielded a single or even a predominant product. Based on these observations it is believed that sodium borohydride is capable of reducing **28** but not selectively and instead a mixture of 1,2 and 1,4 reduction products forms. When tetrabutylammonium borohydride (TBA-$BH_4$), is used as an alternative borohydride reagent, one major product is observed in the $^{31}P$ NMR spectrum. Upon work up a single reduction product is isolated cleanly. Unfortunately the $^{1}H$ NMR spectrum confirmed the identity of the product as the fully saturated dihapto-coordinated indolizidine (**32**, Scheme 4.4). Most notably in the $^{1}H$ NMR Spectrum the alkene resonance around 6.5 ppm indicating **28** is absent. Additionally there are no $^{1}H$ NMR peaks between 4 and 6 ppm implying the iminium had been reduced. Furthermore the anodic wave of **32** is found to be $E_{p,a}$ = +0.42 V confirming the iminium has indeed been reduced. The stereochemistry of **32** will be discussed later in this section.

**Scheme 4.4** The reaction of **89** and TBA-$BH_4$ to form **32**.




**28** **32**

W = {WTp(NO)($PMe_3$)}

While **32** is not the desired product these results reaffirmed the concept of borohydrides being considered "softer" nucleophiles.[7] The reduction product that forms after reacting with TBA-$BH_4$ is likely the 1,4 reduction product (**31**) where the enamine forms and then reacts with a proton followed by a second reduction in solution to give **32**. A stronger hydride is required to form the desired 1,2 reduction product **30**.

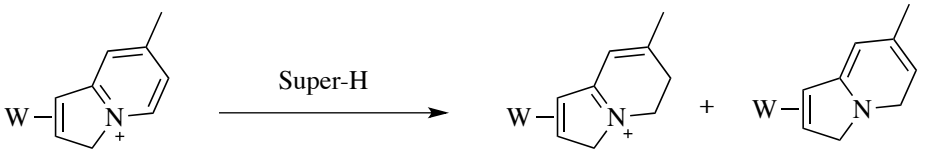
To find a stronger hydride source, aluminum reducing agents were explored as aluminum is less electronegative than boron leaving more electron density centered on the hydrides themselves rather than on the aluminum.[8] An exhaustive study using lithium aluminum hydride (LAH) was conducted but the results were no better than those observed with $NaBH_4$.

Other reducing agents were explored including: DIBAL (diisobutylaluminum hydride), Red-Al® (sodium bix(2-methoxyethoxy)aluminum hydride) and Super-Hydride® (lithium triethylborohydride). While many iterations of each of the reducing agents listed above were explored, Super-Hydride® was the only hydride source able to give a clean single product in the $^{31}P$ NMR spectrum. Unfortunately, after work up the coordinated saturated indolizidine (**32**) is isolated.

Interesting results were observed when the re-aromatized product (**28A**) reacts with Super-Hydride®. A predominant product is observed in the $^{31}P$ NMR spectrum, though upon work up there is a major and minor product. The minor product resembles the peaks of the non-aromatic cyclized product **28** but the major product had several distinct NMR characteristics. The $^{1}H$ NMR spectrum reveals peaks at 5.38 ppm and 4.38 ppm that could represent alkene shifts though both are broadened. There is also a singlet that integrates properly for three protons (relative to the major product) indicating a

methyl group. Based on several multidimensional NMR interactions, complex **33** is proposed (Scheme 4.5). Presently, the $^{1}$H NMR spectrum of **33** lacks geminal proton signals but because of broadening it is possible they are not easily located. Because enamines are very reactive, it is conceivable that a tautomerization is taking place causing the broadening of several resonances. Though an iminium is not associated with the major product according to the HMBC (hetero-nuclear multiple bond correlation) NMR data. Another explanation for the broadening of several shifts could be due to incorporation of the alkyl-boron reagent remaining after the hydride is donated. Further experimentation and characterization is needed to confirm the structure of **33**.

**Scheme 4.5** The reaction of **28A** and SuperH to form the proposed **33**




**28A**

W = {WTp(NO)(PMe$_3$)}

**28 -** Minor product **33** - major product

Despite our best efforts with a variety of reducing agents, no conditions yielded the 1,2 reduction product (**30**). In spite of the difficulty performing a 1,2-reduction on the cyclized product (**28**), attempts were made to functionalize the indolizidine by chemically elaborating the alkene portion before reduction of the iminium.

The initial attempt for activating the unsaturated bond of **28** was by a Simmons-Smith Cyclopropanation as their is precedent for such transformations in tungsten(0) dearomatization chemistry.[11] Unfortunately, only starting material is recovered after several attempts under these conditions.

A great deal of the literature on indolizidines focuses on hydroxylated derivatives like Lentiginosine, Swainsonine and Castanospermine for their biological activity (Figure

4.2).[12] With this in mind experiments were conducted to place hydroxyl groups on the alkene. First attempts were made to form an epoxide with *m*-chloroperoxybenzoic acid (mCPBA), as this reagent has been used to add hydroxyl groups to dihapto-coordinated complexes previously.[13] Unfortunately, all current reactions with mCPBA gave starting material. Because hydroxylation is so prevalent a feature in many indolizidines, alternative conditions were explored.

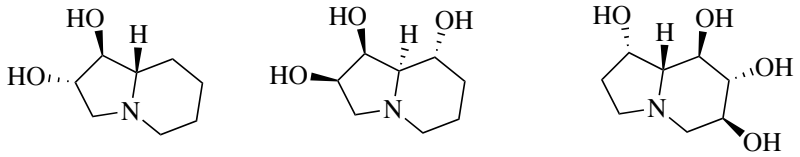
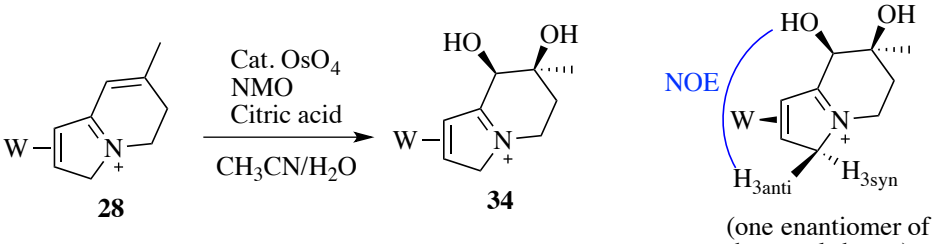



**Figure 4.2** Hydroxylated indolizidines: Lentiginosine, Swainsonine and Castanospermine.

One of the oldest known methods for dihydroxylation uses osmium tetroxide.[14] Despite its cost and toxicity, osmium tetroxide continues to be used to dihydroxylate olefins. The Upjohn dihydroxylation uses catalytic osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) as an oxidant in solution that regenerates the osmium species.[15] A slightly modified version of this procedure that incorporates citric acid is able to dihydroxylate **28** to form **34** (Scheme 4.6).[16] The dihydroxylated product (**35**) is isolated and fully characterized. Under these dihydroxylation conditions the two hydroxyl groups add in a *cis* formation. The exact stereochemistry of the resulting product can be discerned through multidimensional NMR techniques. An NOE (through space) interaction can be seen between the $H3_{anti}$ and an OH group confirming the dihydroxylation occurred on the *anti* face of the indolizidine away from the steric bulk of the metal (Scheme 4.6). It is crucial to note that these reaction conditions require pure starting material. It is believed that any excess phosphorous (like $PMe_3$ from any

decomposition) poisons the osmium catalyst and prevents reactivity yielding starting material.

**Scheme 4.6** *cis*-Dihydroxylation of **28.**



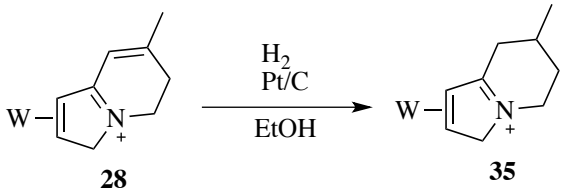

**28** **34**

(one enantiomer of the metal shown)

W = {WTp(NO)($PMe_3$)}

Another method for modification of the alkene of **28** is through catalytic hydrogenation. Over a platinum/carbon catalyst the alkene of **28** is reduced with ease to form **35** (Scheme 4.7**)**. The $^1$H NMR spectrum reveals the loss of an alkene signal, the presence of a methyl doublet and the cyclic voltammegram shows a high anodic wave of $E_{p,a}$ = + 1.15 V indicating the iminium is still intact.

**Scheme 4.7** *cis*-hydrogenation of **28**.

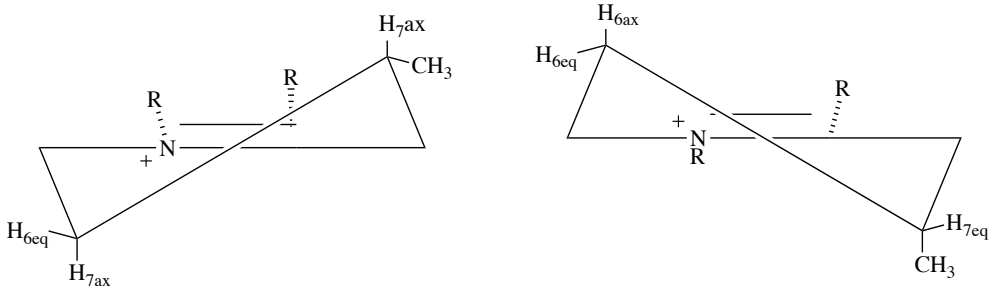



**28** **35**

W = {WTp(NO)($PMe_3$)}

Under *cis* hydrogenation conditions the two hydrogens must add on the same face of the alkene. Because of the steric bulk of the metal, it is assumed that the hydrogenation prefers to add on face of the coordinated-indolizidinium away from the metal. Because the iminium is still intact there is limited mobility in the non-coordinated ring of **35**. A key difference between two proposed products is the orientation of H7. If that methine proton is in an axial position, it creates the twist-boat conformation **A** (Figure 4.3). If,

instead, the methine is found in an equatorial position, it creates an alternative twist-boat confirmation **B** (Figure 4.3).




**A** - H7 in axial position

**B** - H7 in equitorial position

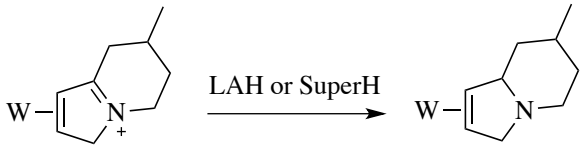
**Figure 4.3** *cis*-hydrogenation products **A** and **B** (5-membered ring and metal not shown).

In order to accurately determine the stereochemistry of **35**, careful analysis of the multidimensional NMR data is required. H7 is found at 2.16 ppm though the precise splitting pattern of H7 is difficult to discern, as it is broadened and very complex. This feature is enlightening because if **35** were in conformation **B** then H7 would be in the equatorial position and it would give rise to a simple quartet as it would not couple strongly to anything other than the methyl. However, because the splitting pattern seems more complex, H7 is likely coupling with several other protons. In order to interact with other protons H7 would have to be in the axial position so to achieve a dihedral angle of ~ 180° which would enable strong coupling to both $H6_{ax}$ and $H8_{ax}$.[17] Both $H6_{ax}$ and $H8_{ax}$ are orientated such that their dihedral angles are 180° with $H7_{ax}$, which dictates there should be large coupling (~ 10 - 12 Hz).[17] Having identified $H6_{ax}$ and $H8_{ax}$, using NOE and HSQC (Hydrogen-carbon single correlation) data, their geminal pairs were easily determined. It is observed that while $H6_{ax}$ and $H8_{ax}$ showed complex splitting because of their dihedral angles with other axial protons, $H6_{eq}$ and $H8_{eq}$ show strong geminal coupling and little to no coupling for any other interactions as expected from equatorial

protons. As an additional experiment, deuterium was used instead of hydrogen. The resulting product showed the disappearance of the $H8_{eq}$ and $H7_{ax}$ protons. Using these data, it is confirmed that **35** is formed with the hydrogens adding to the alkene on the face *anti* to the metal (**A**, Figure 4.3).

After the hydrogenation of **28** to form **35** the iminium can be reduced without the concern of forming a mixture of 1,2 and 1,4 reduction products. Both LAH and Super-Hydride® can reduce the iminium and create the dihapto-saturated indolizidine complex **32** (Scheme 4.8). The iminium is confirmed to be reduced because of the indicative negative shift in the anodic wave from an $E_{p,a}$ = + 1.15 V for **35** to an $E_{p,a}$ = + .42 V for **32**.

**Scheme 4.8** Hydride reduction of **35** to the fully saturated indolizidine complex **32**.




**35** **32**

W = {WTp(NO)($PMe_3$)}

As with the formation of **35** there is a question of which face of the coordinated indolizidine the hydride addition occurred. In previous studies in our lab when an iminium is reduced in close proximity to the metal fragment the hydride normally adds *anti* thus avoiding the steric bulk of the metal.[13] Multidimensional NMR data corroborates this trend in reactivity for **32**. To confirm the identity of H8a, an NOE interaction is observed between it and the H1 proton (Figure 4.4 A). Unfortunately, H8a is broadened and the precise coupling is difficult to ascertain. H8a shows several interesting NOE correlations that confirm the hydride addition is *anti* to the metal. H8a shows NOE interactions with $H8_{eq}$ and $H5_{ax}$, two protons known to be on the face of the

indolizidine *anti* to the metal (Figure 4.4 B). With H8a in this position we can assume the lone pair of nitrogen is pointed downward toward the metal as this confirmation keeps the six-membered ring away from the bulk of the metal. With the lone pair pointed upward the six-membered ring is pushed towards the metal center in an unfavorable interaction (Figure 4.4 C). Based on these data the proposed structure of **32** shows the hydride adding *anti* to the metal and the nitrogen lone pair is facing downward.

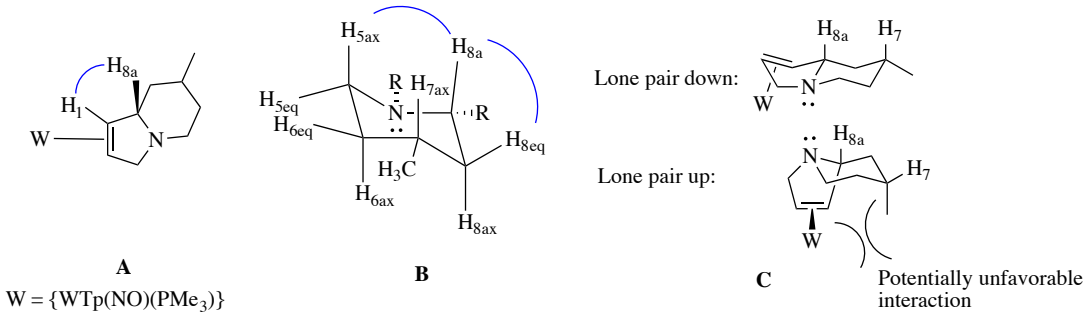
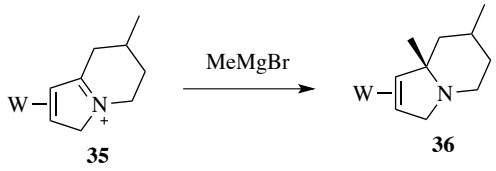



**Figure 4.4** A. NOE interactions with between $H_{8a}$ and H1 (shown in blue). B. NOE interactions with other ring protons *anti* to the metal (5-membered ring and metal not shown). C. Steric effects of lone pair down vs. lone pair up.

While the iminium of **35** is successfully reduced with a hydride (forming **32**), the site itself is very electron-deficient and could conceivably be reacted with an alternative nucleophile. One nucleophile explored was methylmagnesium bromide. This Grignard reagent was used with the goal of adding a methyl to the iminium carbon to create **36** (Scheme 4.9). This would be an interesting reaction as quaternary centers on indolizidines are rare and difficult to synthesize.[18] Unfortunately, all the reaction conditions explored with methylmagnesium bromide gave multiple products as observed by $^{31}$P NMR spectroscopy. Despite a variety of conditions tested, a single product was never isolated. Upon work up of one of these reactions, an oil was isolated and its $^{1}$H NMR spectrum was obtained. Starting material (**35**) is observed but there is also a new set of peaks that could represent **36** because of an indicative methyl singlet observed in

addition to the methyl doublet as expected. **36** was unable to be isolated cleanly and fully characterized.

**Scheme 4.9** Reaction of **35** with MeMgBr to form **36**.

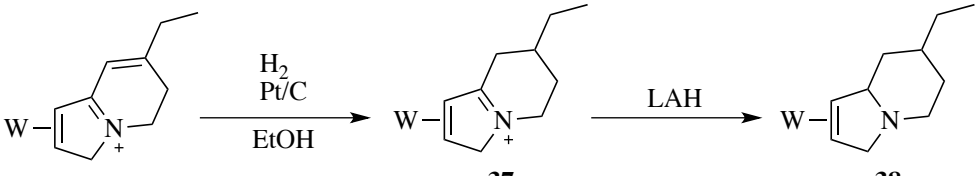



**35** **36**

W = {WTp(NO)(PMe$_3$)}

Because of the success of the hydrogenation and subsequent reduction procedures for **28**, the same conditions were explored with the EVK cyclized product (**29**). It is found that **29** is susceptible to hydrogenation over a platinum catalyst to form **37** (Scheme 4.10). Following hydrogenation, the resulting iminium is reduced with LAH and **38** is isolated (Scheme 4.10). After the iminium is reduced and **38** is formed, the anodic wave of the complex is shifted more negative to $E_{p,a}$ = +0.35 V. Both products **37** and **38** were able to be fully characterized using multidimensional NMR techniques. As with **35** and **32**, both **37** and **38** show both the hydrogens and the hydride add to the face of the indolizidine *anti* to the metal. **38** is also believed to be in the conformation with the nitrogen lone pair facing downward so to prevent an unfavorable steric interaction (see Figure 4.4 C for comparable representation with **32**).

**Scheme 4.10** *cis*-hydrogenation of **29** to form **37**. Subsequent reduction with LAH to form **38**.



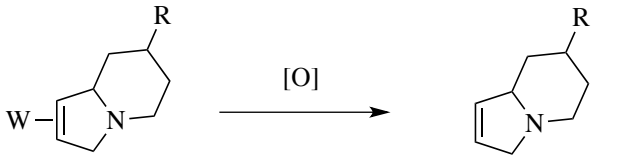

**29** **37** **38**

W = {WTp(NO)(PMe$_3$)}

With the saturated dihapto-indolizidines **32** and **38** in hand, our research efforts focused on oxidation conditions to isolate the dehydroindolizidines, **39** and **40** (Scheme

4.11). An interesting feature of the dehydroindolizidines **39** and **40** is the unsaturated bond that appears after the organic is no longer coordinated to the metal. Once the metal is oxidized, another site of chemical elaboration becomes available. Not only has the metal enabled the formation of an indolizidine core but it has also presented an additional site available for chemical transformations.

**Scheme 4.11** Oxidation of **32** and **38** to yield dehydroindolizidines **39** and **40**.




R = $CH_3$ (**32**)
R = $CH_2CH_3$ (**38**)
W = {$WTp(NO)(PMe_3)$}

R = $CH_3$ (**39**)
R = $CH_2CH_3$ (**40**)

Initial oxidation attempts were performed on **32** and the oxidants explored were ceric ammonium nitrate (CAN) and nitrosonium hexafluorophosphate ($NOPF_6$) because both have shown success in oxidizing similar dihapto-coordinated nitrogen-containing arenes.[11,13] The cleanest results were found using $NOPF_6$ in deuterated acetonitrile. Before the oxidizing agent is added, the complex (**32**) can be seen clearly in the $^1H$ and $^{31}P$ NMR spectra. Once the $NOPF_6$ is added the solution changes color and a significant transformation is observed in both NMR spectra. The dihapto-coordinated complex that is characterized by a resonance in the $^{31}P$ NMR with a $J_{WP} \sim 274$ Hz is no longer present and instead the signals for the $PF_6$ counterion appear with some possible decomposition peaks. Most revealing is the change in the $^1H$ NMR spectrum. Before oxidation there is a clean set of nine resonances for the Tp ligand, a doublet for the $PMe_3$ ancillary ligand as well as several distinct peaks for the coordinated-indolizidine. After oxidation the clean set of Tp peaks and single $PMe_3$ doublet disappear and are replaced with a range of

unknown decomposition products. The coordinated-indolizidine peaks disappear and are replaced by a new set of free dehydroindolizidine (**39**) resonances. The free dehydroindolizidine (**39**) can be seen among the decomposition products by its alkene proton signals around 6 ppm (Figure 4.5).

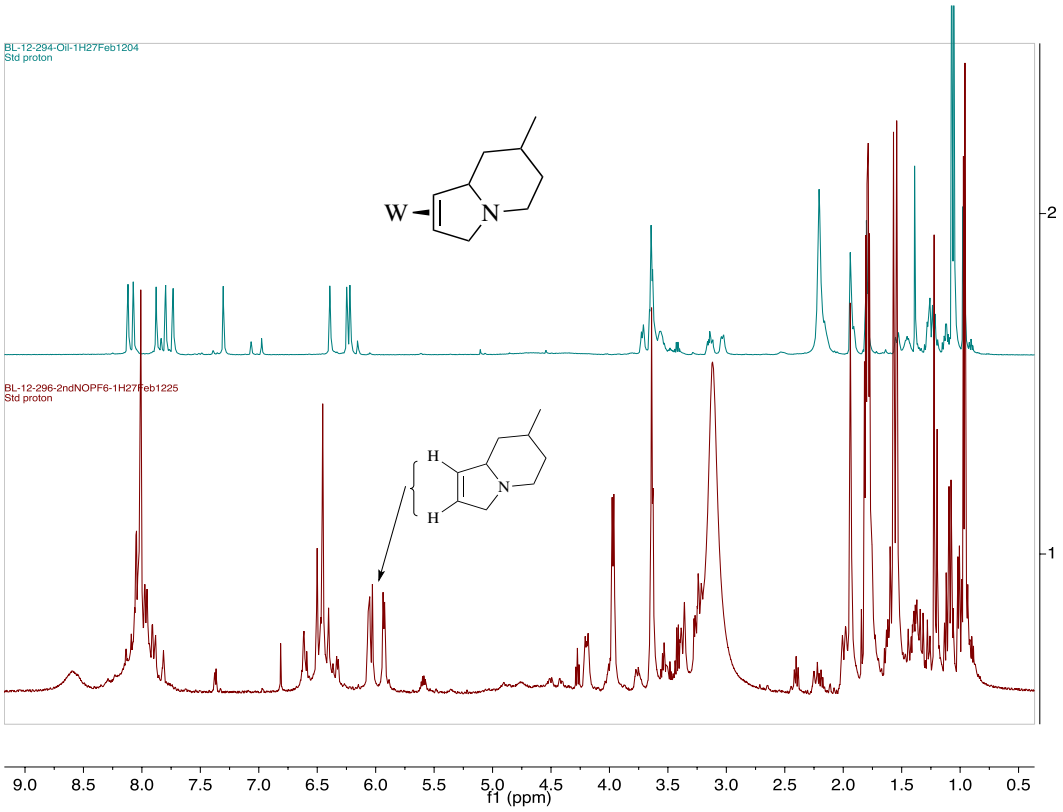


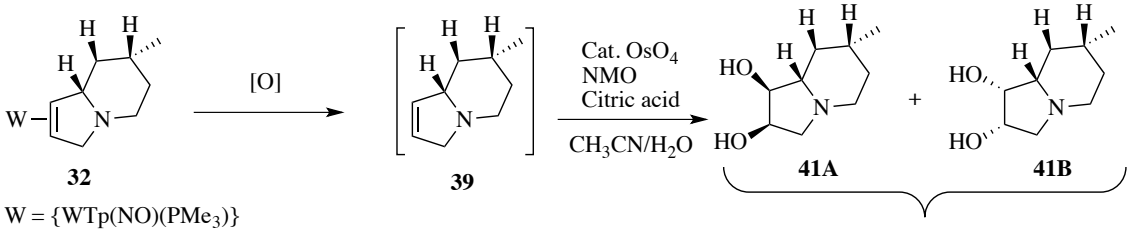

**Figure 4.5** $^{1}$H NMR spectra of dihapto-indolizidine (**32**, top) and free dehydroindolizidine (**39**, bottom) (W = {WTp(NO)($PMe_3$)}).

A great effort was put forward to isolate **39** cleanly. Initial purification attempts included column chromatography and aqueous extractions. Unfortunately, neither of these methods yields a clean product. Because of the small size and low molecular weight of **39** (137 g/mol) it is possible that the desired organic is not isolated because it has been evaporated *in vacuo* during the work-up procedure. There is precedent for smaller indolizidines to be volatile.[19] A method to counteract this volatility is by isolating the

hydrochloride salt of the indolizidine instead of the free indolizidine (**39**).[19] When this method was tested on the isolation of **39** a clean hydrochloride salt of **39** was not isolated, possibly due to complications of scale. The reaction was performed on <100 mg scale of dihapto-coordinated indolizidine complex (**32**) making the relative amount of clean dehydroindolizidine (**39**) in solution miniscule.

Although isolating **39** as its hydrochloride salt was unsuccessful, we proposed another idea to modify **39** and make the molecule bulkier and possibly less volatile. As mentioned previously, hydroxylated indolizidines are of interest in the chemical and biological community.[12] Using the same conditions that were able to dihydroxylate **28**, it was believed that we could dihydroxylate **39** after oxidation but before any work-up. By adding two hydroxyl groups to **39** the added molecular weight should decrease the volatility of the indolizidine. There is also literature precedent for dihydroxylated indolizidines like lentiginosine (see Figure 4.2) to survive column conditions.[20] The Upjohn process that was used previously is also able to dihydroxylate **39** and convert it to the dihydroxylated indolizidine (**41A** and **41B**, Scheme 4.12).[15]

**Scheme 4.12** Oxidation of **33** to form **39**, which is dihydroxylated to form **41**.




It is important to note that when the cyclized MVK adduct (**28**) is hydrogenated to form **35** and subsequently reduced to form **32** those additions occurred on the *anti* face of the coordinated indolizidine likely because of the steric bulk of the metal. However, once the organic is no longer coordinated to the metal, the metal cannot influence the regio- or

stereochemistry of subsequent reactions. In essence, the regio- and stereochemical preferences of any reaction performed on the free dehydroindolizidine (**39**) are subject to the influences of whatever substituents are on the ring. This is pertinent to the dihydroxylation reaction used to create the dihydroxylated indolizidine **41**. The mechanism of the Upjohn dihydroxylation dictates the hydroxyl groups add *cis* creating two potential stereoisomers of **41 (**Scheme 4.12). If the dihydroxylation occurs on the same face of the indolizidine as the hydrogenation and hydride reduction **41A** is formed. If dihydroxylation occurs on the opposite face **41B** is formed (scheme 4.12).

The first indication that the dihydroxylation of **39** was successful is in the $^{1}H$ NMR spectrum. The most notable peaks in **39** were the alkene peaks around 6 ppm that signify the dehydroindolizidine (**39**) is no longer coordinated (see Figure 4.5) but after dihydroxylation these peaks disappear and are replaced by more upfield proton signals just over 4 ppm indicating **41A** or **41B** had formed (Figure 4.6).

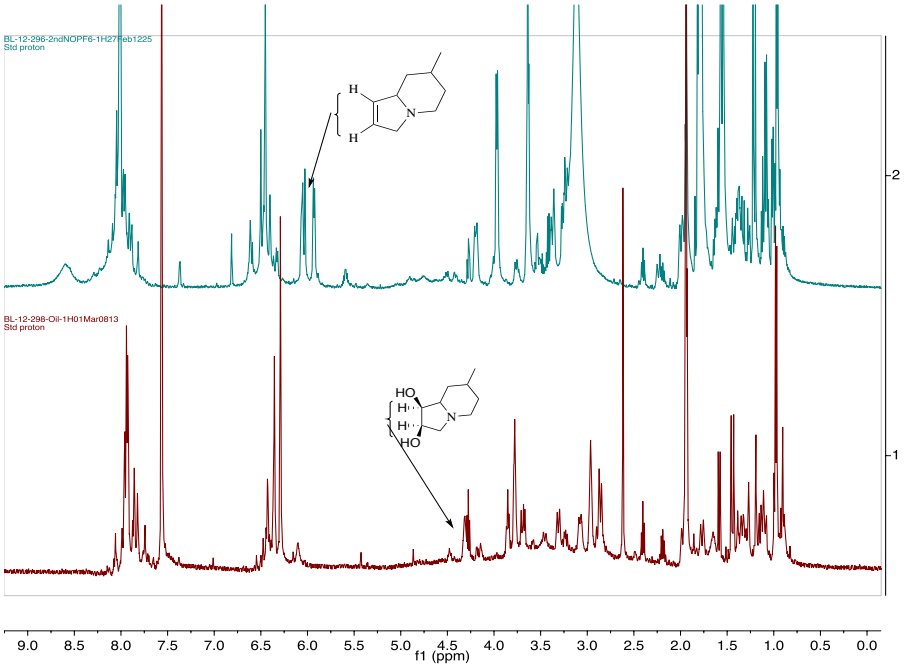
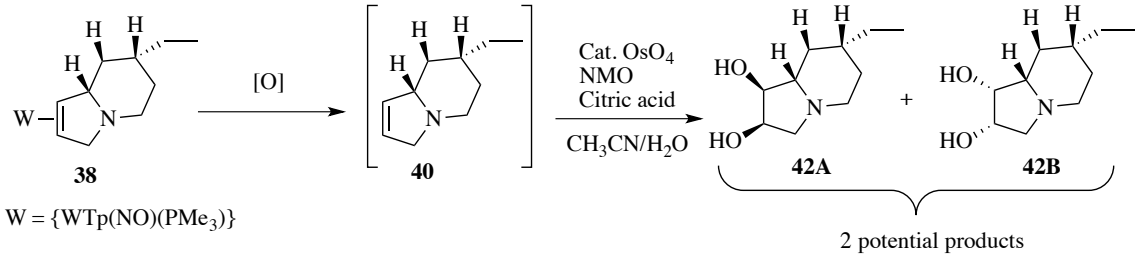


**Figure 4.6** $^1$H NMR spectra of dehydroindolizidine (**39**, top) and the dihydroxylated indolizidine (**41**, bottom).

The product of **41** reveals a major product and a minor product in a 5:1 ratio. Unfortunately, we were unable to fully characterize the dihydroxylated indolizidine (**41**) and identify which stereoisomer is the major product. This dihydroxylated indolizidine (**41**) does resemble Lentiginosine (Figure 4.2) and is found to have a very similar $^1$H NMR spectrum to a Lentiginosine derivative.[21] A sample of **41** was also observed using low-resolution mass spectrometry. Two distinct parent compounds with the correct M/Z ratio were observed possibly representing the two diastereomers. **41** has been submitted for biological screening.

For the EVK cyclized saturated indolizidine product (**38**), oxidation with $NOPF_6$ provides the dehydroindolizidine product (**40**) though it is not isolated. As observed before, the Upjohn dihydroxylation conditions were able to convert **40** to the dihydroxylated product **42** (scheme 4.13). Compared to the dihydroxylation of **39** similar observations are made confirming the dihydroxylation of **40**. Two products for **42** are observed, a major and minor isomer (2:1). Compound **42** is isolated after column chromatography but was unfortunately not fully characterized. As with **41**, the $^1$H NMR spectrum of **42** resembled that of a lentiginosine derivative.[21]

**Scheme 4.13** Oxidation of **38** to form **40**, which is dihydroxylated to form **42**.



## 4.3 Conclusion

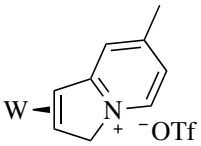
After the successful dihapto-coordination of 2-methylpyrrole to the electron-rich dearomatization fragment {WTp(NO)($PMe_3$)} the 2H-pyrrolium complex is formed. After Michael addition with MVK or EVK and subsequent intramolecular cyclization two indolizidine cores can be isolated. The indolizidine cores are prone to several transformations including hydrogenation followed by hydride reduction to yield dehydroindolizidine systems. Post oxidation of the metal a dihydroxylation can occur and dihydroxylated indolizidines can be isolated. Presently, the MVK cyclized product that has been reduced, oxidized and dihydroxylated has been submitted for biological screening.

## 4.4 Experimental Procedures

**General Methods**. NMR spectra were obtained on a 300, 500, 600 or 800 MHz spectrometer. All chemical shifts are reported in ppm, and proton and carbon shifts are referenced to tetramethylsilane (TMS) utilizing residual $^{1}H$ or $^{13}C$ signals of the deuterated solvents as an internal standard. Phosphorous NMR signals are referenced to 85% $H_3PO_4$ (δ 0.00) using a triphenyl phosphate external standard (δ -16.58). Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra (IR) were recorded as a glaze on a spectrometer fitted with a horizontal attenuated total reflectance (HATR) accessory or an FT-IR spectrometer equipped with a diamond anvil ATR assembly. Electrochemical

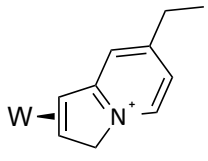
experiments were performed under a dinitrogen atmosphere using a potentiostat. Cyclic volammetry data were taken at ambient temperature (~25 °C) at 100 mV/s in a standard three-electrode cell with a glassy-carbon working electron, *N*,*N*-dimethylacetamine (DMA) or acetonitrile (MeCN) solvent (unless otherwise specified), and tetrabutylammonium hexafluorophosphate (TBAH) electrolyte (approx. 0.5 M). All potentials are reported verses the NHE (normal hydrogen electron) using cobaltocenium hexafluorophosphate ($E_{1/2}$ = -0.78 V), ferrocene ($E_{1/2}$ = +0.55 V), or decamethylferrocene ($E_{1/2}$ = +0.04 V) as internal standard. The peak-to-peak separation was less than 100 mV for all reversible couples. Low-resolution mass spectra were acquired in EI mode, on a Shimadzu GCMS-QP2010. Unless otherwise noted, all synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere. Dimethoxyethane (DME) and chloroform was purified through a column packed with activated basic alumina. Other solvents and liquid reagents were thoroughly purged with dry nitrogen prior to use. Triflate salts of amines were synthesized by addition of a diethyl-ether solution of trifilic acid to the appropriate conjugate base dissolved in diethyl-ether. Deuterated chloroform was purified through a column packed with activated basic alumina. Other deuterated solvents were used as received from Cambridge Isotopes. Deactivated basic alumina was made by stirring basic alumina with water (15% by mass). Pyrazole (Pz) protons of the tris(pyrazolyl)borate (Tp) ligand were uniquely assigned when possible (e.g., "PzA3") using a combination of two-dimensional NMR data and phosphorous-proton NOE interactions. BH peaks (around 4-5 ppm) are not identified due to their quadrupole broadening. All phosphrous NMR spectra are phosphorous-proton decoupled. IR data are used to confirm the presence of a BH group (around 2500 $cm^{-1}$). OH and NH peaks are

not always identified due to exchange with water in the solvent. Compounds: **13**, **16**, **17**, **28** and **29** were previously reported.[3]




**28A**: WTp(NO)($PMe_3$)($\eta^2$-(7-methyl-indolizinium)][OTf]: Under an ambient atmosphere **13** (3.2445 g, 4.420 mmol), in a 50 mL round bottom flask charged with a stirbar. Added chloroform (13 mL) followed by methyl vinyl ketone (1.3679 g, 19.52 mmol) and triethylamine (.4815 g, 4.758 mmol). The reaction stirred for ~ 6 hours. Transferred reaction solution to 250 mL round bottom flask. Added chloroform (65 mL) and pyrrolidine (1.3988 g, 19.67 mmol) to the flask. The reaction stirred for ~ 16 hours and then more methyl vinyl ketone (.1728 g, 2.465 mmol) and pyrrolidine (.0852 g, 1.198 mmol) were added. The reaction stirred. After 7 days, the reaction was dry loaded onto deactivated alumina. Set up a 350 mL medium frit with ~ 2 cm of deactivated alumina. Added alumina with reaction mixture and eluted with ethyl acetate (~ 300 mL) to remove red-brown eluent. Eluted with 40:60 acetonitrile: ethyl acetate (500 mL) and collected yellow-brown band. Concentrated to oil. In a 500 mL round bottom flask, picked oil up in minimal dichloromethane and then added ethyl acetate (250 mL). Evaporating compound till precipitate was seen and then put round bottom in freezer at -15 °C overnight.

Collected a brown precipitate **28A** (.9096 g, 1.159 mmol, 26% yield). Note: starting material (**13**) for this reaction was very dirty and possibly contained a great excess of 2-methylpyrrole. $^{1}$H NMR ($CDCl_3$, 600 MHz, δ): 8.28 (d, *J* = 6.8, 1H, H5), 8.09 (d, *J* = 2.0, 1H, Pz3A), 7.93 (d, *J* = 2.0, 1H, Pz3B), 7.80 (d, *J* = 2.3, 1H, Pz5B), 7.76 (d, *J* = 2.3, 1H, Pz5C), 7.65 (d, *J* = 2.3, 1H, Pz5A), 7.56 (s, 1H, H8), 7.48 (d, *J* = 2.1, 1H, Pz3C), 7.01 (dd, *J* = 6.5, 1.4, 1H, H6), 6.35 (t, *J* = 2.2, 1H, Pz4B), 6.31 (t, *J* = 2.2, 1H, Pz4C), 6.25 (t, *J* = 2.1, 1H, Pz4A), 6.11 (dd, *J* = 14.8, 6.6, 1H, H3-anti), 5.80 (d, *J* = 14.8, 1H, H3-syn), 4.30 (dd, *J* = 8.4, 1.0, 1H, H1), 2.55 (dt, *J* = 6.7, 2.0, 1H, H2), 2.50 (s, 3H, $CH_3$), 1.20 (d, *J* = 8.6, 9H, $PMe_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 169.1 (C8a), 144.3 (Pz3b), 141.8 (Pz3C), 140.7 (Pz3A), 138.3(C7), 137.5 (Pz5C or Pz5B), 137.0 (Pz5C or Pz5B), 136.3 (Pz5A), 122.2 (C5), 121.7 (C6), 121.3 (C8), 107.5 (Pz4B), 107.1 (Pz4C), 106.3 (Pz4A), 66.3 (C3), 57.9 (d, *J* = 9.7, C1), 53.9 (C2), 22.3 ($CH_3$), 13.6 (d, *J* = 29.5, $PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -13.53, $J_{WP}$ = 274. CV ($CH_3CN$): $E_{p,a}$ = +1.04 V. IR: $\nu_{BH}$ = 2499 cm$^{-1}$, $\nu_{NO}$ = 1574 cm$^{-1}$.

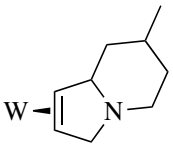



**30A**: WTp(NO)($PMe_3$)(η$^2$-(7-ethyl-indolizinium)][OTf]: Under a nitrogen atmosphere, **13** (1.6714 g, 2.277 mmol) was placed in an oven dried vial. Triethylamine (.2598 g, 2.567 mmol), ethyl vinyl ketone (.8460 g, 10.06 mmol), and chloroform (~ 7 mL total) were added to the vial. The reaction sat for just under 5 hours. The reaction was placed in

a fume hood and transferred to a 100 mL round bottom flask with chloroform (35 mL) and pyrrolidine (.7174 g, 10.09 mmol). The reaction stirred for ~ 20 hours. Added ethyl vinyl ketone (.0845 g, 1.005) and pyrrolidine (.0426 g, 5.992 mmol). The reaction stirred for 26 days. A precipitate was observed in the round bottom. The solution was decanted and concentrated to an oil. The oil was picked up in minimal DCM and precipitated in stirring ether (~ 1.6 L). A brown precipitate was collected on a 150 mL M frit. The precipitate was dried in a dessicator over night to yield **30A** (1.3446 g, 1.685 mmol, 74% yield). Note: $^{1}$H NMR of this precipitate was impure, column conditions were attempted. Cyclized product likely minor product (10% or less).

Column conditions: Impure **30A** (.0534 g, .0669 mmol), was dry loaded on deactivated basic alumina and set on a column of deactivated basic alumina loaded with ethyl acetate. Eluted with ethyl acetate to remove a colored eluent. A solution of acetonitrile and ethyl acetate (50:50) was used to collect a yellow band that was concentrated to an oil that was clean **30A** (.0230 g, .0288 mmol, 43.1% yield). $^{1}$H NMR ($CDCl_3$, 600 MHz, δ): 8.32 (d, *J* = 6.4, 1H, H6), 8.10 (d, *J* = 1.9, 1H, Pz3A), 7.95 (d, *J* = 1.9, 1H, Pz3B), 7.80 (d, *J* = 2.3, 1H, Pz5B), 7.77 (d, *J* = 2.2, 1H, Pz5C), 7.66 (d, *J* = 2.3, 1H, Pz5A), 7.57 (s, 1H, H8), 7.53 (d, *J* = 2.0, 1H, Pz3C), 7.06 (dd, *J* = 6.4, 1.5, 1H, H5), 6.37 (t, *J* = 2.2, 1H, Pz4B), 6.33 (t, *J* = 2.2, 1H, Pz4C), 6.28 (t, *J* = 2.2, 1H, Pz4A), 6.16 (dd, *J* = 14.8, 6.4, 1H, H3-Anti), 5.82 (d, *J* = 14.8, 1H, H3-Syn), 4.38 (dd, *J* = 8.1, 1.0, 1H, H1), 2.60 (td, *J* = 7.3, 2.2, 2H, $CH_2$), 2.52 (q, *J* = 7.3, 1H, H2), 1.22 (d, *J* = 8.5, 1H, $PMe_3$), 1.03 (t, *J* = 7.3, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 169.2 (C8a), 161.1 (C7), 144.2 (Pz3B), 141.8 (Pz3C), 140.7 (Pz3A), 138.6 (C6), 137.4 (Pz5C), 137.0 (Pz5B), 136.3 (Pz5A), 121.0 (C5), 120.1 (C8), 107.5 (Pz4B), 107.1 (Pz4A), 106.3 (Pz4C), 66.3 (C3), 58.0 (d, *J* = 9.6,

C1), 53.9 (C2), 35.5 ($CH_2$), 13.6 (d, $J$ = 30.0, $PMe_3$), 7.73 ($CH_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -13.6, $J_{WP}$ = 282. CV ($CH_3CN$): $E_{p,a}$ = 1.07 V. IR: $\nu_{BH}$ = 2509 $cm^{-1}$, $\nu_{NO}$ = 1577 $cm^{-1}$.




**32**: WTp(NO)($PMe_3$)($\eta^2$-(7-methyl-hexahydroindolizine):

**Tetrabutylammonium borohydride, HCl method**: Under a nitrogen atmosphere **28** (0.2730 g, 0.3472 mmol) was placed in an oven-dried vial. Acetonitrile (3 mL) was added and the solution stirred. Tetrabutylammonium borohydride (TBA-$BH_4$, 0.1829 g, 0.7108 mmol) was then added. The reaction stirred ~ 1 min. The vial was then brought out of the box and precipitated in stirring ether (250 mL). The precipitate was collected on a 150 mL fine porosity fritted funnel. To the filtrate added a stirbar and stirred. Added 4M HCl solution in dioxane (.5 mL, 2.00 mmol) and formed a white precipitate. The precipitate was collected on a 60 mL medium porosity fritted funnel. The precipitate was rinsed through the frit with non-dried chloroform (~ 50 mL). The chloroform was washed with 1M NaOH (2 x 50 mL) and DI water (1 x 50 mL). The organic layer was dried over magnesium sulfate. After removing the drying agent, the organic layer was concentrated to a yellow oil **32** (0.1435 g, 0.2242 mmol, 65% yield).

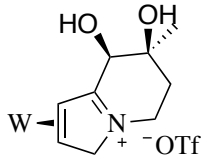
**Tetrabutylammonium borohydride, $Na_2CO_3$ method**: Under a nitrogen atmosphere **28** (0.0425 g, 0.0541 mmol) was placed in an oven-dried vial. Added acetonitrile (.6 mL)

and transferred to oven-dried NMR tube with TBA-$BH_4$ (0.0181 g, 0.0703 mmol). The reaction was allowed to react ~ 10 minutes. Took outside of the box and precipitated in 50 mL stirring ether. The precipitate was collected and the filtrate was washed with sat. $Na_2CO_3$ (1 x 50 mL) and DI water (1 x 50 mL). The organic layer was dried over magnesium sulfate. After removing the drying agent, the organic layer was concentrated *in vacuo* to a yellow oil **32** (0.0166 g, 0.0259 mmol, 48% yield).

**Super-hydride method:** Under a nitrogen atmosphere **28** (0.0996 g, 0.1264 mmol) was placed in an oven-dried vial and added acetonitrile (1 mL) making a heterogeneous solution. Added this heterogeneous solution to an oven-dried vial with 1M Super-H® (0.2 mL, 0.2 mmol). Swirled and then rinsed back into original vial. Then added more 1M Super-H® (0.2 mL, 0.2 mmol). The solution was precipitated in stirring ether (50 mL). To the filtrate added a stirbar and stirred. Added 4M HCl solution in dioxane (0.2 mL, 0.8 mmol) and formed a white precipitate. The precipitate was collected on a 30 mL medium porosity fritted funnel. The precipitate was rinsed through the frit with dichloromethane (~ 3 mL). The dichloromethane was washed with 1M NaOH (2 x 2 mL). The organic layer was dried over magnesium sulfate. After removing the drying agent, the organic layer was concentrated to a yellow oil of **32** (0.0475 g, 0.2242 mmol, 59% yield).

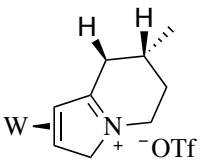
**Beginning with 35**: **35** (0.1009 g, 0.1280 mmol) was placed in an oven-dried vial. Added distilled THF (~ 1 mL) and the solution became mostly heterogeneous. Added 1M LAH in THF (0.25 mL, .2500 mmol) and the solution darkened and became homogeneous. After ~ 1 min added few drops of methanol. In a fume hood added to stirring ether (100 mL) and collected precipitate on 30 mL fine porosity fritted funnel. Washed filtrate with

sat. $Na_2CO_3$ (2 x 100 mL) then collected organic layer and dried over magnesium sulfate. after removing the drying agent, the organic layer was concentrated to a yellow oil of **32** (0.0358 g, 0.0559 mmol, 44% yield). $^1$H NMR ($CD_3CN$, 600 MHz, δ): 8.11 (d, $J$ = 1.7, 1H, Pz3A), 8.07 (d, $J$ = 1.7, 1H, Pz3B), 7.88 (d, $J$ = 2.3, 1H, Pz5B), 7.80 (d, $J$ = 2.2, 1H, Pz5C), 7.73 (d, $J$ = 2.3, 1H, Pz5A), 7.31 (d, $J$ = 1.8, 1H, Pz3C), 6.39 (t, $J$ = 2.2, 1H, Pz4B), 6.25 (t, $J$ = 2.2, 1H, Pz4A), 6.22 (t, $J$ = 2.2, 1H, Pz4C), 3.74 (dd, $J$ = 9.0, 1.5, 1H, H3-syn), 3.64 (buried m, 1H, H8a), 3.58 (d, $J$ = 9.0, 1H, H3-anti), 3.14 (ddd, $J$ = 13.4, 8.8, 4.4, 1H, H1), 3.05 (dd, $J$ = 10.3, 2.0, 1H, H5eq), 2.18 (td, $J$ = 10.3, 2.0, 1H, H5ax), 1.92 (broad m, 1H, H8eq), 1.55 (dd, $J$ = 12.0, 2.5, 1H, H6eq), 1.46 (m, 1H, H7ax), 1.28 (dd, $J$ = 8.2, 1.4, 1H, H2), 1.26 (buried m, 1H, H6ax), 1.21 (buried m, 1H, H8ax), 1.06 (d, $J$ = 8.1, 9H, $PMe_3$), 0.97 (d, $J$ = 6.6, 3H, $CH_3$). $^{13}$C NMR ($CD_3CN$, 600 MHz, δ): 143.3 (Pz3B), 143.2 (Pz3A), 141.5 (Pz3C), 137.6 (Pz5C), 137.2 (Pz5B), 136.7 (Pz5A), 107.6 (Pz4B), 107.0, (Pz4A), 106.7 (Pz4C), 73.6 (C8a), 63.3, (C1), 61.3 (C3), 57.8 (C2), 52.9 (C5), 43.4 (C8), 35.9 (C6), 33.2 (C7), 23.0 ($CH_3$), 13.7 (d, $J$ = 28.0, $PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -13.0, $J_{WP}$ = 274. CV ($CH_3CN$): $E_{p,a}$ = 0.42 V. IR: $\nu_{BH}$ = 2488 cm$^{-1}$, $\nu_{NO}$ = 1535 cm$^{-1}$.



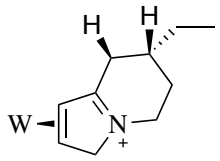

**34**: WTp(NO)($PMe_3$)($\eta^2$-(7-methyl-7,8-dihydroxyindolizidinium)][OTf]: Under a nitrogen atmosphere **28** (0.0527 g, 0.0760 mmol) was put in an oven-dried vial with

acetonitrile (~ 1 mL). To this, a solution of *N*-methylmorpholine *N*-oxide (0.0247 g, 0.2108 mmol) and citric acid (0.0255 g, 0.1327 mmol) in DI water (~ 1 mL). This biphasic solution stirred for ~ 1 minute. Then added 2.5% OsO4 solution (.1 mL, 0.0080 mmol). The reaction stirred for 23.5 hours. Vial taken out of glovebox and placed in fume hood. Added sat. $Na_2CO_3$ (~ 3 mL) and extracted aqueous layer with ethyl acetate (2 x 3mL). Collected organic layers and dried over magnesium sulfate. Filtered off drying agent and concentrated to oil *in vacuo*. Oil picked up in minimal dichloromethane and precipitated in stirring ether (50 mL). Tan precipitate **34** collected on 15 mL fine porosity fritted funnel (0.0230 g, 0.0280 mmol, 42% yield). $^{1}$H NMR ($CDCl_3$, 600 MHz, δ): 8.08 (d, *J* = 1.8, 1H, Pz3B), 7.98 (d, *J* = 1.6, 1H, Pz3A), 7.84 (d, *J* = 2.4, 1H, Pz5B), 7.77 (d, *J* = 2.2, 1H, Pz5C), 7.64 (d, *J* = 2.3, 1H, Pz5A), 7.53 (d, *J* = 1.8, 1H, Pz3C), 6.44 (t, *J* = 2.2, 1H, Pz4B), 6.33 (t, *J* = 2.2, 1H, Pz4C), 6.26 (t, *J* = 2.2, 1H, Pz4A), 6.02 (dd, *J* = 8.2, 1.7 1H, H3-syn), 5.75 (t, *J* = 8.2 1H, H3-Anti), 4.38 (ddd, *J* = 8.8, 6.6, 2.8, 1H, H1), 4.28 (dt, *J* = 15.1, 5.2, 1H, H5ax), 4.05 (d, *J* = 9.6, 1H, H8), 3.82 (dd, *J* = 15.1, 6.5, 1H, H5eq), 2.65 (dd, *J* = 5.6, 0.6, 1H, H2), 2.23 (dd, *J* = 14.4, 5.2, 1H, H6eq), 2.04 (ddd, *J* = 17.4, 11.3, 7.2, 1H, H6ax), 1.88 (bs, 2H, OH), 1.49 (s, 3H, $CH_3$), 1.20 (d, *J* = 8.8, 9H, $PMe_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 188.9 (iminium), 144.0 (Pz3B), 142.0 (Pz3C), 141.0 (Pz3A), 137.6 (Pz5C), 137.3 (Pz5B), 136.4 (Pz5A), 107.9 (Pz4B), 107.5 (Pz4C), 106.5 (Pz4A), 100.1 (C3), 72.6 (C8), 69.0 (C7), 66.4 (C2), 59.1 (d, *J* = 8.6, C1), 39.8 (C5), 32.9 (C6), 25.6 ($CH_3$), 13.2 (d, *J* = 30.4, $PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -13.6, $J_{WP}$ = 266. CV ($CH_3CN$): $E_{p,a}$ = +1.46 V. IR: $\nu_{BH}$ = 2506 cm$^{-1}$, $\nu_{NO}$ and $\nu_{CN}$ = 1575 cm$^{-1}$, $\nu_{OH}$ = 3347 cm$^{-1}$



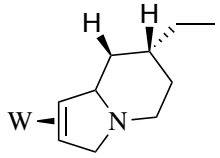

**35**: WTp(NO)($PMe_3$)($\eta^2$-(7-methyl-7,8-dihydroindolizidinium)][OTf]: **28** (0.2413 g, 0.3069 mmol) was placed in a reaction tube with 5% Pt on activated carbon (0.1723 g, 0.0442 mmol) and absolute ethanol (8 mL) a stirbar was added. The reaction tube was sealed and pressurized with hydrogen (50 psi). The reaction stirred for 23 hours. The reaction tube was vented and the reaction solution was filtered through a 30 mL medium porosity frit with ~1 inch of Celite®. The frit was then rinsed with dichloromethane (~ 50 mL). The filtrate was concentrated to dryness *in vacuo*. The resulting oil was picked up in minimal dichloromethane and precipitated in stirring ether (~ 250 mL). A tan precipitate (**35**) was collected on a 30 mL fine porosity fritted funnel (0.1525 g, 0.1935 mmol, 63% yield). $^1$H NMR ($CDCl_3$, 600 MHz, δ): 8.02 (d, *J* = 1.7, 1H, Pz3B), 7.99 (d, *J* = 1.5, 1H, Pz3A), 7.83 (d, *J* = 1.9, 1H, Pz5B), 7.74 (d, *J* = 2.1, 1H, Pz5C), 7.67 (d, *J* = 2.2, 1H, Pz5A), 7.62 (d, *J* = 2.2, 1H, Pz3C), 6.41 (t, *J* = 2.2, 1H Pz4B), 6.32 (t, *J* = 2.1, 1H, Pz4C), 6.27 (t, *J* = 2.1, 1H, Pz4A), 5.74 (dd, *J* = 16.0, 5.0, 1H, H3-syn), 5.00 (d, *J* = 16.0, 1H, H3-anti), 4.23 (td, *J* = 8.4, 2.0 1H, H1), 3.94 (dd, *J* = 14.3, 4.1, 1H, H5eq), 3.79 (td, *J* = 14.3, 4.1, 1H, H5ax), 3.65 (dd, *J* = 18.2, 2.0, 1H, H8eq), 2.43 (td. *J* = 6.5, 2.0, 1H, H2), 2.16 (m, 1H, H7ax), 2.09 (dd, *J* = 18.8, 10, 1H, H8ax), 2.03 (d, *J* = 16.0, 1H, H6eq), 1.67 (ddd, *J* = 16.0, 10.8, 4.5 1H, H6ax), 1.19 (d, *J* = 8.4, 9H, $PMe_3$), 1.17 (d, *J* = 6.9, 3H, $CH_3$ in equatorial position). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 191.8 (C=N), 143.9 (Pz3B),

142.2 (Pz3C), 140.1 (Pz3A), 137.3 (Pz5C), 137.2 (Pz5B), 136.4 (Pz5A), 107.6 (Pz4B), 107.5 (Pz4C), 106.2 (Pz4A), 66.9 (C3), 62.5 (d, $J$ = 8.2, C1), 56.5 (C2), 45.6 (C5), 36.8 (C8), 30.0 (C6), 25.4 (C7), 21.1 ($CH_3$), 13.9 (d, $J$ = 29.5, $PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -14.5, $J_{WP}$ = 269. CV ($CH_3CN$): $E_{p,a}$ = +1.15 V. IR: $\nu_{BH}$ = 2506 $cm^{-1}$, $\nu_{NO}$ and $\nu_{CN}$ = 1566 $cm^{-1}$.



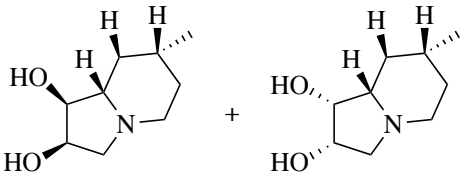

**37**: [WTp(NO)($PMe_3$)($\eta^2$-(7-ethyl-7,8-dihydroindolizidinium)][OTf]: **29** (0.0504 g, 0.0630 mmol) was placed in a reaction tube with a stir bar. 5% Pt on activated carbon (0.0348 g, 0.0630 mmol) and absolute ethanol (2 mL) were added. The reaction tube was sealed and pressurized with hydrogen (50 psi). The reaction stirred for 23 hours. The reaction tube was vented and the reaction solution was filtered through a 15 mL medium porosity frit with ~0.5 inches of Celite®. The frit was then rinsed with dichloromethane (~ 10 mL). The filtrate was concentrated to dryness *in vacuo*. The resulting oil was picked up in minimal dichloromethane and precipitated in stirring ether (~ 50 mL). A tan precipitate (**37**) was collected on a 30 mL fine porosity fritted funnel (0.0263 g, 0.0328 mmol, 52% yield). $^1$H NMR ($CDCl_3$, 600 MHz, δ): 8.00 (d, $J$ = 1.9, 1H, Pz3B), 7.98 (d, $J$ = 1.9, 1H, Pz3A), 7.82 (d, $J$ = 2.4, 1H, Pz5B), 7.74 (d, $J$ = 2.1, 1H, Pz5C), 7.66 (d, $J$ = 2.4, 1H, Pz5A), 7.53 (d, $J$ = 2.2, 1H, Pz3C), 6.39 (t, $J$ = 2.2, 1H, Pz4B), 6.28 (t, $J$ = 2.2, 1H, Pz4C), 6.24 (t, $J$ = 2.3, 1H, Pz4A), 5.72 (dd, $J$ = 15.9, 5.6, 1H, H3-anti), 4.99 (dt, $J$ = 15.9, 2.1 1H, H3-syn), 4.14 (tt, $J$ = 9.0, 1H, H1), 3.94 (dd, $J$ = 14.5, 5.4, 1H, H5eq), 3.78

(dt, $J$ = 14.5, 4.6, 1H, H5ax), 3.53 (dd, $J$ = 15.1, 2.9, 1H, H8eq), 2.40 (dt, $J$ = 6.6, 1.4, 1H, H2), 2.08 (m, 2H, H6eq and H8ax), 1.92 (m, 1H, H7), 1.61 (m, 1H, H6ax), 1.52 (m, 1H, -$CH_2$-), 1.42 (m, 1H, -$CH_2$), 1.17 (d, $J$ = 8.6, 9H, $PMe_3$), .99 (t, $J$ = 7.2, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 191.6 (iminium), 143.8 (Pz3B), 141.9 (Pz3C), 140.0 (Pz3A), 137.4 (Pz5C), 137.2 (Pz5B), 136.4 (Pz5A), 107.6 (Pz4B), 107.4 (Pz4C), 106.2 (Pz4A), 66.9 (C3), 62.5 (C1), 56.4 (C2), 45.8 (C5), 35.0 (C8), 31.8 (C7), 28.3 ($CH_2$), 27.5 (C6), 13.8 (d, $J$ = 27.0, $PMe_3$), 11.0 ($CH_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -14.6, $J_{WP}$ = 269. CV ($CH_3CN$): $E_{p,a}$ = 1.14 V. IR: $\nu_{BH}$ = 2515 cm$^{-1}$, $\nu_{NO}$ =1562 or 1625 cm$^{-1}$ and $\nu_{CN}$ = 1562 or 1625 cm$^{-1}$.



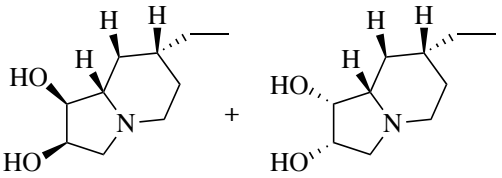

**38**: WTp(NO)($PMe_3$)(η$^2$-(7-ethyl--hexahydroindolizine)][OTf]: **37** (0.0153 g, 0.0191 mmol) was placed in an oven-dried vial. Added distilled THF (~ 0.5 mL). Added 1M LAH in THF (0.05 mL, 0.05 mmol) and the solution darkened. After ~ 1 min added few drops of methanol. In a fume hood added to stirring ether (20 mL) and collected precipitate. Washed filtrate with sat. $Na_2CO_3$ (3 x 20 mL) then collected organic layer then DI water (1 x 20 mL). Collected organic layers and dried over magnesium sulfate. After removing the drying agent, the organic layer was concentrated to a yellow oil **38** (0.0059 g, 0.0090 mmol, 47% yield). $^1$H NMR ($CD_3CN$, 600 MHz, δ): 8.11 (d, $J$ = 1.9, 1H, Pz3A), 8.07 (d, $J$ = 1.8, 1H, Pz3B), 7.88 (d, $J$ = 2.3, 1H, Pz5B), 7.80 (d, $J$ = Pz5C), 7.74 (d, $J$ = 2.4, 1H, Pz5A), 7.31 (d, $J$ = 2.1, 1H, Pz3C), 6.39 (t, $J$ = 2.2, 1H, Pz4B), 6.25

(t, $J$ = 2.3, 1H, Pz4A), 6.22 (t, $J$ = 2.2, 1H, Pz4C), 3.71 (dd, $J$ = 7.5, 2.0, 1H, H3-syn), 3.56 (m, 1H, H3-anti), 3.56 (m, 1H, H8a), 3.15 (ddd, $J$ = 13.5, 8.7, 4.3, 1H, H1), 3.04 (d, $J$ = 9.5, 1H, H5), 2.15 (buried m, 1H, H5), 1.98 (buried m, 1H, H8), 1.59 (d, $J$ = 9.2, 1H, H6), 1.32 (m, 2H, ethyl), 1.27 (m, 4H, H2, H6, H7 and H8), 1.07 (d, $J$ = 8.2, 9H, $PMe_3$), .93 (t, $J$ = 7.5, 3H, $CH_3$). $^{13}C$ NMR ($CD_3CN$, 600 MHz, δ): 143.2 (Pz3B), 141.5 (Pz3A), 140.9 (Pz3C), 137.6 (Pz5C), 137.2 (Pz5B), 136.7 (Pz5A), 107.6 (Pz4B), 107.0 (Pz4C or Pz4A), 106.7 (Pz4C or Pz4A), 73.6 (C8a), 63.6 (C1), 61.0 (C3), 58.0 (C2), 52.9 (C5), 41.0 (C8), 40.0 (C7), 33.6 (C6), 30.6 (ethyl), 13.8 ($PMe_3$), 11.8 ($CH_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -12.6, $J_{WP}$ = 271. CV (DMA): $E_{p,a}$ = 0.35 V. IR: $\nu_{BH}$ = 2480 $cm^{-1}$, $\nu_{NO}$ = 1559 $cm^{-1}$.




**41**: 7-methyloctahydroindolizine-1,2-diol: In a fume hood **32** (0.0707 g, 0.1105 mmol), was placed in a vial with deuterated acetonitrile (~ 0.6 mL). To this solution added $NOPF_6$ (0.0389 g, 0.2224 mmol). The solution turned green and the organic **39** could be observed in the $^1H$ NMR spectrum. Took NMR tube and added to vial and rinsed in with some more acetonitrile (~ 2 mL). Evaporated under nitrogen purge till about ~ 1 mL total volume. In a separate vial put *N*-methylmorpholine-*N*-oxide (NMO, 0.0447 g, 0.3814 mmol), citric acid (0.0320 g, 0.1666 mmol) and DI water (1 mL). Added water solution to acetonitrile and let stir ~ 5 minutes. Added 2.5 % $OsO_4$ solution (0.6 mL, 0.0479

mmol) and the reaction stirred for 28 hours. For work up added sat. $Na_2CO_3$ (3 mL). Extracted aqueous layer with ethyl acetate (3 x 3 mL). Collected organic layer and dried over magnesium sulfate. Filtered off drying agent and concentrated to oil. Set up silica column in Pasteur pipet. Loaded with 50:50 ethyl acetate: hexanes with 28% $NH_4OH$ (few drops). Eluted impurities with 75:25 ethyl acetate: hexanes. Collected yellow band with a gradient of ethyl acetate, 20:80 acetonitrile: ethyl acetate and 50:50 acetonitrile: ethyl acetate. After concentration of yellow band, a thin film was collected **41** (0.0017 g, 0.0099 mmol, 9% yield). Note: only $^1$H NMR obtained and shifts resemble the peaks for an analogous indolizidine: 1-*epi*-lentiginosine.[21] Major product: minor product (5:1). $^1$H NMR ($CDCl_3$, 600 MHz, δ): Major Isomer: 5.39 (m, 2H), 4.26 (dt, *J* = 6.9, 5.5, 1H), 3.64 (t, *J* = 7.4, 1H), 3.53 (dd, *J* = 10.2, 6.8, 1H), 3.01 (m, 1H), 2.43 (m, 3H), 2.26 (dd, *J* =10.8, 5.1), 2.16 (dt, *J* = 12.2, 2.8), 2.04 (s, 1H), 1.66 – 1.63 (m, 2H), .97 (d, *J* = 6.6, 3H). LRMS: M = 171 observed.



**42**: 7-ethyloctahydroindolizine-1,2-diol: In a fume hood **38** (0.0086 g, 0.0131 mmol), was placed in a vial with deuterated acetonitrile (~ 0.6 mL). To this solution added $NOPF_6$ (0.0048 g, 0.0274 mmol). The solution turned green and the organic **40** could be observed in the $^1$H NMR spectrum. Put NMR tube inside a glove-box. Under a nitrogen atmosphere added NMR tube to an oven dried vial and rinsed in with some more

acetonitrile (~ .7 mL). In a separate vial put *N*-methylmorpholine-*N*-oxide (NMO, 0.0047 g, 0.0401 mmol), citric acid (0.0037 g, 0.0193 mmol) and DI water (0.8 mL). Added water solution to acetonitrile and let stir ~ 2 minutes. Added 2.5 % $OsO_4$ solution (0.03 mL, 0.0024 mmol) and the reaction stirred for 25.5 hours. For work up added sat. $Na_2CO_3$ (3 mL). Extracted aqueous layer with ethyl acetate (3 x 3 mL). Collected organic layer and dried over magnesium sulfate. Filtered off drying agent and concentrated *in vacuo*. Set up silica column in Pasteur pipet. Loaded with ethyl acetate and 28% $NH_4OH$ (few drops added to bulk ethyl acetate). Eluted impurities with ethyl acetate and then acetonitrile to remove a green band. After the green band had come off the column a colorless eluent was collected. The colorless eluent was concentrated *in vacuo* to yield a colorless oil (0.0005 g, 0.0027 mmol, 21% yield). Note: only $^1$H NMR obtained and peaks resemble the peaks for an analogous indolizidine: 1-*epi*-lentiginosine.[21] Major isomer: minor isomer: 4.02 (ddd, $J$ = 12.3, 7.1, 5.2, 1H), 3.50 (dd, $J$ = 11.1, 4.7, 1H), 3.44 (d, $J$ = 6.3, 1H), 3.42 (m, 1H), 3.34 (d, $J$ = 9.5, 6.8, 1H), 2.90 (ddd, $J$ = 6.7, 4.3, 2.5, 1H), 1.98 (quintet, $J$ = 2.51, 4H), 1.91 (quintet, $J$ = 2.5, 4H), 1.74 (ddd, $J$ = 10.7, 8.4, 2.5, 1H), 1.64 (m, 1H), 1.28 (m, 1H), 1.11 (dd, $J$ = 12.3, 4.4, 1H), 0.78 (q, $J$ = 11.6, 1H).

## 4.5 References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# Chapter 5

## Synthesis of Quinolizidines via the Electron-rich Dearomatization of Substituted Pyridines

## 5.1 Introduction to pyridine

Pyridine is an aromatic molecule with 6π electrons and a nitrogen heteroatom. Unlike pyrrole (see Section 3.1) the lone pair on the nitrogen of pyridine is orthogonal to the aromatic π system in a non-bonding $sp^2$ orbital (Figure 5.1). The resonance structure of pyridine is distinct from pyrrole in that the lone pair is not a part of the aromatic π-system and does not partake in the resonance structures.

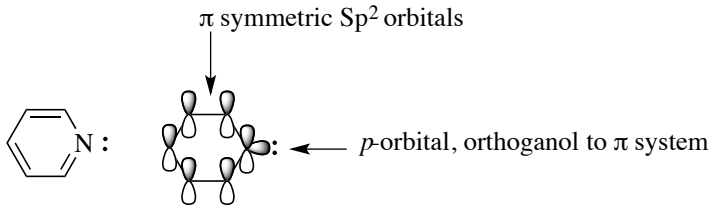
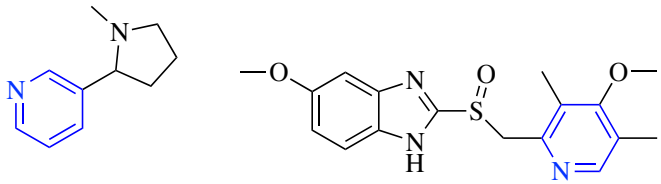



**Figure 5.1** Orbital diagram of pyidine.

There are many pyridine-based molecules that show interesting biological activity. Some show therapeutic qualities such as, antiretrovirals, analgesics, anti-inflammatory agents and others.[1-3] Two famous biologically active molecules with pyridine in their structures are nicotine and the pharmaceutical Nexium® (Figure 5.2). Because of pyridine's aromaticity, it is able to undergo a variety of substitution reactions to form larger molecules with aromaticity remaining present as a stabilizing effect.




Nicotine Nexium

**Figure 5.2** Nicotine and Nexium two biologically active molecules with pyridine.

Pyridines and their pyridinium analogs are more inclined to undergo nucleophilic rather than electrophilic substitution reactions, though a good leaving group must be

present beforehand. After a nucleophile reacts with an aromatic pyridine, the resulting resonance structures can be seen in Figure 5.3. When the nucleophile adds at the ortho (C2) or para (C4) position the negative charge ends up on the nitrogen, which is a favorable interaction. Because of these advantageous interactions, the ortho (C2) or para (C4) positions are the most likely spots for nucleophilic substitution to take place.

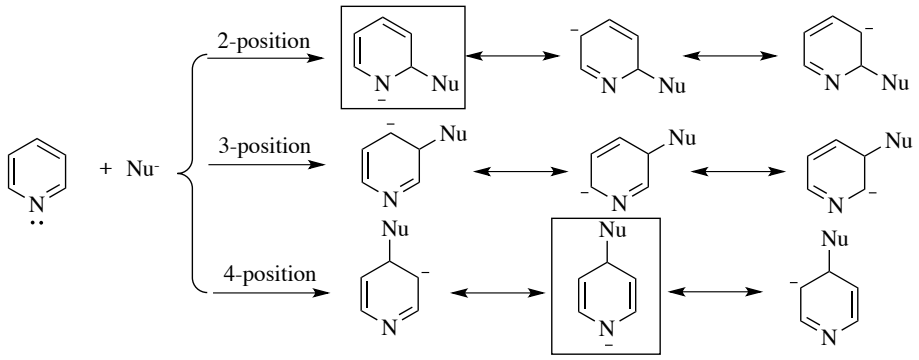



**Figure 5.3** Resonance structures available for a nucleophilic substitution of pyridine (boxes represent more stable resonance structures).

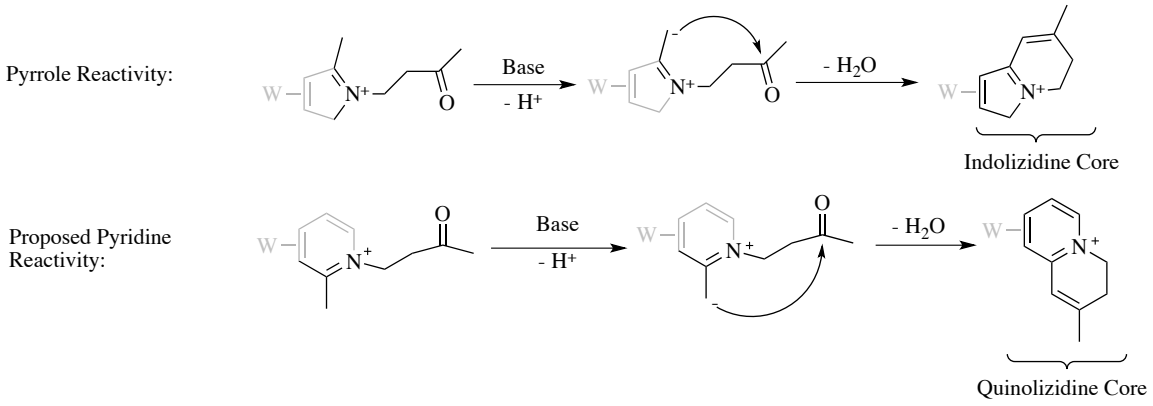
While pyridine is known for many substitution reactions (when a leaving group is present) there is little literature on alternative ways to modify this arene. One method is through the use of electron-rich dearomatization, which is able to activate pyridine to increased reactivity.

## 5.2 Significance of the Dearomatization of Pyridine

In the previous chapters, pyrrole was in focus as a means of isolating indolizidine analogs through cyclization with an enone under electron-rich dearomatization conditions (see Chapters 3 and 4). Upon scrutinizing the reaction pathway that formed the indolizidine, it occurred to us that this reaction mechanism might be more generally

applicable than originally considered. Initially, dearomatized pyrrole is able to undergo a Michael addition to form the Michael adduct, which subsequently is able to perform an intramolecular cyclization to form an indolizidine core. The key feature of interest on the dihapto-coordinated 2H-2-methylpyrrolium complex is the methyl group on the iminium carbon (Scheme 5.1). The methyl is able to be deprotonated likely because of stabilization from being in conjugation with the iminium. It was proposed that a dearomatized alkylpyridinium complex with a similar methyl might be able to perform the same intramolecular cyclization to form a quinolizidine ring system (Scheme 5.1). It is in this light that the dearomatization of pyridines will be explored.

**Scheme 5.1** Observed pyrrole intramolecular cyclization, proposed pyridine intramolecular cyclization.

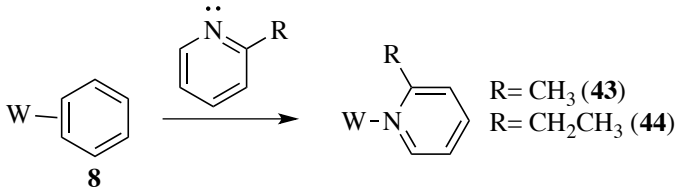



## 5.3 Previous Dearomatization of 2-alkylpyridines via {WTp(NO)(PMe$_3$)}

Although chronologically, disubstituted pyridines were explored before monosubstituted analogs, for the purpose of this dissertation the mono-substituted pyridines will be discussed first.

In order to have the potential for the intramolecular cyclization seen in Scheme 5.1 it is necessary to have the alkyl group on the carbon adjacent to the nitrogen (with the metal bound across carbons 3 and 4). Alkylpyridines such as: 2-methylpyridine (2-picoline) and 2-ethylpyridine were explored. Both pyridines were previously studied using electron-rich dihapto-coordination. When either pyridine is in solution with the W($\eta^2$-benzene) complex (**8**) a $\kappa^1$ product forms (2-picoline [**43**] and 2-ethylpyridine [**44**], Scheme 5.2).[4] Despite the difficulty in isolation of a precipitate of the $\kappa^1$ products, they can be identified by their distinct blue color and large $J_{WP}$ = ~ 435 Hz.[5] While it was thought the bulk of the alkyl groups might dissuade coordination through the nitrogen this was proven false. Having substituents at the 2 and 6 positions *was* enough to prevent coordination through nitrogen's lone pair but that will be discussed later in this chapter.

**Scheme 5.2** Formation of W($\kappa^1$-alkylpyridine) complexes.



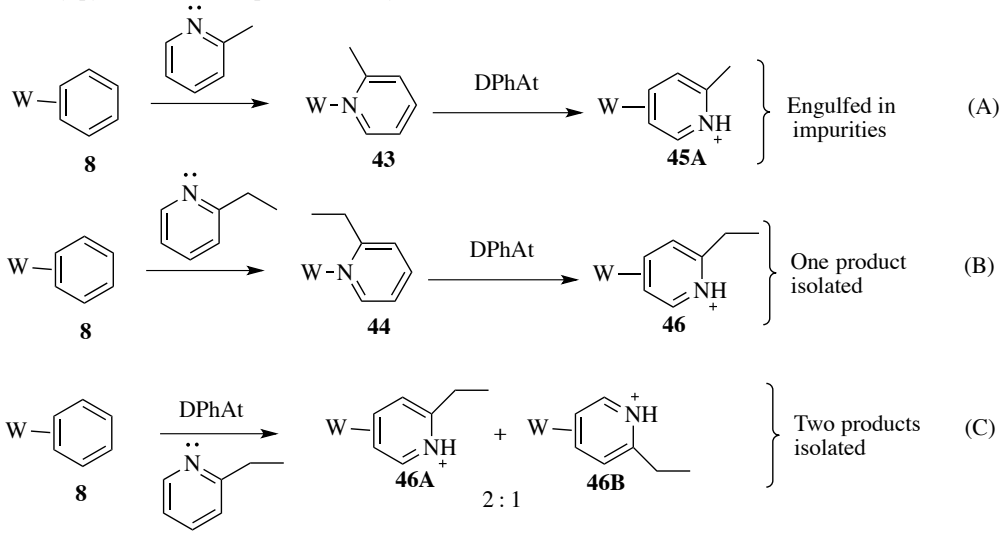

**8**

W = {WTp(NO)($PMe_3$)}

Attempts were made to convert the $\kappa^1$ products (**43** and **44**) to their respective dihapto-coordinated products using dihphenylammonium triflate (DPhAt *p*Ka ~ 0.78). After the formation of the undesired $\kappa^1$ product, acid is added and ideally the desired $\eta^2$-product is formed.[4] When this was initially attempted for 2-picoline the product that formed was not a clean precipitate of the dihapto-coordinated 2-picolinium complex (**45A** [**45A** coordination diastereomer presented to compare to that observed for **46**] Scheme 5.3 A, one coordination diastereomer shown). Instead the product was very impure and could not be confirmed or characterized. However, addition of DPhAt to the

2-ethylpyridine converts the $\kappa^1$ product (**44**) to a dihapto product (**46**, scheme 5.3 B).[4] Interestingly, under these conditions only one coordination diastereomer was observed. Alternatively, when W($\eta^2$-benzene) (**8**) is put in solution with 2-ethylpyridne with acid already in solution, two coordination diastereomers are observed, nitrogen up and nitrogen down (Scheme 5.3 C).[4]

**Scheme 5.3** Attempts to isolate the dihapto-subsituted pyridininum complexes: (A) 2-picoline (B) 2-ethylpyridne (C) 2-ethylpyridine with acid present initially.




W = {WTp(NO)($PMe_3$)}

An interesting note on the coordination diastereomers that formed is the presence of the proton on the iminium carbon (**45** and **46**). This proton has a downfield resonance > 9 ppm as it is deshielded as part of the iminium. Unfortunately this is not the desired formation as required for the proposed intramolecular cyclization (see Scheme 5.1). In addition to this undesired feature, the 2-ethylpyridinium complex was not pursued as the W($\eta^2$-2H-2-ethylpyrrolium) complex showed no signs of intramolecular cyclization (see Chapter 3). Presently, continued efforts were put forth to dihapto coordinate 2-picoline, form the coordinated 2-picolinium complex (**45**) and encourage intramolecular cyclization to form a quinolizidine.

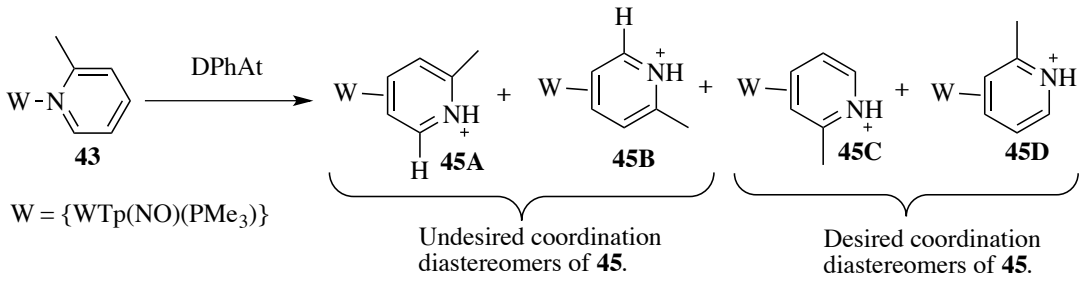
## 5.4 Results and Discussion, 2-picoline

For the present study, in addition to using W($\eta^2$-benzene) (**8**) as starting material, W($\eta^2$-1,3-dimethoxybenzene) (**8A**) was used as the two complexes have similar substitution half lives ($t_{1/2}$) and both substitute cleanly for other aromatics. Additionally, **8A** has been isolated as a single enantiomer, which gives the potential for isolating enantiopure organic molecules.[6]

As observed for other similarly substituted pyridines, when 2-picoline is put in solution with **8** or **8A**, the bright blue-green $\kappa^1$ product (**43**) forms as confirmed through $^{31}$P NMR spectroscopy by the observation of a signal with a large $J_{wp}$ = ~ 435 Hz. For the 2-ethylpyridine analog, addition of DPhAt to a solution of the $\kappa^1$ product (**44**) results in conversion to the dihapto product (**46**), which can be isolated as a pure product.[4] However, when **43** is subjected to similar reaction conditions, a clean product is not isolated.

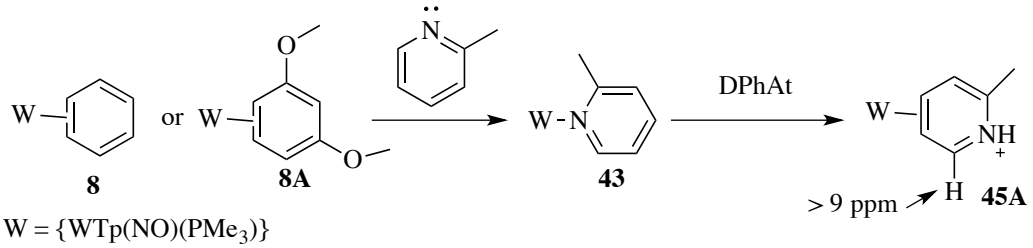
Upon protonation of the $\kappa^1$ product (**43**), if a dihapto product forms, there are several coordination diastereomers that could be isolated. The undesired complexes (**45A** and **45B**, Scheme 5.4) are bound across carbons 4 and 5. Alternatively, the desired complexes (**45C** and **45D** Scheme 5.4) are bound across carbons 3 and 4. In this coordination mode, the methyl group is on the carbon of the iminium and is therefore more likely to undergo the desired intramolecular cyclization to form a quinolizidine.

**Scheme 5.4** Possible isomers that could be forming after acid addition to **43**.




When **8** is put in solution with 2-picoline and allowed to react overnight, the $\kappa^1$ product (**43**) forms. Addition of DPhAt to the reaction solution results in an immediate change of color from bright blue-green to a light brown. After 20 minutes, addition of the reaction solution to pentane results in a precipitation of a brown solid, which is triturated and isolated as an impure solid. Multiple tungsten products are observed based on the presence of several $PMe_3$ doublets around 1 ppm in the $^1$H NMR spectrum. Of particular note is the observation of a peak above 9.0 ppm that is indicative of a proton on an iminium carbon. Comparison of the integration of this proton with other protons in the $^1$H NMR spectrum suggests that this proton is part of the major product isolated under these conditions. Based on this evidence it is believed that under these conditions, the major product of this experiment is the undesired 4,5-bound isomer of the dihapto-coordinated 2-picolinium complex (**45A**, Scheme 5.5).

**Scheme 5.5** Isolation of dihapto-coordinated 2-methylpyridinium complex (**45**).




Attempts to isolate a cleaner 2-picolinium complex involved using a variety of different acids. Reactions involving anilinium triflate (*p*Ka ~ 5), 2-picolinium triflate

(*p*Ka ~ 5), and triflic acid leveled in DME (*p*Ka ~ -2) all showed similar reactivity with **43** and all resulted in formation of a similarly impure product.

To better understand the transformation of **43** to **45A**, DPhAt was added to a sample of **43** formed *in situ* and the reaction was monitored periodically over 23 h by $^{31}$P NMR. Three products were observed during the course of the experiment. After 0.3 h, two main products are present as evidenced by signals at -14.29 ($J_{WP}$ = 291 Hz) and -7.10 ($J_{WP}$ = 283) ppm. At this time there was also a small peak at -11.03 ($J_{WP}$ not observed due to proximity to baseline). As the reaction progressed the peak at -14.29 ppm diminished rapidly, the peak at -7.10 ppm disappeared more slowly and the peak at -11.03 ($J_{WP}$ = 298 Hz) ppm grew to be the major product. Some smaller peaks around -11.03 were also observed. The $^{31}$P NMRs can be seen in Figure 5.4.

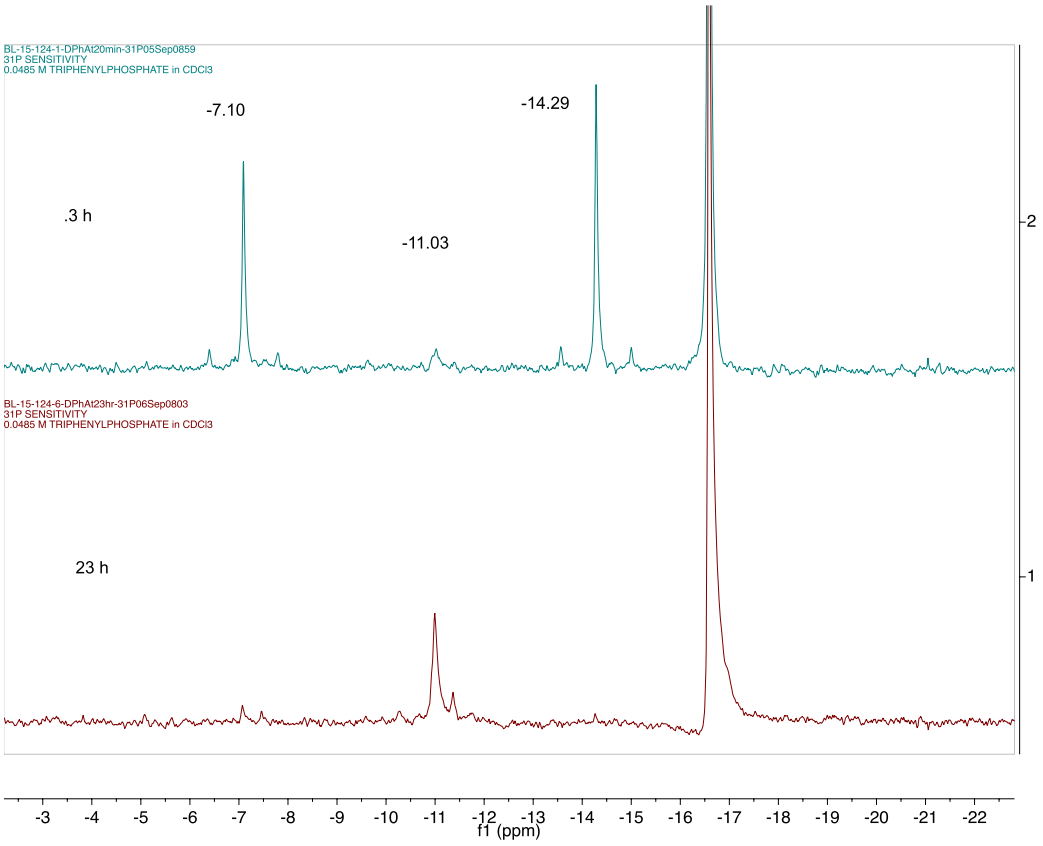



**Figure 5.4** NMRs after addition of DPhAt to **43**, top: .3 h, bottom: 23 h.

Upon the addition of acid to **43** several potential products can be considered (see Scheme 5.4). The preference for the coordination of 2-picolinium across carbons 3 and 4 (or carbons 4 and 5, for an asymmetric pyridine such as 2-picoline) is based on previous dihapto-coordination of pyridine.[4,7] For the desired chemistry, of these four structures, 3,4 coordinated isomers (**45C** and **45D**) are of interest because of their positioning of a methyl group, as opposed to a proton, on the iminium carbon. The non-preferred isomer **45A** (or **45B**, bound across carbons 4 and 5) is believed to be the major product of the precipitated reaction described initially. However, because of the multiple products seen in the $^{31}$P NMR spectra at various time points under acidic conditions it is possible that one or both of the desired coordination isomers form during the course of the reaction.

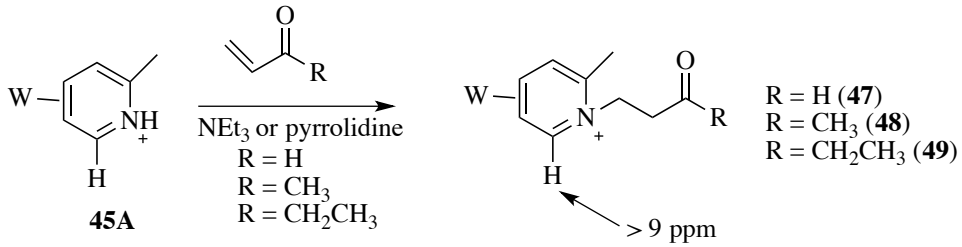
When W($\eta^2$-benzene) (**8**) is dissolved in a 2-ethylpyridine solution containing DPhAt, two 4,5-coordination diastereomers of **46** form (**46A** and **46B**, Scheme 5.3 C) and can be isolated. Attempts to form two isomers of **45** under similar conditions were unsuccessful. However, addition of the $\kappa^1$ complex (**43**, formed *in situ)* to diethyl ether acidified with triflic acid (triflic acid leveled in ether *p*Ka ~ - 2) results in an immediate color change from bright blue-green to dark purple and the precipitation of an oily solid. The $^1$H NMR spectrum of the isolated material reveals several species in solution. However, it also shows two resonances at 6.82 and 6.09 ppm, which are consistent with uncoordinated alkene protons and, significantly, no iminium proton signal above 9 ppm is observed. These observations imply that the undesired coordination diastereomer of **45A** that had been isolated previously might not be present in solution and the new $^1$H NMR spectrum is consistent with either of the desired 3,4-coordination diastereomers (**45C** or **45D**), which have the methyl on the iminium carbon. In addition to these data the $^{31}$P

NMR spectrum reveals a peak around -15 ppm with a $J_{WP}$ = 290 Hz. The other peaks at -11 and – 7 ppm that were seen in previous substitution experiments were also observed, although as minor peaks. Overall, these data suggest that while the same three isomers of **45** are produced as impure mixtures in the two synthetic methodologies described above, it is possible to influence the major product formed through careful control of reaction conditions, specifically, the method of acid addition and precipitation.

Unfortunately, attempts at separating or purifying the product mixture formed from this ether acidification method to cleanly isolate what is thought to be the desired, 3,4-coordination diastereomer of **45** (could be **45C** or **45D**) were ultimately unsuccessful. For this reason, the identity of the major coordination diastereomer in this mixture was not conclusively determined, although it is believed to be either **45C** or **45D** for reasons presented above.

Despite the inability to remove impurities present in the precipitation of **45**, experiments were conducted to determine whether a Michael addition could occur at the pyridine nitrogen of these 2-picolinium complexes. When the suspected undesired 4,5-coordination diastereomer (**45A**) is put in solution under basic conditions the immediate result is a color change back to the blue-green shade of the $\kappa^1$ product (**43**). To circumvent this issue, base is added to a solution of the 2-picolinium complex already containing the Michael acceptor. Under these conditions Michael adducts were formed with acrolein (**47**), MVK (**48**) and EVK (**49**, Scheme 5.6) as 4,5-bound coordination diastereomers as confirmed by the presence of proton signals downfield of 9 ppm. Precipitation of these Michael adducts results in partial separation of this mixture.

**Scheme 5.6** Michael addition of **45A** with acrolein (**47**), MVK (**48**) and EVK (**49**).

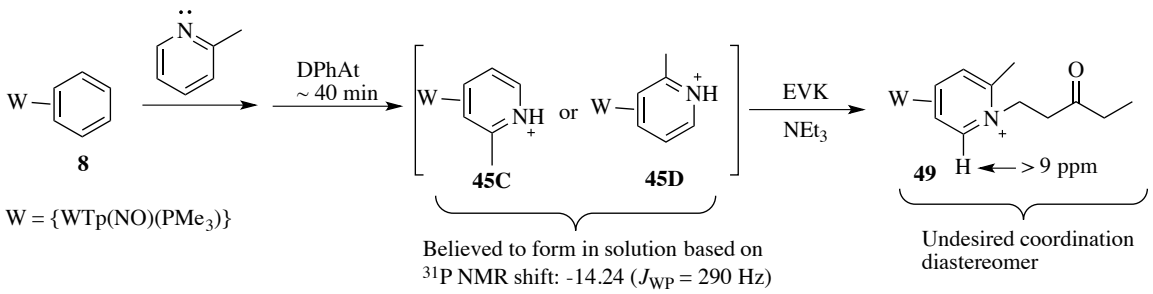



When a similar Michael addition with MVK is performed on the impure sample of the 3,4-bound coordination diastereomer (**45C** or **45D**) a metal complex forms. However, the product isolated when using **45C** or **45D** is missing some of the $^{1}$H NMR features expected from an MVK adduct, either **48** or another coordination diastereomer. Because of the inability to clean and more precisely identify this product or the starting material for this reaction, research efforts focused on the reactivity of the 4,5-bound coordination isomer: **45A**.

An alternative method for a Michael addition to **45A** involves forming the $\kappa^{1}$ product (**43**) and then taking the solution to dryness *in vacuo* to remove any excess 2-picoline. After the solution has dried, dimethoxyethane (DME) is added followed by just over one equivalent of DPhAt. After 40 minutes, EVK (as an example) is added followed by two equivalents of triethylamine resulting in the formation of the EVK addition product (**49**, Scheme 5.7). $^{31}$P NMR spectra taken 30 minutes after acid addition and then again after EVK addition can be seen in Figure 5.5. Most notable is the presence of the peak at -14.24 ($J_{WP}$ = 290 Hz) after acid is added. This signal corresponds to what is believed to be a 3,4-bound coordination diastereomer of the 2-picolium complex (**45C** or **45D**) (*vide supra*). Addition of a Michael acceptor to this isomer would potentially yield the alternative, desired 3,4-bound Michael adduct of the 2-picolinium complex. However, based on the $^{1}$H NMR spectrum of the isolated product after EVK was added, only the

4,5-bound isomer of the Michael adduct is isolated (**49**). It was anticipated that using the desired coordination diastereomers **45C** or **45D**, the Michael addition might create the desired form of the Michael adduct. However, based on the $^{1}$H NMR spectra of the isolated product, only one product was isolated and it was the undesired coordination diastereomer (**49**).

**Scheme 5.7** Alternative procedure for Michael addition to **45**.



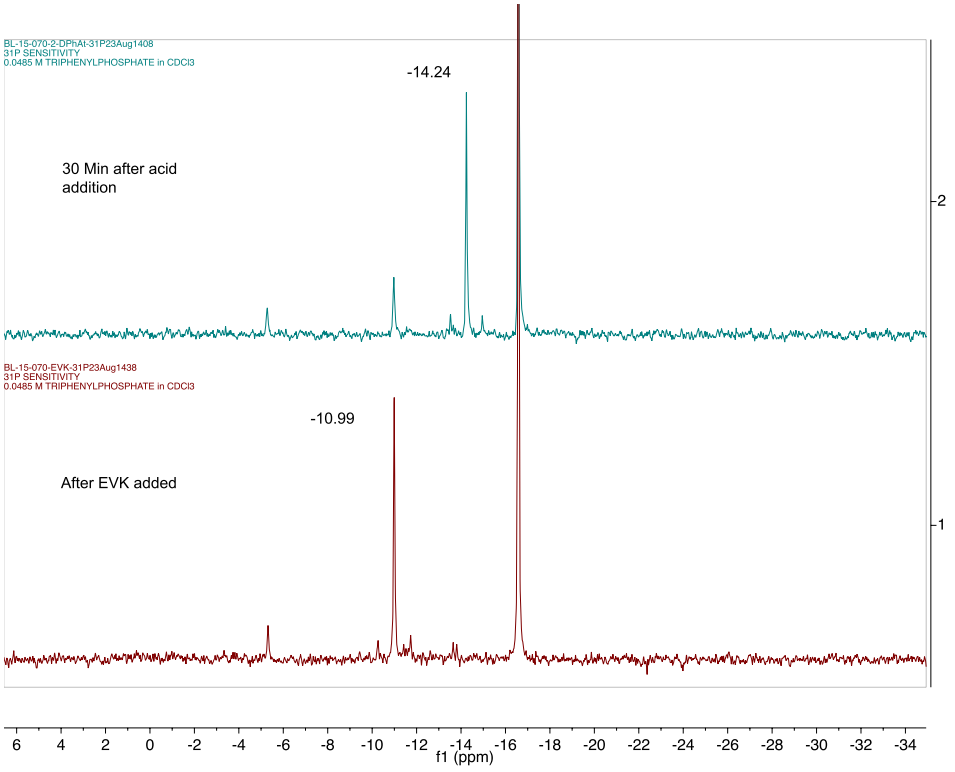
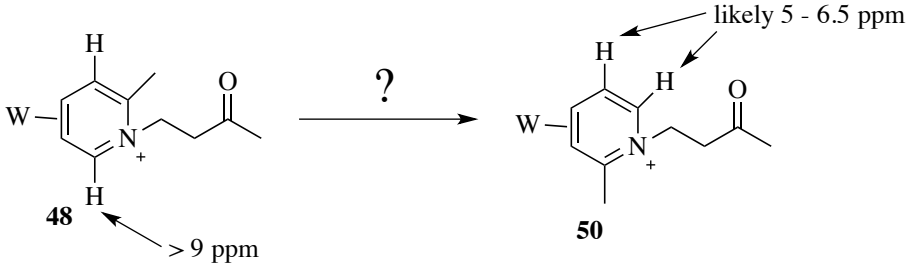




**Figure 5.5** Top: $^{31}$P NMR after addition of DPhAt; Bottom: $^{31}$P NMR after EVK added.

This experiment is significant because it shows that even when multiple isomers of **45** are present in the reaction mixture and even when the major isomer is not the 4,5-bound isomer, **45A**, only one coordination diastereomer, the 4,5-bouund isomer of the Michael adduct is formed suggesting either a kinetic or thermodynamic barrier to the direct formation of the desired 3,4-bound isomers of the Michael adducts.

Conditions were explored to convert the undesired, 4,5-bound coordination diastereomer of the Michael adducts to the desired 3,4-bound isomers. Initial tests involved the use of the MVK adduct (**48**) and conversion to the desired 3,4-bound isomer (**50**, Scheme 5.8).

**Scheme 5.8** Conversion of undesired **48** to desired **50**.




In an attempt to convert the MVK adduct (**48**) to the desired 3,4-bound coordination diastereomer (**50**) (Scheme 5.9), solutions of the Michael adduct were heated. When a solution of **48** in deuterated chloroform is heated at 60 °C for five days, the resulting $^{1}$H NMR spectrum shows a mixture of free 2-picoline and a new metal complex. Although full characterization data for the precipitate that formed was not obtained, the disappearance of the iminium proton signal at 9 ppm as well as the presence of two new alkene resonances around 6.7 and 6.0 ppm in the $^{1}$H NMR spectrum support the formation of the desired 3,4-bound coordination diastereomer of the MVK adduct (**50**, Figure 5.6)

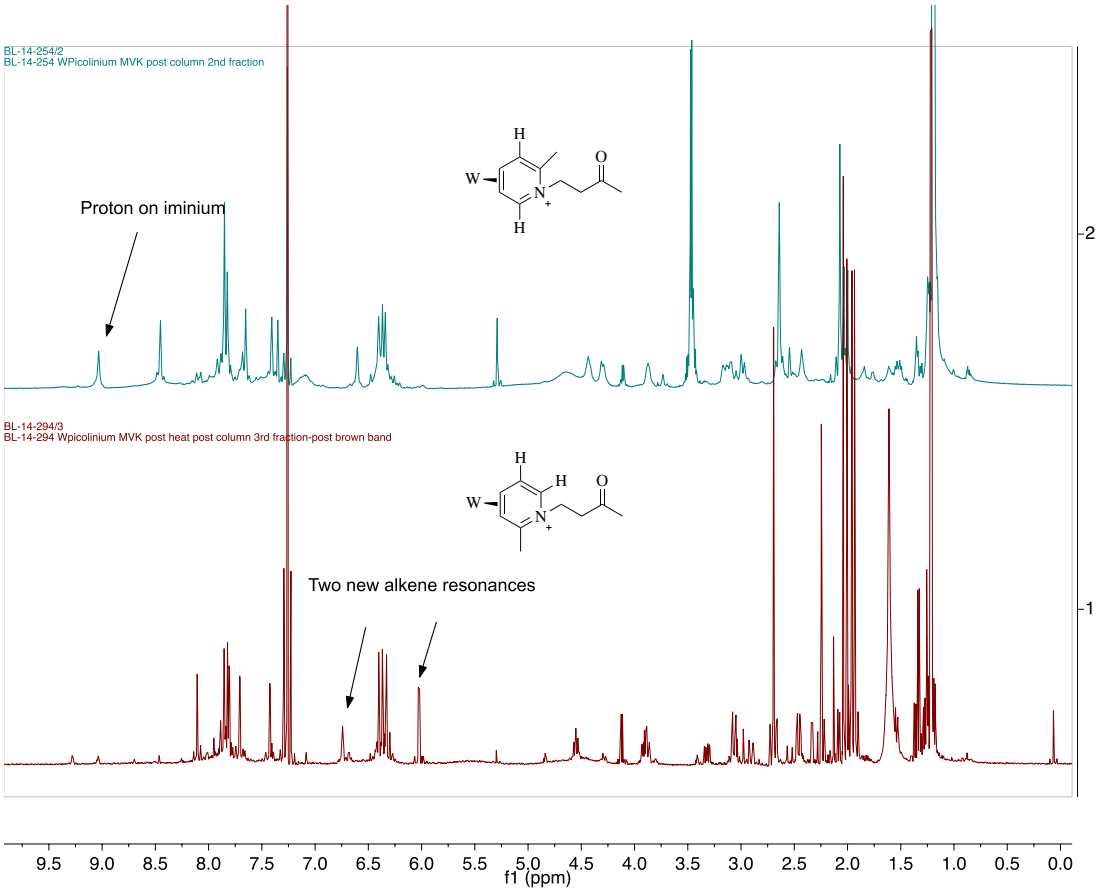
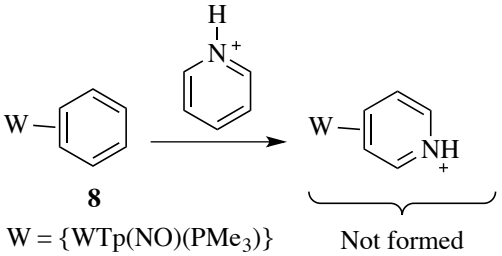



**Figure 5.6** Top: $^{1}$H NMR spectra of undesired coordination diastereomer of **48**. Bottom: $^{1}$H NMR spectrum of what might be the desired coordination diastereomer **50**.

To achieve isomerization from the 4,5-bound picolinium MVK adduct, **48**, to the desired 3,4-bound adduct, **50**, requires an interfacial isomerization of the metal as the metal must bind the opposite face of the picolinium. One possible pathway that could allow this transformation is the complete dissociation of the metal from the ligand followed by subsequent association on the opposite face. However, it is more probable that the metal will suffer oxidative decomposition in the presence of a pyridinium triflate salt. The basis for this stems from an experiment where **8** is put in solution with methylpyridinium triflate and the metal suffers oxidative degradation (Scheme 5.9).[8]

**Scheme 5.9** Previous results of **8** in the presence of a pyridinium salt (no $\eta^2$ product forms).




While complete dissociation of the pyridine is unlikely, there is precedent for an oxidative addition to occur at pyridine's C4-H bond. As will be discussed later in this chapter, the dihapto 2,6-lutidine complex exists as an equilibrium mixture of the dihapto-coordination isomer and the C4-H oxidative addition product.[9] If this oxidative addition were to occur for the 2-picolinium complex, it could provide a route to the desired 3,4-bound isomer, **50**, via rotation about the W-C bond followed by reductive elimination.

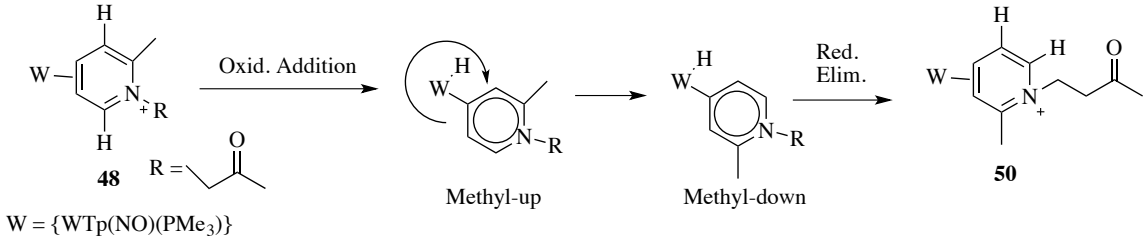



**Figure 5.7** Potential reaction pathway involving oxid adition, rotation, followed by red elim to give **50**.

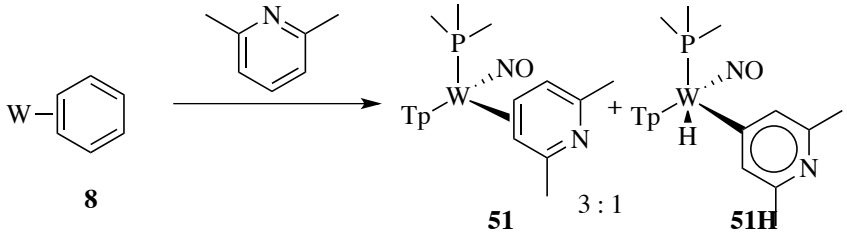
With the goal of forming a quinolizidine core from the suspected 3,4-bound MVK adduct (**50**), the product isolated from the heating experiment above was put in solution with pyrrolidine, resulting in the formation of a new metal complex as evidenced by the presence of a full set of Tp signals as well as a $PMe_3$ doublet signal in the $^1H$ NMR spectrum. Unfortunately, no peaks belonging to the organic ligand were easily identifiable, so this complex could not be identified, although it does not resemble any other known 2-picolinium complex. Because of the difficulty in isolating or definitively

characterizing the 3,4-bound coordination diastereomer of the Michael adduct (**50**) and the inability to form the cyclized quinolizidine core, the chemistry of 2-picolium complexes was not investigated further and the coordination of 2,6-lutidine was explored instead.

## 5.5 Previous Dearomatization of 2,6-lutidine via {WTp(NO)($PMe_3$)}

2,6-lutidine was first explored as an alternative to pyridine for electron-rich tungsten(0) dearomatization. While pyridine prefers to coordinate through its lone pair, 2,6-lutidine is dihapto-coordinated easily to the tungsten(0) fragment, {WTp(NO)($PMe_3$)} because the two methyl groups prevent $\kappa^1$ coordination.[8] When W($\eta^2$-benzene) (**8**) is in solution with 2,6-lutidine, the dihapto-coordinated product (**51**) forms as well an oxidative addition product at lutidine's C4-H bond (**51H**) in a 3:1 ratio **(**Scheme 5.10).[9]

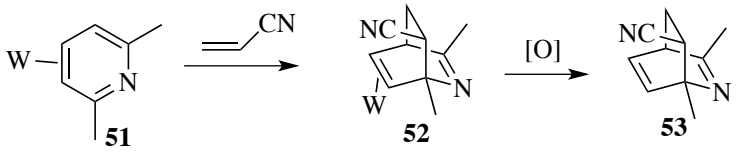
**Scheme 5.10** Formation of W($\eta^2$-2,6-lutidine) (**51**) and the oxidative addition product (**51H**).




Despite the appearance of the oxidative addition product (**51H**), the reactivity of dearomatized lutidine (**51**) was explored. One of the most interesting reactions afforded by the dearomatization of lutidine is a Diels-Alder reaction leading to a bicyclic species (**52**, Scheme 5.11). After subsequent oxidation a bicyclic organic (**53**) can be isolated.

This reaction is significant because pyridine does not normally undergo Diels-Alder-type reactivity. Under electron-rich dearomatization conditions dihapto-coordinated lutidine (**51**) is activated towards increased reactivity.[9]

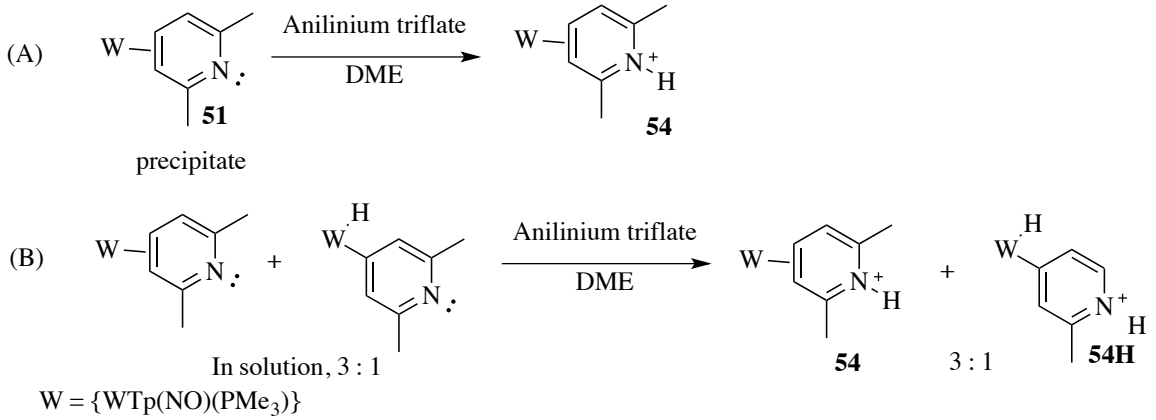
**Scheme 5.11** Diels-Alder reaction of **51** and acrylonitrile to the organic **53**.




**51** **52** **53**

In addition to the formation of the neutral 2,6-lutidine complex (**51**) upon the addition of the weak acid anilinium triflate (*p*Ka ~ 5) the protonated dihapto-lutidinium complex (**54**) forms (Scheme 5.12).[9] The procedure for isolating the W($\eta^2$-2,6-lutidinium) complex (**54**) requires the addition of dissolved anilinium triflate directly to the solid complex (Scheme 5.12 A). This method yields the desired complex (**54**). Instead, if the dihapto-lutidine complex is in solution followed by the addition of an acid, two protonated products are observed: the desired complex (**54**) as well as the protonated oxidative addition product (**54H**, Scheme 5.12 B).[9] This implies that the oxidative addition product exists in solution and converts to the $\eta^2$-product upon precipitation.

**Scheme 5.12** Protonation products of dihapto-coordnated lutidine (**51**).

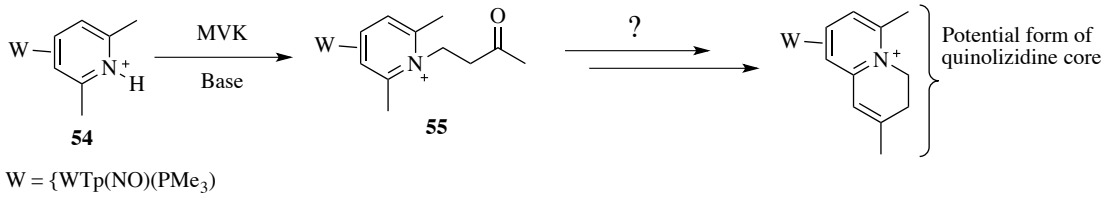


Using the conditions described in Scheme 5.13 A, the protonated lutidinium complex (**54**) is formed easily. Unlike the examples of protonated 2-picoline discussed in Section 5.4 not only is the dihapto-lutidinium complex (**54**) pure (aside from trace anilinium triflate) it exists in the correct coordination mode as the nitrogen is directly between two methyl groups. The present study will explore the reactivity of the protonated lutidnium complex (**54**).

## 5.6 Results and Discussion, 2,6-lutidine

In addition to using the W($\eta^2$-benzene) complex (**8**) as starting material, W($\eta^2$-1,3-dimethoxybenzene) (**8A**) can also be used because of its similarities in aromatic substitution ability to **8**. In order to potentially form a quinolizidine ring system from **54**, a Michael addition must first take place (MVK example seen in Scheme 5.13).

**Scheme 5.13** Michael addition of MVK to W($\eta^2$-2,6-lutidinum) to potentially form a quinolizidine.




**54** **55**

W = {WTp(NO)($PMe_3$)}

The W($\eta^2$-2,6-lutidnium) complex (**54**) has been previously synthesized but no Michael additions at the nitrogen have been attempted. For this experiment the strength of the base is particularly important because if **54** is deprotonated it will revert to its direct precursor **51** and **51H**. The base must be strong enough to deprotonate **54** but also weak enough to allow the Michael addition to complete. An example of an inappropriate base for this purpose is potassium *tert*-butoxide. When **54** is in solution with a Michael

acceptor and potassium *tert*-butoxide products **51** and **51H** are observed immediately and a Michael addition does not occur.

The weaker base triethylamine was attempted as it shows success with a Michael addition for the 2H-2-methylpyrrolium complex (see Chapter 3). Unfortunately when **54** is in solution with a Michael acceptor and triethylamine the reaction progresses slowly. After 6 days the reaction appeared to be approximately 10% complete. After 14 days the reaction showed two new products growing in the $^{31}$P NMR spectrum but starting material was still the major product by at least 2:1.

This was an interesting occurrence because both dihapto-coordinated pyridinium[10] and dihapto-coordinated 2-picolinium (**45**) were able to be deprotonated by triethylamine and successfully perform a Michael addition. **54**'s reluctance to be deprotonated by triethylamine could indicate that **54**'s N-H proton is *less* acidic than dihapto-coordinated pyridinium or 2-picolinium (**45**). Alternatively, a noted difference between pyridine, 2-picoline and 2,6-lutidine is the increase in steric bulk around the nitrogen. It is possible that the methyl groups on 2,6-lutidine make it difficult for a base to remove the proton. A smaller base might allow for the deprotonation of **54** more quickly than triethylamine.

An alternative to triethylamine is pyrrolidine. Although both triethylamine and pyrrolidine are similar in base strength, pyrrolidine has shown reactivity distinct from triethylamine. Most notably, pyrrolidine is capable of encouraging intramolecular cyclization of a 2H-2-methylpyrrolium Michael adduct (see Chapter 3) while triethylamine cannot. In this light, it was found that when **54** is in solution with pyrrolidine and MVK under similar conditions as the triethylamine experiment, after 6

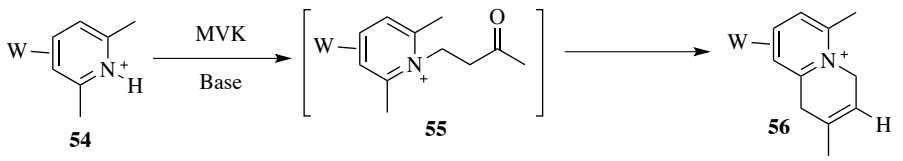
days the products are seen in a 1.5:1 ratio to starting material. This is in direct contrast to the triethylamine experiment, which only resulted in 10% product formation after 6 days.

If the pyrrolidine reaction is allowed to continue for 13 days, two new peaks are observed in the $^{31}P$ NMR spectrum. At first glance it appears to be a single broad peak but after closer investigation there are two peaks in very close proximity implying there are two products formed. Upon precipitation of the resulting solution, two products were observed in the $^{1}H$ NMR spectrum, both were distinct from starting material.

In an effort to increase the speed of this reaction and possibly isolate a single product, less solvent was used to increase the concentration of the reactants in solution. Under more concentrated conditions **54** reacts with MVK and pyrrolidine yielding two products as observed previously, though after much less time has elapsed. Upon work-up, two products are observed in the precipitate isolated from the MVK/pyrrolidine experiment the ratio of major to minor product appears to be 3:1.

Upon scrutinizing the $^{1}H$ NMR spectrum of the major product, an interesting observation was made. The MVK adduct (**55**) is expected to have one alkene resonance for the alkene proton on the lutidinium ring and three methyl singlets for the two methyl groups on the ring as well as the methyl on the methyl vinyl ketone portion. However, in the $^{1}H$ NMR spectrum of the major product there were two alkene peaks and only two methyl singlets. After careful multidimensional NMR analysis the major product in solution was not **55** but the cyclized, quinolizidinium complex (**56**, Scheme 5.14).

**Scheme 5.14** Formation of MVK adduct (**55**) *in situ* followed by cyclization to **56**.




W = {WTp(NO)($PMe_3$)}

Using multidimensional NMR data, it is observed that the alkene resonance at 6.90 ppm shows NOE interactions with the $PMe_3$ ligand, the H1 proton and the methyl at C9 confirming its presence on the lutidinium ring (Figure 5.8). The other alkene resonance showed NOE interactions with the other methyl singlet at C5 and the geminal set of protons as C7 (Figure 5.8). Using these interactions, the structure of the major product in solution was confirmed to be **56**.

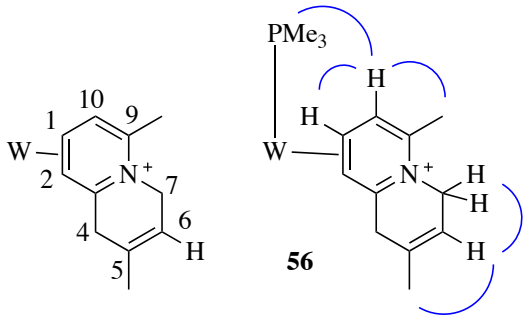
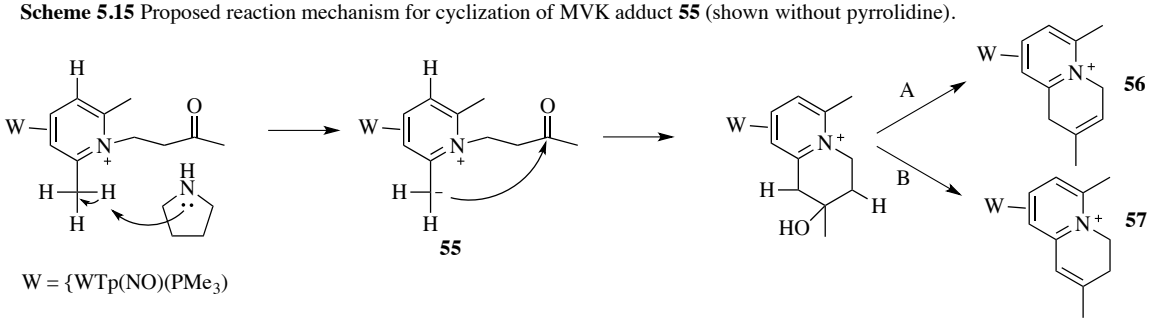



**Figure 5.8** NOE interactions (in blue) confirming structure of **56**.

The structure of **56** seems to have formed from a slightly different intramolecular cyclization mechanism when compared to the cyclization of the 2H-2-methylpyrrolium MVK adduct (see Chapter 3). The most notable distinction is the location of the new unsaturated bond in the second ring. In the proposed mechanism of cyclization, the alkene forms away from the remainder of the π-system of the ring (**56**, Scheme 5.15 A) though it also could have formed in conjugation with the ring (**57**, Scheme 5.15 B). NOTE: Scheme 5.16 shown without influence of pyrrolidine.

**Scheme 5.15** Proposed reaction mechanism for cyclization of MVK adduct **55** (shown without pyrrolidine).




W = {WTp(NO)($PMe_3$)}

A clear distinction between **56** and **57** in the NMR data is the NOE interactions of the alkene resonance on the second ring. For the structure of **57** the alkene resonance in the second ring would be expected to show an NOE interaction with the adjacent methyl, a Tp proton and the proton at H2. However, that alkene resonance only sees NOE correlations with the geminal set and the methyl indicating **56** is indeed the structure of the quinolizidine core formed.

With the structure of the major isomer of the product confirmed our attention was drawn to the identity of the minor isomer. Because the minor isomer is present in such small quantities some of the peaks are difficult to single out because of impurities in the baseline. From our best determination it is observed that the minor product has one alkene resonance at 6.81 ppm, a proton at 4.20 ppm (likely H1), a methyl singlet around 2.70 ppm and potentially another methyl singlet at 1.80 ppm. Using NOE correlations, the alkene resonance shows interactions with the $PMe_3$ ligand, the H1 proton at 4.20 ppm and with a methyl singlet at 2.70 ppm. These data indicate that the minor product has a similar dihapto-coordinated structure of lutidine to the major product (**56**). With this information and the appearance of only one alkene resonance, three structures are proposed for the minor product. Aside from starting material (which the minor product is not), the product is considered to be: the MVK adduct (**55**), or the cyclized but not eliminated product where either water (**58**) or pyrrolidine (**59**) is not eliminated (Figure 5.9).

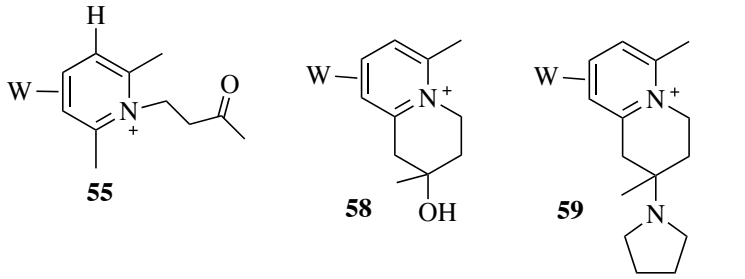
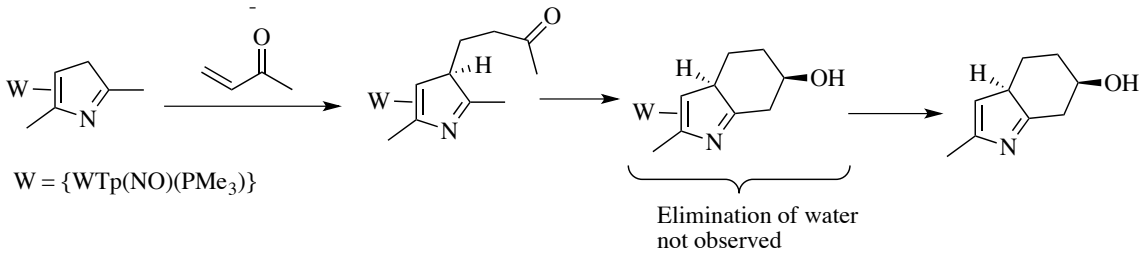



**Figure 5.9** MVK adduct (**55**), cyclized but not eliminated product: water (**58**) and pyrrolidine (**59**).

In order to form the cyclized product **56**, the reaction mechanism must first go through the MVK adduct (**55**). Because **56** can be isolated, it is unexpected that the reaction would stall at the Michael adduct, **55**, and not proceed with the intramolecular cyclization. However, for the non-elimination quinolizidine rings **58** and possibly **59** there is precedent for the reaction to stop at such a phase. When studying the dihapto-coordination of 2,5-dimethylpyrrole, it is observed that after a Michael addition at the 3 position, an intramolecular cyclization takes place forming an indole core without elimination of the alcohol that forms (see Section 2.5 or Scheme 5.16).[11] The indole core with the alcohol present is likely more favorable than if an elimination were to take place.[11]

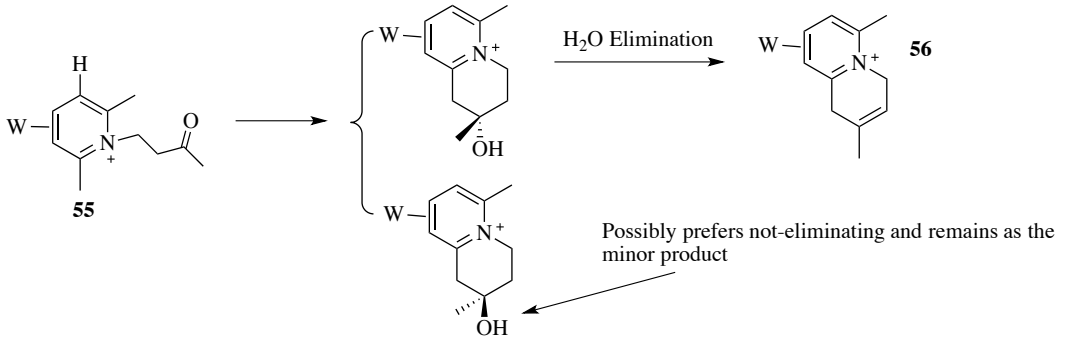
**Scheme 5.16** Synthesis of a tetrahydroindole from 2,5-dimethylpyrrole.




It is possible to consider this quinolizidine system in a similar capacity. It is conceivable that after the Michael addition and ring closure portion of the cyclization take place, an elimination might *not* occur and instead the alcohol remains in the final product (or possibly an amine because of pyrrolidine). When the intramolecular

cyclization takes place on the Michael adduct (**55**) it is possible that two alcohol products form depending on which face of the ketone is attacked by the nucleophilic carbon of the methyl. It is plausible that if the metal has no influence on the steric interactions of the alkyl chain, then multiple products could form with the alcohol anti or syn to the metal (Scheme 5.18, Note: the alcohol product chosen to perform elimination is random and elimination could be of pyridine; alcohol shown for convenience). The two products that form differ only in the position of the alcohol. While this might seem like a small difference it could be the deciding factor between elimination or not. It is possible that the cyclized product with the alcohol *syn* to the metal (just as an example) is able to undergo a simple elimination to form **56**. Conversely, the cyclized product where the alcohol is *anti* to the metal might experience a different steric environment giving it a preference to remain as an alcohol rather than eliminate. It has been suggested that if an E2 elimination mechanism were taking place that the elimination could be selective based on the position of the leaving group in an antiperiplaner position. If one leaving group is removed, the elimination product forms, while the alternative conformation does not allow such elimination because the leaving group is not in the proper position to eliminate. Unfortunately an –OH peak in the $^{1}$H NMR is difficult to determine and the IR was inconclusive.

**Scheme 5.17** Possible reaction pathway for elimination to form **56**.



Because of the level of impurities and the small amount of the minor product present, the identity and full characterization details of the minor product were not obtained.

To isolate a cleaner product, alternative conditions were explored. Using pyrrolidine and MVK, various solvents were tested including: DME, DMF, acetonitrile, acetone and methanol. All show starting material even after extended periods of time. Neither raising the temperature or the use of trimethylsilyl triflate (TMS-OTf) as a Lewis Acid increased reactivity. As an alternative base, 8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was explored. Unfortunately, DBU yields the same results as pyrrolidine.

To explore conditions that might increase the speed of the reaction, acrolein experiments were conducted because acrolein is more reactive than MVK. When monitoring $^{31}P$ NMR spectra of acrolein reactions with either DBU or pyrrolidine a new peak is formed but after work up a clean product has not been isolated. Further experiments are currently underway using acrolein and ethyl vinyl ketone (EVK) to compare their reactivity to MVK.

**5.7 Conclusion**

Using the electron-rich dearomatization agent, {WTp(NO)($PMe_3$)} 2-picoline can be dihapto-coordinated in its 2-picolinium form. Michael additions successfully occur on the nitrogen of the 2-picolinium complex using acrolein, MVK and EVK. The

coordination diastereomer formed of dihapto-coordinated 2-picolinium is not the desired form and when the MVK adduct is converted to the proposed desired coordination mode it did not show signs of intramolecular cyclization. When 2,6-lutidine is dearomatized and protonated, a dihapto-coordinated lutidinium complex forms and can undergo a Michael addition followed by intramolecular cyclization to form a coordinated quinolizidininium core. Using the method of electron-rich dearomatization, a quinolizidine core was formed beginning with 2,6-lutidine.

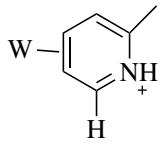
## 5.8 Experimental

**General Methods**. NMR spectra were obtained on a 300, 500, 600 or 800 MHz spectrometer. All chemical shifts are reported in ppm, and proton and carbon shifts are referenced to tetramethylsilane (TMS) utilizing residual $^{1}H$ or $^{13}C$ signals of the deuterated solvents as an internal standard. Phosphorous NMR signals are referenced to 85% $H_3PO_4$ (δ 0.00) using a triphenyl phosphate external standard (δ -16.58). Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra (IR) were recorded as a glaze on a spectrometer fitted with a horizontal attenuated total reflectance (HATR) accessory or an FT-IR spectrometer equipped with a diamond anvil ATR assembly. Electrochemical experiments were performed under a dinitrogen atmosphere using a potentiostat. Cyclic volammetry data were taken at ambient temperature (~25 °C) at 100 mV/s in a standard three-electrode cell with a glassy-carbon working electron, *N*,*N*-dimethylacetamine (DMA) or acetonitrile (MeCN) solvent (unless otherwise specified), and

tetrabutylammonium hexafluorophosphate (TBAH) electrolyte (approx. 0.5 M). All potentials are reported verses the NHE (normal hydrogen electron) using cobaltocenium hexafluorophosphate ($E_{1/2}$ = -0.78 V), ferrocene ($E_{1/2}$ = +0.55 V), or decamethylferrocene ($E_{1/2}$ = +0.04 V) as internal standard. The peak-to-peak separation was less than 100 mV for all reversible couples. Unless otherwise noted, all synthetic reactions were performed in a glovebox under a dry nitrogen atmosphere. Dimethoxyethane (DME) and chloroform were purified through a column packed with activated basic alumina. Other solvents and liquid reagents were thoroughly purged with dry nitrogen prior to use. Triflate salts of amines were synthesized by addition of a diethyl-ether solution of trifilic acid to the appropriate conjugate base dissolved in diethyl-ether. Deuterated chloroform was purified through a column packed with activated basic alumina. Other deuterated solvents were used as received from Cambridge Isotopes. Deactivated basic alumina was made by stirring basic alumina with water (15% by mass) in ethyl acetate. Pyrazole (Pz) protons of the tris(pyrazolyl)borate (Tp) ligand were uniquely assigned when possible (e.g., "PzA3") using a combination of two-dimensional NMR data and phosphorous-proton NOE interactions when available. BH peaks (around 4-5 ppm) are not identified due to their quadrupole broadening. All phosphrous NMR spectra are phosphorous-proton decoupled IR data are used to confirm the presence of a BH group (around 2500 $cm^{-1}$). OH and NH peaks are not always identified due to exchange with water in the solvent. Compounds: **8**, **8A**, **43**, **44**, **46**, **51**, **51H**, **52 - 54** were previously reported.[4,5,9]

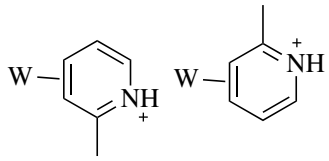
**45: Unconfirmed complexes due to impurities upon isolation**

**45A:**

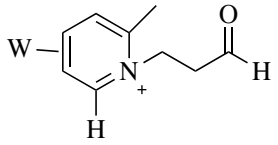


[WTp(NO)(PMe$_3$)($\eta^2$-4,5-2-picolinium)][OTf]: **8** (0.5021 g, 0.8640 mmol) was placed in an oven-dried vial charged with a stirbar. 2-picoline (0.7917 g, 8.504 mmol) in DME (~ 6 mL) was added and the solution stirred. The reaction turned blue-green within five minutes. After 18.5 hours, a solution of DPhAt (0.2857 g, 0.8948 mmol) in DME (~ 1 mL) was added. The reaction darkened and was allowed to stir for ~ 15 minutes. The reaction solution was precipitated in stirring pentane (250 mL) and a precipitate was collected on a 30 mL medium porosity fritted funnel. The precipitate was dissolved in minimal DCM and placed in a 125 mL filter flask with a stirbar. To the stirring DCM, ether (50 mL) was added and a precipitate formed as well as a glaze on the bottom of the filter flask. A precipitate was collected on a 30 mL medium porosity fritted funnel. This procedure was repeated three to 4 times to collect all the precipitate that would come from the oil. When the precipitates from each collection was combined it yielded impure **45** (0.4506 g, .6031 mmol, 69% yield). Note: Yield likely over-estimating as NMR spectra very impure. Product was not fully characterized.

**45C** or **45D**

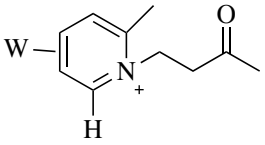


[WTp(NO)($PMe_3$)($\eta^2$-3,4-2-picolinium)][OTf]: **8A** (0.0523 g, 0.0816 mmol) was placed in an oven-dried vial. A solution of 2-picoline (0.0387 g, .4157 mmol) in DME (~ 1 mL) was added and the reaction stirred for ~ 15 hours. Ether (~ 50 mL) was placed in a 50 mL Erlenmeyer flask with a stirbar and triflic acid (0.0240 g, 0.1599 mmol) was added. The reaction solution was added to the stirring ether/acid solution. The reaction immediately changed from bright blue-green to purple brown. When the reaction was filtered through a 15 mL fine porosity frit a residue was collected. Upon dissolving the residue in minimal DCM and upon concentration of the DCM *in vacuo* yielded an oil that shows signs of **45C** or **45D** (0.0782 g, .1047 mmol, > 100% yield). Note: Product contained a multitude of other species. $^1$H NMR ($CDCl_3$, 600 MHz, δ): Notable peaks: 6.82 (m, 1H, H5 or H6), 6.34 (t, 1H, Tp4), 6.32 (t, 1H, Tp4), 6.22 (t, 1H, Tp4), 6.09 (m, 1H, H5 or H6), 3.66 (m, 1H), 2.72 (s, 3H, $CH_3$).




**47**: [WTp(NO)($PMe_3$)($\eta^2$-3,4--2-picolinium-*N*-propionaldehyde)][OTf]: **8A** (0.1050 g, 0.1638 mmol) was placed in an oven-dried vial with a stirbar. A solution of 2-picoline (0.0728 g, 0.7820 mmol) and DME (~ 1.5 mL) was added and the reaction stirred for 15.5 hours before being concentrated *in vacuo* for 5 hours. To the concentrated glaze a solution of DPhAt (0.0720 g, 0.2255 mmol) in DME (~ 1mL) was added and stirred for 10 minutes. Several drops of acrolein (0.0907 g, 1.617 mmol) were added followed by triethylamine (0.0403 g, 0.3983 mmol) in DME (~ .5 mL). The reaction solution was then precipitated in stirring ether (~ 100 mL) and a precipitate was collected on a 15 mL fine

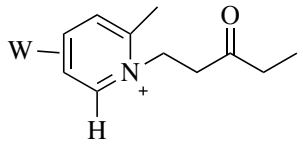
porosity fritted funnel. A brown precipitated was dried to give **47** (0.105 g, 0.1285 mmol, 78% yield). $^{1}$H NMR ($CDCl_3$, 600 MHz, δ): 9.65 (s, aldehyde), 9.07 (s, 1H, H3), 9.07 (d, 1H, Tp), 8.48 (d, 1H, Tp), 7.85 (d, 2H, Tp), 7.83 (d, 1H, Tp), 7.63 (d, 1H, Tp), 7.42 (d, 1H, Tp), 6.61 (d, $J$ = 4.1, 1H, H6), 6.40 (t, 1H, Tp), 6.36 (t, 1H, Tp), 6.34 (t, 1H, Tp), 4.52 (t, $J$ = 11.1, H8), 4.35 (d, $J$ = 15.2, H8), 3.89 (dd, $J$ = 12.3, 6.2, 1H, H1), 3.17 (m, 2H, H9), 2.65 (s, 3H, $CH_3$), 2.47 (t, $J$ = 4.9, H2), 1.19 (d, $J$ = 9.0, 9H, $PMe_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 199.5 (carbonyl), 174.0 (iminium), 147.0 (Tp), 144.9 (Tp), 141.3 (Tp), 137.8 (Tp), 137.3 (Tp), 136.4 (Tp), 127.0 (C5) 127.0 (C6), 107.6 (Tp), 107.4 (Tp), 107.3 (Tp), 67.5 (d, $J$ = 12.5, C1), 58.8 (C2), 48.0 (C8), 47.1 (C9), 16.9 ($CH_3$), 12.5 ($PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -11.8, $J_{WP}$ = 294. CV (DMA): $E_{p,a}$ = 0.71 V. IR = $\nu_{BH}$ = 2519 cm$^{-1}$, $\nu_{CO}$ = 1714 cm$^{-1}$, $\nu_{NO}$ and $\nu_{iminium}$ = 1584 cm$^{=1}$.




**48**: [WTp(NO)($PMe_3$)(η$^2$-3,4-2-picolinium-*N*-butan-2-one)][OTf]:

**Using triethylamine**: In an NMR tube put **45A** (0.0488 g, 0.0653 mmol), followed by chloroform (~ .6 mL) and methyl vinyl ketone (0.0338 g, 0.4822 mmol). The NMR tube was inverted several times to confirm homogeneity. Triehtylamine (0.0127 g, 0.1255 mmol) was added and the NMR tube was inverted. The reaction was allowed to react for 3 hours before being concentrated to an oil *in vacuo*. The oil was dissolved in minimal DCM and precipitated in stirring ether (50 mL). A brown precipitate was collected on a 15 mL medium porosity fritted funnel yielding **48** (0.0391 g, 0.0470 mmol, 72% yield).

**Using pyrrolidine**: In an NMR tube put **45A** (0.0504 g, 0.0675 mmol), followed by chloroform (~ .6 mL) and methyl vinyl ketone (0.0381 g, 0.5436 mmol). The NMR tube was inverted several times to confirm homogeneity. Pyrrolidine (0.0167 g, 0.2348 mmol) was added and the NMR tube was inverted. The reaction was allowed to react for 3.5 hours before being concentrated to an oil *in vacuo*. The oil was dissolved in minimal DCM and precipitated in stirring ether (50 mL). A brown precipitate was collected on a 15 mL medium porosity fritted funnel yielding **48** (0.0418 g, 0.0502 mmol, 74% yield). $^{1}$H NMR ($CDCl_3$, 600 MHz, δ): 9.04 (d, $J$ = 2.6, 1H, H3), 8.46 (d, 1H, Pz3A or Pz5A), 7.86 (d, 1H, Pz3B), 7.85 (d, 1H, Pz5B), 7.82 (d, 1H, Pz5C), 7.66 (d, 1H, Pz3A or Pz5A), 7.43 (d, 1H, Pz3C), 6.63 (d, $J$ = 4.1, 1H, H6), 6.42 (t, 1H, Pz4A), 6.37 (t, 1H, Pz4B), 6.35 (t, 1H, Pz4C), 4.44 (dt, $J$ = 14.0, 2.5, 1H, H8), 4.31 (d, $J$ = 14.0, 1H, H8), 3.90 (ddd, $J$ = 12.0, 5.6, 1H, H1), 3.12 (dd, $J$ = 19.1, 9.1, 1H, H9), 2.98 (d, $J$ = 19.1, 1H, H9), 2.66 (s, 3H, picolinium $CH_3$), 2.45 (t, $J$ = 5.6, 1H, H2), 2.08 (s, 3H, MVK $CH_3$), 1.20 (buried d, 9H, $PMe_3$). $^{13}$C NMR ($CDCl_3$, 800 MHz, δ): 206.6 (carbonyl), 174.1 (iminium), 167.9 (C3), 146.7 (Pz3A or Pz5A), 144.9 (Pz5B), 141.3 (Pz3C), 137.8 (Pz5C), 137.3 (Pz3B), 136.3 (Pz3A or Pz5A), 128.5 (C5), 127.0 (C6), 107.5 (Pz4C), 107.4 (Pz4B and Pz4A), 67.5 (d, $J$ = 12.1, C1), 58.7 (C2), 49.5 (C8), 44.8 (C9), 30.2 (MVK $CH_3$), 17.0 (picolinium $CH_3$), 12.6 (d, $J$ = 30.2, $PMe_3$). $^{31}$P NMR ($CDCl_3$, 500 MHz, δ): -11.9, $J_{WP}$ = 294. CV (DMA): $E_{p,a}$ = 0.72 V. IR = $\nu_{BH}$ = 2516 cm$^{-1}$, $\nu_{CO}$ = 1716 cm$^{-1}$, $\nu_{NO}$ and $\nu_{iminium}$ = 1598 cm$^{=1}$.



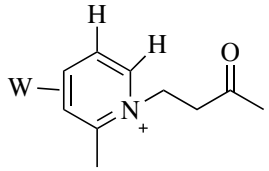
**49**: [WTp(NO)($PMe_3$)($\eta^2$-3,4-2-picolinium-*N*-pentan-3-one)][OTf]:

**Using triethylamine**: In an oven-dried vial put **45A** (0.1071 g, 0.1434 mmol), followed by chloroform (~ 1 mL) and ethyl vinyl ketone (0.1101 g, 1.309 mmol). The vial was shaken to confirm homogeneity. To the vial, triethylamine (0.0262 g, 0.2589 mmol) was added and the reaction was allowed to sit for ~ 30 minutes. The reaction solution was precipitated in stirring ether (100 mL) and a precipitate was collected on a 15 mL medium porosity fritted funnel yielding a brown precipitate **49** (0.0865 g, 0.1022 mmol, 73% yield).

**Directly from 8**: In an oven dried vial put **8** (0.3115 g, 0.5361 mmol), followed by a solution of 2-picoline (0.2486 g, 2.67 mmol) in DME (~ 4 mL) and a stirbar. The reaction stirred for ~ 15 hours before being concentrated to an oil *in vacuo* for 5 hours. A solution of DME (~ 1 mL) and DPhAt (0.2168 g, 0.6790 mmol) was added and the solution stirred for ~ 30 minutes. Ethyl vinyl ketone (0.5392 g, 6.411 mmol) was added and the reaction stirred for 2 minutes. Triethylamine (0.1186 g, 1.172 mmol) was then added and the reaction stirred for ~ 20 minutes. The reaction solution was precipitated in stirring ether (250 mL) and the resulting precipitate was collected on a 30 mL medium porosity fritted funnel to give a brown precipitate: **49** (0.2959 g, 0.3493 mmol, 66% yield).

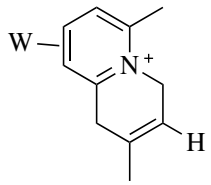
$^1$H NMR ($CDCl_3$, 600 MHz, δ): 9.05 (d, *J* = 5.3, 1H, H3), 8.42 (d, *J* = 1.2, 1H, Pz3A), 7.85 (d, *J* = 2.1, 2H, Pz3B and Pz5B), 7.83 (d, *J* = 1.3, 1H, Pz5C), 7.66 (d, *J* = 1.2, 1H, Pz5A), 7.42 (d, *J* = 1.1, 1H, Pz3C), 6.62 (d, *J* = 5.5, 1H, H6), 6.41 (t, *J* = 1.8, 1H, Pz4A), 6.37 (t, *J* = 2.1, 1H, Pz4C), 6.35 (t, *J* = 1.9, 1H, Pz4B), 4.48 (ddd, *J* = 14.2, 9.6, 4.2, 1H,

H8), 4.31 (dt, $J$ = 14.2, 4.2, 1H, H8), 3.89 (dd, $J$ = 12.2, 7.0, 1H, H1), 3.08 (m, 1H, H9), 2.96 (m, 1H, H9), 2.45 (t, $J$ = 7.0, 1H, H2), 2.36 (m, 2H, H10), 1.20 (d, $J$ = 9.1, 9H, $PMe_3$), .93 (t, $J$ = 7.3, 3H, H11). $^{13}C$ NMR ($CDCl_3$, 800 MHz, δ): 209.4 (carbonyl), 174.2 (iminium), 146.6 (Pz4A), 144.8 (Pz3B or Pz5B), 141.3 (Pz3C), 137.8 (Pz3B or Pz5B), 137.3 (Pz5C), 136.4 (Pz5A), 127 (C4), 107.5 (Pz4A, 4B, or 4C), 107.4 (Pz4A, 4B, or 4C), 107.3 (Pz4A, 4B, or 4C), 67.5 (d, $J$ = 11.6, C1), 58.7 (C2), 49.4 (C8), 43.6 (C9), 35.9 (C10), 17.0 (C7), 12.6 (d, $J$ = 30.3, $PMe_3$), 7.7 (C11). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -11.9, $J_{WP}$ = 293. CV (DMA): $E_{p,a}$ = 0.69 V. IR = $\nu_{BH}$ = 2519 $cm^{-1}$, $\nu_{CO}$ = 1712 $cm^{-1}$, $\nu_{NO}$ and $\nu_{iminium}$ = 1589 $cm^{=1}$.




**50**: [WTp(NO)($PMe_3$)($\eta^2$-3,4-2-picolinium-*N*-butan-2-one)][OTf]: Took a sample of **48** (0.0239 g, 0.0287 mmol), in an NMR tube with deuterated chloroform. Put in an oil bath at 60 °C for 5 days. NMR tube removed from oil bath 3 – 4 times over the course of 5 days for a $^1H$ NMR checks. After 5 days, the NMR solution was precipitated in stirring ether (50 mL) and the precipitate was collected on a 15 mL fritted funnel to yield **50** (0.0193 g, 0.0232 mmol, 81% yield). Column conditions tested: Neutral alumina and eluted with 10% acetonitrile in ethyl acetate to remove junk followed by 100% acetonitrile to collect product (0.0063 g, 0.0076 mmol, 26% recovery). $^1H$ NMR ($CDCl_3$, 600 MHz, δ): 8.11 (d, $J$ = 2.1, 1H, Tp), 7.85 (d, $J$ = 2.4, 1H, Tp), 7.82 (d, $J$ = 1,4, 1H, Tp), 7.80 (d, $J$ = 2.4, 1H, Tp), 7.70 (d, $J$ = 2.4, 1H, Tp), 7.42 (d, $J$ = 1.6, 1H, Tp), 6.74 (dd, $J$ = 7.0, 4.5, 1.4, 1H, H6), 6.40 (t, $J$ = 2.3, 1H, Tp), 6.37 (t, $J$ = 2.1, 1H, Tp), 6.33 (t, $J$

= 2.5, 1H, Tp), 6.02 (d, *J* = 7.2, 1H, H5), 4.55 (ddd, *J* = 13.7, 11.3, 1.8, 1H, H7), 3.90 (m, 1H, H1), 3.32 (ddd, *J* = 13.5, 11.3, 2.5, 1H, H7), 3.08 (m, 2H, H8), 2.69 (s, 3H, $CH_3$), 2.34 (d, *J* = 7.7, 1H, H2), 2.25 (s, 3H, MVK $CH_3$), 1.21 (d, *J* = 8.9, 9H, $PMe_3$).




**56**: [WTp(NO)($PMe_3$)($\eta^2$-2,6-dimethyl-1,4-dihydroquinolizin-5-ium)][OTf]: In an oven dried vial put **51** (0.1999 g, 0.2626 mmol) and a stirbar. Added chloroform (.6 mL), pyrrolidine (0.0385 g, 0.5425 mmol) and methyl vinyl ketone (0.1963 g, 2.801 mmol) to the reaction solution. The reaction stirred for 45 minutes before chloroform (.3 mL) was added. The reaction stirred for 46 hours. The reaction solution was then concentrated to oil and left *in vacuo* for 1.5 hours. Took oil and rinsed through a 3 cm of Celite® before being concentrated back to an oil. The oil was picked up in minimal DCM and precipitated in stirring ether (200 mL). A precipitate was collected on a 30 mL medium porosity fritted funnel (0.1911 g, 0.2352 mmol, 90% yield). Took **56** (0.1005 g, 0.1237 mmol) and dry loaded on neutral alumina. Set up a 15 mL course porosity fritted funnel with 1.5 inches of neutral alumina and loaded with 10% acetonitrile in ethyl acetate. Eluted with 10% acetonitrile in ethyl acetate followed by 20% acetonitrile in ethyl acetate. Collected an initial band, pink band and a yellow band. The pink bands were concentrated down *in vacuo* to yield an oil of **56** (.0290 g, .0357 mmol, 29% recovery). $^1$H NMR (Acetone-D, 600 MHz, δ): $^1$H NMR (Acetone-D): 8.16 (d, *J* = 2.3, 1H, Pz5C), 8.08 (d, *J* = 2.3, 1H, Pz5A), 8.03 (d, *J* = 2.1, 1H, Pz3B), 8.02 (d, *J* = 2.3, 1H, Pz3A), 7.72

(d, $J$ = 2.1, 1H, Pz3C), 7.64 (d, $J$ = 2.0, 1H, Pz5B), 6.90 (d, $J$ = 5.1, 1H, H10), 6.49 (t, $J$ = 2.3, 1H, Pz4C), 6.45 (t, $J$ = 2.3, 1H, Pz4B), 6.43 (t, $J$ = 2.1, 1H, Pz4A), 6.03 (m, 1H, H6), 4.99 (d, $J$ = 18.3, 1H, H7), 4.92 (d, $J$ = 18.3, 1H, H7), 4.30 (ddd, $J$ = 13.7, 8.1, 5,1, 1H, H1), 2.79 (s, 3H, 11-$CH_3$), 2.64 (d, $J$ = 8.1, 1H, H2), 2.58 (m, 1H, H4), 2.47 (m, 1H, H4), 1.96 (s, 3H, 12-$CH_3$), 1.37 (d, $J$ = 9.0, 9H, $PMe_3$). $^{13}C$ NMR (Acetone-D, 800 MHz, δ): 182.7 (Iminium), 146.2 (Pz3B or Pz3A), 144.2 (Pz5B), 142.4 (Pz3C), 138.8 (Pz5C), 138.5 (Pz5A), 138.3 (Pz3B or Pz3A), 137.6 (C5 or C9), 128.7 (C5 or C9), 125.1 (C10), 119.4 (C6), 108.0 (Pz4B, Pz4C, or Pz4a), 108.0 (Pz4B, Pz4C, or Pz4A), 107.4 (Pz4B, Pz4C or Pz5A), 68.6 (d, $J$ = 12.5, C1), 63.4 (C2), 48.0 (C7), 39.8 (C4), 20.7 (C12), 16.5 (C11), 12.9 (d, $J$ = 30.6, $PMe_3$). $^{31}P$ NMR ($CDCl_3$, 500 MHz, δ): -10.8, $J_{WP}$ = 295. CV (DMA): $E_{p,a}$ = 0.72 V. IR = $\nu_{BH}$ = 2501 $cm^{-1}$, $\nu_{NO}$ and $\nu_{iminium}$ = 1582 $cm^{=1}$.

## 5.9 References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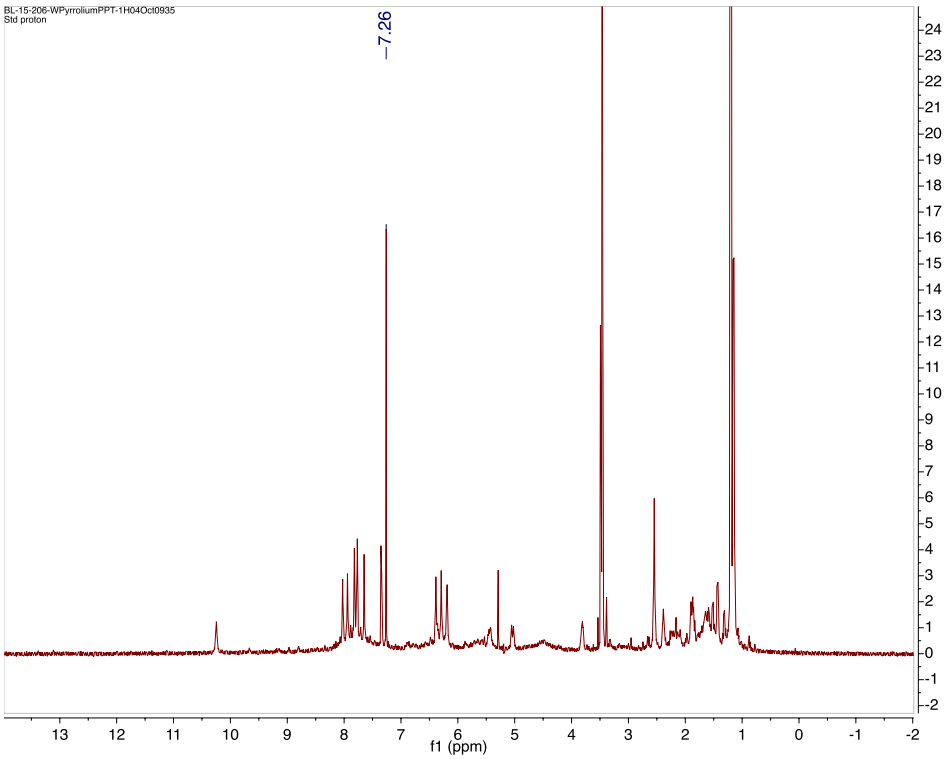
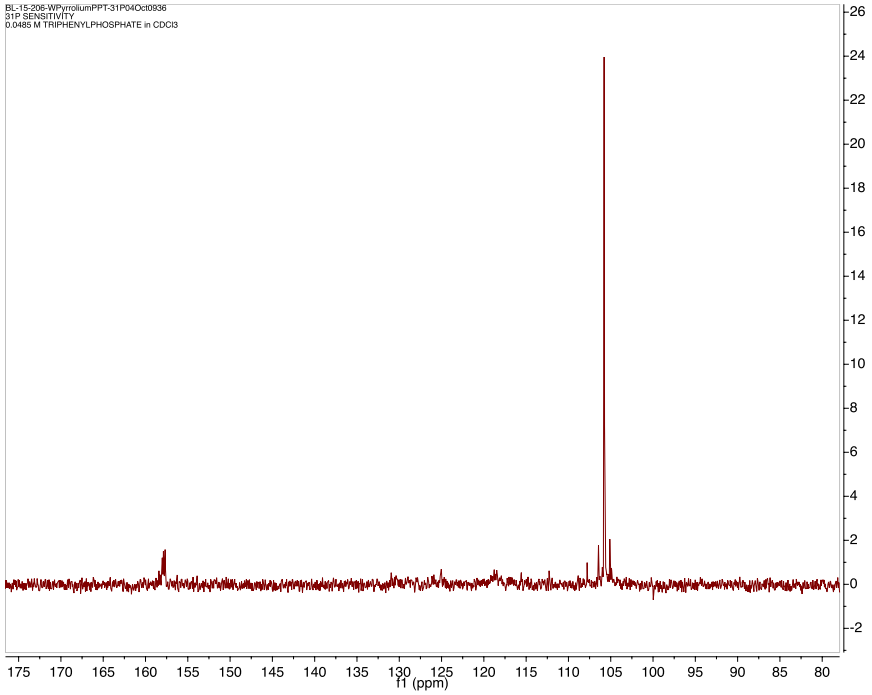
# Appendix

Compound **13** – $^{1}$H NMR




Compound **13** - $^{31}$P NMR



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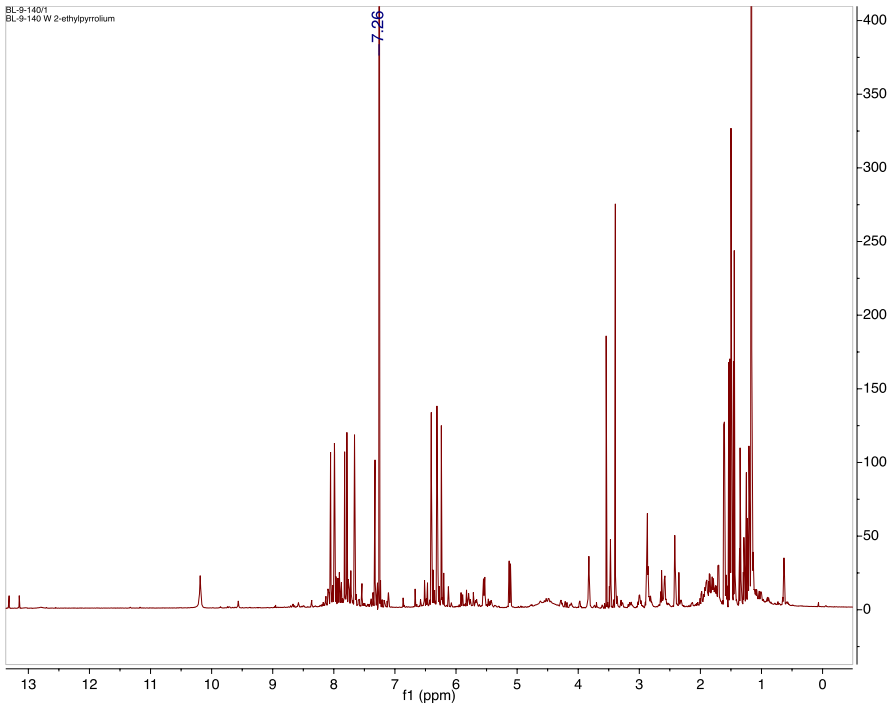
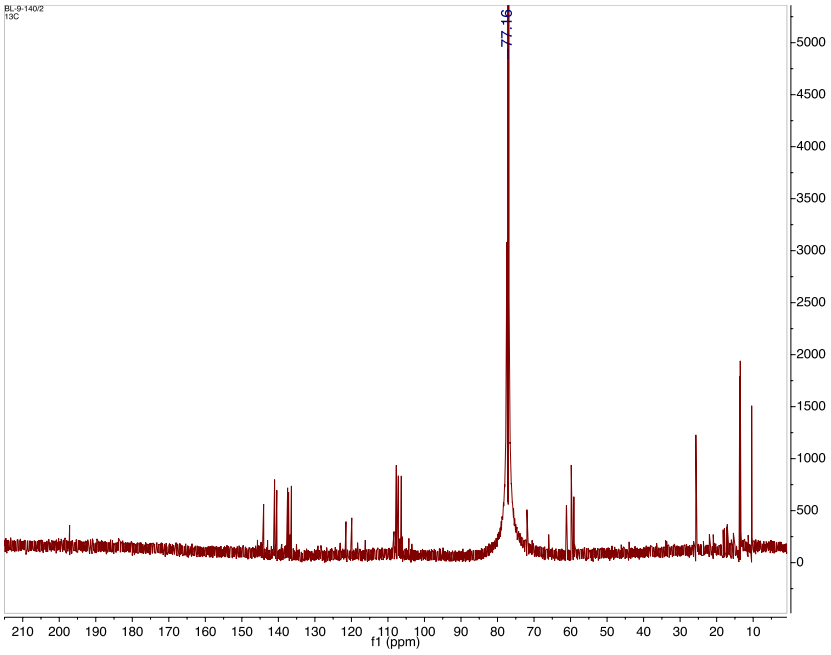



Compound **15** – $^{13}$C NMR



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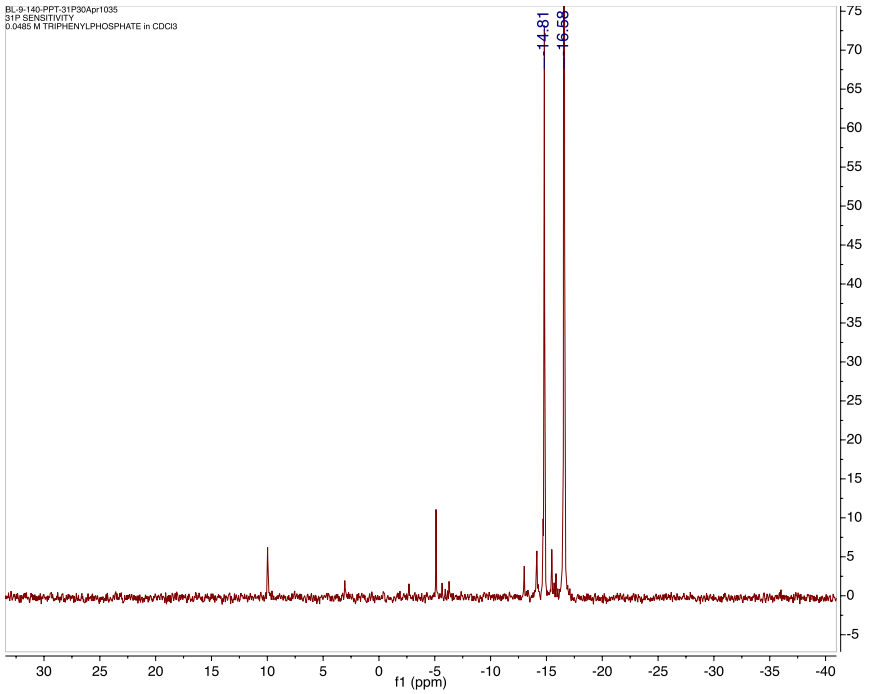

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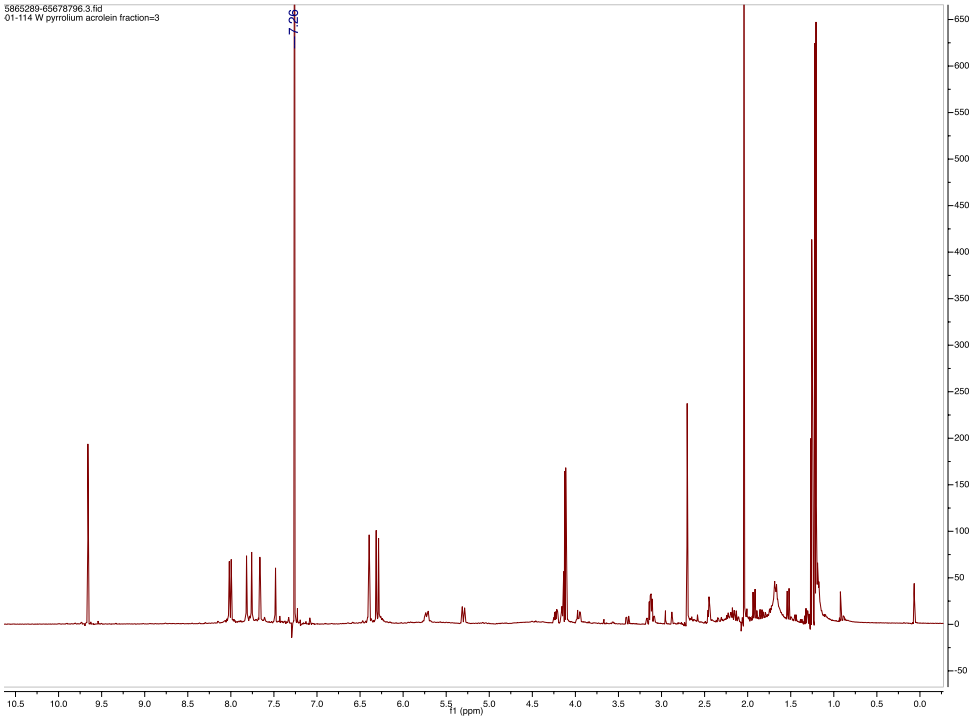
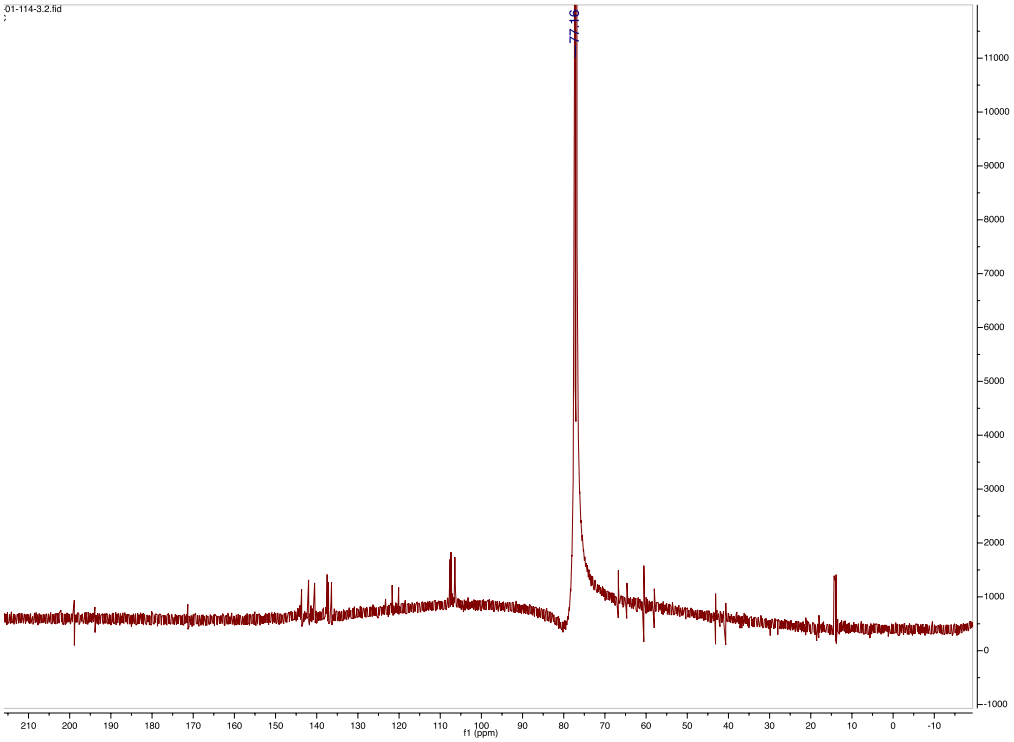
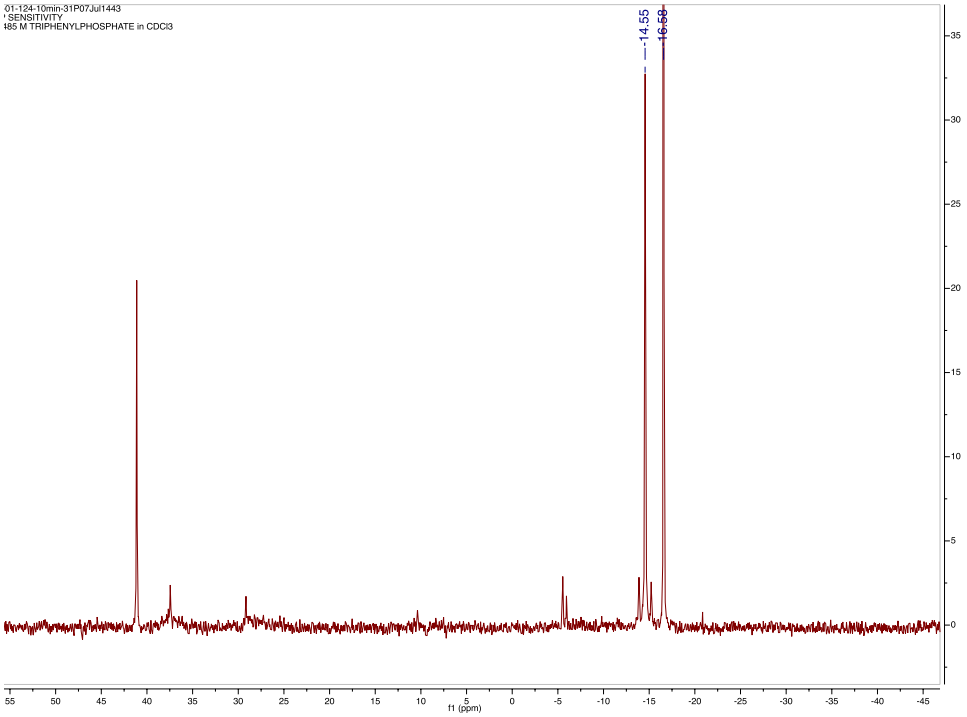



Compound **23** – $^{13}$C NMR



Compound **23** – $^{31}$P NMR



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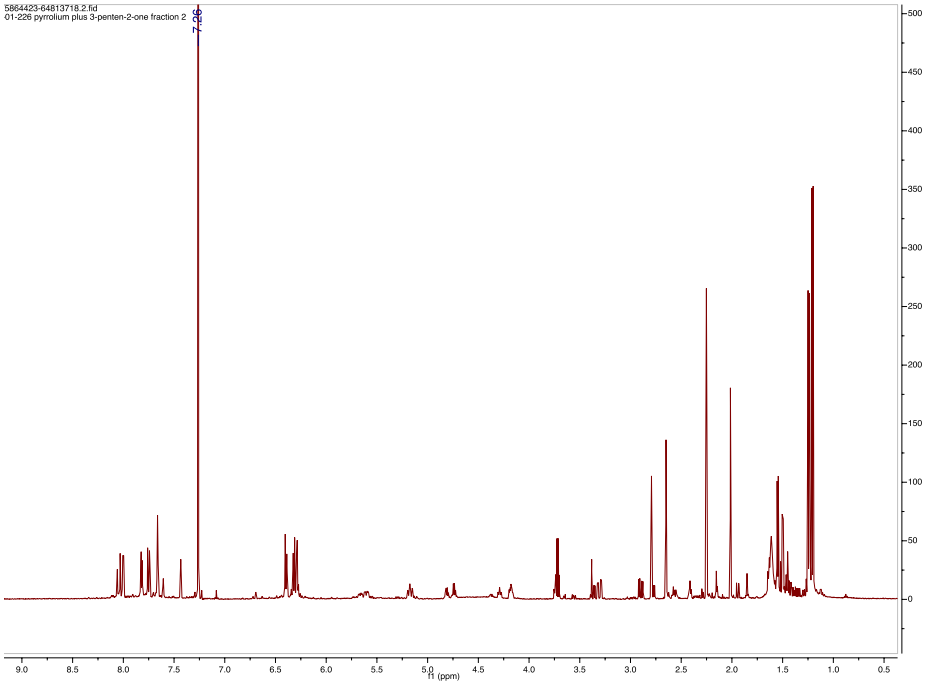


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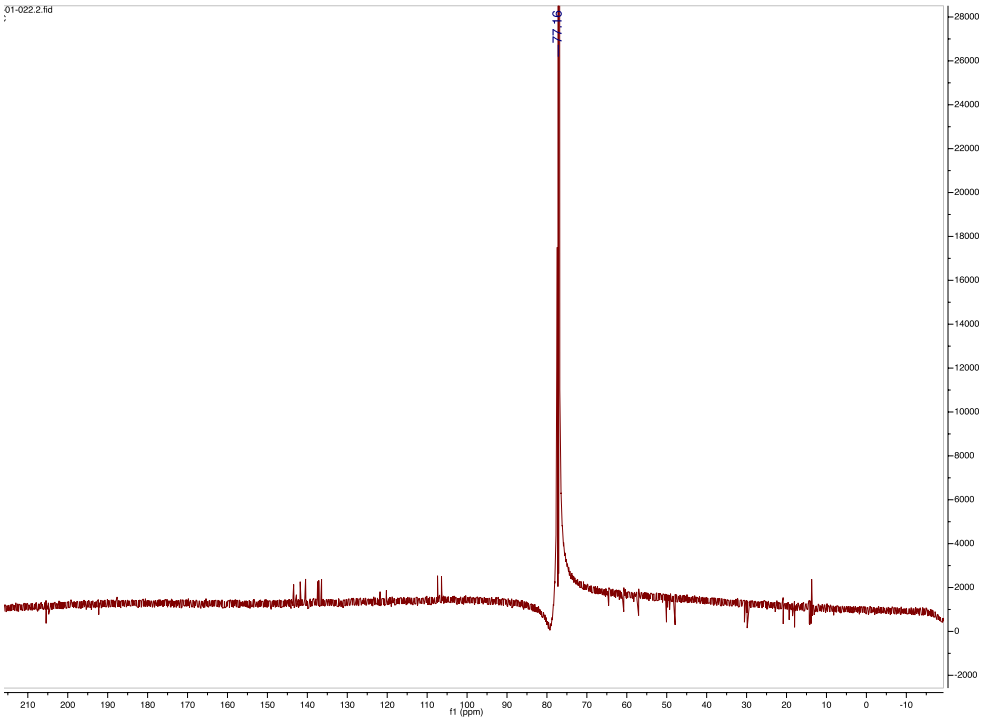
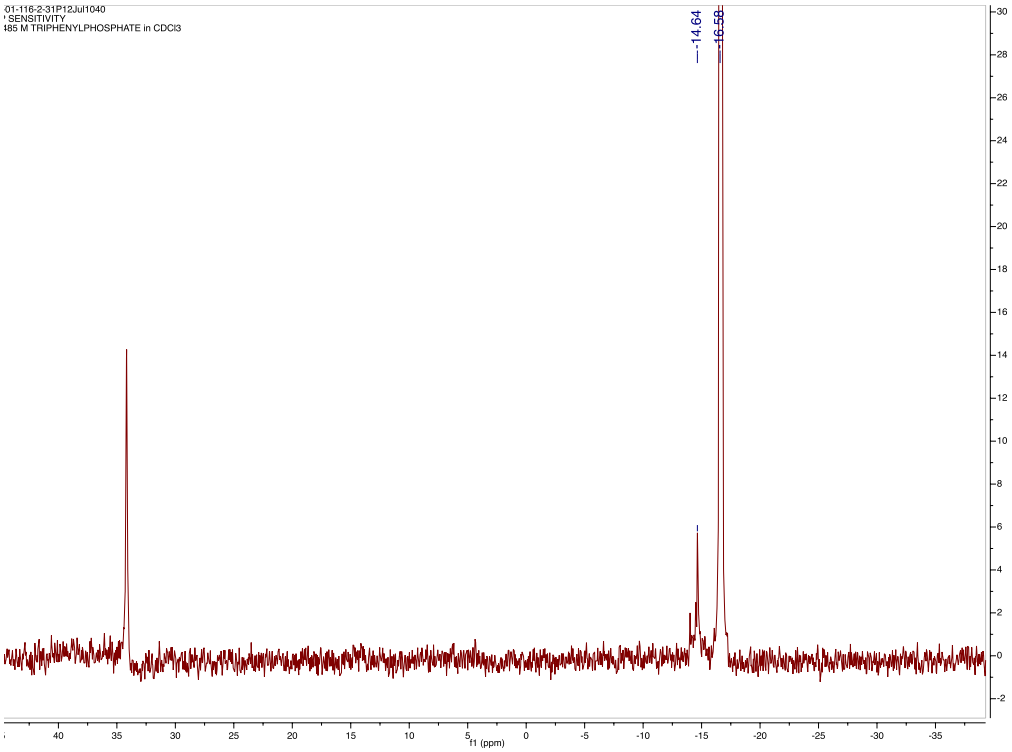


Compound **24**– $^{31}P$ NMR



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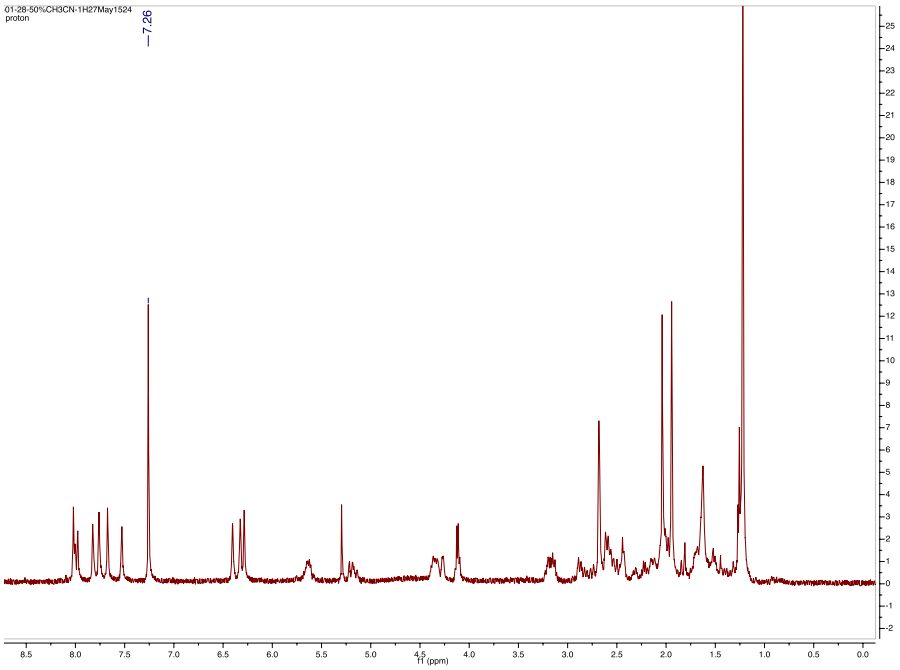


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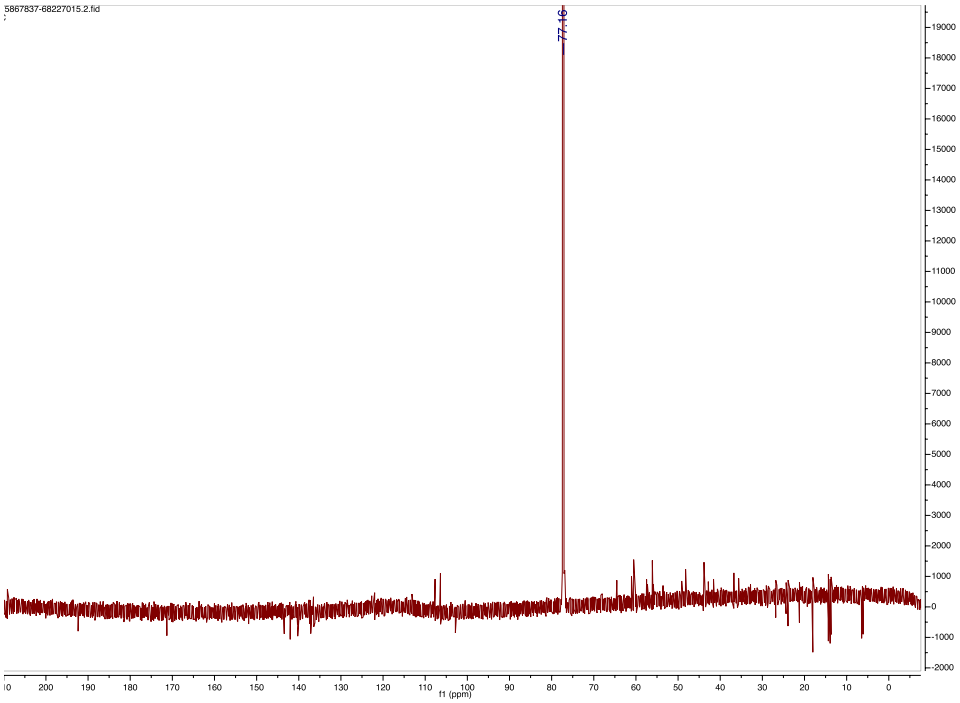

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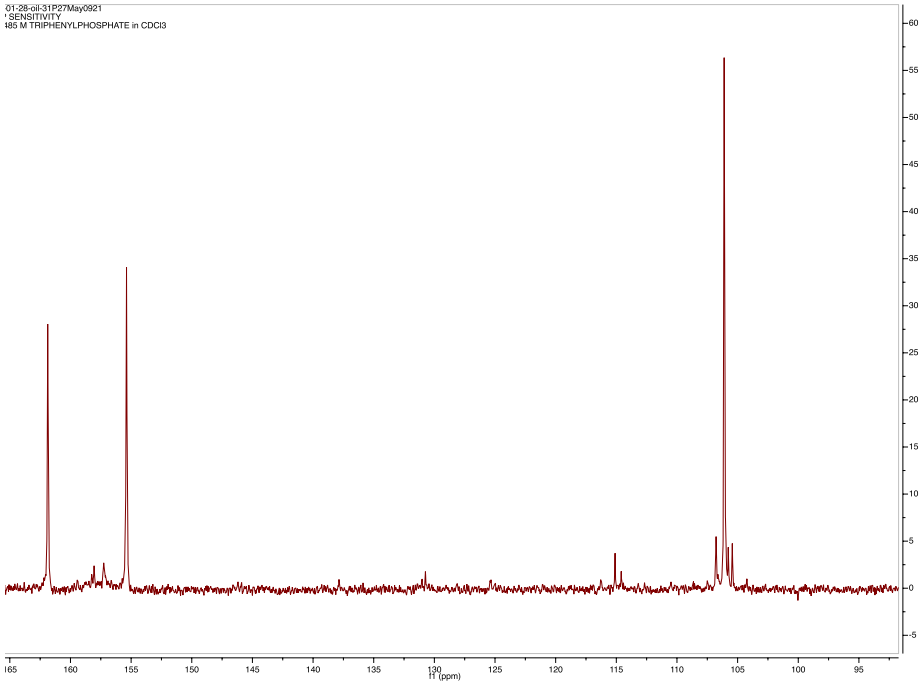

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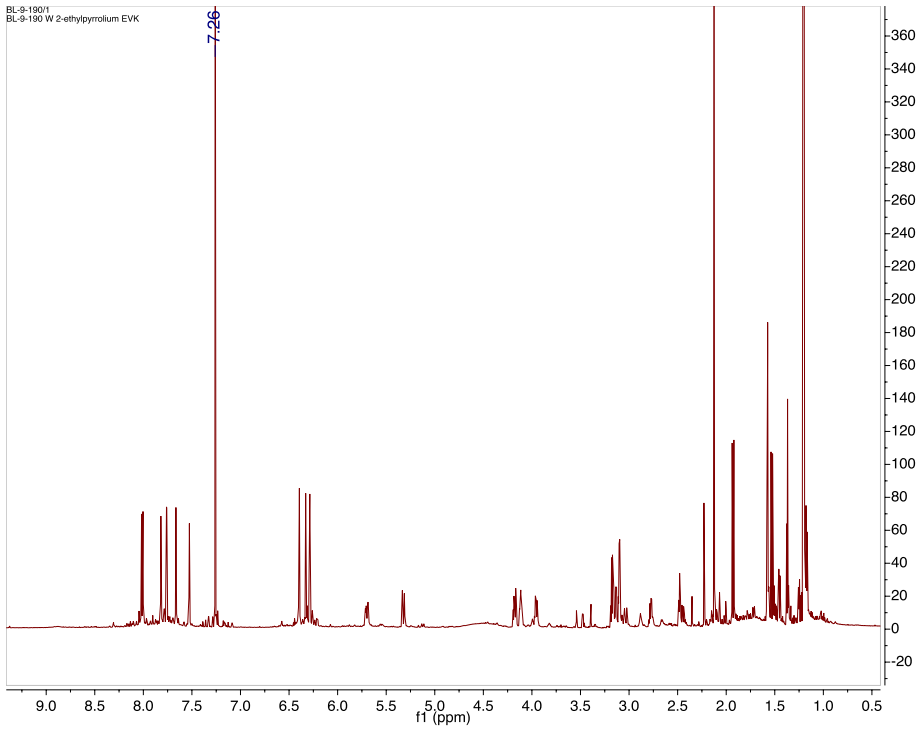
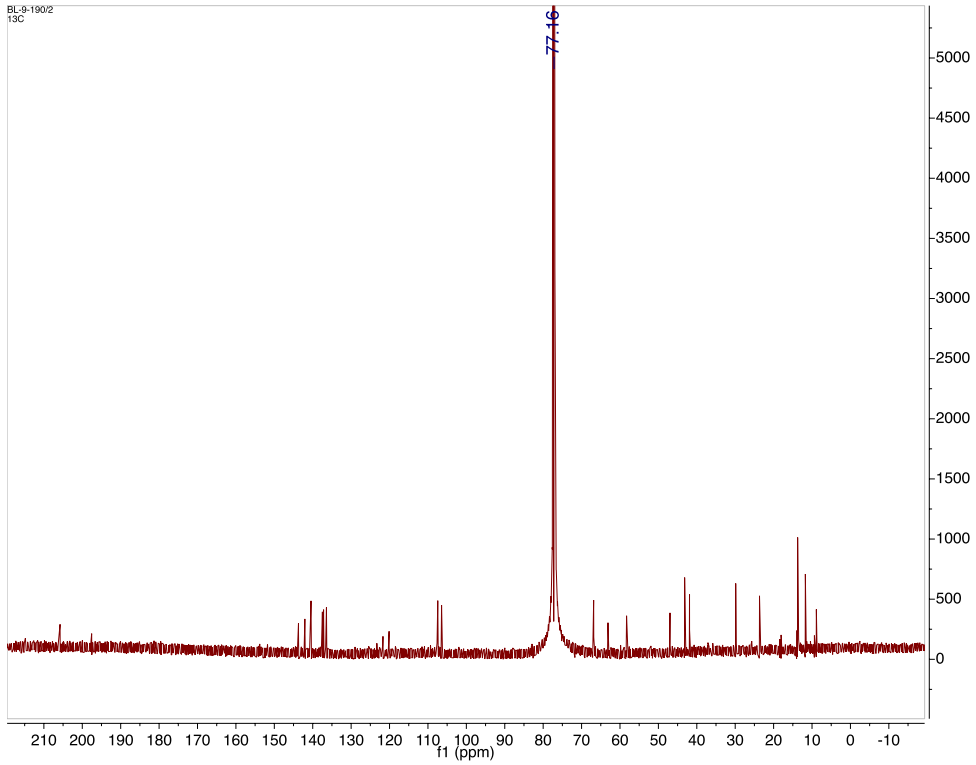



Compound **26** – $^{13}$C NMR



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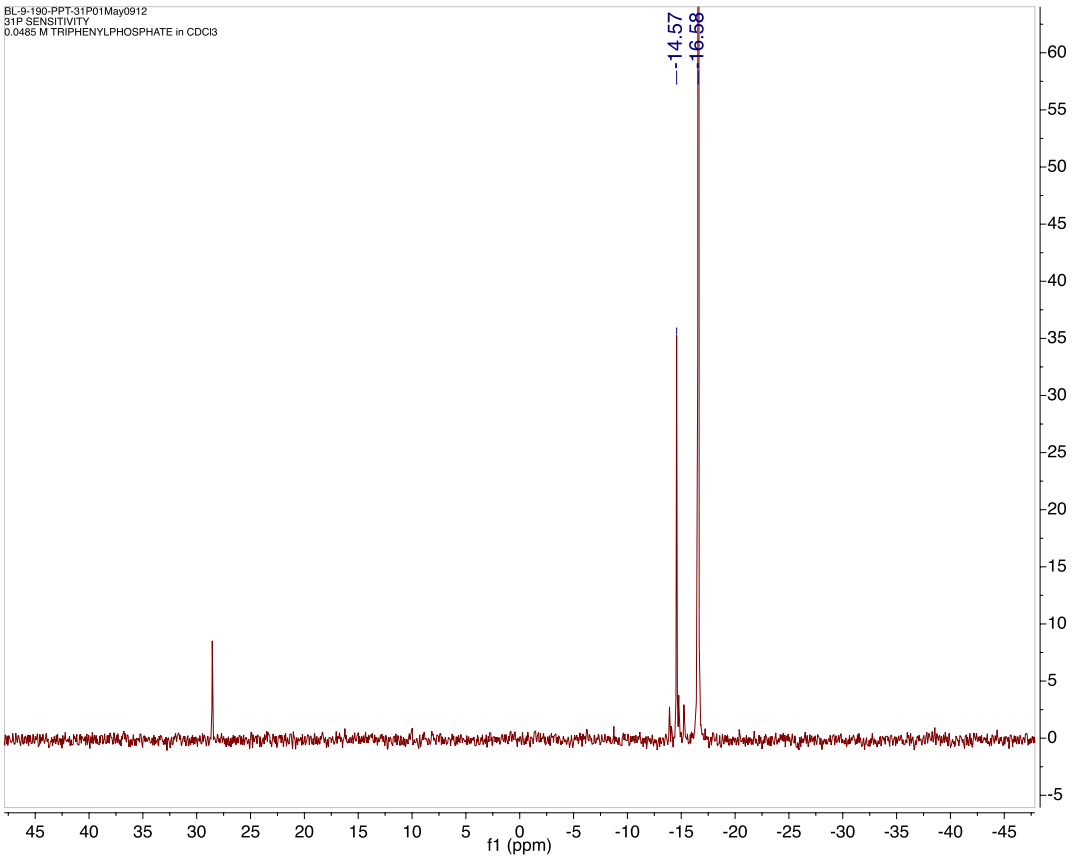

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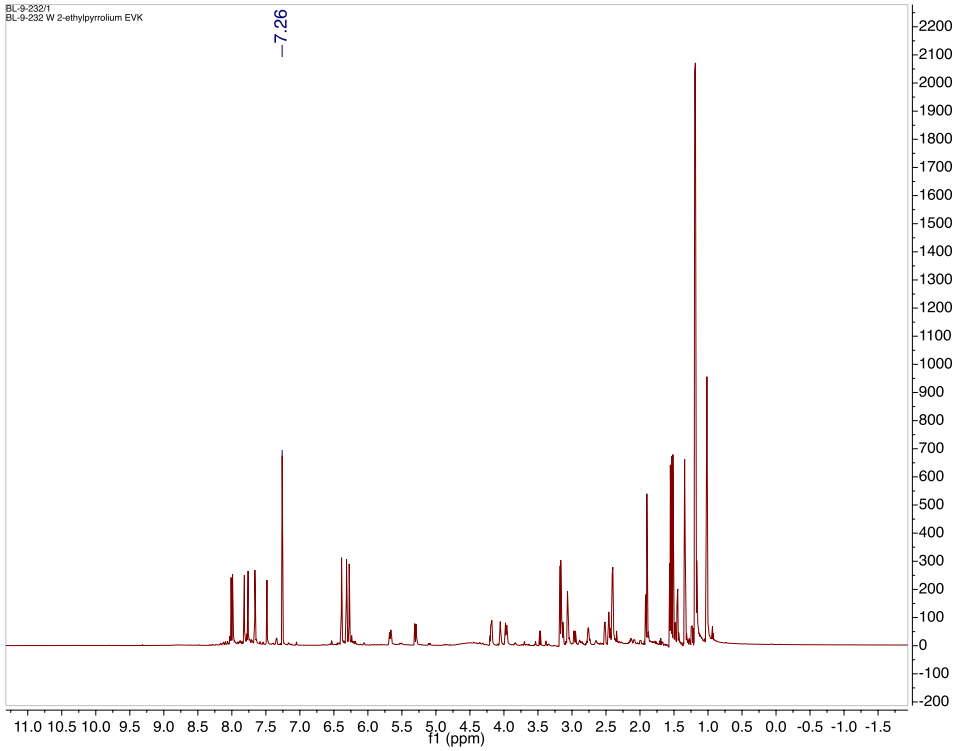


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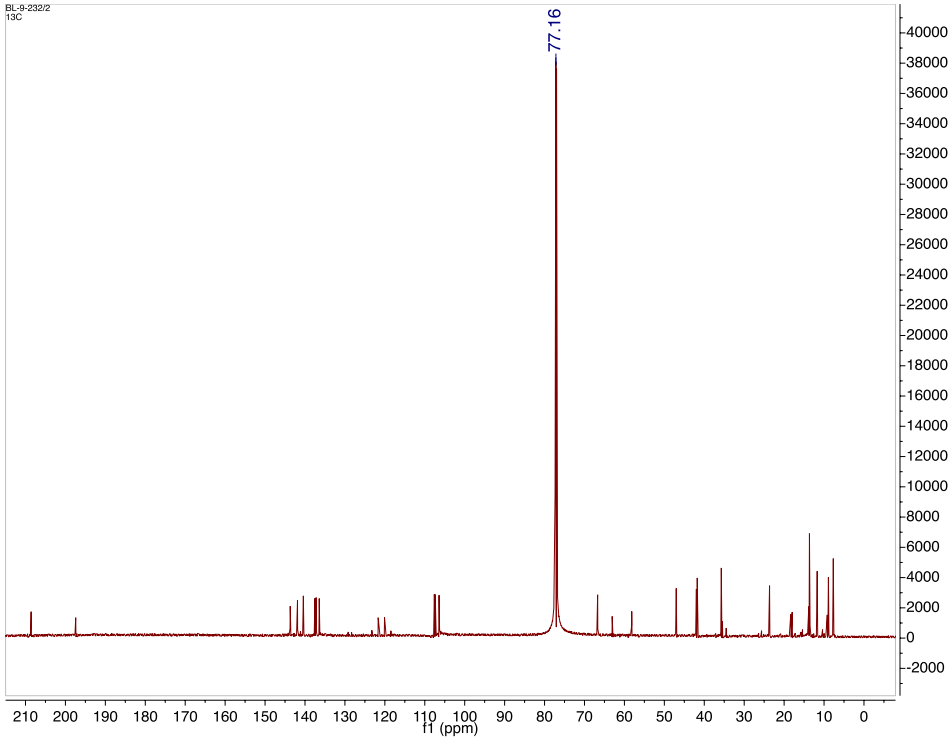

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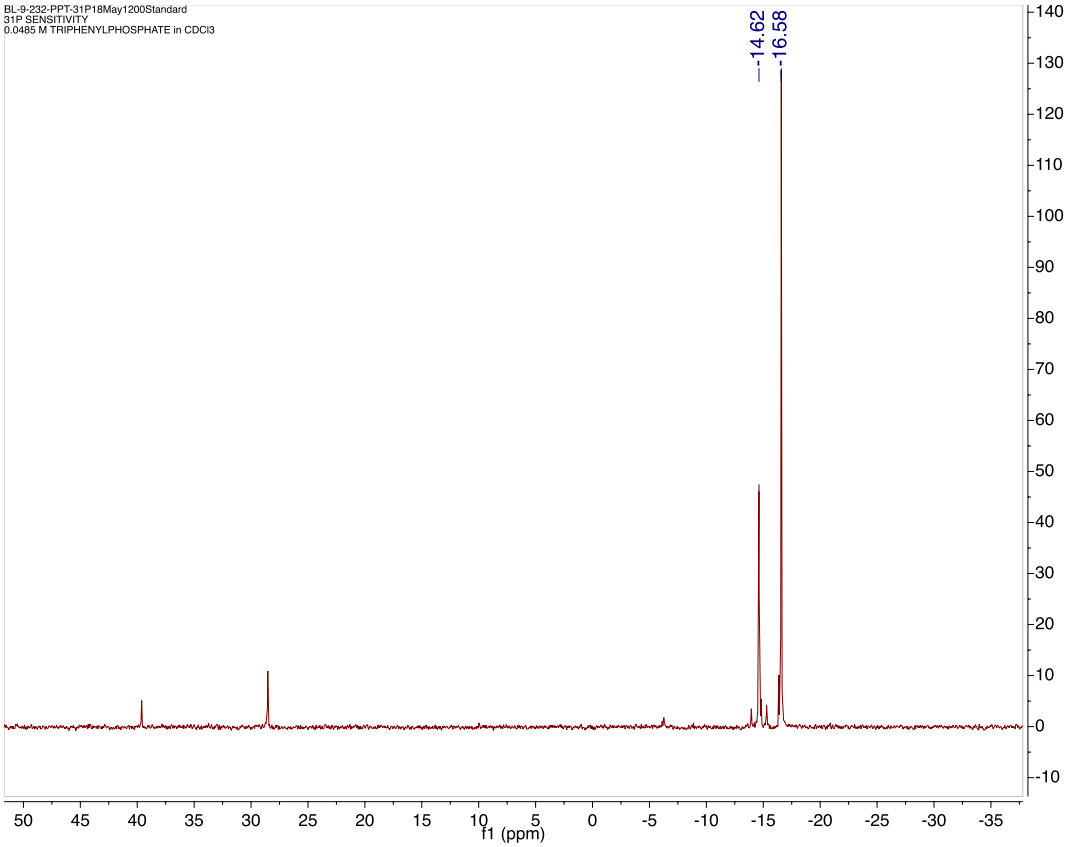
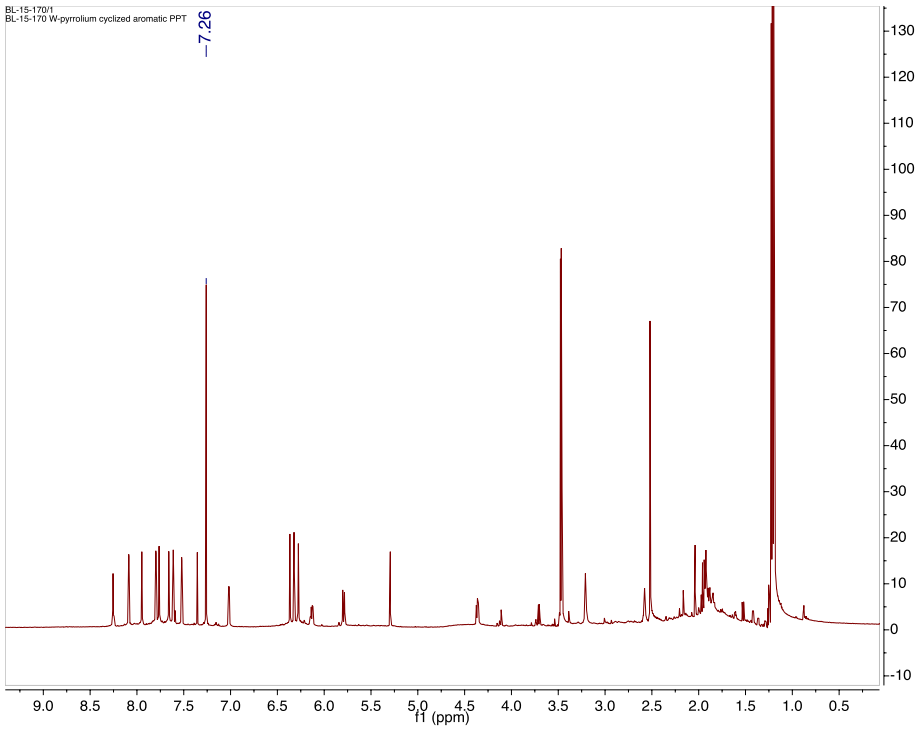


Compound **28A** – $^{1}$H NMR

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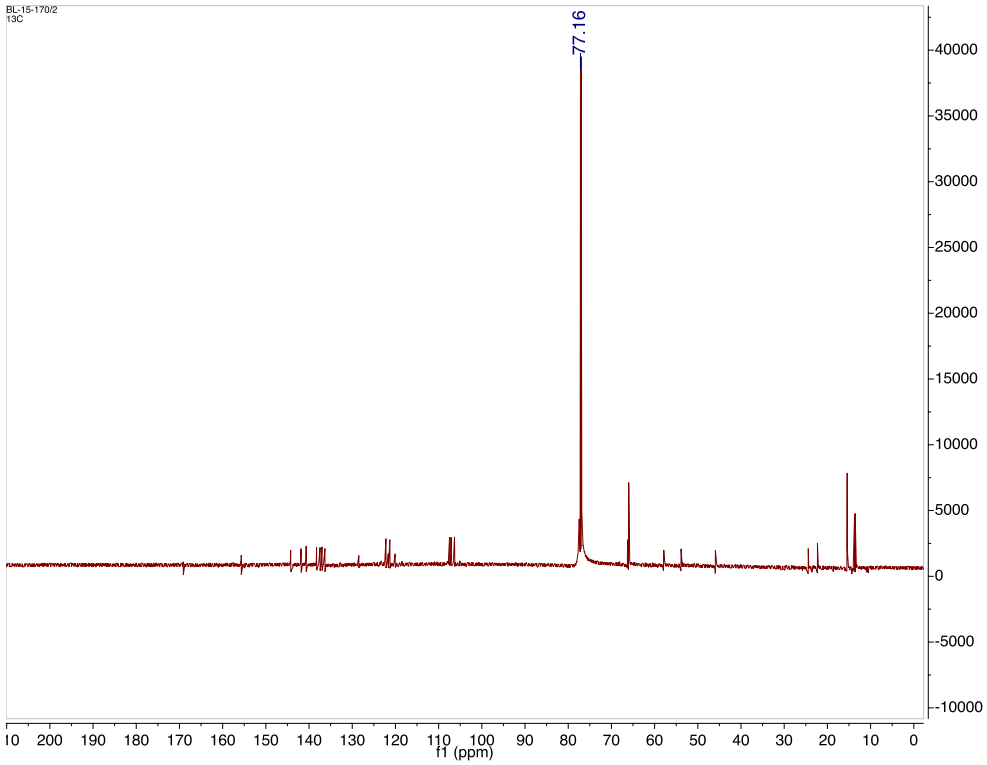
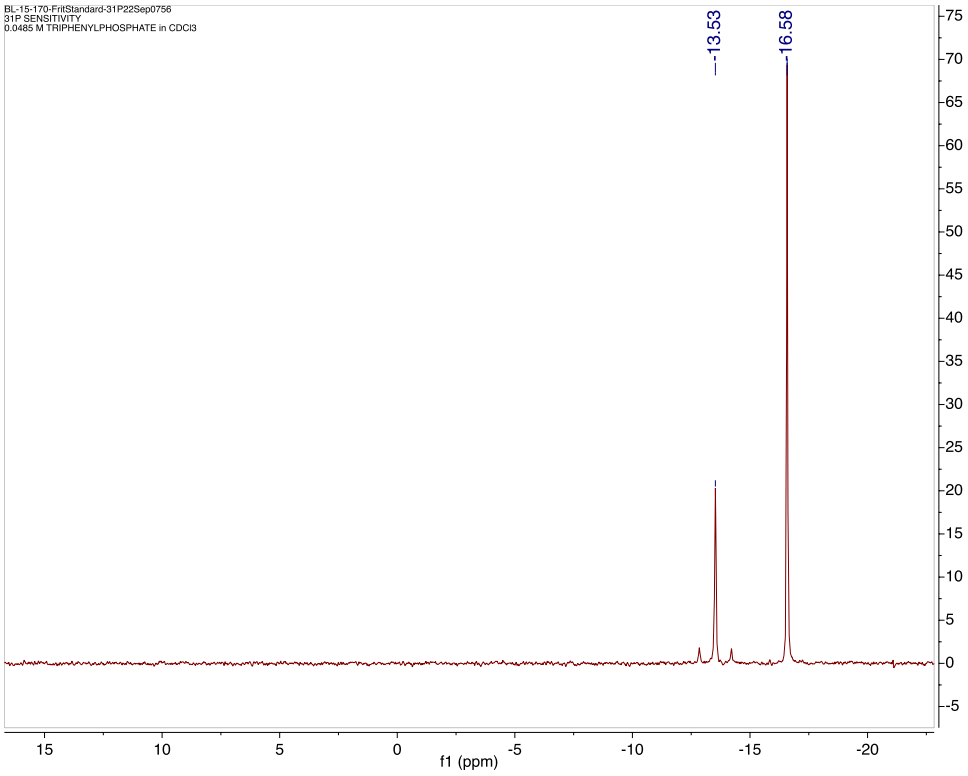
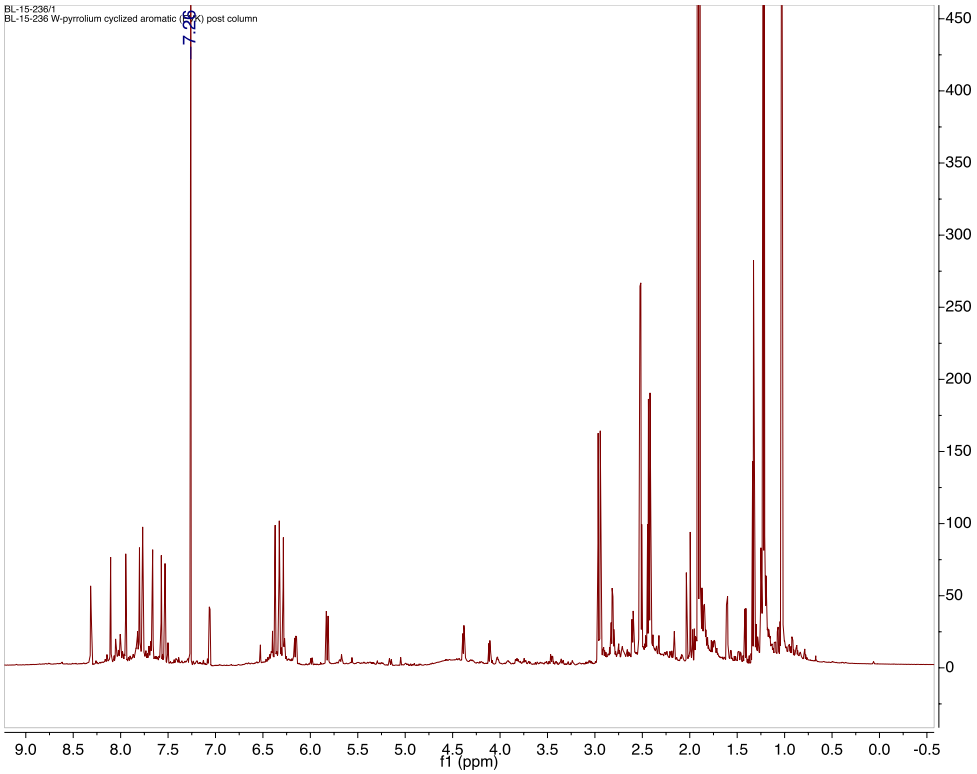


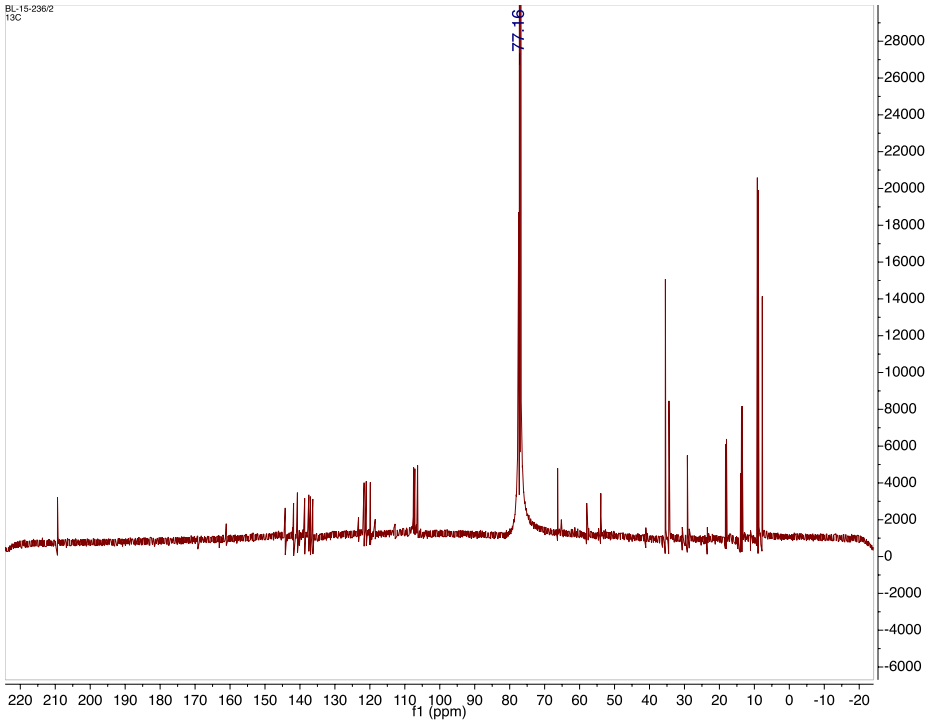
Compound **28A** – $^{31}P$ NMR



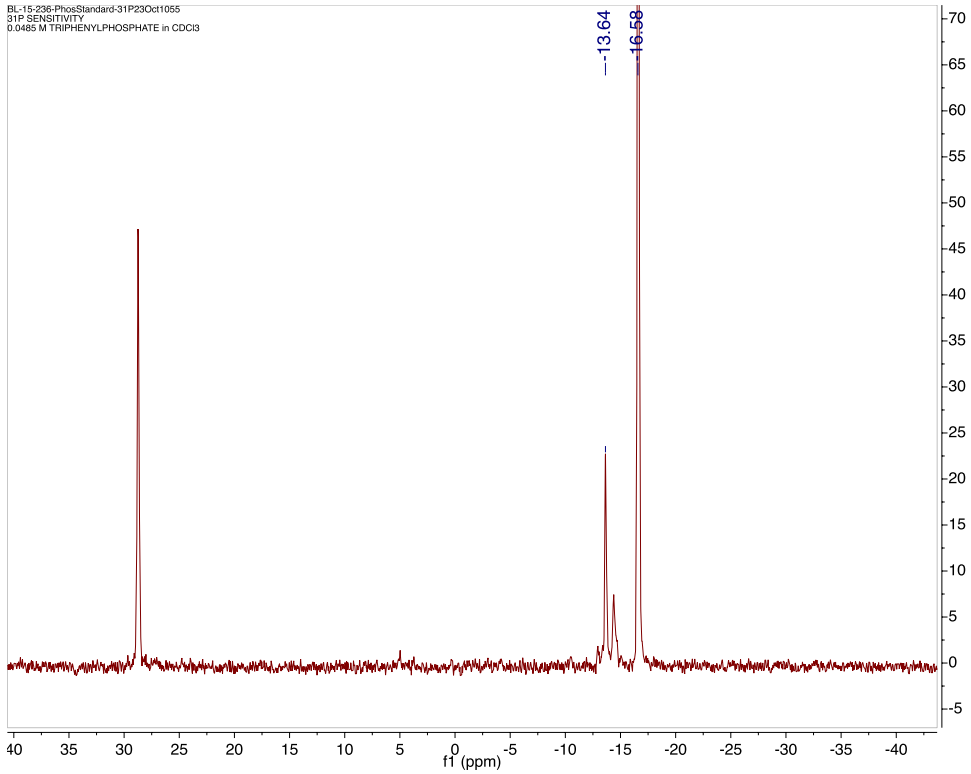
Compound **30A** - $^{1}$H NMR



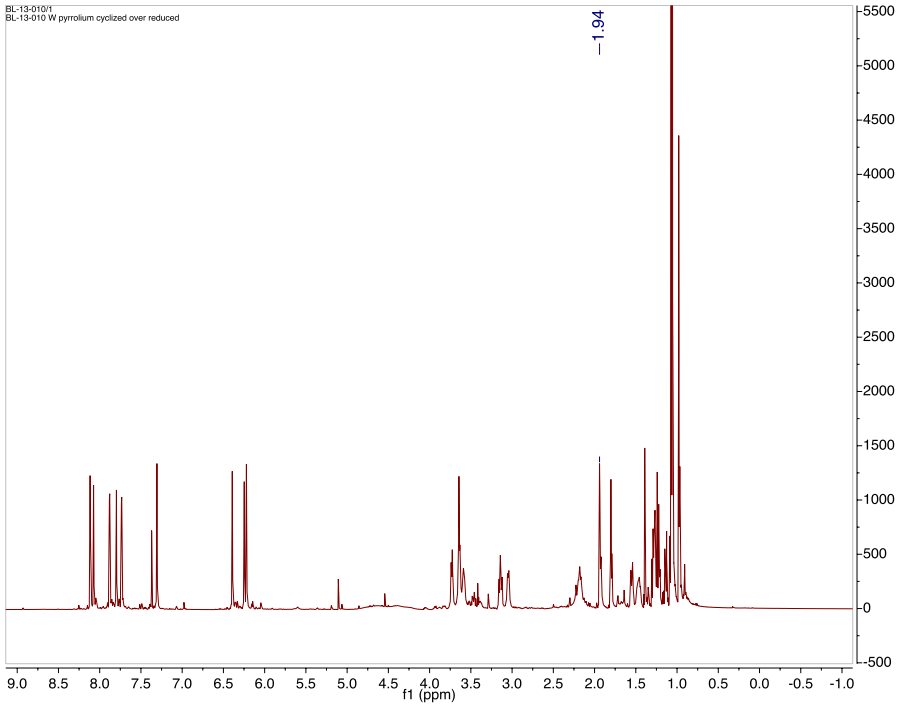

Compound **30A** – $^{13}$C NMR



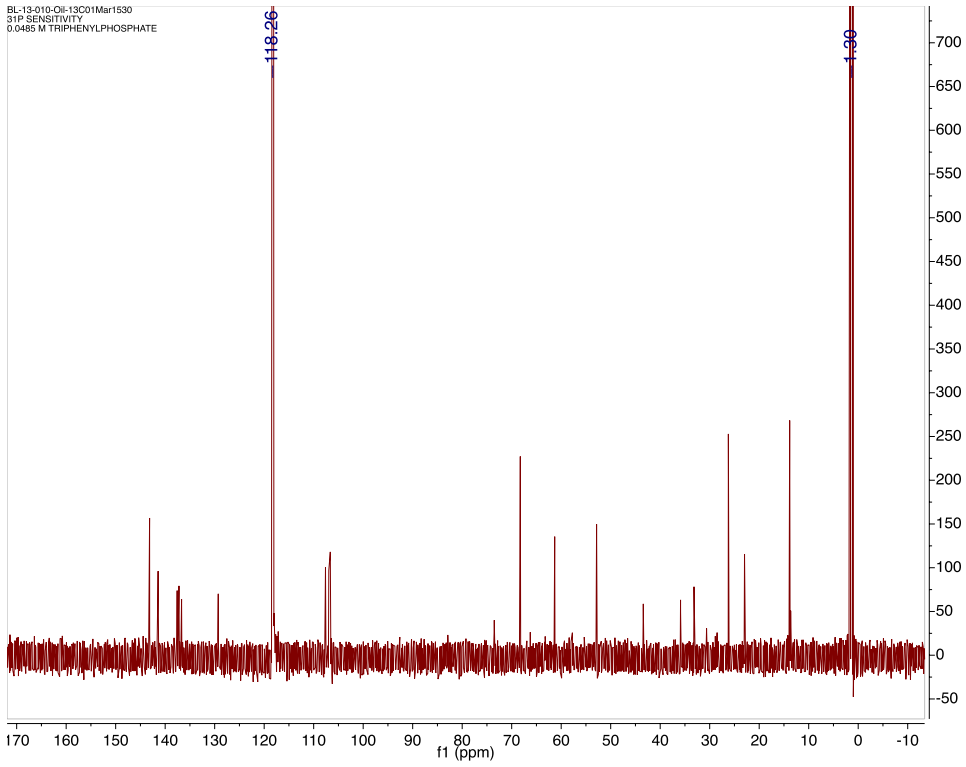
Compound **30A** – $^{31}P$ NMR



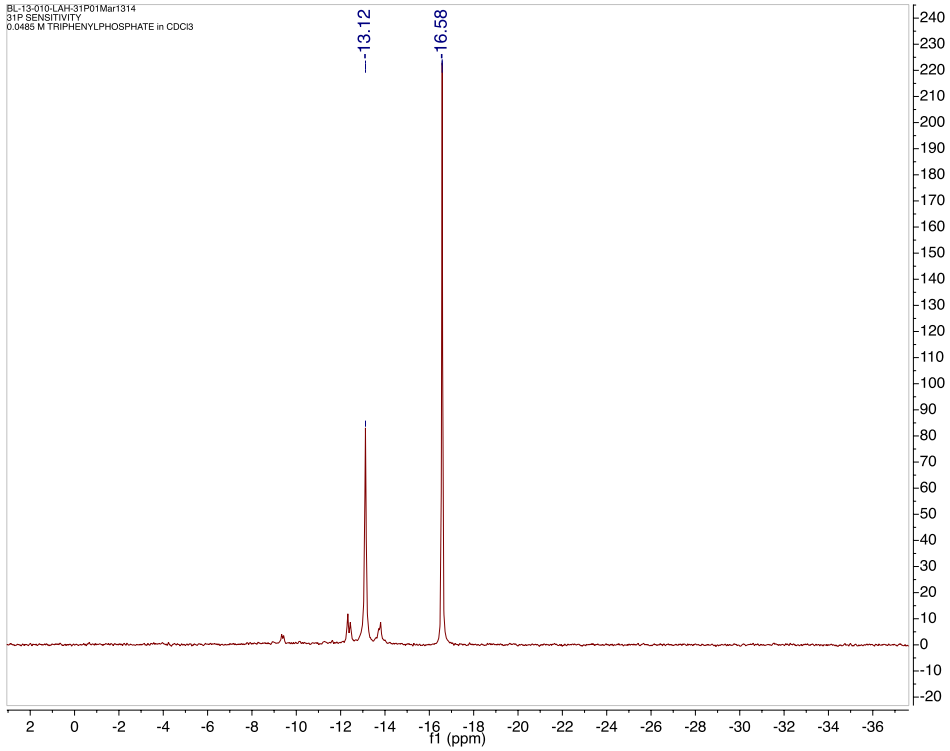
Compound **32** – $^{1}$H NMR



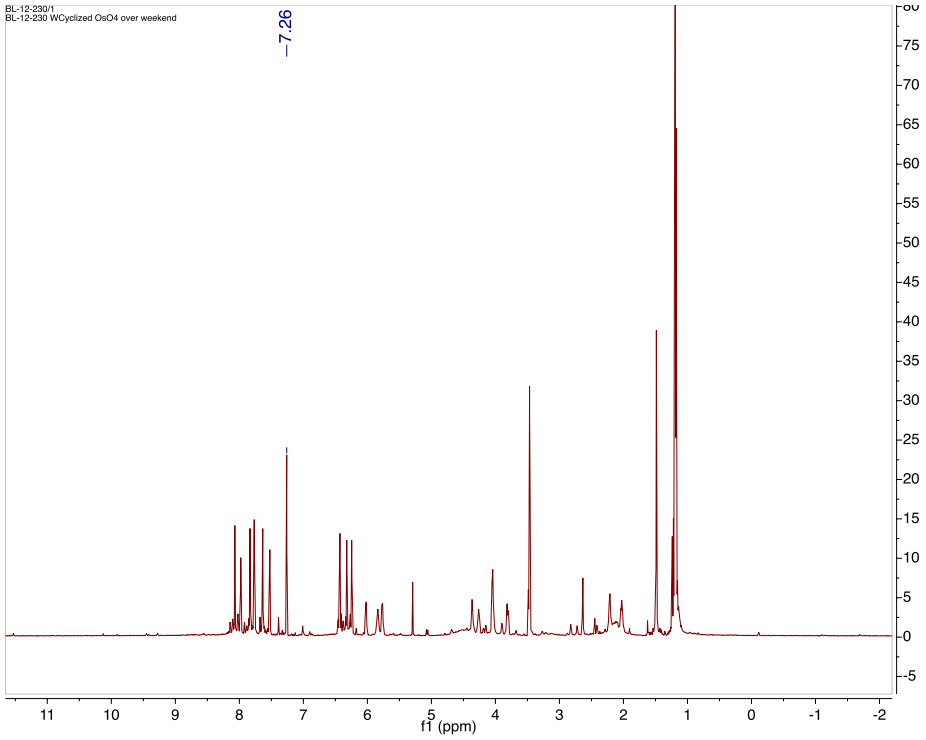

Compound **32** - $^{13}$C NMR



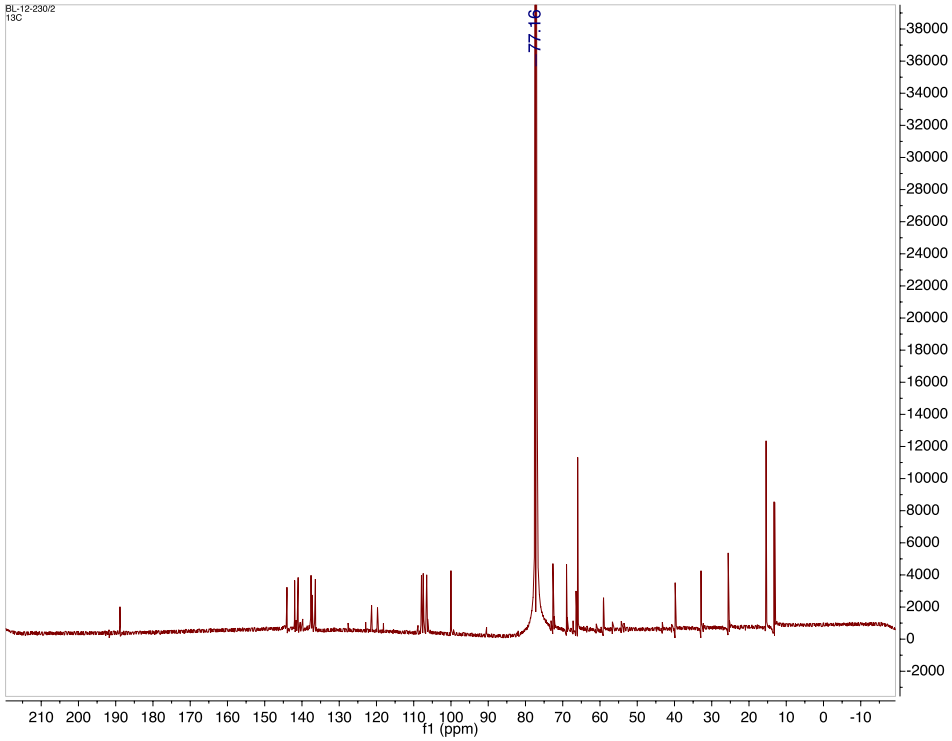
Compound **32** - $^{31}$P NMR



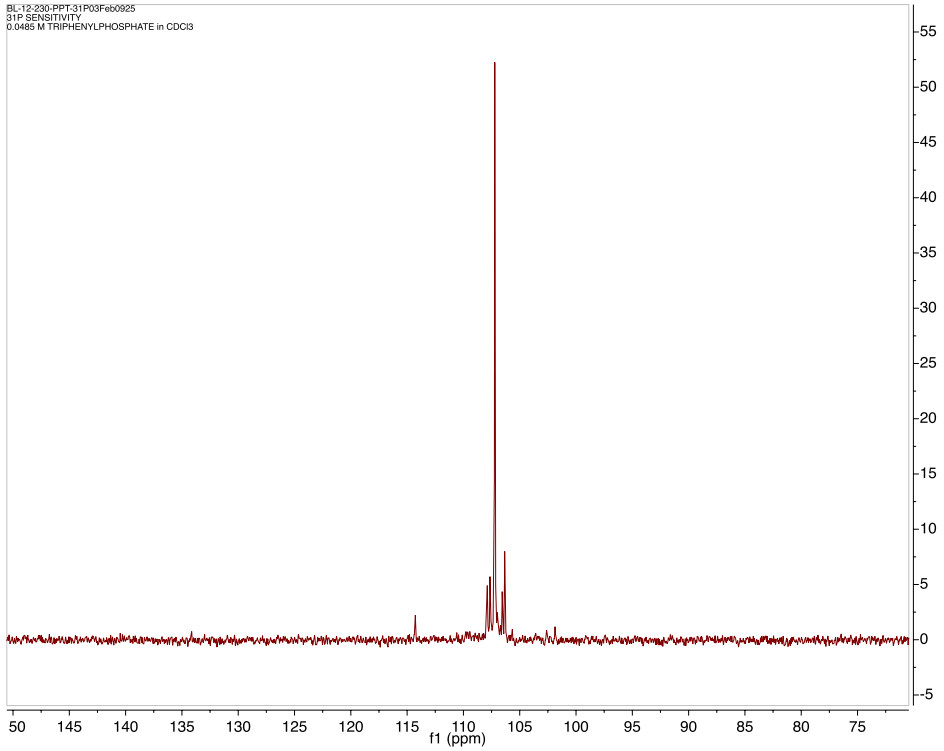
Compound **34** – $^{1}$H NMR



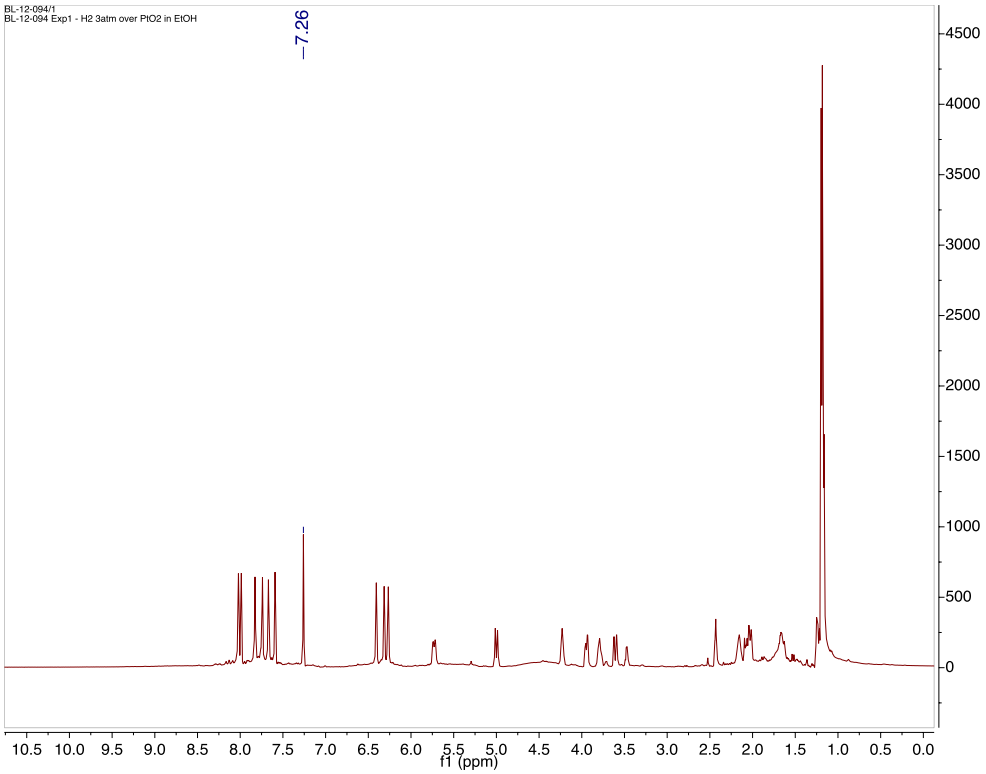

Compound **34** – $^{13}$C NMR



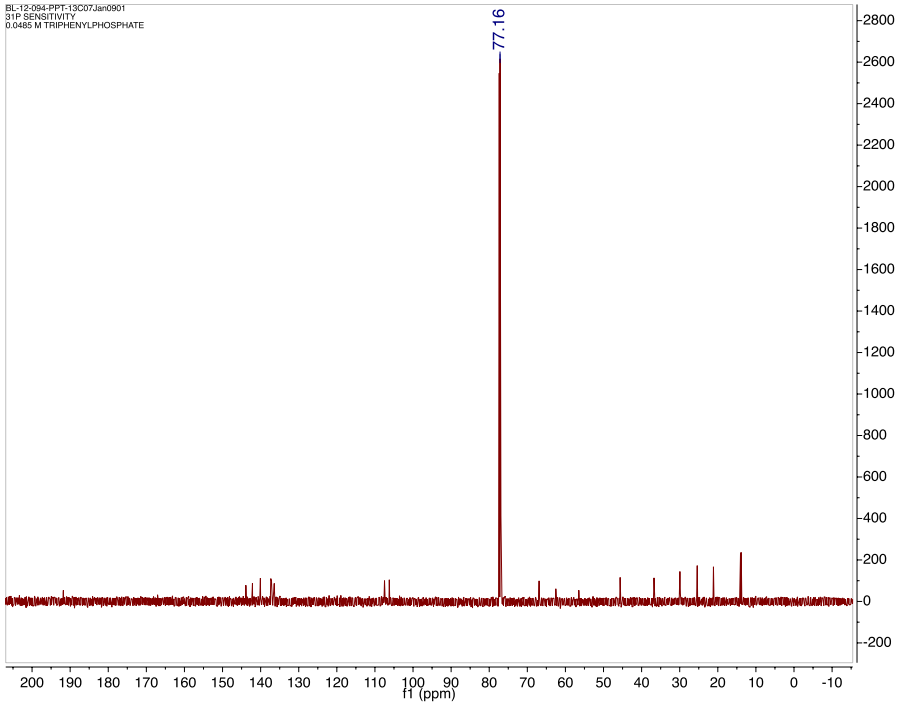
Compound **34** – $^{31}$P NMR



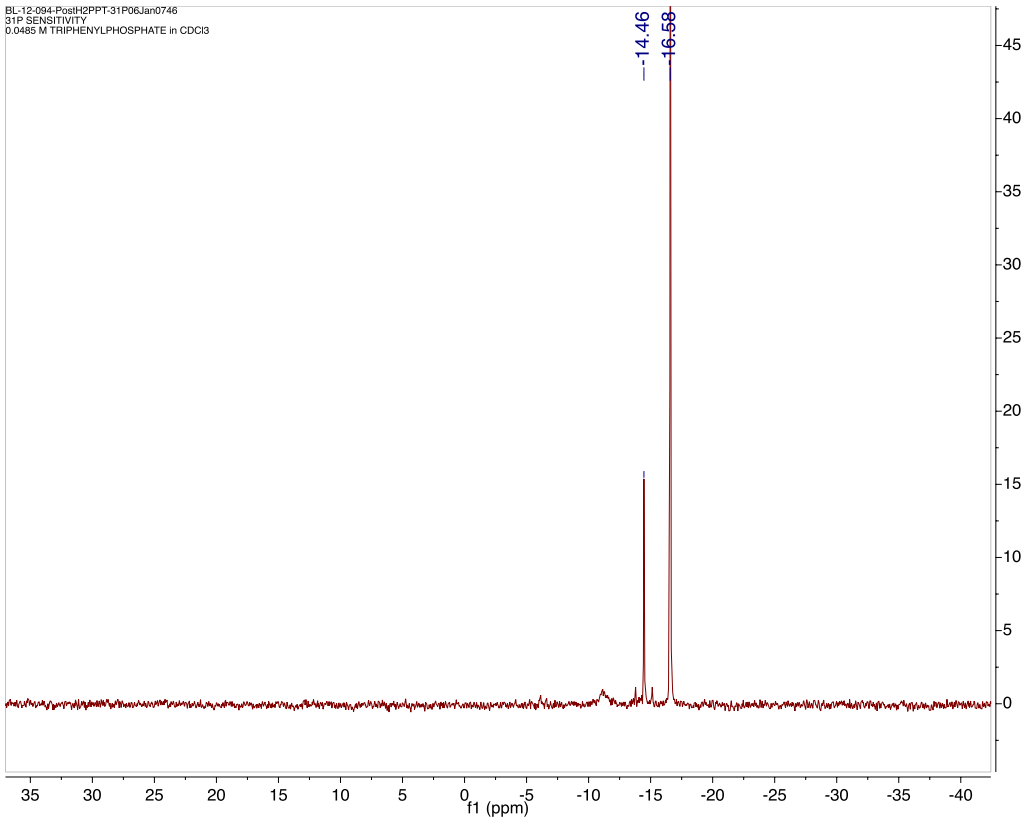
Compound **35** – $^{1}$H NMR



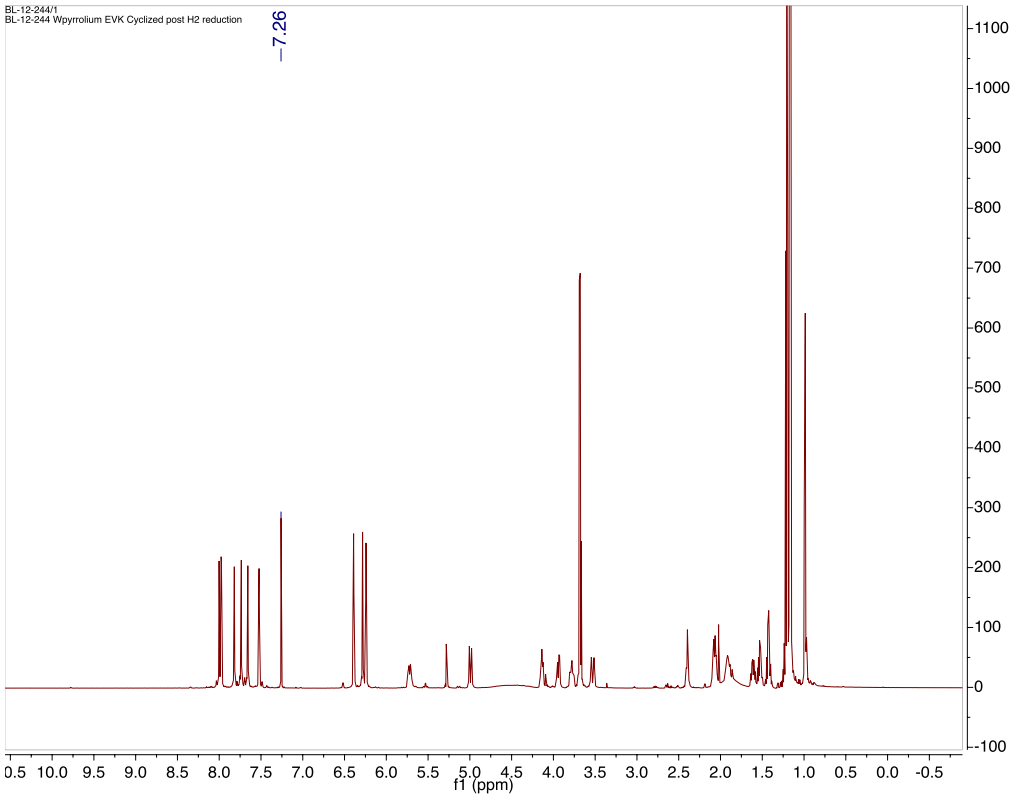

Compound **35** – $^{13}$C NMR



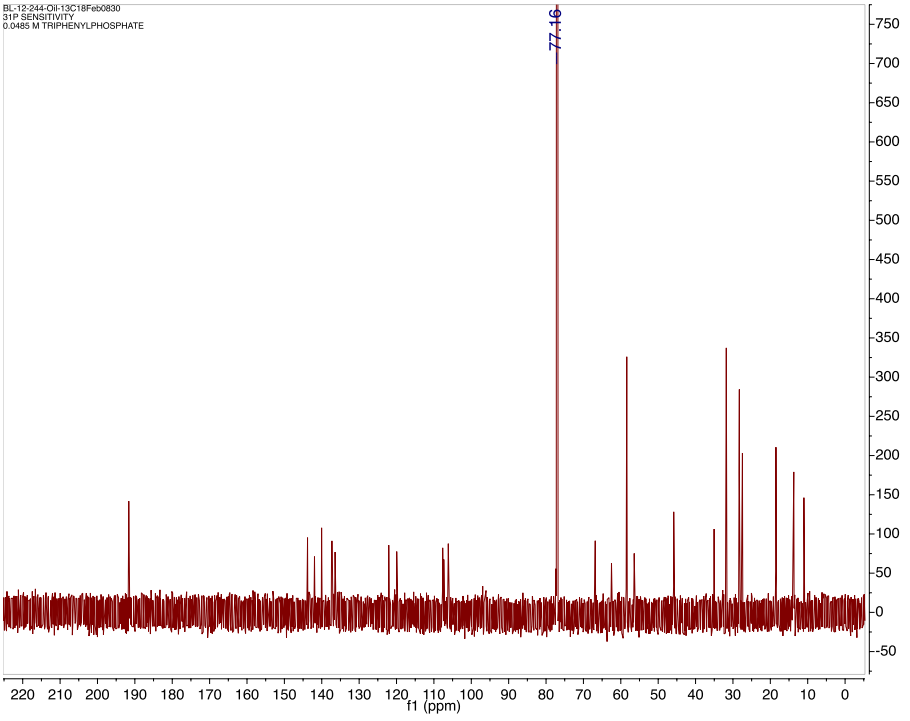
Compound **35** – $^{31}P$ NMR



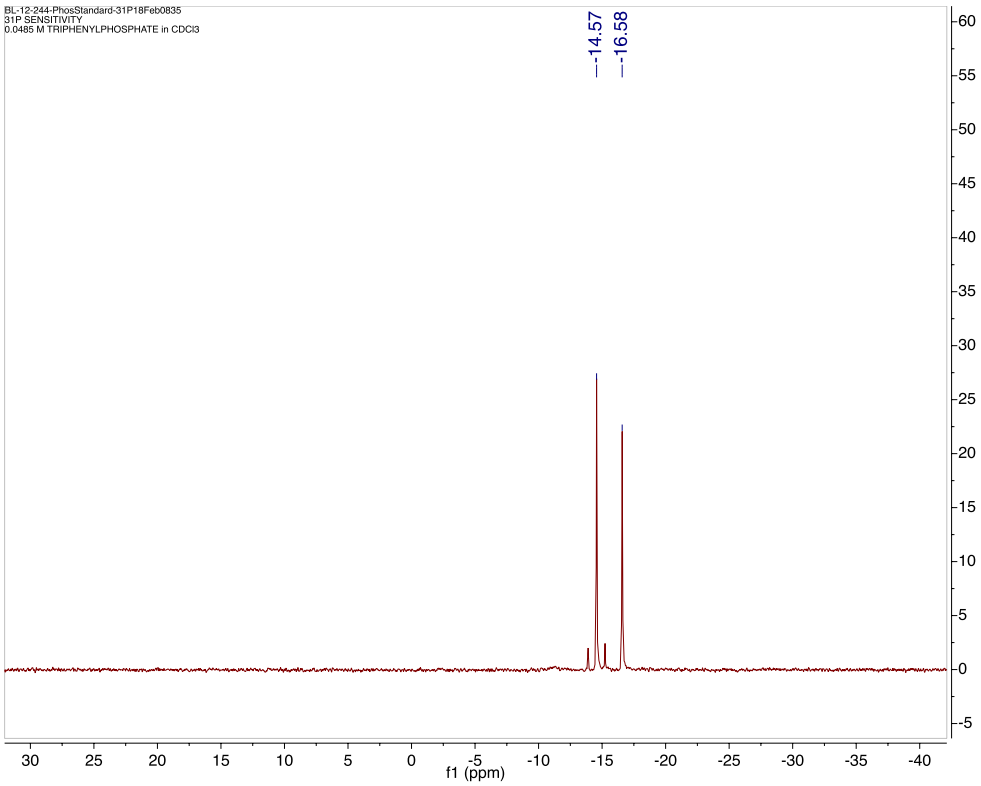
Compound **37** – $^{1}$H NMR



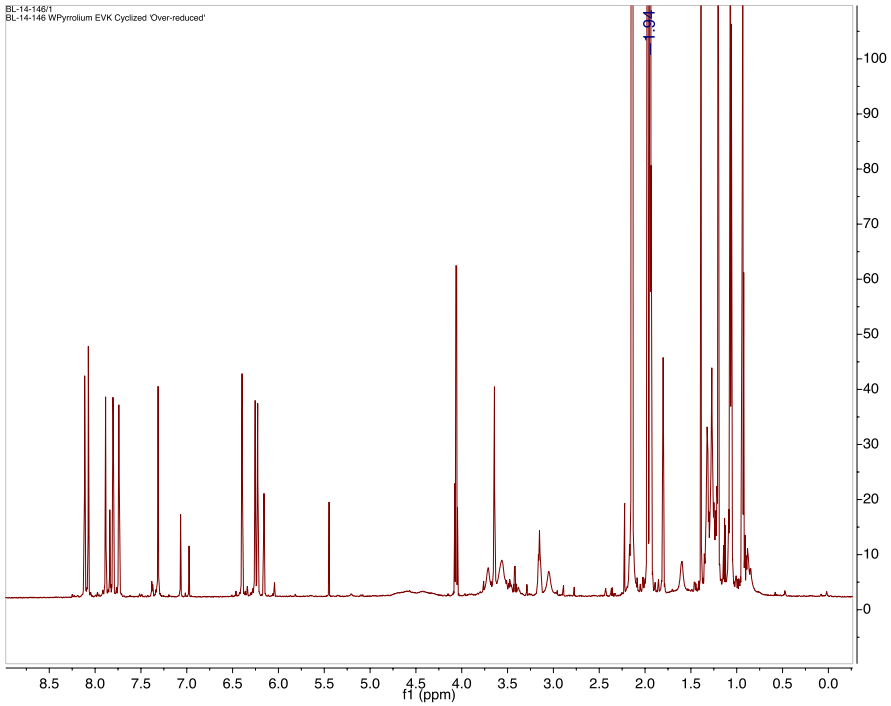

Compound **37** – $^{13}$C NMR



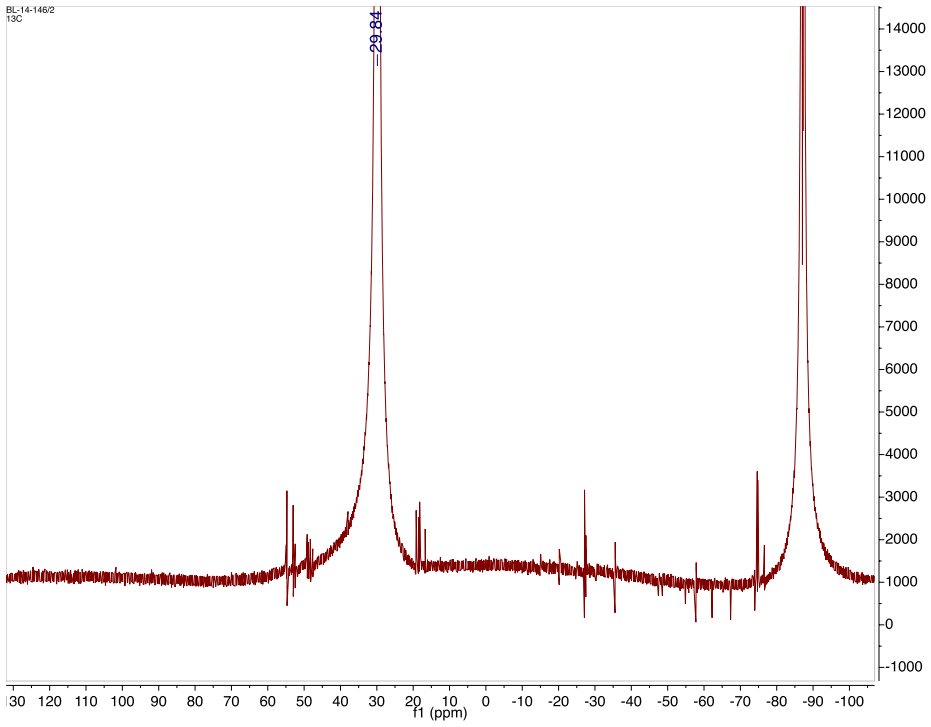
Compound **37** – $^{31}$P NMR



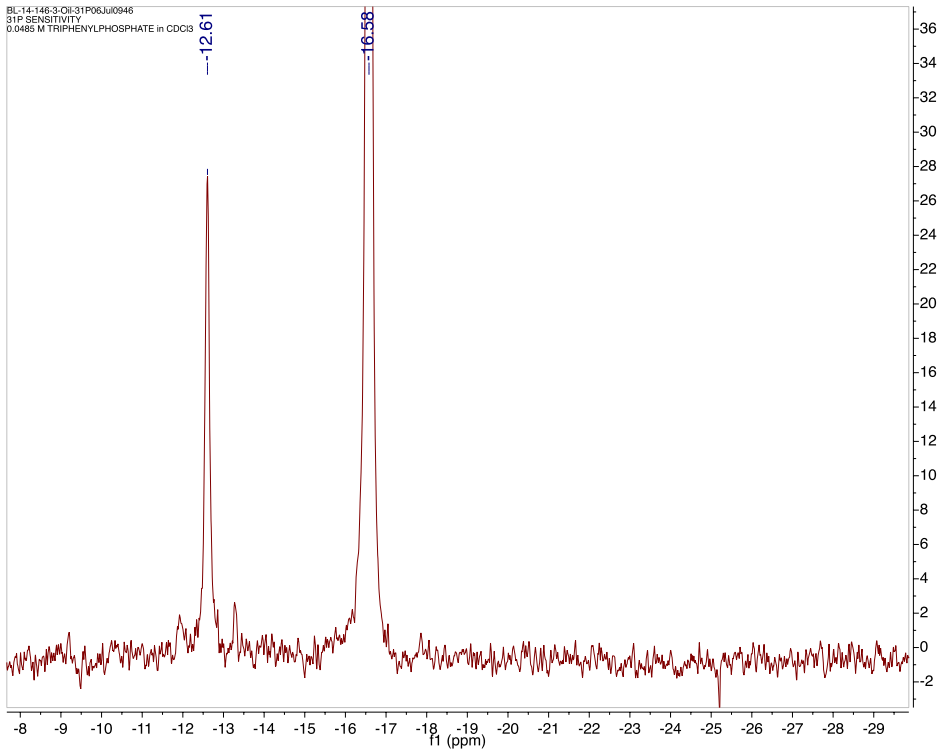
Compound **38** – $^{1}$H NMR



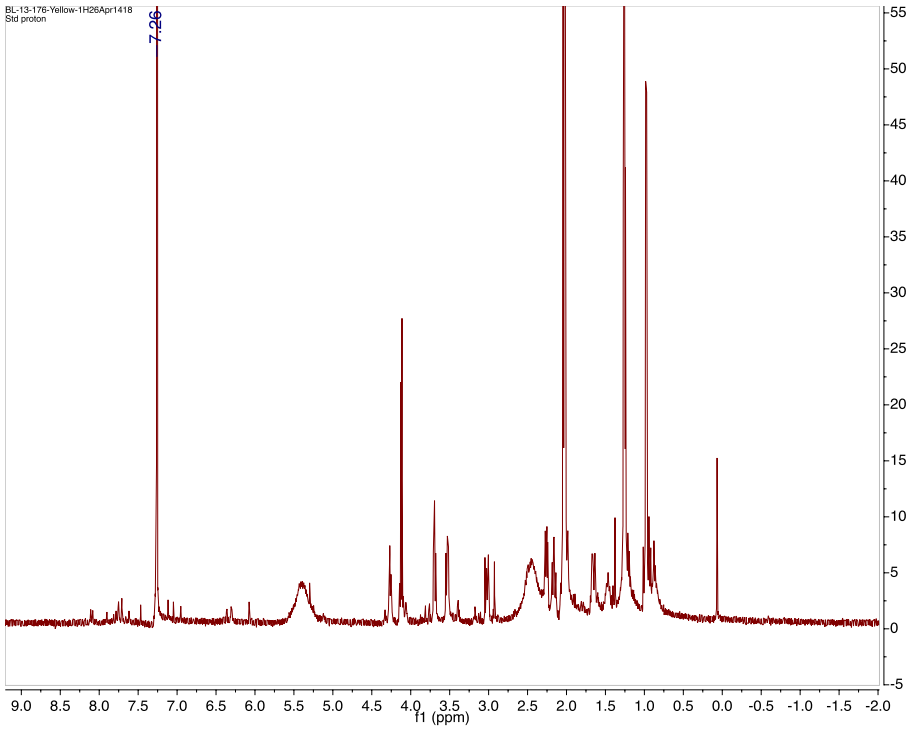

Compound **38** - $^{13}$C NMR



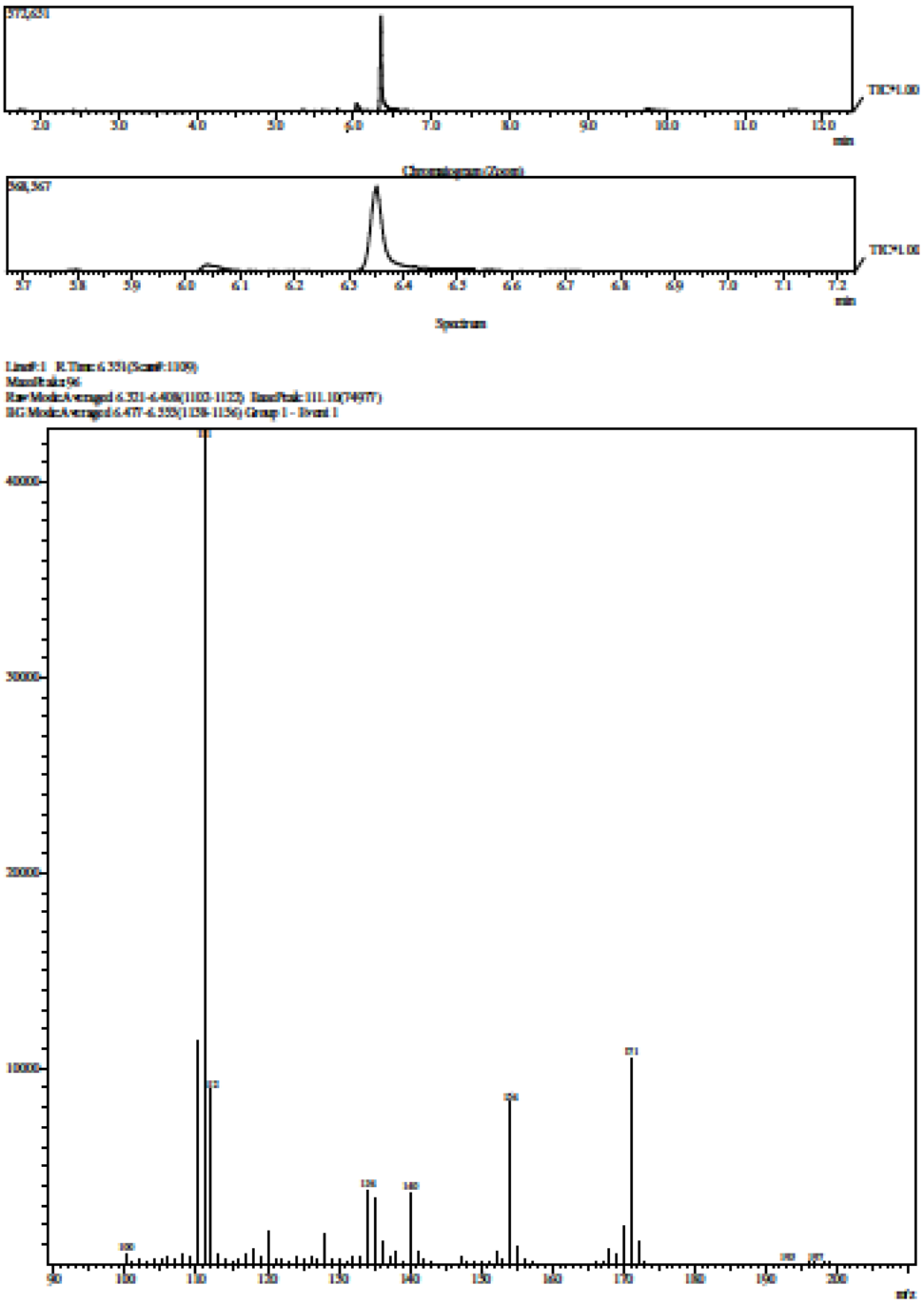
Compound **38** - $^{31}$P NMR



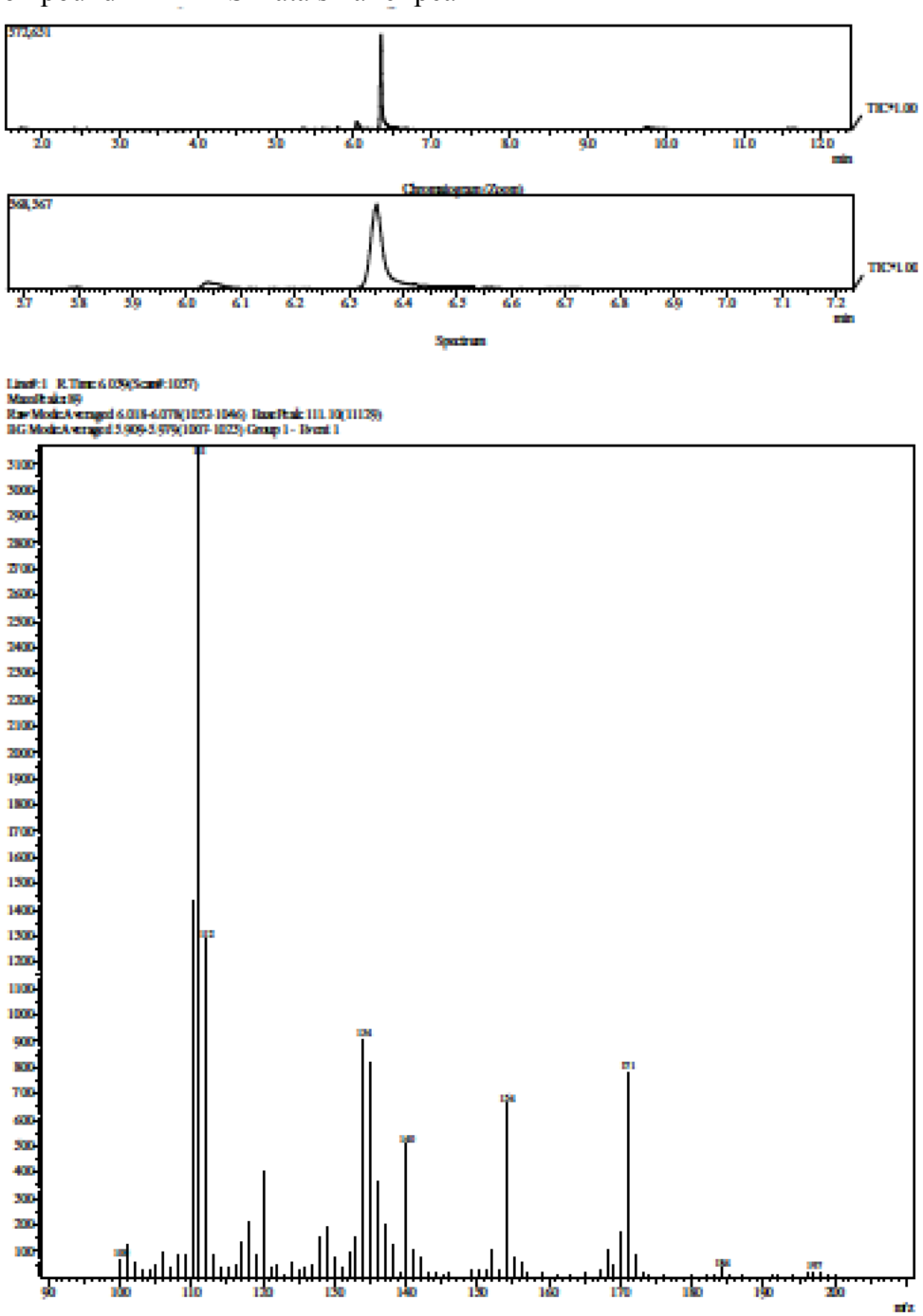
Compound **41** – $^{1}$H NMR



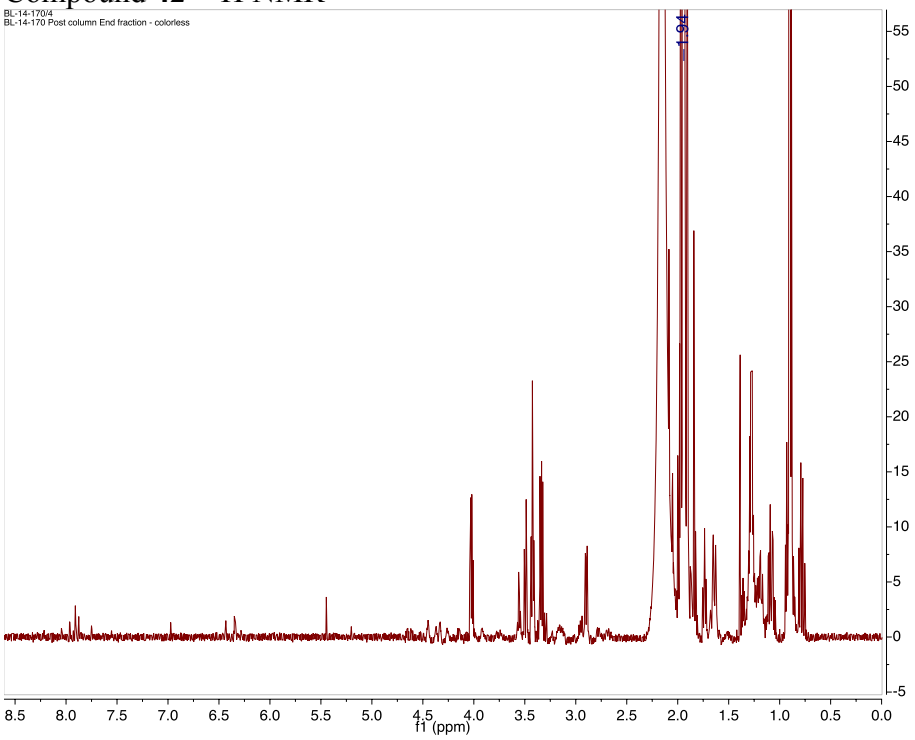
Compound **41** LRMS Data larger peak



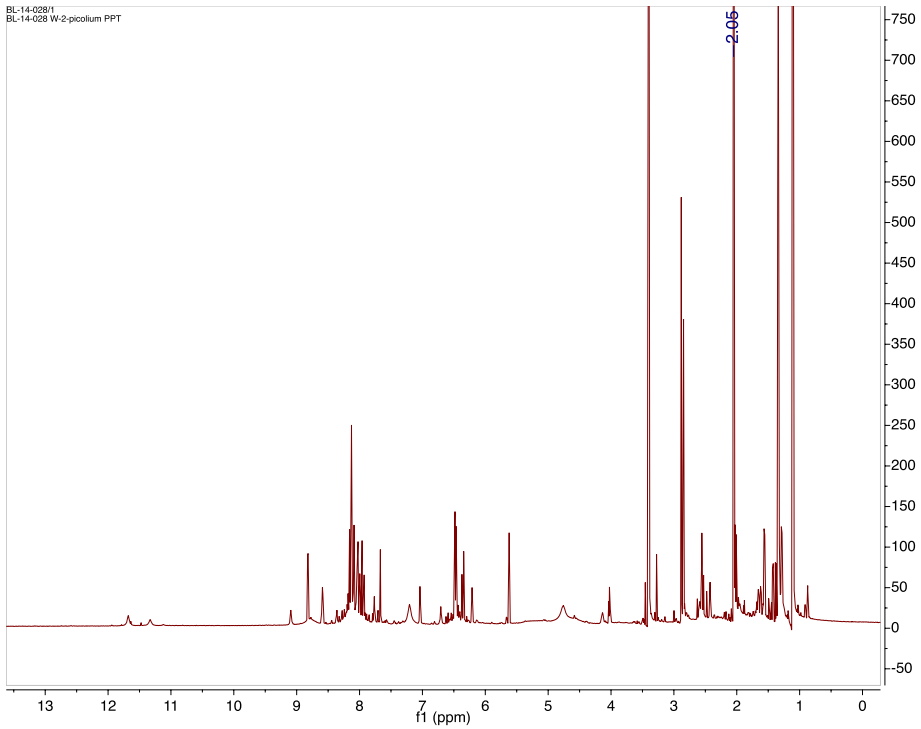
Compound **41** LRMS Data smaller peak



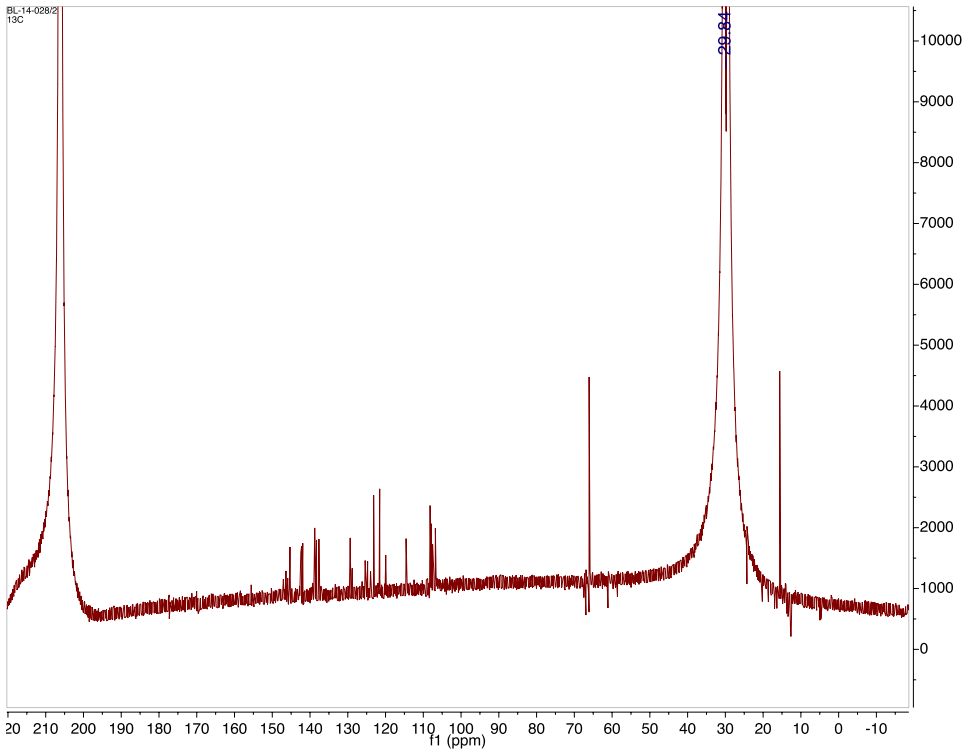
Compound **42**– $^{1}$H NMR



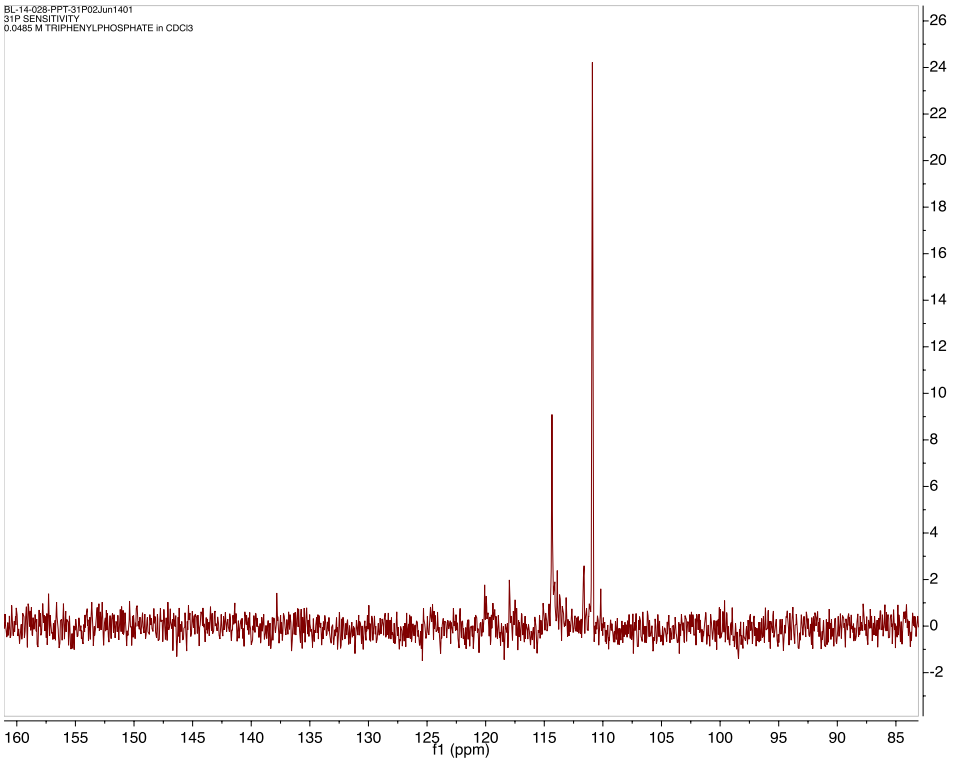
Compound **45A** impure – $^{1}$H NMR



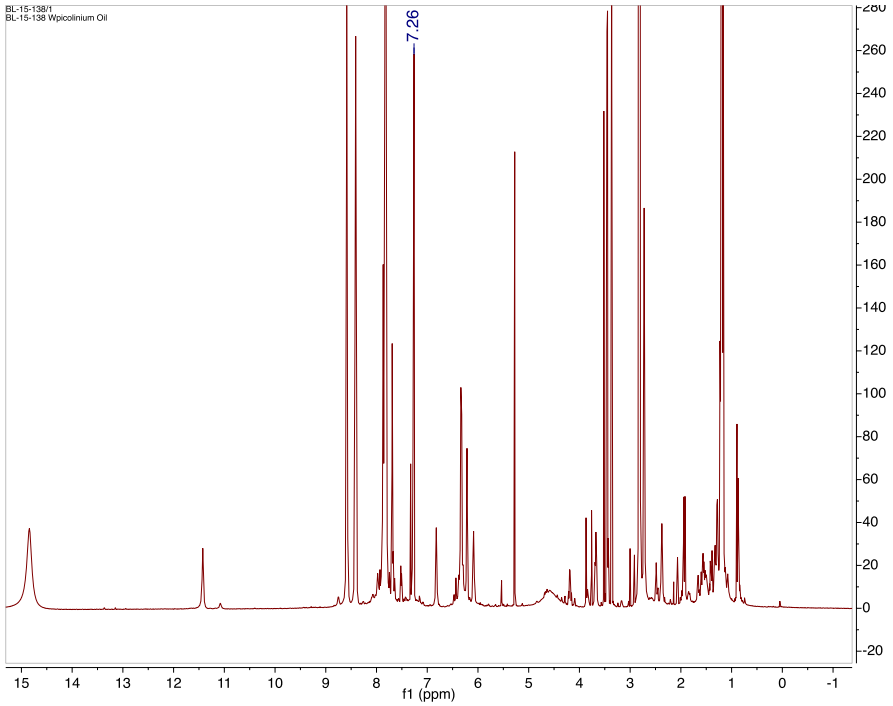

Compound **45A** impure – $^{13}$C NMR



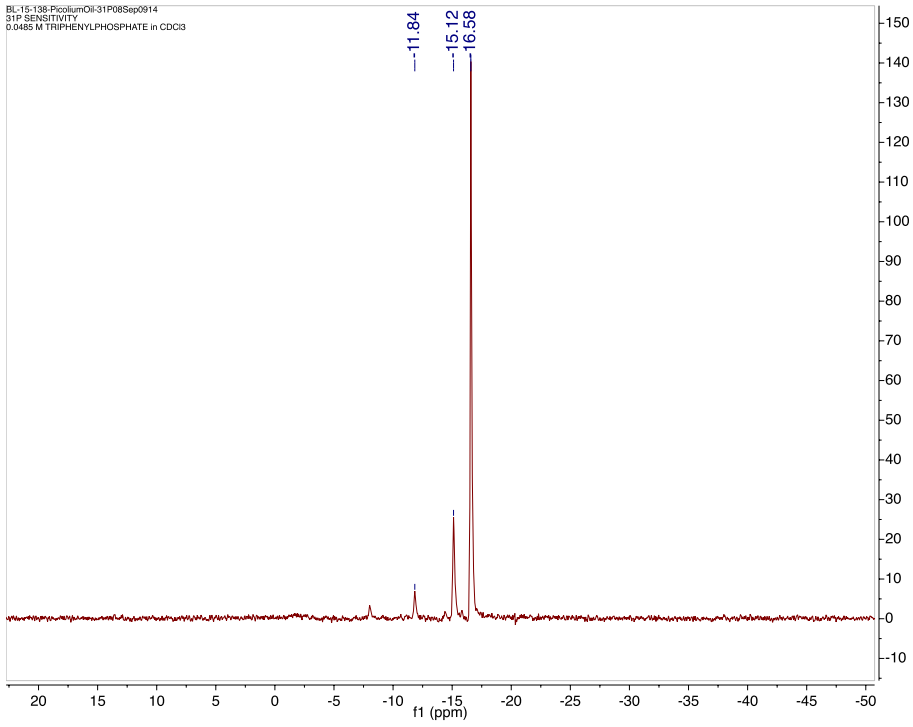
Compound **45A** – $^{31}$P NMR



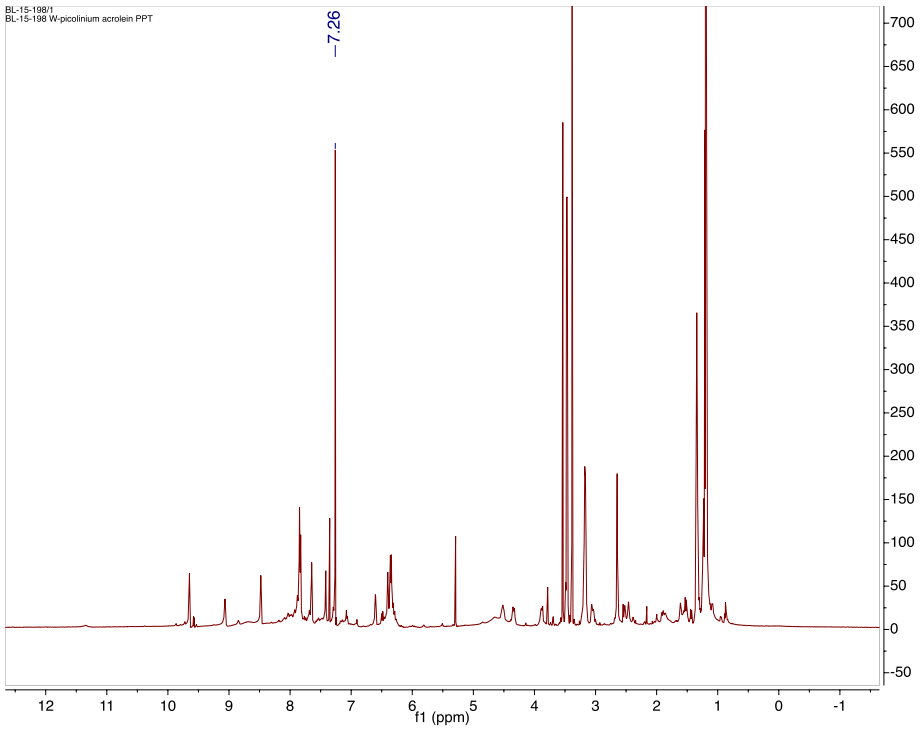
Compound **45C** or **45D** impure – $^{1}$H NMR



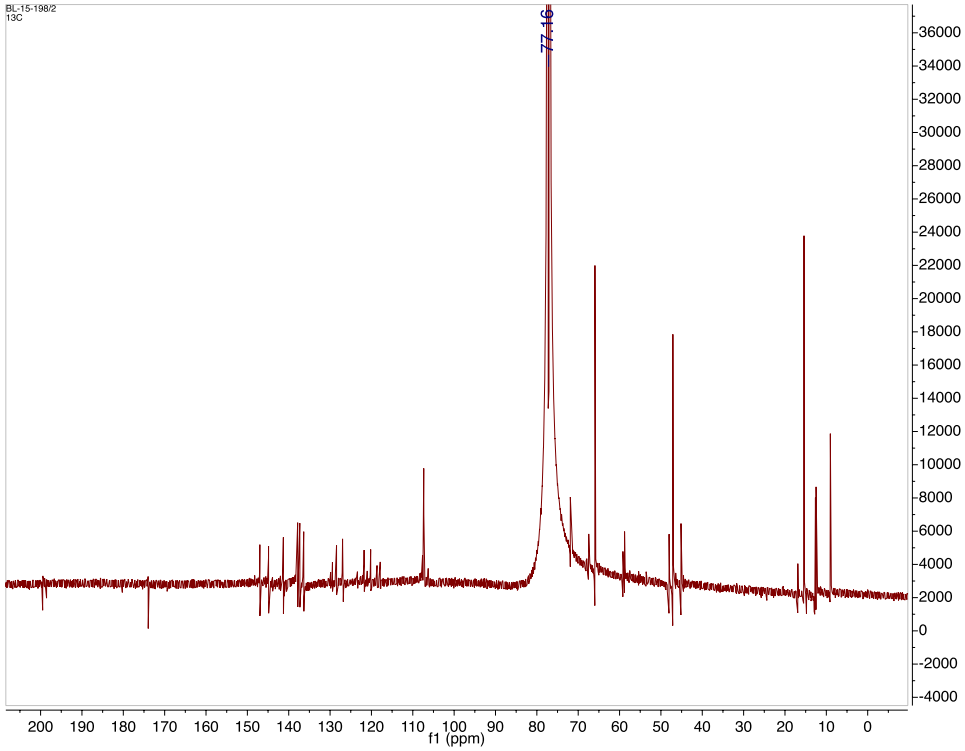

Compound **45C** or **45D** impure – $^{31}$P NMR



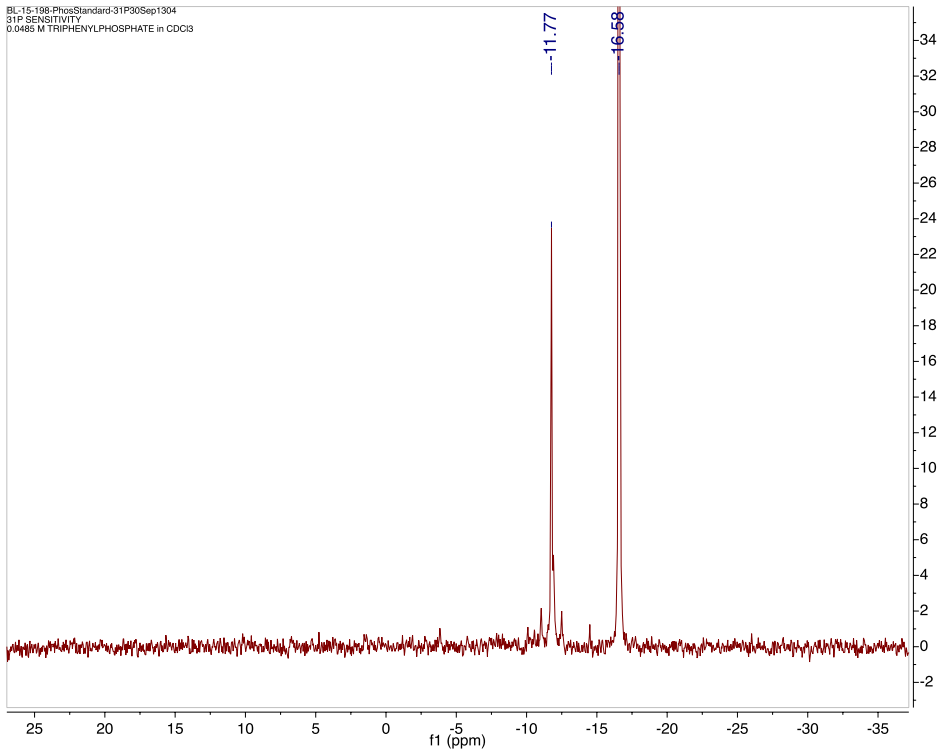
Compound **47** – $^{1}$H NMR



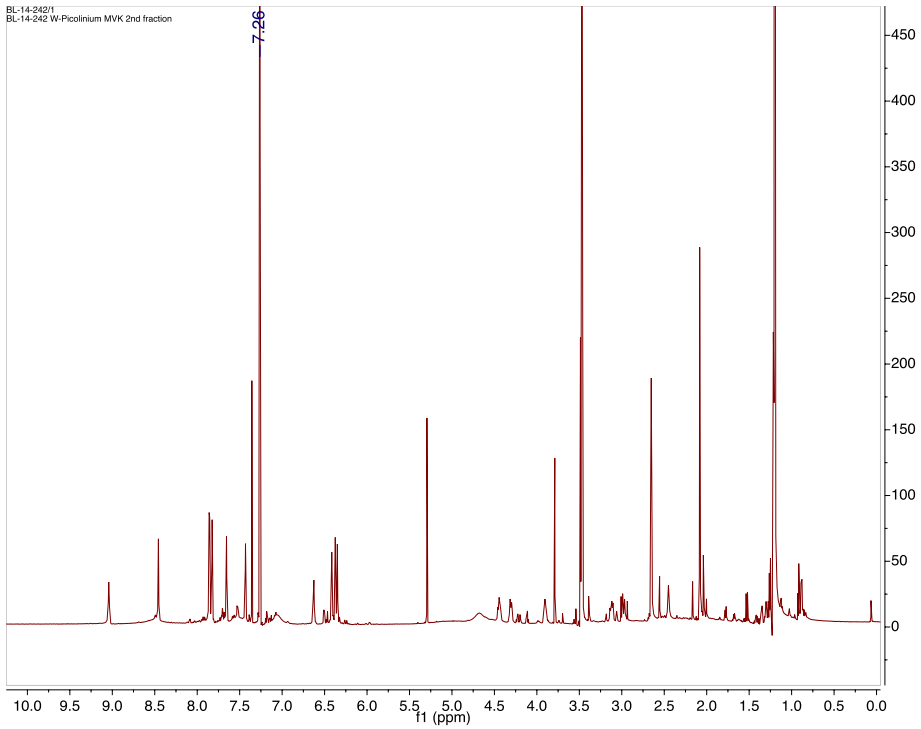

Compound **47** – $^{13}$C NMR



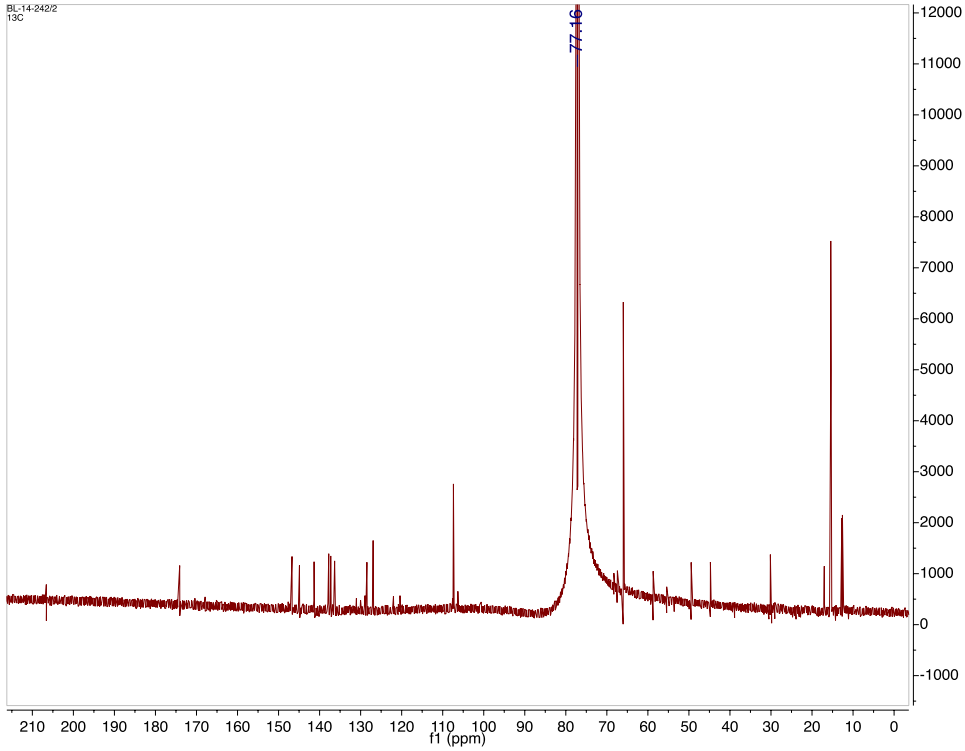
Compound **47** – $^{31}$P NMR



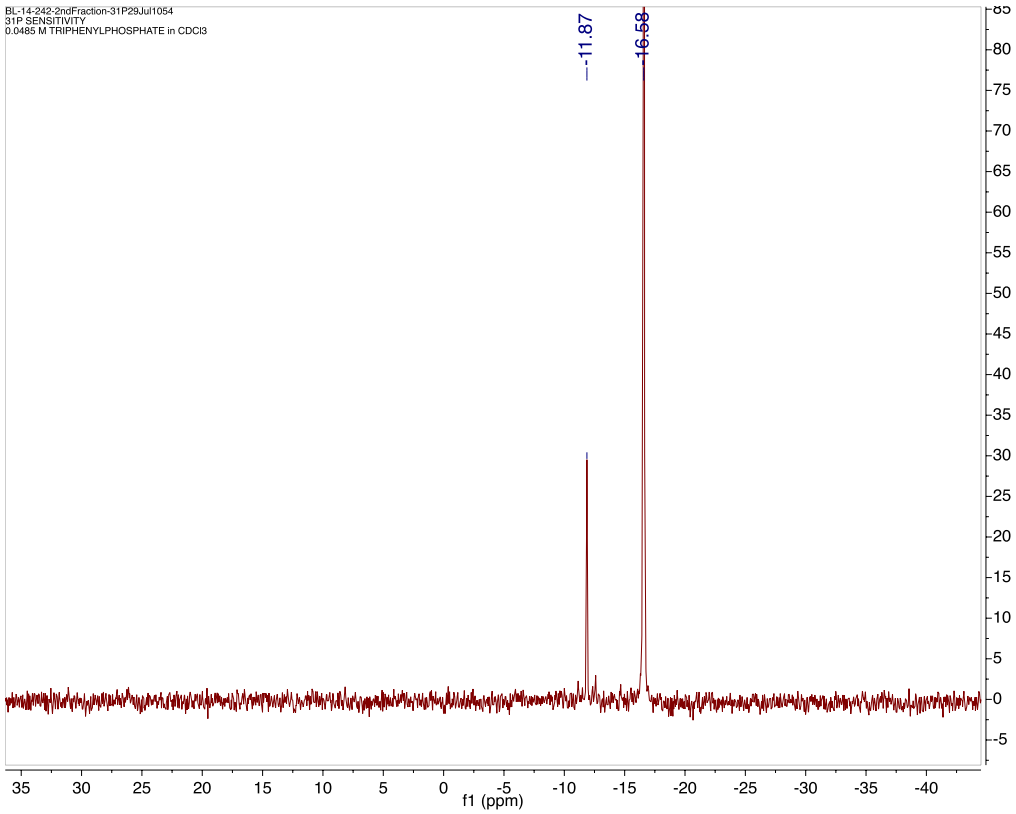
Compound **48** – $^{1}$H NMR



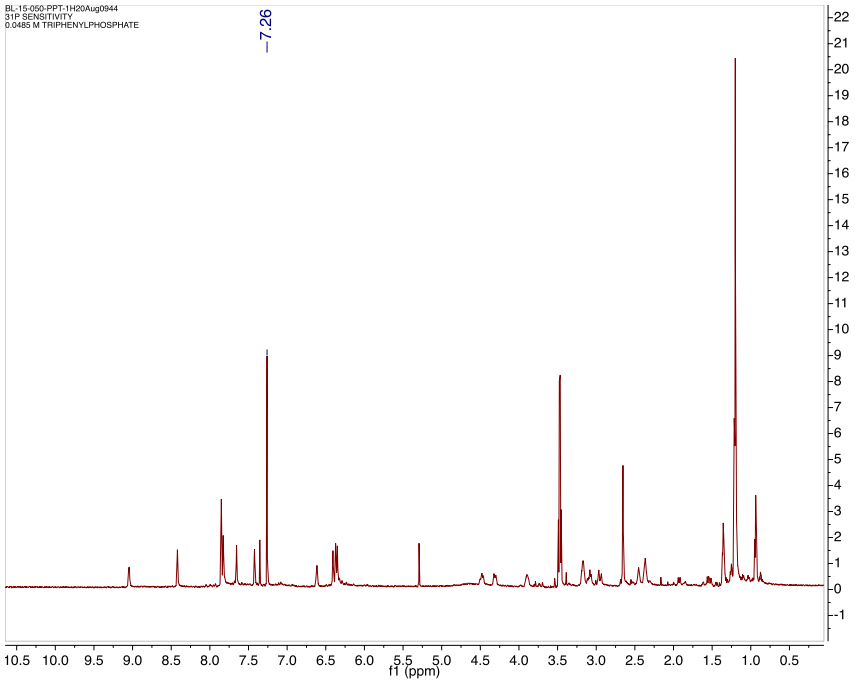

Compound **48** – $^{13}$C NMR



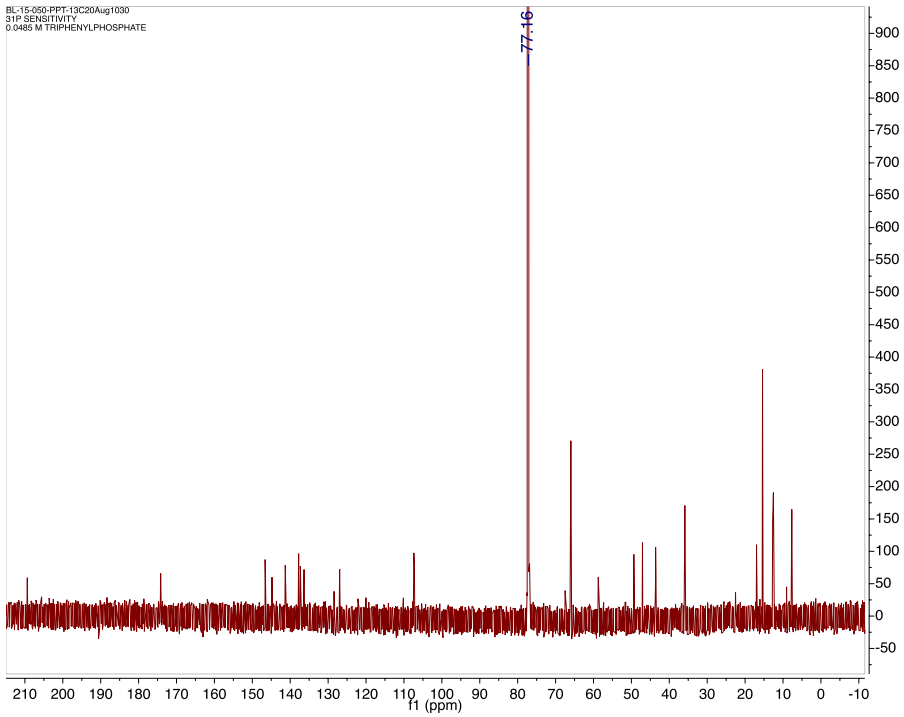
Compound **48** – $^{31}P$ NMR



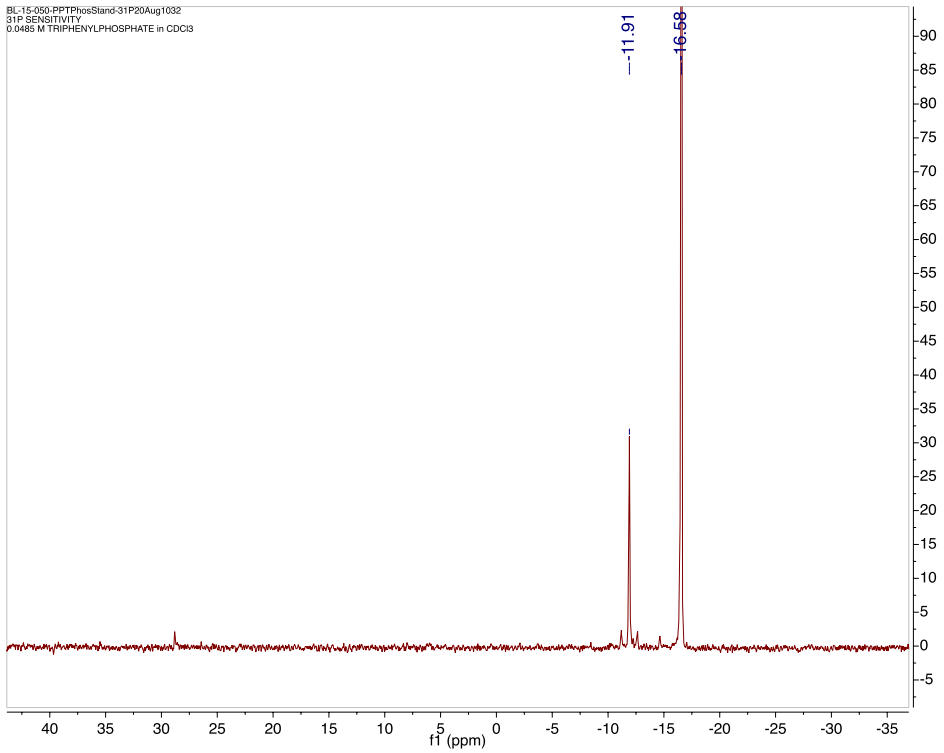
Compound **49** – $^{1}$H NMR



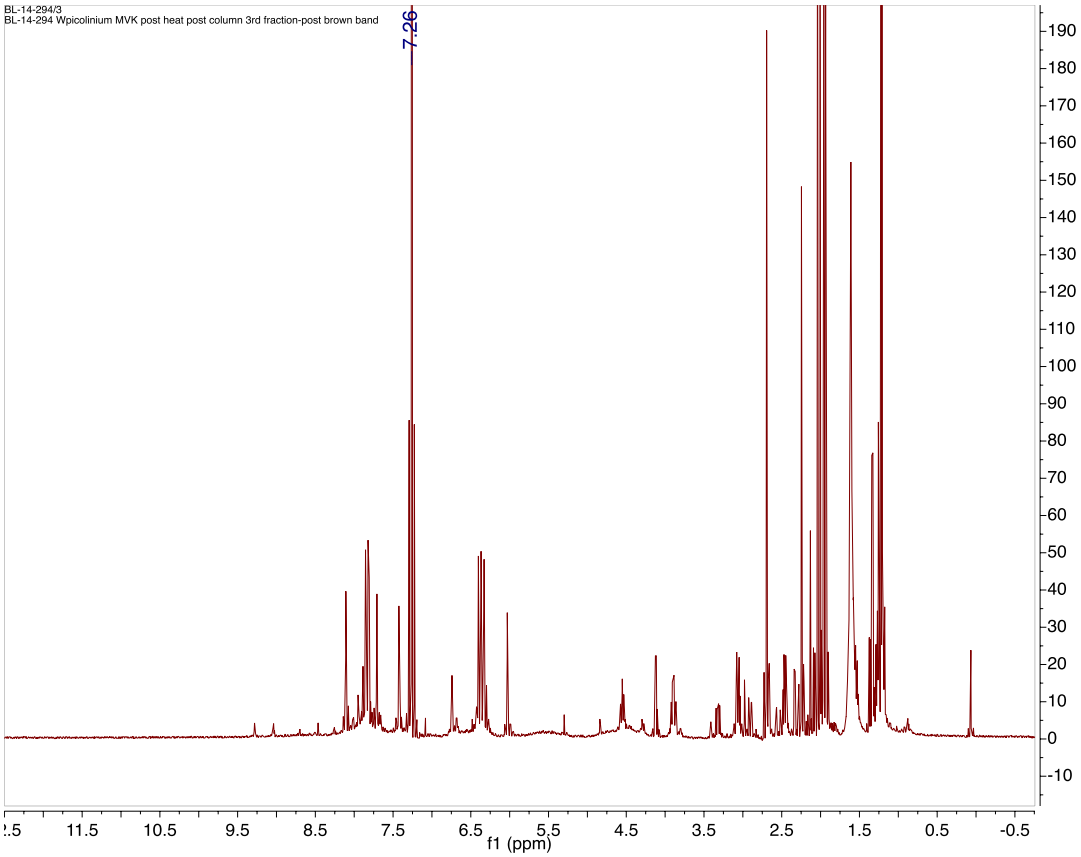

Compound **49** – $^{13}$C NMR



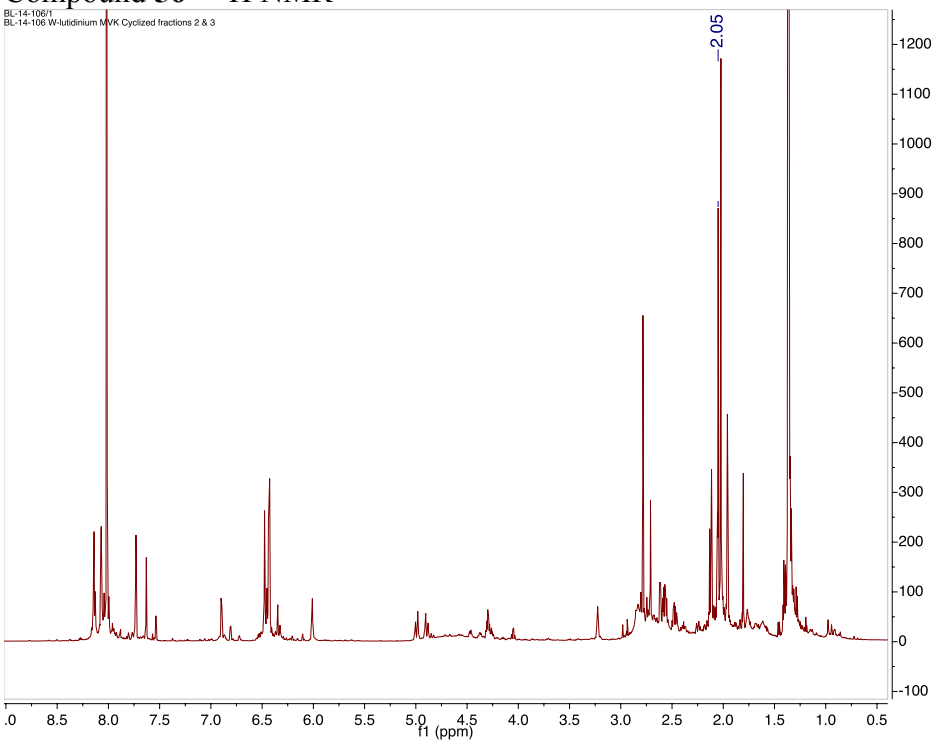
Compound **49** – $^{31}$P NMR



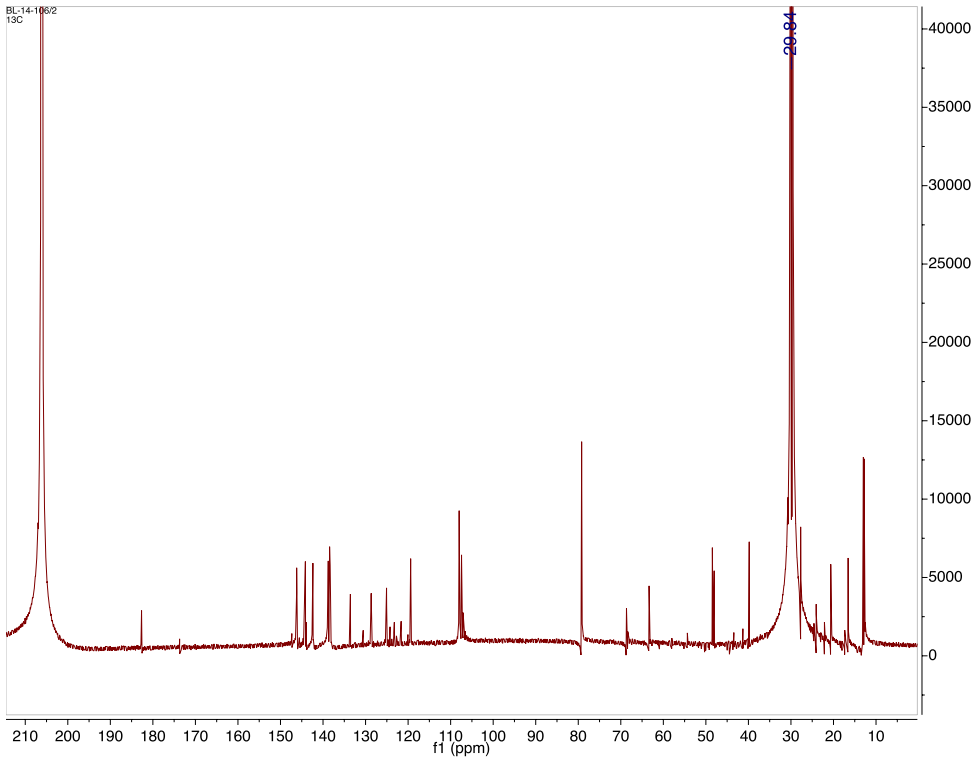
Compound **50** – $^{1}$H NMR



Compound **56** – $^{1}$H NMR




Compound **56** – $^{13}$C NMR



Compound **56** – $^{31}$P NMR