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Studies directed Towards the Iridium Catalyzed Synthesis of New Carbon-Nitrogen Bonds.

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Studies directed Towards the Iridium Catalyzed Synthesis of New Carbon-Nitrogen Bonds

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
Chemistry

by

Maria Lindsay
B.S., Chemistry, Minnesota State University, Moorhead, 2010
May 2017
To my loving husband Kent,
I could not have completed this journey without you.
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Abstract

Amines are ubiquitous in nature and serve a variety of functions in living organisms. Because of this fact amines are of great biological and pharmaceutical interest. The iridium catalyst (pentamethylcyclopentadienyl) iridium dichloride dimer ([Cp*IrCl₂]₂) has been used in a number of ways to synthesize new carbon-nitrogen bonds. These studies were directed toward the development of a method for the iridium catalyzed N-alkylation of alpha-amino acid esters as well as the development of a strategy for synthesis of the natural product Lehmizidine 275A.

We have optimized a method for the N-alkylation for alpha-amino acid esters. Using this method, we have N-alkylated a series of alpha-amino acid esters with a variety of alcohols. We have shown that the N-alkylation of the alpha-amino acid esters works consistently and gives the desired products in moderate to high yields. We have examined the effect of this method on the chiral center of the obtained products by analyzing their optical rotation. Evaluation of these specific rotations indicated racemization was occurring but it is believed that any loss of the chiral center is due to the reaction conditions.

Amphibian alkaloids are of great interest to the pharmaceutical and academic communities due to their biological activities. Unfortunately, they are not naturally available in large quantities which makes total synthesis the most common method of generating these compounds for evaluation. One amphibian alkaloid class of interest to us are the Lehmizidines. These are bicyclic ring structures consisting of a 7-member and 5-member ring with a nitrogen bridgehead. The alkaloid, Lehmizidine 275A, was selected as a target for a general synthetic approach. This synthetic approach required the synthesis of novel diols. The construction of these diols along with a method for the synthesis of the azepane ring is presented here.

Keywords: Iridium, catalysis, N-alkylation, alpha-amino acid esters, diols, lehmizidine, N-heterocyclization
Chapter 1: Introduction

1.1. Amines

The International Union of Pure and Applied Chemistry defines an amine as a “compound formally derived from ammonia by replacing one, two or three hydrogen atoms by hydrocarbyl groups, and having the general structures RNH₂ (primary amines), R₂NH (secondary amines), R₃N (tertiary amines).”¹ Amines are ubiquitous in nature; serving a variety of functions in living organisms, some of which include bioregulation, neurotransmission, and defense against predators. A majority of nitrogen-containing compounds that are of biological significance are also pharmaceutically important. Drugs are designed based on their ability to imitate or obstruct the actions of natural amine compounds produced by the body (Figure 1).

![Chemical structures of morphine, oxycodone, met-enkephalin, prozac, zoloft, and serotonin](image)

**Figure 1:** Examples of synthetic and naturally produced amine compounds.

Synthetic opioids (morphine or oxycodone) prescribed for pain mimic the natural opioids (endorphins or enkephalins)² produced by the body enough to stimulate their receptors.³ Prozac or Zoloft are examples of compounds that obstruct the actions of an amine compound produced by the body. These compounds are known as selective serotonin re-uptake inhibitors (SSRIs)
and are used in the treatment of depression. They target the transport protein that removes serotonin from the synapse (the space between neurons) and returns it to the sending neuron. As long as a SSRI is occupying the transporter, serotonin cannot return to the sending neuron. This means the concentration of serotonin will build up in the synapse where it will stimulate more receiving neurons and produce a much larger serotonin impact than would occur in the absence of these compounds.²

Alpha-chiral amines are those having a stereogenic center on the carbon immediately next to the nitrogen. A stereogenic center is an atom (usually a carbon) whose substituents are all different.⁴ Many alkaloids and natural products contain alpha-chiral amines (Figure 2). Amino acid esters can be used as building blocks in the synthesis of these more complex structures as they already possess the desired functional group.

![Figure 2: Example of an Alpha-chiral amine and compounds containing this functional group.](image)

1.2. Traditional Synthesis of Amines

Ammonia is directly or indirectly the basic building block for all amines. So while only a minority of the ammonia produced on an annual basis is used for the synthesis of more complex amines this “minor amount” still adds up to several million tons of amine products.⁵ Amines are used in a variety of other industries as well. They are present in the synthesis of dyes, polymers⁴, electrodes for organic electronics⁶ and are used in the capture of CO₂ at fossil fuel plants.⁷ They are also used as intermediates in the synthesis of agricultural chemicals, animal nutrients, and surfactants.⁸

1.2.1. Ammonia and alcohol

The reaction of ammonia with alcohols is one of the most common industrial methods for the production of small alkyl amines. One of the reasons this process is so popular is that the amination of alcohols affords water as the only by-product. However, the reaction temperature
and pressure can vary quite significantly depending on what alcohols or catalysts are being used and sometimes a mix of products (primary, secondary, and tertiary amines) are obtained. One such example of this is the industrial synthesis of methyamine from methanol and ammonia. These reagents are combined over an alumina-oxide catalyst at temperatures ranging from 300-500°C and pressures between as high as 15-30 bar (Scheme 1).

\[
\begin{align*}
\text{NH}_3 & \quad + \quad R-OH \quad \xrightarrow{\text{catalyst}} \quad \text{-H}_2\text{O} \quad \rightarrow \quad R-NH_2 & \quad + \quad R-NH & \quad + \quad N-R
\end{align*}
\]

**Scheme 1:** General synthesis of amines from ammonia and methanol

### 1.2.2. Alkyl and aryl halides

This reaction proceeds through an S\text{N}2 reaction to produce the final product. However, since both the starting material (ammonia) and the product (the amine) are nucleophilic they compete to react with the alkyl halide. This results in a product that is a mixture of primary, secondary, and tertiary amines unless a large excess of ammonia is used. This reaction is problematic not only because equimolar amounts of the ammonium salt are produced that can be an issue to deal with on the large scale, but the alkyl halide reagents used are often quite toxic (Scheme 2).

\[
\begin{align*}
X \quad \text{CH}_2 & \quad + \quad \text{excess NH}_3 \quad \rightarrow \quad \text{H}_2\text{N} \quad \text{CH}_2 & \quad + \quad \text{NH}_4^+ \quad \text{X}^- & \quad + \quad \text{NH}_3
\end{align*}
\]

**Scheme 2:** General synthesis of amines from alkyl halides and ammonia.

### 1.2.3. Reductive amination

This two-step reaction is one of the most frequently used methods of synthesizing secondary and tertiary amines. It involves the treatment of a carbonyl compound with a hydroxylamine to form an imine intermediate. The imine intermediate can then be reduced with a variety of reagents as demonstrated in **Scheme 3** to produce the final amine. While this reaction is incredibly useful some of its reagents could be considered unsuitable for large scale reactions. For example, lithium aluminum hydride produces heat, aluminum salts and hydrogen gas on workup, so care needs to be taken when scaling up this reaction. Sodium cyanoborohydride is toxic and produces toxic byproducts like cyanide and sodium cyanide. It
can be replaced with sodium triacetoxyborohydride but this compound is water sensitive so care must be taken in that aspect. 

1.3. Hydrogen Transfer or the “Borrowing Hydrogen” Methodology

One of the more recent procedures that has come into use for the synthesis of amines is the “borrowing hydrogen” method. This method employs an organo-metallic transition metal catalyst. The catalyst removes or “borrows” two hydrogens from the alcohol. This oxidation of the alcohol to a carbonyl allows it to react with the amine where it undergoes a condensation reaction to produce an imine. The catalyst then gives the hydrogens it has been “borrowing” to the imine. This action serves to hydrogenate the imine which produces the desired amine product and to regenerate the catalyst. A general mechanism for this catalytic cycle is shown in Figure 3. 

Figure 3: General borrowing hydrogen mechanism
In 1981, Grigg et al demonstrated the first use of a homogeneously catalyzed version of this methodology to when they used rhodium to N-alkylate pyrrolidine and primary amines in yields ranging from 37-98%. They also showed that in addition to rhodium, ruthenium and iridium based catalysts could be used to perform the same transformations (Scheme 4).\textsuperscript{11}

\begin{equation}
\text{NH} + \text{H}_2\text{C}−\text{OH}_\text{excess} \xrightarrow{[\text{RhH}(\text{PPh}_3)_4] \text{(5 mol\%)} \text{reflux, 4h}}} \text{N}−\text{CH}_3
\end{equation}

\textit{Scheme 4: Review of Grigg et al. - Ru-catalyzed synthesis of N-methylpyrrolidine.}

In the years following this discovery others used a variety of ruthenium based catalysts in alcohol aminations, however, most of these systems required high temperatures (~180°C) and were limited to simple primary alcohols.\textsuperscript{12,13} One notable exception was the use of a ruthenium catalyst in the synthesis of indoles demonstrated in 1990 by Tsuji et al. They reported that their reaction worked without the need for a hydrogen acceptor as was noted by the spontaneous evolution of hydrogen over the course of the reaction (Scheme 5). In general, the yields of the indoles synthesized from 2-aminophenethyl and 2-nitrophenethyl alcohols were good to excellent, however, it was noted that the choice of solvent, temperature, or catalyst could have a marked effect on the yield. For example reactions run in toluene at 80°C only gave the indole in 30% yield.\textsuperscript{14}

\begin{equation}
\text{R}−\text{NH}_2 + \text{RuCl}_2(\text{PPh}_3)_3 \text{toluene, reflux, 6h} \rightarrow \text{R}−\text{N}−\text{H} + \text{H}_2\uparrow
\end{equation}

\textit{Scheme 5: Review of Tsuji et al. - Ru-catalyzed synthesis of indoles.}

1.4. Pentamethylcyclopentadienyl iridium dichloride dimer [Cp*IrCl\textsubscript{2}]

The use of this method for the N-alkylation of amines is attractive because it is often atom economical, it does not generate harmful byproducts and alcohols tend to be more readily available and are usually more economical to purchase than most corresponding alkyl halides or carbonyls. It has been shown that the iridium catalysts are more reactive\textsuperscript{15-17} than the ruthenium catalysts and so they are preferred for most N-alkylations. The catalyst of choice is often
[Cp*IrCl₂₂, it is both air and moisture stable and it has displayed high catalytic versatility. This organometallic compound has the formula (C₅(CH)₃IrCl₂)₂ but it is often abbreviated [Cp*IrCl₂₂. It is an orange diamagnetic solid with C₂ᵥ symmetry and each of the two metals are pseudo-octahedral as demonstrated in Figure 4.¹⁸,¹⁹

**Figure 4:** (Pentamethylcyclopentadienyl)iridium(III) chloride dimer

Kang et al. first prepared this compound in 1969 using hydrated iridium trichloride (IrCl₃·5H₂O) and hexamethyl Dewar benzene. Unfortunately, this method gave very low yields (9%); upon optimization they found that they were able to obtain significantly higher yields (85%) by reacting the (IrCl₃·5H₂O) with 1-(1-chloroethyl)pentamethylcyclopentadiene in methanol at 65°C under nitrogen for 20 hours (Scheme 6).¹⁹

**Scheme 6:** Review of Kang et al. - Two methods for the synthesis of [Cp*IrCl₂₂

1.5. Compounds synthesized using [Cp*IrCl₂₂

Since Grigg et al. first demonstrated its use in the N-alkylation of amines [Cp*IrCl₂₂ has been employed as the catalyst in numerous hydrogen transfer reactions. While these
transformations include the oxidation of alcohols and carbon-carbon bond formation this review will be focusing on reactions involving the formation of carbon-nitrogen bonds.

1.5.1. N-alkylation of Amines with Alcohols Catalyzed by a Cp*Ir Complex

As previously discussed the N-alkylation of amines with alcohols using borrowing hydrogen method is an attractive method it is often atom economical, it does not generate harmful byproducts and alcohols tend to be more readily available and are usually more economical to purchase than most corresponding alkyl halides or carbonyls. In 2003 Fujita et al.\textsuperscript{15} demonstrated that when \([\text{Cp}^*\text{IrCl}_2]_2\) was combined with potassium carbonate (\(\text{K}_2\text{CO}_3\)) the N-alkylation of amines with alcohols would proceed under much milder conditions than previously described (Scheme 7)\textsuperscript{15}.

\[
\text{R}_1\text{N}^{+}\text{R}_2 + \text{OH}^+ \xrightarrow{[\text{Cp}^*\text{IrCl}_2]_2 (5.0 \text{ mol}\% \text{Ir})} \text{K}_2\text{CO}_3 (5.0 \text{ mol}\%) \text{ toluene} \rightarrow \text{R}_1\text{N}^{+}\text{R}_2
\]

Scheme 7: Ir-catalyzed N-alkylation of amines

They also showed that the monoalkylated amine was formed as the sole product. This selectivity was an advantage as multi-alkylation products are often an issue with some of the more traditional methods of synthesizing amines. An examination of the reaction using primary and secondary amines demonstrated that it would tolerate a range of primary and secondary amines and resulted in the amine products being obtained in good to excellent yields.

Fujita et al. further expanded on the use of basic additives and found that the N-alkylations preformed using sodium bicarbonate (\(\text{NaHCO}_3\)) would give the product in excellent yields as well. They noted that a variety of weak bases were effective at producing the amine products but the use of stronger bases slowed the reactions.\textsuperscript{20} Using their optimized reaction conditions (Scheme 8)\textsuperscript{20} they N-alkylated a variety of substrates including anilines, primary amines, and secondary amines.
Scheme 8: Ir-catalyzed N-alkylation of anilines with primary and secondary alcohols.

The reaction of anilines with primary and secondary alcohols was selective for the mono-alkylated products and proved to be tolerant of methyl, methoxy, cyano, ester, nitro, chloro, and bromo substituents. A small amount of dialkylated product was only obtained after reacting aniline with an excess of 1-octanol (2.6 equiv) for 40 hours which indicates that the second alkylation was slow to occur. All products were obtained in high yields but it was found that a higher catalyst loading (5.0 mol % Ir) was required to achieve these yields for the benzyl alcohols with electron withdrawing substituents.

The subsequent exploration the of primary amines with primary and secondary alcohols (Scheme 9) found that these reactions also gave excellent yields even when run at lower temperatures in some instances. However, the primary amines proved to be less selective than the anilines. When benzylamine was reacted with an excess of 1-octanol (2.6 equiv.) for 40 hours; where the aniline/1-octanol di-alkylated product was only obtained in 36% yield the benzylamine/1-octanol di-alkylated product was obtained in 80% yield. This method for the N-alkylation of secondary amines was also used with various alcohols to synthesize tertiary amines. It was found that overall these reactions gave good to excellent yields as well.

The two exceptions noted were the combination of N-isopropylbenzylamine with benzyl alcohol and the combination of benzylamine with cyclohexanol; the yields of the first reaction was determined to be due to a need for steric hindrance around the amine and the second reaction only gave the product in 44% yield at 110°C; an increase in the reaction temperature to 130°C was required to improve the yield to 88%.

Scheme 9: Ir-catalyzed N-alkylation of primary amines with primary and secondary alcohols.
Fujita et al. proposed possible mechanisms (Figure 5)\textsuperscript{20} for the N-alkylation of primary and secondary amines respectively. In the case of the primary amine they felt that the first step (a) of the reaction was the formation of an alkoxo-iridium species that would coordinate with the amine. Beta-hydrogen elimination of the alkoxo group would then leave an iridium hydride coordinated with the amine and the aldehyde (or ketone) formed through the borrowing hydrogen step (b). A condensation step (c) coordinated by the iridium would lead to the formation of an imine-iridium hydride and water as a byproduct. The C=N of the imine could then be inserted into the iridium-hydride bond (d) at which point an amide-alkoxide exchange would occur and the product would be released (e). Another amine could then be coordinated with the left over alkoxo-iridium species to restart the catalytic cycle (f). The proposed catalytic cycle for the secondary amines was very similar to that of the primary amines. The main difference was that the condensation step (g) involved an additional proton resulting in an iminium ion coordinated with the iridium hydride. The C=N of the iminium ion would then be inserted into iridium-hydride bond in step (h). Fujita et al. posited this would be followed by the release of the product and formation of the proton (i) that participates in the condensation step (g). Finally, the active species would be regenerated (f).
Figure 5: Fujita et al. proposed mechanisms for N-alkylation of primary and secondary amines

Given the presence of nitrogen heterocycles in a large variety of biologically active compounds and natural products Fujita et al.\textsuperscript{21} also sought to apply this mild iridium catalyzed method of N-alkylation to the synthesis of these ring systems (Scheme 10).\textsuperscript{21}
A variety of diols were cyclized using various primary amines in the presence of NaHCO$_3$ and [Cp*IrCl$_2$]$_2$. The reaction of benzylamine with unsubstituted and substituted diols gave the cyclic amines in good to excellent yields (72-94%). The reaction of benzylamine with benzo-fused diols required higher catalyst loading to achieve good yields (63-76%) and in the case of 1,2-benzenedimethanol the addition of NaHCO$_3$ did not improve the yield. The use of a secondary amine like aniline required higher catalyst loading and higher reaction temperatures to obtain the cyclic product in good yield (70%). It was noted that the addition of an electron donating group improved the yield significantly (90%).

The asymmetric synthesis of (S)-2-Phenylpiperidine was also examined using this method (Scheme 11).$^{21}$ It was found that when (R)-1-phenylethylamine and 1-phenyl-1,5-pentanediol were reacted together with potassium acetate (KOAc) and [Cp*IrCl$_2$]$_2$ in toluene for 17 hours a diastereomeric mixture of the cis/trans N-(1-phenylethyl)-2-phenylpiperidines in a 76% yield with a 92% diastereomeric excess (de) was obtained. The enantiomeric excesses (ee) of these compounds were 86% ee and 93% ee, respectively. When the mixture of diastereomers was hydrogenated, (S)-2-phenylpiperidine was obtained in 78% ee and 96% yield.
Building on this work\textsuperscript{15,21} Nordstrøm and Madsen\textsuperscript{22} showed that [Cp*IrCl\textsubscript{2}]\textsubscript{2} could be used to catalyze the synthesis of piperazines from primary and secondary diols. They found that when using NaHCO\textsubscript{3} (5 mol \%) in conjunction with the catalyst the reaction worked equally with toluene or water as solvents giving yields of 94\% and 96\% respectively. Interestingly, while conducting optimization reactions they discovered that the use of trifluoroacetic acid (10\%) gave excellent yields (98\%) when used for reactions run in water. This discovery indicated that the condensation could be promoted by both acids and bases. However, for the general reaction they chose to use NaHCO\textsubscript{3} as it produced excellent yields in both solvents tested (Scheme 12).\textsuperscript{22}

![Scheme 12](image)

\textit{Scheme 12:} Ir-catalyzed synthesis of a bicyclic piperazine.

Using their optimized conditions, Nordstrøm and Madsen sought to ascertain the scope of the reaction by cyclizing a series of primary and secondary diols with a variety of amines; good to excellent yields were obtained in all cases. Notably, it was found in cases where new stereocenters were installed the diastereoselectivity was dependent on the choice of solvent with water displaying more selectivity than toluene. Reactions involving secondary amines or alcohols required higher temperatures to reach completion indicating that they reacted slower than the primary amines or alcohols and using trifluoroacetic acid instead of NaHCO\textsubscript{3} did not improve the rate of conversion. No racemization was observed when optically pure (1S, 2S)-1,2-diamino-1,2-diphenylethane was reacted with ethylene glycol, however, the reaction required almost three days to reach complete conversion when using NaHCO\textsubscript{3} as the base. In this case when NaHCO\textsubscript{3} was exchanged for trifluoroacetic acid both the yield and speed of conversion were improved.

The synthesis of 1,4-dibenzypiperazine from N, N’-dibenzyl-1,2-diaminoethane and ethylene glycol was accomplished in good yields using both water and toluene as a solvent but when attempts were made to generate the molecule from benzylamine and ethylene glycol using the same conditions the yields were only moderate. Alternatively, reacting benzylamine with
ethylene glycol in the absence of a solvent at a higher temperature saw complete conversion of the reagents to the product, 1,4-dibenzylpiperazine.

Since the secondary amines and alcohols were slower to react an alternative route was developed for the synthesis of the substituted piperazines. This one pot protocol involved the participation of two different diols reacting with one amine to form a piperazine. The diols were added sequentially; the first was allowed to react to completion with the primary amine before the addition of the second. Since the conversion of the secondary amine was slower than the primary amine the diol added initially would primarily react with the benzylamine. It was found that conducting the reactions in water gave higher yields than reactions conducted without solvent at a higher temperature (Scheme 13).

Scheme 13: Ir-catalyzed one pot synthesis of substituted piperazines.

Having previously demonstrated the versatility of their method for the N-alkylation of primary and secondary amines, Fujita et al. expanded its use to the N-alkylation of sulfonamides. Using a very small amount of [Cp*IrCl2]2 (0.05%-Ir) and potassium t-butoxide (KOTBu) as a base, p-toluenesulfonamide was N-alkylated with benzyl alcohol in refluxing toluene. These reaction conditions gave the mono-alkylated product in nearly quantitative yield. In a reversal from results observed with the primary and secondary amines, stronger bases were more effective, as the milder bases (sodium carbonate (Na2CO3), potassium carbonate (K2CO3), and cesium carbonate (Cs2CO3)) only gave yields up to 80%.
N-alkylation of p-toluenesulfonamide with a variety of primary alcohols was performed (Scheme 14)\(^{23}\) and in general all reactions gave the expected mono-alkylated product in good to excellent yield with no formation of di-alkylated product. However, with the aliphatic cases it was necessary to significantly increase the amount of base (5.0–20 mol%) and catalyst (0.25–1.0 mol % Ir) used. The N-alkylation of p-toluenesulfonamide with various secondary alcohols was also examined. These reactions took place in refluxing xylene instead of toluene. The reactions with saturated cyclic secondary alcohols gave good to high yields but the N-alkylation with 1-phenylethanol only resulted in a moderate yield of the desired product. Sulfonamides other than p-toluenesulfonamide were also subjected to these reaction conditions; it was found that it was necessary to increase the catalyst loading to improve the yields for electron-rich sulfonamides. This was not necessary in the reactions involving electron-poor sulfonamides.

Finally, to verify that the N-alkylation was occurring through a hydrogen borrowing catalytic cycle they ran two experiments of note. First, they isolated and characterized the catalytically active species. They did this by combining \([\text{Cp}^*\text{IrCl}_2]_2\) with \(p\)-toluenesulfonamide (TsNH\(_2\)) (2 equiv.) and KOTBu (2 equiv) in toluene at room temperature for five minutes. At this point a dinuclear complex \([\text{(Cp}^*\text{Ir)}_2(\mu\text{-NTs})_2]\) which had bridging ligands was found to have formed quantitatively (Scheme 15).\(^{23}\)

![Scheme 14: Ir-catalyzed N-alkylation of p-toluenesulfonamide with various primary and secondary alcohols.](attachment:Scheme14.png)

**Scheme 14:** Ir-catalyzed N-alkylation of \(p\)-toluenesulfonamide with various primary and secondary alcohols.

When this complex was used for the N-alkylating reaction between \(p\)-toluenesulfonamide and benzyl alcohol it had comparable catalytic activity to \([\text{Cp}^*\text{IrCl}_2]_2\). Secondly, they used \(^1\text{H}\)
NMR to monitor the reaction of \( p \)-toluenesulfonamide with benzyl alcohol in deuterated toluene at 100°C in the presence of \([\text{Cp}^*\text{IrCl}_2]_2\) (10 mol % Ir) and KOTBu (40 mol %). After the reaction had progressed for one hour the N-alkylated product was observed along with small amounts of benzaldehyde and the imine intermediate. Continued observation saw an increase in the amount of product produced but no change in the amount of benzaldehyde or imine intermediate generated (Scheme 16).\(^{23}\) The presence of these two specific side products support the hydrogen borrowing mechanism.

Scheme 16: NMR study of the Ir-catalyzed N-alkylation of \( p \)-toluenesulfonamide with benzyl alcohol.

More recently Fujita’s method of iridium catalyzed N-alkylation under basic conditions has been expanded to aminosugars.\(^{24}\) Cumpstey et al. N-alkylated a series of carbohydrates bearing primary amines and protected hydroxyl groups.\(^{24}\) They found that when using non-carbohydrate alcohols such as cyclohexanol to N-alkylate the amines the reaction proceeded without base affording the products in excellent yields (Scheme 17).\(^{24}\)

Scheme 17: Ir-catalyzed N-alkylation of protected aminosugars with primary and secondary alcohols.
It was also noted that the use of substrates containing a primary amine and one unprotected hydroxy group gave similar results. In those cases, epimerization or amination of the unprotected hydroxy groups was not observed. On the basis of these results Cumpstey et al. alkylated the aminosugar α-Man-10 with a variety of alcohols (Scheme 18). It was found that this aminosugar was insoluble in toluene, likely due to the number of unprotected hydroxyl groups it possessed, however using the N-alkylating alcohol as the solvent proved to be a good substitute. In this case, the secondary alcohols gave secondary amines and primary alcohols gave tertiary amines due to two consecutive alkylations occurring.

![Scheme 18](image)

Scheme 18: Ir-catalyzed N-alkylation of an unprotected aminosugar with various primary and secondary alcohols.

Cumpstey et al. also sought to combine two carbohydrates by N-alkylating the primary amine of one with the secondary alcohol of another. They found then when the reaction conditions reported in Scheme 18 were applied to the combination of a carbohydrate alcohol and carbohydrate amine no product was formed. However, the addition of an inorganic base, such as the ones typically associated with this reaction, resulted the formation of the desired product. Use of NaHCO₃ at 160°C gave the product in 66% yield while the use of Cs₂CO₃ only required temperatures of 120°C to afford the product in 78% yield. Both results contrasted with those observed by Fujita et al. regarding the coupling of benzyl alcohol and anilines where a base was needed for any iridium catalyzed N-alkylation and milder bases like NaHCO₃ gave better yields than stronger bases. To further examine the reactivity of these carbohydrates a series of control reactions were run (Scheme 19). It was found that without the addition of the carbohydrate alcohol the sugar product failed to form. Additionally, it was noted that all products isolated were single diastereomers and epimerization was not observed of either the...
secondary carbohydrate alcohols or the chiral centers vicinal to the intermediate carbonyl. Finally, since the primary carbohydrate alcohols reacted more quickly than the secondary it was possible to regioselectively control the functionalization of the final product.

![Scheme 19: Example N-alkylation of an aminosugar with a carbohydrate alcohol.](image)

**1.5.2. Solvent-free, Base-free, Room-temperature, or Microwave-mediated, Iridium Catalyzed N-alkylations.**

One of the biggest benefits to the hydrogen borrowing methodology is its lack of toxic side products. Additional improvements are still possible as the use of solvents such as toluene or xylene are not considered as environmentally friendly. Efforts have been made on that front to extend these methods to the production of amines without solvent or base. Also, it has been shown that conducting reactions\(^\text{25,26}\) in the microwave leads to much shorter reactions times in comparison to conventional heating methods.

As mentioned before, ammonia is the primary source for all amines so the use of it or its ammonium salts as a nitrogen source for the synthesis of more complex amines is an important objective in catalytic organic synthesis. Because ammonium salts are more safely and easily handled than ammonia Fujita et al. chose to subject these compounds to iridium-catalyzed N-alkylation. A series of ammonium salts were treated with benzyl alcohol in the presence of a transition metal catalyst and base without the use of any additional solvent. They found that
using ammonium acetate (NH$_4$OAc) and reacting it with benzyl alcohol (3.6 equiv.) at 130°C gave optimal yields (Scheme 20).$^{17}$

$$\text{NH}_4\text{OAc} + \text{RCH}_2\text{OH} \xrightarrow{[\text{Cp}\ast\text{IrCl}_2]_2 (1.0-5.0 \text{ mol}\% \text{Ir}) \text{NaHCO}_3} \text{130°C, 17h} \text{N(CH}_2\text{R)}_3$$

**Scheme 20:** Ir-catalyzed tri-alkylation of ammonium acetate with primary alcohols.

This set of reaction conditions was then used to synthesize a series of tri-alkylamines from various primary alcohols. It was found that the benzylic alcohols gave higher yields (70-92%) than the aliphatic alcohols (55-73%). It was also noted that the aliphatic alcohols required an increase in the equivalents of alcohol used, an increase in reaction temperature and an increase in both base and catalyst loading to obtain these yields.

When attempts were made to synthesize secondary amines in the same manner using the smaller salts and only two equivalents of an alcohol the tri-alkylamine was obtained in 35% along with trace amounts of the dialkylated product. Surprisingly, secondary amines were synthesized in good to excellent yields by using ammonium tetrafluoroborate (NH$_4$BF$_4$). When using this larger salt with primary alcohols the secondary amines were the major product and any tertiary amine products were obtained in trace amounts. When NH$_4$BF$_4$ was reacted with secondary alcohols only the secondary amine products were obtained. It was posited that the selectivity of NH$_4$BF$_4$ for the di-alkylation over the tri-alkylation was due to steric hindrance since the same degree of selectivity was not observed with smaller ammonium salts (Scheme 21).$^{17}$

$$\text{NH}_4\text{BF}_4 + \text{RCH}_2\text{OH} \xrightarrow{[\text{Cp}\ast\text{IrCl}_2]_2 (1.0-5.0 \text{ mol}\% \text{Ir}) \text{NaHCO}_3} \text{140°C, 17h} \text{R-NH-R} + \text{R-NH-R}$$

**Scheme 21:** Ir-catalyzed multi-alkylation of ammonium tetrafluoroborate with primary and secondary alcohols.
Carbamates are synthetic intermediates used in the production of a variety of biologically active compounds such as agrochemicals or pharmaceuticals. Also, similarly to ammonium salts carbamates can be considered an equivalent for ammonia as removal of the alkoxy carbonyl group is a facile procedure. Typically, the N-alkylations of carbamates are conducted using one of the traditional methods for the synthesis of amines such as reductive amination or reaction with alkyl halides.

Given the importance of these intermediates Fujita et al. examined the possibility of applying their N-alkylation method to carbamates and amides. They found that when n-butyl carbamate was reacted with benzyl alcohol (2 equiv) at 130°C for 17 hours in the presence of [Cp*IrCl₂]₂ without additional solvent or base the mono-alkylated product was obtained in 57% yield. None of the di-alkylated product was obtained, indicating that the reaction was selective for mono-alkylation. After exploring a variety of reaction conditions, they found the best yields (94%) were obtained when they combined n-butyl carbamate with benzyl alcohol (4 equiv) at 130°C for 17 hours in the presence of sodium acetate (NaOAc) and [Cp*IrCl₂]₂ without additional solvent (Scheme 22).

Using these reaction conditions, they further explored the N-alkylation of n-butyl carbamate with various primary alcohols; all products were obtained in moderate to excellent yields. They found that reaction was tolerant of both electron donating and electron withdrawing substituents on the aromatic ring of the alcohol although in some cases increased loading of the catalyst and the base was required. Benzamides were subjected to the same reaction conditions and it was found that they produced the similar results. The reactions involving benzamides as reagents were equally tolerant to electron donating and electron withdrawing substituents and gave similar yields. Reactions with several secondary alcohols were attempted but no products were obtained.
They also noted that the \( n \)-butoxycarbonyl group on the \( N \)-alkylated \( n \)-butylcarbamate could be easily removed through reflux in a basic methanol/water mixture as demonstrated in Scheme 23.\(^{16}\) This system can then be used as a new method for transforming an alcohol into a primary amine through the \( N \)-alkylated intermediates.

Recently Li et al. reported on the \( N \)-alkylation of 2-aminobenzothiazoles\(^{28}\) (1 equiv) with a variety of alcohols (5 equiv) in the presence of \([\text{Cp}^*\text{IrCl}_2]_2\) (0.2 mol\% ) and sodium hydroxide (NaOH) (20 mol\%). All reactions were conducted without solvent at 150°C and afforded the alkylated amino-azole products in excellent yields (Scheme 24).\(^ {28}\) A similar investigation of functionalized 2-aminobenzothiazoles, 2-aminothiazoles, and amino-oxazoles with 1-butanol also gave alkylated products in excellent yields in all cases. It was noted that in some instances a stoichiometric amount of base was required to bring the reaction to complete conversion but that no 3-alkyl-2-iminoazoline isomers or di-alkylated 2-(\( N \)-dialkylamino)azole products were not observed in any of the test cases.

**Scheme 24:** Solventless Ir-catalyzed \( N \)-alkylation of various amino-azoles with a variety of alcohols.

Additional reactions were conducted to gather information about the catalytic cycle. After the reaction of 4,5-diphenylthiazole-2-amine with benzaldehyde afforded only (Z)-\( N \)-benzyldiene-4,5-diphenylthiazole-2-amine in 45\% yield it was reacted with benzyl alcohol using their general method for the \( N \)-alkylation of amino-azoles. This reaction gave them almost stoichiometric amounts of benzaldehyde and \( N \)-benzyl-4,5-diphenylthiazol-2-amine (Scheme 25).\(^ {28}\)
Scheme 25: Condensation of amino-azole with benzaldehyde and Ir-catalyzed hydrogen transfer between an imine and alcohol.

Using this information, a mechanism was proposed for the catalytic cycle that would account for the N-alkylation step’s regioselectivity. They determined that in the condensation process the exocyclic nitrogen was favored by the aldehyde over the endocyclic nitrogen (Scheme 26).²⁸

Scheme 26: Li et al. Proposed mechanism for Ir-catalyzed N-alkylation of amino-azoles.
Zhang et al. noted that new C-C bonds had been formed under iridium-catalyzed, solvent-
free, microwave-mediated conditions and sought to apply this methodology to synthesis of
amines. After conducting a series of optimization reactions with benzylamine and 1,5-
pentanediol, they found that the best yields were obtained when the reaction was run without
solvent or base and heated to 140°C for 1h in the microwave. Use of a solvent and conventional
heating required long reaction times to obtain comparable yields and lower microwave
temperatures gave significantly lower yields. The addition of base to the reaction also lowered
yields (Scheme 27).

![Scheme 27: Microwave-assisted Solvent-free, Baseless, Ir-catalyzed N-alkylation of amines with
primary and secondary alcohols.]

Having obtained an optimal set of conditions Zhang et al. wished to evaluate the scope of
the reaction and applied it to the mono-, di- and tri-alkylation of amines with various alcohols.
To examine the potential of mono-alkylation a series of primary and secondary amines were
reacted with a variety of primary and secondary alcohols; to ensure complete conversion the
reaction temperature was adjusted from 140°C for 1 hour to 160°C for 1 hour. It was found that
all products were good yields and that the reaction tolerated a wide range of alcohols.

The di-alkylation of amines was used to generate N-heterocycles from diols. A series of
functionalized benzylamines were reacted with 1,5-pentanediol, 1,6-hexanediol, or 1,7-
heptanediol form the corresponding heterocycles. The products were obtained in good yields in
all cases although the 5- and 7-member rings required a temperature increase to 160°C to reach
completion. It is interesting to note when comparing the same heterocycles produced in both
studies that the method used by Fujita et al. produced higher isolated yields than this method
(Figure 6).
Finally, the tri-alkylation of an amine was explored using NH$_4$OAc as the nitrogen source. Zhang et al. reacted NH$_4$OAc with several functionalized benzyl alcohols using the higher temperatures required for the mono-alkylations. To ensure complete conversion they also employed four equivalents of the alcohol; these reaction conditions resulted in moderate to good yields.

Earlier the iridium-catalyzed N-alkylation of amides as reported by Fujita et al.$^{16}$ was discussed. This method requires the reagents to be refluxed in toluene for 17 hours in the presence of a base. Studies by Xu et al.$^{30}$ showed that this process could be accomplished under solvent-free conditions using a variety of transition metal catalysts (including iridium) and Williams et al.$^{31}$ expanded on this by demonstrating the use of microwave-mediated, solvent-free conditions to conduct their Ru-catalyzed N-alkylation of amides. Members of our group noted that these methods were limited to the use of primary alcohols as alkylating agents and sought to develop a protocol with wide substrate tolerance that employed the more environmentally friendly solvent-free, microwave-mediated reaction conditions.$^{32}$ A series of optimization reactions resulted in microwave-mediated conditions that did not require base or solvent to afford product yields that were similar to results reported by those using conventional methods$^{16}$ (Scheme 28).$^{32}$

Scheme 28: Ir-catalyzed N-alkylation of amides with primary alcohols under microwave-mediated, solvent-free, base-free conditions.
With the optimal reaction conditions in hand the scope of the method was evaluated through the synthesis of a series of N-substituted benzylamides. It was found that the reaction conditions were equally tolerant of electron-donating, electron-withdrawing, and halogen functional groups on the benzyl alcohols with the alkylated amide products afforded in high yields. The only exception to this was the 4-nitrobenzy alcohol, the amide product was obtained as an intractable mixture, this poor yield was consistent with previous reports regarding the reactivity of the nitro derivative in other systems.\textsuperscript{15,20} Reactions using primary alkanols, acetamide or substituted benzamides also afforded the amide products in good to high yields (60-85%).

![Scheme 29](image)

**Scheme 29**: Ir-catalyzed N-alkylation of benzamide with secondary alcohols under microwave-mediated, solvent-free, base-free conditions.

Following the success of amides treated with primary alcohols the investigation was expanded to secondary alcohols. It was found that both acyclic and cyclic secondary alcohols could be used for the N-alkylation of benzamide under the general reactions conditions. In all cases the amide product was obtained in good yields (65-78%), even when a sterically hindered alcohol was employed for the N-alkylation (**Scheme 29**)\textsuperscript{32}.

**1.6. Iridium Catalyzed Synthesis of Natural Products.**

Our group has long had an interest in the synthesis of bicyclic amphibian alkaloids. Structures like these are of interest both because they may be of pharmaceutical importance and because developing a general method for the synthesis of the base ring structure could then allow for access to other more complex structures. Our focus recently has been the use of an iridium catalyst and borrowing hydrogen methodology in the synthesis of natural products. This methodology has proved efficacious in the both the enantioselective synthesis of Noranabasamine\textsuperscript{33} and in the synthesis of nicotine and anabasine derivatives.\textsuperscript{34}

The total synthesis of noranabasamine as reported by our group (**Scheme 30**) employed a commercially available brominated pyridine 49 as the base on which to build the rest of the
three-ring structure. This pyridine (49) was combined with n-butyllithium and δ-valerolactone to give ketone 50 which was subsequently reduced to provide the diol 51. The diol (51) and (R)-1-phenylethylamine were then combined in toluene with the iridium catalyst ([Cp*IrCl₂]₂) and heated at 110°C in a sealed pressure tube. This reaction gave the two diastereomers of the 2-substituted piperidine 52a and 52b with a diastereomeric ratio of 52a:52b 95:5. This reaction was repeated using (S)-1-phenylethylamine and the resulting diastereomers 53a and 53b were obtained with a diastereomeric ratio of 53a:53b 95:5. The piperidine ring system underwent hydrogenation to remove the N-substitution and then was subjected to treatment with phosphoryl trichloride which gave the chlorinated analogues 54 and 55. Finally to obtain both enantiomers of noranabasamine, Fu and coworkers’ Suzuki-Miyaura coupling conditions²⁹ were applied to 54 and 55.
Scheme 30: Total synthesis of Noranabasamine.

Reagents and conditions: (a) (i) n-BuLi, Et₂O, -78°C; (ii) δ-valerolactone, 98%; (b) BH₃·SMe₂, toluene, 40°C, 88%; (c) (i) (R)-1-phenyethylamine, KOAc, [Cp*IrCl₂]₂, toluene, 110°C, (ii) chromatographic separation, 72%, dr = 95:5; (d(i) (S)-1-phenyethylamine, KOAc, [Cp*IrCl₂]₂, toluene, 110°C, (ii) chromatographic separation, 69%, dr = 95:5; (e) (i) H₂, Pd/C, EtOH, 55°C; (ii) POCl₃, 120°C; (f) 3-pyridineboronic acid, Pd₂(dba)₃, PCy₃, K₃PO₄, dioxane/H₂O, 100°C, 18h
As discussed earlier the synthesis of N-heterocycles from diols as described by Fujita et al.\textsuperscript{21} had been modified by Zhang et al.\textsuperscript{29} and shown to work under microwave-mediated, solvent-free, base-free conditions. Members of our group sought to exploit this method for the green synthesis of natural products like nicotine and anabasine derivatives.\textsuperscript{34} However, they found that the lack of base and solvent resulted in poor yields.

\[
\begin{array}{c}
\text{NH}_2R_n \quad \text{[Cp*IrCl}_2\text{]}_2 (5.0 \text{ mol}\% \text{Ir}) \\
\text{Na}_2\text{CO}_3 (5.0 \text{ mol}\%) \\
\text{H}_2\text{O, 110°C, MW, 2h}
\end{array}
\]

\( n = 1 \text{ or } 2 \)

**Scheme 31**: Optimized reaction conditions for the iridium-catalyzed synthesis of nicotine and anabasine derivatives.

Conventional or microwave heating with base using either toluene as a solvent gave some improvement but it was not substantial. Exchanging the toluene for water as a solvent resulted in significant improvements in product yields. They found the optimum reaction conditions to be microwave irradiation of the reagents at 110°C for 2 hours in the presence of [Cp*IrCl\textsubscript{2}]\textsubscript{2} and Na\textsubscript{2}CO\textsubscript{3} with water as a solvent (Scheme 31).\textsuperscript{34} Using these conditions, they were able to synthesize a series of nicotinic and anabasine analogues from commercially available pyridines. The preparation of the diol employs methodology developed in our laboratory\textsuperscript{35} and is illustrated below in Scheme 32.\textsuperscript{34} The 3-bromopyridine (57a) or 5-bromo-2-methoxypyridine (57b) was dissolved in diethyl ether at -78°C and treated with \(n\)-butyllithium. \(\gamma\)-Butyrolactone or \(\delta\)-valerolactone were subsequently added to the reaction mixture to produce the hydroxy ketones 58 or 59. The hydroxy ketones were then subjected to reduction with sodium borohydride in methanol affording the desired diols 60 and 61. The N-heterocyclization process was conducted by the addition of the diol to a stirred solution of [Cp*IrCl\textsubscript{2}], Na\textsubscript{2}CO\textsubscript{3}, and water in a microwave reactor tube. This solution was treated with an amine and then irradiated at 110°C for 2 hours thus affording the final products in good yields.
Scheme 32: Synthesis of nicotine and anabasine derivatives.

1.7. Conclusion

In summary, the borrowing hydrogen methodology is a powerful tool for the N-alkylation of amines and thus the synthesis of new carbon-nitrogen bonds. Chapter two will discuss the use of this methodology in the N-alkylation of chiral amino acid esters and chapter three will examine both a novel synthetic route for difficult to obtain diols and the use of the borrowing hydrogen methodology for cyclizing these diols with amines to form N-heterocycles.
1.8. References


Chapter 2: Iridium Catalyzed N-alkylation of Amino Acid Esters

2.1. Abstract

Amines are ubiquitous in nature and serve a variety of functions in living organisms. Because of this fact amines are of great biological and pharmaceutical interest. The iridium catalyst (pentamethylcyclopentadienyl) iridium dichloride dimer ([Cp*IrCl₂]₂) has been used in a number of ways to synthesize new carbon-nitrogen bonds. These studies were directed toward the development of a method for the iridium catalyzed N-alkylation of alpha-amino acid esters. A range of alpha-amino acid esters were N-alkylated with a variety of alcohols. The resultant products were evaluated for racemization of the alpha-carbon chiral center.

We have optimized a method for the N-alkylation for alpha-amino acid esters. Using this method, we have N-alkylated a series of alpha-amino acid esters with a variety of alcohols. We have shown that the N-alkylation of the alpha-amino acid esters works consistently and gives the desired products in moderate to high yields. We have examined the effect of this method on the chiral center of the obtained products by analyzing their optical rotation. Evaluation of these specific rotations indicated racemization was occurring but it is believed that any loss of the chiral center is due to the reaction conditions.

2.2. Introduction

Amines are ubiquitous in nature; serving a variety of functions in living organisms, some of which include bioregulation, neurotransmission, and defense against predators. A majority of nitrogen-containing compounds that are of biological significance are also pharmaceutically important. Many of these are natural products that contain alpha-chiral amines (Figure 7). Alpha-chiral amines are those having a stereogenic center on the carbon immediately next to the nitrogen. A stereogenic center is an atom (usually a carbon) whose substituents are all different. Amino acid esters can be used as building blocks in the synthesis of these more complex structures as they already possess the desired functional group.
Traditionally amines are synthesized using one of several methods. Two of the most common methods for making amines are reductive amination and the alkylation of amines by alkyl halides. Unfortunately, both reactions are problematic in that they can produce toxic or unwanted side products and in the case of the alkyl halides stoichiometric amounts of halogenated salts. The importance of amines has led to a great deal of investigation into the use of transition metal catalysts and borrowing hydrogen methodology in the amination of alcohols with much success being reported. While the transition metals are often expensive they are reusable and the only byproduct of the reaction is water.

Our group has employed the catalyst \([\text{Cp*IrCl}_2]^2\) in the formation of new carbon-nitrogen bonds for use in medicinally interesting compounds over the last ten years. We have used these methods in the N-alkylation of amines and amides with alcohols and diols and have used them in the course of synthesizing natural products such as noranabasamine and nicotine and anabasine derivatives. In our review of the literature we could not find any instance where the simple \([\text{Cp*IrCl}_2]^2\) catalyzed “borrowing hydrogen” reaction had been applied to the N-alkylation of chiral amino acid esters. Previous reported instances of enantioselective iridium-catalyzed N-alkylation employed a derivative form of \([\text{Cp*IrCl}_2]^2\) or iridium catalysts in conjunction with chiral ligands.

We therefore sought to apply this methodology to alpha-amino acid esters. Our goal was to develop a suitable method for the N-alkylation of alpha-amino acid esters that maintained the existing chiral center without requiring the use of a specialized Cp*Ir derivative.
2.3. Results and Discussion

For the purposes of optimization, a series of L-alpha amino acid esters were chosen to give a range of aliphatic and aromatic side chains along with primary and secondary amines. All alpha-amino acid esters were purchased in their hydrochloride salt form and free-based immediately prior to use (Figure 8).

![Selected alpha-amino acid esters](image)

**Figure 8**: Selected alpha-amino acid esters.

2.3.1. Optimization of Reaction Conditions: Achiral substrate

Initially we explored making the reaction more environmentally friendly by substituting water for toluene as the solvent. The reaction of the amine and benzyl alcohol was performed in a heavy walled pressure reactor tube at temperatures sufficient to bring the solution to reflux inside the vessel. Using the original method put forth by Fujita et al as a baseline we ran the N-alkylation in toluene using K$_2$CO$_3$, using these conditions we obtained nearly quantitative yields. In contrast, when the reaction was run using only water as a solvent it yielded an intractable mixture that proved impossible to purify. Noting that Fujita and co-workers had achieved success using a gentler base (NaHCO$_3$) and that in some cases it had been observed that stronger bases could retard the reaction we changed bases. We also noticed the low solubility of the catalyst in water and so positing that this might be influencing the rate of reaction we added a co-solvent. Using a small amount of THF as a co-solvent solved the purification issue but the final
product was obtained in low yields. The low yields prompted us to increase the amount of catalyst used; this was found to significantly increase the yield of the final product. We found that increasing the amount of co-solvent beyond 20% did not have any improvement on overall yields (Scheme 33, Table 1).

![Scheme 33: N-alkylation of achiral substrate.]

Table 1: Optimization of N-alkylation of achiral substrate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst Loading</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>5 mol % metal</td>
<td>K₂CO₃</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>5 mol % metal</td>
<td>K₂CO₃</td>
<td>IM</td>
</tr>
<tr>
<td>3</td>
<td>Water</td>
<td>5 mol % metal</td>
<td>NaHCO₃</td>
<td>IM</td>
</tr>
<tr>
<td>4</td>
<td>Water/20%THF</td>
<td>5 mol % metal</td>
<td>NaHCO₃</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Water/20%THF</td>
<td>10 mol % metal</td>
<td>NaHCO₃</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>Water/30%THF</td>
<td>10 mol % metal</td>
<td>NaHCO₃</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>Water/40%THF</td>
<td>10 mol % metal</td>
<td>NaHCO₃</td>
<td>67</td>
</tr>
</tbody>
</table>

IM = Intractable Mixture.

2.3.2. Optimization of Reaction Conditions: Chiral substrates

Using the reaction conditions obtained from the achiral substrate optimization we turned to the N-alkylation of the selected alpha amino acid esters. Unfortunately, we found that the alpha-amino acid esters produced the same intractable mixture when using the water/THF solvent system. Even using the baseline reaction conditions that had produced quantitative yields in the achiral system only gave moderate yields when the alpha-amino acid esters were N-alkylated. Confronted with these results we explored the reaction further, our findings are summarized in Table 2. We found that using an excess of either the amino acid ester or the alcohol did not have a significant effect on the yield of the reaction. However, we did find that the amino acid ester was prone to self-condensation and hydrolysis under these reaction conditions therefore to counter these issues we used a slight excess of the alcohol in an attempt to maximize the yield of the desired product over these side products. We also found that yields
were improved by not subjecting the reaction to any sort of extraction prior to chromatographic purification. We believe that products may have some water solubility thus resulting in a decreased yield if this step was taken. As some work had been done in our group in synthesizing compounds similar to this using microwave reactors\textsuperscript{12,13} this was also a method we explored. Unfortunately, while we did see comparable yields to the conventional method this heating method led to a complete loss of the chiral center on all products tested. We found that for a few amino acid esters yields were improved significantly by decreasing the run times to 8 or 9 hours. However, in most cases comparable or better yields were obtained at run times of 16 to 20 hours (Scheme 34, Table 2).

Scheme 34: General N-alkylation of alpha-amino acid esters

Table 2: Optimization of chiral substrate conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid</th>
<th>AA (eq.)</th>
<th>Alcohol (eq.)</th>
<th>Solvent</th>
<th>Base</th>
<th>Heating method</th>
<th>Run time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenylalanine ethyl ester</td>
<td>1</td>
<td>1.1</td>
<td>20%THF 80%Water</td>
<td>NaHCO\textsubscript{3}</td>
<td>conventional</td>
<td>18.5</td>
<td>IM</td>
</tr>
<tr>
<td>2</td>
<td>Phenylalanine ethyl ester</td>
<td>1.1</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Proline Benzyl Ester</td>
<td>1.2</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>7.5</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Proline Benzyl Ester</td>
<td>1</td>
<td>1.5</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>8</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Proline Benzyl Ester</td>
<td>1.5</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>microwave</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Proline Benzyl Ester</td>
<td>1.2</td>
<td>1</td>
<td>acetonitrile</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>microwave</td>
<td>1.3</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>Proline Benzyl Ester</td>
<td>1.2</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>7.5</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Proline Benzyl Ester</td>
<td>1</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>microwave</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>Proline methyl ester</td>
<td>1.2</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>Proline methyl ester</td>
<td>1.5</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>11</td>
<td>Tyrosine methyl ester</td>
<td>1.2</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>12</td>
<td>Tyrosine methyl ester</td>
<td>1.5</td>
<td>1</td>
<td>toluene</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>conventional</td>
<td>9</td>
<td>34</td>
</tr>
</tbody>
</table>

IM = Intractable Mixture
2.3.3. Scope of Optimized Reaction

Having determined the best reaction conditions for most of the selected alpha-amino acid esters we turned our attention to assessing the scope and limitations of the developed method. As shown in Table 3 N-alkylation of the chosen alpha-amino acid esters with benzyl alcohol gave moderate to good yields. The only exception is methionine methyl ester; in this case, the lack of product is likely due to the sulfur group on the amino acid ester poisoning the catalyst. As shown in Table 4 N-alkylation of phenylalanine methyl ester with a variety of alcohols gave moderate to good yields in almost all cases. Here the only exception was the 4-nitrobenzyl alcohol which afforded only an intractable mixture. This yield is consistent with the slow reactivity of the nitro functional group reported in other systems.4,5,12
<table>
<thead>
<tr>
<th>Amino Acid Ester</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 5" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 20" /></td>
<td>0</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 21" /></td>
<td>42</td>
</tr>
<tr>
<td><img src="image" alt="Structure 7" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 22" /></td>
<td>39</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 23" /></td>
<td>70</td>
</tr>
<tr>
<td><img src="image" alt="Structure 9" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 24" /></td>
<td>39</td>
</tr>
<tr>
<td><img src="image" alt="Structure 10" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 25" /></td>
<td>48</td>
</tr>
</tbody>
</table>
Table 4: N-alkylation of phenylalanine methyl ester with various alcohols.

<table>
<thead>
<tr>
<th>Amino Acid Ester</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="12" alt="Image" /></td>
<td><img src="22" alt="Image" /></td>
<td>39</td>
</tr>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="14" alt="Image" /></td>
<td><img src="26" alt="Image" /></td>
<td>54</td>
</tr>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="15" alt="Image" /></td>
<td><img src="27" alt="Image" /></td>
<td>59</td>
</tr>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="16" alt="Image" /></td>
<td><img src="28" alt="Image" /></td>
<td>IM</td>
</tr>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="17" alt="Image" /></td>
<td><img src="29" alt="Image" /></td>
<td>43</td>
</tr>
<tr>
<td><img src="7" alt="Image" /></td>
<td><img src="18" alt="Image" /></td>
<td><img src="30" alt="Image" /></td>
<td>23*</td>
</tr>
</tbody>
</table>

IM = Intractable Mixture, *Product was obtained was the amino acid, methyl ester had been hydrolyzed.
2.3.4. Optical Rotation

To examine any effects this method of N-alkylation and these reaction conditions were having on the chiral center of the alpha-amino acid ester we analyzed the specific rotation of several of the products obtained (Table 5). We compared these specific rotations to known values\textsuperscript{16} to determine if racemization was occurring. In all cases, we found some degree of racemization.

Table 5: Observed optical rotations of selected N-alkylated amino acid esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid Ester_Alcohol</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhenylalanineOMe_BnOH</td>
<td>18</td>
<td>24</td>
<td>91% (-)</td>
</tr>
<tr>
<td>2</td>
<td>PhenylalanineOme_BnOH</td>
<td>21</td>
<td>24</td>
<td>64% (-)</td>
</tr>
<tr>
<td>3</td>
<td>PhenylalanineOme_BnOH</td>
<td>10</td>
<td>15</td>
<td>34% (-)</td>
</tr>
<tr>
<td>4</td>
<td>ProlineOBn_BnOH</td>
<td>8</td>
<td>51</td>
<td>23% (-)</td>
</tr>
<tr>
<td>5</td>
<td>ProlineOBn_BnOH</td>
<td>17</td>
<td>45</td>
<td>12% (-)</td>
</tr>
<tr>
<td>6</td>
<td>PhenylalanineOMe_4-methoxy-BnOH</td>
<td>17</td>
<td>54</td>
<td>79% (-)</td>
</tr>
</tbody>
</table>

It is believed that the racemization was an effect of the reaction conditions rather than introduced during the catalytic cycle. As demonstrated in Figure 9, removal of a hydrogen at the alpha carbon could lead to racemization. Small amounts of base were required for this reaction to run and equally small amounts of hydrogen chloride are generated in situ. Unfortunately, attempts to generate the N-alkylation product from reactions run without base gave only a self-condensation product.

![Figure 9: Possible racemization mechanism](image)

Figure 9: Possible racemization mechanism
2.4. Conclusion

We have optimized a method for the N-alkylation for alpha-amino acid esters. Using this method, we have N-alkylated a series of alpha-amino acid esters with a variety of alcohols. We have shown that the N-alkylation of the alpha-amino acid esters works consistently and gives the desired products in moderate to high yields. We have examined the effect of this method on the chiral center of the obtained products by analyzing their optical rotation. Evaluation of these specific rotations indicated racemization was occurring but it is believed that any loss of the chiral center is due to the reaction conditions as opposed to the catalytic cycle.
2.5. Experimental Section

General Methods

Chemicals were purchased from Alfa Aesar, Oakwood Chemicals, Acros Organics, TCI Chemicals, and Sigma Aldrich unless otherwise noted. Anhydrous toluene was purchased from Mallinckrodt Baker, Inc, and used without further purification. Dichloromethane (DCM) was purchased from Fisher Scientific and used without further purification. All solvents were used under argon or nitrogen unless otherwise noted. Thin layer chromatography (TLC) 20 x 20 cm glass plates pre-coated with 250 μm silica gel were purchased from Sorbent Technologies and used to monitor reactions via visualization with shortwave UV light, iodine, phosphomolybdic acid (PMA), or ninhydrin stains. Chromatography is in reference to flash column chromatography on silica gel (Silica Gel 60, 230-400 mesh). Proton and carbon NMR were recorded on a variety of Varian 400MHz, 500MHz, and 600MHz nuclear magnetic resonance spectrometers. All spectra were obtained at ambient temperature in deuterated chloroform (CDCl₃) from Cambridge Isotope Laboratories, Inc. ¹H NMR chemical shifts are reported in δ values (ppm) relative to chloroform-d (7.26 ppm). ¹³C NMR chemical shifts are reported in δ values (ppm) relative to chloroform-d (77.0 ppm).

General Procedure A: Freebasing of Alpha-Amino Acid Esters

Alpha-amino acid ester hydrochlorides (4-6) (1 equiv) were dissolved in DCM (30-50 mL) at room temperature. To this solution 1M NaOH (1.1 equiv) was added slowly. The reaction flask was capped loosely with a septum and the solution was stirred vigorously for 1h. The solution was then transferred to a separatory funnel and the organic layer separated from the aqueous layer. The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the alpha-amino acid esters (4-6) as free amines.

General Procedure B: Freebasing of Alpha-Amino Acid Esters

Alpha-amino acid ester hydrochloride salts (7-10) (1 equiv) were dissolved in DCM (50-100 mL) and the resulting solution was extracted with a saturated K₂CO₃ solution (3 x 50-100 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the alpha-amino acid esters (7-10) as free amines.
Alanine methyl ester (4)

\[
\begin{align*}
\text{O} & \\
\text{NH}_2 & \\
\text{O} &
\end{align*}
\]

General Procedure A. The alpha-amino acid ester was obtained as a clear, watery liquid (0.753 g, 50%).

\textsuperscript{1}H NMR (300 MHz, Chloroform-\(d\)) \(\delta\) 3.49 (s, 3H), 3.33 (q, \(J = 7.0\) Hz, 1H), 1.56 (s, 2H), 1.10 (d, \(J = 7.0\) Hz, 3H).

Methionine methyl ester (5)

\[
\begin{align*}
\text{S} & \\
\text{NH}_2 & \\
\text{O} & \\
\text{O} &
\end{align*}
\]

General Procedure A. The alpha-amino acid ester was obtained as a clear, watery liquid (0.560 g, 58%).

\textsuperscript{1}H NMR (300 MHz, Chloroform-\(d\)) \(\delta\) 3.47 (s, 3H), 3.33 (dd, \(J = 8.3, 4.9\) Hz, 1H), 2.36 (t, 2H), 1.84 (s, 3H), 1.82 – 1.67 (m, 1H), 1.61 – 1.46 (m, 1H), 1.38 (s, 2H).

Proline methyl ester (6)

\[
\begin{align*}
\text{N} & \\
\text{H} & \\
\text{O} & \\
\text{O} &
\end{align*}
\]

General Procedure A. The alpha-amino acid ester was obtained as a pale yellow watery liquid (0.647 g, 83%).

\textsuperscript{1}H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 3.67 (dd, \(J = 8.7, 5.7\) Hz, 1H), 3.63 (s, 3H), 3.02 – 2.94 (m, 1H), 2.85 – 2.78 (m, 1H), 2.09 – 1.98 (m, 1H), 1.81 – 1.71 (m, 1H), 1.71 – 1.62 (m, 2H).
Phenylalanine methyl ester (7)

\[
\begin{array}{c}
\text{O} \\
\text{NH}_2
\end{array}
\]

General Procedure B. The alpha-amino acid ester was obtained as a colorless oil (0.424 g, 98%).

\(^1\)H NMR (400 MHz, Chloroform-\text{d}) \(\delta\) 7.31 – 7.13 (m, 5H), 3.75 – 3.65 (m, 4H), 3.05 (dd, \(J = 13.5, 5.2\) Hz, 1H), 2.83 (dd, \(J = 13.5, 7.9\) Hz, 1H), 1.42 (s, 2H).

Proline benzyl ester (8)

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C} \quad \text{O}
\end{array}
\]

General Procedure B. The alpha-amino acid ester was obtained as a pale, yellow oil (0.867 g, 96%).

\(^1\)H NMR (400 MHz, Chloroform-\text{d}) \(\delta\) 7.47 – 7.16 (m, 5H), 5.14 (s, 2H), 3.78 (dd, \(J = 8.6, 5.8\) Hz, 1H), 3.11 – 2.98 (m, 1H), 2.93 – 2.82 (m, 1H), 2.45 (s, 1H), 2.18 – 2.04 (m, 2H), 1.90 – 1.65 (m, 2H).

Phenylalanine ethyl ester (9)

\[
\begin{array}{c}
\text{O} \\
\text{NH}_2
\end{array}
\]

General Procedure B. The alpha-amino acid ester was obtained as a colorless oil (0.769 g, 91%).

\(^1\)H NMR (400 MHz, Chloroform-\text{d}) \(\delta\) 7.32 – 7.07 (m, 5H), 3.75 – 3.59 (m, 4H), 3.02 (dd, \(J = 13.5, 5.2\) Hz, 1H), 2.80 (dd, \(J = 13.5, 7.9\) Hz, 1H), 1.44 (s, 2H).
Tyrosine methyl ester (10)

Tyrosine methyl ester hydrochloride (10) (0.657 g, 2.84x10^{-3} mol) was dissolved in Ethyl Acetate (75 mL) and the resulting solution was extracted with a saturated K₂CO₃ solution (3 x 75 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford tyrosine methyl ester (10) as a free amine. The alpha-amino acid ester was obtained as a white powder (0.454 g, 82%).

¹H NMR (400 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.71 – 3.68 (m, 1H), 3.02 (dd, J = 13.7, 5.1 Hz, 1H), 2.80 (dd, J = 13.7, 7.7 Hz, 1H), 1.60 (s, 2H).

General procedure C: Optimization of achiral reaction conditions:
To a reaction vial equipped with a stir bar was added aniline (1.5 equiv) followed by a base (5 mol%), [Cp*IrCl₂]₂ (5-10 mol%-Ir), and a solution of benzyl alcohol (1 equiv) in solvent (0.5 mL). The vial was flushed with nitrogen and sealed with a screw cap. The reaction mixture was stirred and heated for 17 h at 110°C. The mixture was concentrated under pressure to remove the toluene and the residue was purified by flash chromatography to afford the N-alkylated product.
**General Procedure C:** Aniline (81.7 mg, 0.878 mmol), benzyl alcohol (62.4 mg, 0.577 mmol), NaHCO₃ (2.1 mg, 0.025 mmol), [Cp*IrCl₂]₂ (20.8 mg, 0.0261 mmol) and THF:H₂O (1:4, 0.5mL). Purified by flash chromatography (SiO₂, 1:4 Ethyl Acetate/hexanes) to afford the product (13) (70.8 mg, 67%) as a dark red oil.

**1H NMR** (400 MHz, Chloroform-d) δ 7.52 – 7.24 (m, 5H), 6.88 – 6.71 (m, 5H), 4.41 (s, 2H), 4.09 (s, 1H).

**General procedure D: N-alkylation of Alpha-Amino Acid Esters:**
To a reaction vial equipped with a stir bar was added a free-based alpha amino acid ester (5-10) (1-1.5 equiv) followed by K₂CO₃ (5 mol%), [Cp*IrCl₂]₂ (5 mol%-Ir), and a solution of alcohol (12, 14-18) (1-1.5 equiv) in toluene (1-2 mL). The vial was flushed with nitrogen and sealed with a screw cap. The reaction mixture was stirred and heated for 8-20h at 110°C. The mixture was concentrated under pressure to remove the toluene and the residue was purified by flash chromatography to afford the N-alkylated alpha-amino acid ester.

**Methyl-2-(benzylamino)-4-(methylthio)butanoate (20)**

General Procedure D: Free-based alpha amino acid ester (5) (3.4 mmol), alcohol (12) (4.2 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 1:4 Ethyl acetate/hexanes) The desired product (20) was not obtained (0 mg, 0%).
Methyl-1-benzylpyrrolidine-2-carboxylate (21)

General Procedure D: Freebased alpha amino acid ester (6) (1.5 mmol), alcohol 12) (1.0 mmol) and toluene (1 mL). Reaction mixture was heated for 9 h. Purified by preparative TLC (SiO$_2$, 1:4 Ethyl Acetate/hexanes) to afford the product (21) (95 mg, 43%) as a yellow oil.

$^1$H NMR (600 MHz, Chloroform-d) δ 7.34 – 7.19 (m, 5H), 3.87 (d, J = 12.8 Hz, 1H), 3.63 (s, 3H), 3.56 (d, J = 12.7 Hz, 1H), 3.24 (t, J = 7.7 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.38 (q, J = 8.4 Hz, 1H), 2.16 – 2.07 (m, 1H), 1.98 – 1.84 (m, 2H), 1.80 – 1.72 (m, 1H).

$^{13}$C NMR (150 MHz, Chloroform-d) δ 174.6, 138.4, 129.4, 128.5, 128.3, 127.4, 74.8, 65.5, 58.8, 53.5, 51.8, 29.5, 23.2.

Methyl-2-(benzylamino)-3-phenylpropanoate (22)

General Procedure D: Free-based alpha amino acid ester (7) (5.2 mmol), alcohol (12) (6.3 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO$_2$, 1:3 Ethyl acetate/hexanes) to afford the product (22) (545 mg, 39%) as a yellow oil.

$^1$H NMR (600 MHz, Chloroform-d) δ 7.36 – 7.21 (m, 10H), 3.88 (d, J = 13.3 Hz, 1H), 3.70 (d, J = 13.3 Hz, 1H), 3.67 (s, 3H), 3.62 (t, J = 6.9 Hz, 1H), 3.07 – 2.99 (m, 2H), 2.01 (s, 1H).

$^{13}$C NMR (150 MHz, Chloroform-d) δ 175.2, 139.9, 137.7, 129.6, 129.5, 127.7, 128.5, 128.5, 127.4, 127.2, 127.0, 126.9, 62.4, 62.3, 52.2, 51.7, 40.0.
Benzyl-1-benzylpyrrolidine-2-carboxylate (23)

General Procedure D: Freebased alpha amino acid ester (8) (1.2 mmol), alcohol (12) (1.0 mmol) and toluene (1 mL). Reaction mixture heated for 8 h. Purified by preparative TLC (SiO₂, 1:4 Ethyl Acetate/hexanes) to afford the product (23) (207 mg, 70%) as a yellow oil.

**¹H NMR (400 MHz, Chloroform-d)** δ 7.47 – 7.22 (m, 10H), 5.19 – 5.09 (m, 2H), 3.96 (d, J = 12.7 Hz, 1H), 3.59 (d, J = 12.8 Hz, 1H), 3.35 (dd, J = 8.9, 6.1 Hz, 1H), 3.10-3.04 (m, 1H), 2.43 (q, J = 8.3 Hz, 1H), 2.23 – 2.09 (m, 1H), 2.08 – 1.73 (m, 3H).

**¹³C NMR (100 MHz, Chloroform-d)** δ 174.1, 138.7, 136.3, 129.4, 129.4, 128.8, 128.5, 128.5, 128.5, 127.3, 66.5, 65.4, 58.8, 53.4, 29.6, 23.3.

Ethyl-2-(benzylamino)-3-phenylpropanoate (24)

General Procedure D: Free-based alpha amino acid ester (9) (5.3 mmol), alcohol (12) (6.4 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 1:4 Ethyl acetate/hexanes) to afford the product (24) (621 mg, 41%) as a yellow oil.

**¹H NMR (600 MHz, Chloroform-d)** δ 7.35 – 7.20 (m, 10H), 4.14 (q, J = 7.0 Hz, 2H), 3.88 (d, J = 13.2 Hz, 1H), 3.71 (d, J = 13.2 Hz, 1H), 3.59 (t, J = 7.0 Hz, 1H), 3.06 – 2.99 (m, 2H), 2.03 (s, 1H), 1.19 (t, J = 7.3 Hz, 3H).

**¹³C NMR (600 MHz, Chloroform-d)** δ 174.7, 140.0, 137.7, 129.6, 128.6, 128.5, 128.3, 127.3, 127.1, 126.9, 126.7, 62.4, 60.8, 60.7, 60.5, 52.2, 40.1, 14.5, 14.4.
Methyl-2-(benzylamino)-3-(4-hydroxyphenyl)propanoate (25)

General Procedure D: Free-based alpha amino acid ester (10) (3.3 mmol), alcohol (12) (4.2 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 1:19 MeOH/DCM) to afford the product (25) (450 mg, 48%) as a yellow oil.

**¹H NMR (600 MHz, Chloroform-d):** δ 7.29 – 7.17 (m, 5H), 6.95 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.07 (s, 1H), 3.80 (d, J = 13.1 Hz, 1H), 3.65 (d, J = 13.5 Hz, 4H), 3.53 (t, J = 6.8 Hz, 1H), 3.46 (s, 1H), 2.90 (d, J = 6.8 Hz, 2H).

**¹³C NMR (150 MHz, Chloroform-d):** δ 175.2, 155.3, 139.0, 130.4, 128.7, 128.6, 128.5, 128.3, 127.5, 127.4, 115.8, 115.7, 74.8, 74.8, 62.3, 62.1, 52.3, 52.2, 52.1, 52.0, 51.9, 38.7.
Methyl-2-((4-methoxybenzyl)amino)-3-phenylpropanoate (26)

General Procedure D: Free-based alpha amino acid ester (7) (3.7 mmol), solution of alcohol (14) (4.5 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 1:4 Ethyl acetate/hexanes) to afford the product (26) (591 mg, 54%) as a yellow oil.

\[
\begin{align*}
\text{1H NMR (600 MHz, Chloroform-d)} & \delta 7.28 (t, J = 7.4 \text{ Hz}, 2\text{H}), 7.25 - 7.14 (m, 5\text{H}), 6.83 (d, J = 8.6 \text{ Hz}, 2\text{H}), 3.79 - 3.73 (m, 4\text{H}), 3.64 (s, 3\text{H}), 3.60 (d, J = 12.1 \text{ Hz}, 1\text{H}), 3.56 (t, J = 6.9 \text{ Hz}, 1\text{H}), 2.97 (d, J = 6.9 \text{ Hz}, 2\text{H}), 1.90 (s, 1\text{H}).
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR (600 MHz, Chloroform-d)} & \delta 175.2, 158.9, 137.6, 131.9, 129.5, 128.6, 126.8, 113.9, 62.2, 55.3, 51.6, 51.6, 39.9. \quad [\alpha]_D^{25} = -3.97^\circ
\end{align*}
\]
Methyl-2-((4-bromobenzyl)amino)-3-phenylpropanoate (27)

\[
\begin{align*}
\text{General Procedure D:} & \quad \text{Free-based alpha amino acid ester (7) (3.5 mmol), alcohol (15) (4.3 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO}_2, 1:9 \text{ Ethyl acetate/hexanes) to afford the product (27) (719 mg, 59\%) as a yellow oil.} \\
1^H \text{ NMR (600 MHz, Chloroform-d)} & \quad \delta \text{ 7.36 – 7.01 (m, 9H), 3.73 (d, } J = 13.6 \text{ Hz, 1H), 3.61 (s, 3H), 3.53 (d, } J = 13.6 \text{ Hz, 1H), 3.45 (t, } J = 6.9 \text{ Hz, 1H), 2.98 – 2.84 (m, 2H), 2.29 (s, 1H).} \\
13^C \text{ NMR (600 MHz, Chloroform-d)} & \quad \delta \text{ 175.0, 138.7, 137.3, 131.6, 129.9, 129.3, 128.6, 126.8, 120.9, 51.9, 51.3, 39.8.} \\
[\alpha]_D^{25} & \quad = -4.60^\circ
\end{align*}
\]

Methyl-2-((4-nitrobenzyl)amino)-3-phenylpropanoate (28)

\[
\begin{align*}
\text{General Procedure D:} & \quad \text{Free-based alpha amino acid ester (7) (3.5 mmol), alcohol (16) (4.5 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO}_2, 2:3 \text{ Ethyl acetate/hexanes). The desired product (27) was not obtained (0g, 0\%).}
\end{align*}
\]
Methyl-2-(cyclohexylamino)-3-phenylpropanoate (29)

![Chemical structure of methyl-2-(cyclohexylamino)-3-phenylpropanoate (29)]

General Procedure D: Free-based alpha amino acid ester (7) (4.4 mmol), alcohol (17) (5.5 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 7:13 Ethyl acetate/hexanes) to afford the product (27) (485 mg, 43%) as a yellow oil.

**¹H NMR (600 MHz, Chloroform-d)** \( \delta \) 7.26 – 7.10 (m, 5H), 3.61 (t, \( J = 7.1 \) Hz, 1H), 3.55 (s, 3H), 2.93 – 2.80 (m, 2H), 2.33 – 2.25 (m, 1H), 1.98 (s, 1H), 1.83 – 1.48 (m, 4H), 1.18 – 1.03 (m, 4H), 0.92 (q, \( J = 10.6 \) Hz, 2H).

**¹³C NMR (600 MHz, Chloroform-d)** \( \delta \) 175.7, 171.2, 137.5, 129.3, 129.2, 128.5, 128.4, 126.8, 126.7, 60.5, 60.4, 60.2, 55.3, 55.2, 51.7, 51.6, 42.1, 40.3, 34.2, 34.1, 26.1, 25.0, 24.8, 14.4, 14.3. \( [\alpha]_{D}^{25} = + 1.00^\circ \)

Methyl-2-(butylamino)-3-phenylpropanoate (30)

![Chemical structure of methyl-2-(butylamino)-3-phenylpropanoate (30)]

General Procedure D: Free-based alpha amino acid ester (7) (3.1 mmol), alcohol (18) (3.9 mmol) and toluene (2 mL). Reaction mixture was heated for 17 h. Purified by flash chromatography (SiO₂, 3:17 Ethyl acetate/hexanes) to afford the hydrolyzed product (30) (170 mg, 23%) as a yellow oil.

**¹H NMR (600 MHz, Chloroform-d)** \( \delta \) 7.28 – 7.09 (m, 5H), 6.22 (s, 1H), 3.61 (t, 1H), 3.07 (dd, \( J = 13.5, 6.0 \) Hz, 1H), 2.93 (dd, \( J = 13.5, 7.9 \) Hz, 1H), 2.61 – 2.53 (m, 2H), 2.05 (s, 1H), 1.51 – 1.40 (m, 2H), 1.32 – 1.16 (m, 2H), 0.85 (q, \( J = 7.2 \) Hz, 3H).

**¹³C NMR (150 MHz, Chloroform-d)** \( \delta \) 176.2, 173.9, 136.8, 129.5, 128.7, 127.1, 64.9, 62.9, 47.7, 39.2, 31.5, 30.7, 29.9, 21.4, 20.4, 19.2, 14.1, 13.9. \( [\alpha]_{D}^{25} = + 0.00^\circ \)
2.6. References


Chapter 3: Iridium Catalyzed Synthesis of Substituted Azepanes from Diols

3.1. Abstract

Amphibian alkaloids are of great interest to the pharmaceutical and academic communities due to their biological activities. Unfortunately, they are not naturally available in large quantities which makes total synthesis the most common method of generating these compounds for evaluation. One amphibian alkaloid class of interest to us are the Lehmizidines. These are bicyclic ring structures consisting of a 7-member and 5-member ring with a nitrogen bridgehead. The alkaloid, lehmizidine 275A, was selected as a target for a general synthetic approach. This synthetic approach required the synthesis of novel diols. The construction of these diols along with a method for the synthesis of the azepane ring is presented here.

3.2. Introduction

3.2.1. Alkaloids

Alkaloids comprise a group of compounds that have a basic often cyclic nitrogen containing functional group. Some common, well known examples of alkaloids are nicotine, which is an alkaloid from the tobacco plant, morphine, which is isolated from the opium poppy plant, and cocaine, which is obtained from the leaves of the coca plant (Figure 10).1–3

Figure 10: Examples of common plant alkaloids.

In nature, these compounds are generated by both plants and some animals as a means of defense against predators. Amphibians like frogs and toads store alkaloids obtained through
their diet in granular skin glands for secretion; the irritating properties of these compounds on the mucous membrane tissues and their antimicrobial activity thus allow them to serve as a chemical defense for the amphibians. These alkaloids are generally lipophilic in nature and a large number are biologically active. As of 2005 over 800 such compounds representing 24 structural categories had been reviewed and classified by Daly, Spande, and Garraffo. The diversity of structural features and biological activities present in these compounds produced great interest both academically and in the pharmaceutical world. Unfortunately, obtaining the necessary amounts of these compounds needed for toxicity and biological activity tests proved to be difficult as isolating the alkaloid from the natural source produced very small amounts; 100μg to 20mg per frog depending on the alkaloid. Due to this lack of natural source material for study, total synthesis of these natural products is the most common method of generating material for toxicology, biological activity tests and for structure elucidation study.

3.2.2. Lehmizidines

One of the categories identified by Daly, Spande and Garraffo are the Lehmizidines. These compounds are isolated from the Colombian dendrobatid frog (*dendrobates lehmanni*) from which they take their name. This izidine alkaloid (Figure 11) consists of a 7-member ring and a 5-member ring. Coding for these structures is based on the category assigned, the nominal molecular weight and an identifying letter, the latter two are given in bold-face text. The structure and substitution pattern for 275A was established by mass spectral analyses while comparison to the four synthetic diastereomers of perhydro-275A was used establish the relative configuration of the structure. To date, nine alkaloids have been placed in the Lehmizidine category (Table 6); the structures for all of these compounds remain tentative.

![Figure 11: General structure of a lehmizidine.](image-url)
Table 6: Absolute configuration of lehmizidine is unknown. **Relative configuration is as shown in Figure 11 and other structures are believed to have similar configurations.

<table>
<thead>
<tr>
<th>Lehmi</th>
<th>R</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>275A**</td>
<td>(CH₂)$_7$C≡CH</td>
<td>H</td>
</tr>
<tr>
<td>275G</td>
<td>(CH₂)$_5$CH=CHCH=CH₂</td>
<td>H</td>
</tr>
<tr>
<td>277A</td>
<td>(CH₂)$_3$CH=CH₂</td>
<td>H</td>
</tr>
<tr>
<td>289A</td>
<td>C$<em>9$H$</em>{13}$O (=O, C≡CH)</td>
<td>H</td>
</tr>
<tr>
<td>289D</td>
<td>(CH₂)$_3$CH=CHC≡CH</td>
<td>OH</td>
</tr>
<tr>
<td>291C</td>
<td>C$<em>9$H$</em>{15}$O</td>
<td>H</td>
</tr>
<tr>
<td>291F</td>
<td>(CH₂)$_3$C≡CH</td>
<td>OH</td>
</tr>
<tr>
<td>293F</td>
<td>C$<em>9$H$</em>{17}$O (=O)</td>
<td>H</td>
</tr>
<tr>
<td>293I</td>
<td>(CH₂)$_7$CH=CH₂</td>
<td>OH</td>
</tr>
</tbody>
</table>

3.2.3. Synthesis of Lehmizidine 275A-Garaffo et al.\textsuperscript{6}

In 2001, Garaffo and co-workers definitively identified the relative configuration of Lehmizidine 275A and reported the first total synthesis of this structure.\textsuperscript{6} Based on their HREIMS and GC-FTIR findings they knew that this compound had a molecular formula of C$_{19}$H$_{33}$N and a nine carbon side chain with an acetylene functional group at the end. The relative configuration was nailed down through comparison of the original amphibian alkaloid to its synthetic perhydro-diastereomers (Figure 12).\textsuperscript{6}

Figure 12: Isolated amphibian alkaloid and synthetic perhydro-diastereomers.
Reductive amination of a triketone was used to obtain this mixture of diastereomers and gas chromatography was used to separate the mixture. Analysis of the GC-retention times indicated that third diastereomer (6c) eluted at the same time as 275A. They then designed two syntheses to determine the relative configuration of 6c and consequently 275A.

The first synthesis (shown below in Scheme 35) employed the use of reductive amination to generate a mixture of cis/trans pyrrolidine ketals designated 5a and 5b. These were then deprotected and cyclized to form the desired diastereomers (6a, 6b, 6c, 6d). It was noted that the major products from the cis/trans mixture were 6b and 6d. Even when pure cis-5a was deprotected and cyclized the major product generated was 6b. This was an indication that the pyrrolidine ring in 6b was cis and therefore trans in 6d.

Scheme 35: Synthesis of perhydro-275A diastereomers starting from a pyrrolidine.

Reagents and Conditions: (a) CH₂=CHMgBr; (b) PCC; (c) thiazolium salt, Et₃N, 57%; (d) NH₄OAc; (e) NaCNBH₃, 90% (two steps); (f) N-chlorosuccinimide; (g) KOH; (h) H₂, Rh/Al₂O₃; (i) H⁺
Since the trans pyrrolidine diastereomers were difficult to obtain through this initial synthesis the secondary synthesis was employed. This route builds the 7-member ring first and then pyrrolidine ring. As illustrated in Scheme 36 this was accomplished by synthesizing the ketoacetal (7) from methyl vinyl ketone and a brominated acetal through a nickel-catalyzed conjugate addition. The ketone group on (7) was then converted to a secondary amine through titanium-mediated reductive amination yielding the aminoacetal (8). The deprotection of this compound in the presence of potassium cyanide produced the desired cyanoazepane (9). The nitrile group was then subjected to Grignard addition with 2-(2-bromoethyl)-1,3-dioxane to produce (12). It was found that removal of the benzyl group gave a 1:1 cis/trans mixture of the dioxanyl azepanes (13a and 13b). When these azepanes were further deprotected in the presence of potassium cyanide and then the bicyclic products were treated with Grignard reagent n-nonylmagnesiumbromide the diastereomers 6a, 6b, 6c, and 6d were produced in a 45:13:11:31 ratio. It was found that when starting with the pure cis dioxanyl azepane (12a) and subjecting it to the treatment just outlined only the diastereomers 6b and 6d were obtained. This was an indication that the azepane ring in these diastereomers was cis and therefore that the azepane ring in 6a and 6c was trans. After hydrogenating the isolated natural alkaloid lehmizidine 275A to remove the terminal alkyne, it was co-injected with the four diastereomers 6a-d. The GC retention time of 275A matched that of 6c thus confirming the relative configuration assignment made by Garraffo and co.
Scheme 36: Synthesis of perhydro-275A diastereomers starting from an azepane.

Reagents and conditions: (a) Ni, Py, 97%; (b) Ti(OPr)₄/PhCH₂NH₂; (c) NaCNBH₃, 60% (two steps); (d) H⁺; (e) KCN; (f) NH₄CO₂H/Pd/C, 70%; (g) BrMg-n-C₉H₁₉, 80% (three steps); (h) N-chlorosuccinimide; (i) KOH; (j) H₂/Rh/Al₂O₃; (k) BrMg-C₂H₅
3.2.4. Synthesis of Lehmizidine 275A-Lesma, Sacchetti, and Silvani

Lesma, Sacchetti, and Silvani were the second group to report a total synthesis of 275A in their article published in 2010. Their synthesis of the bicyclic ring structure started with the pyrrolidine ring and built to the intramolecular cyclization of azepane ring leaving the addition of the terminal alkyne on the seven-carbon side chain for last (Scheme 37). They used as their starting point commercially available L-pyroglutamic which was converted to the methyl lactamol 14 using chemistry established by Aggarwal, Astle, and Rogers-Evans. The lactamol then had a butylene chain added using but-3-enylmagnesium and a CuBr·Me₂S complex. Once this chain was added the Boc group was removed and the desired trans-diastereomer (15) was isolated using chromatographic separation. This compound was then protected with a benzyl group to give 16 which was then sequentially reduced with lithium aluminum hydride and treated with tosyl chloride. This provided the tosylate 17 which was then used in a Grignard addition reaction along with 6-(t-butyldimethylsilyloxy)hexyl iodide, t-BuLi, and CuI to synthesize the trans-pyrrolidine 18. It was then combined with methyl vinyl ketone in a cross-coupling reaction to give the pyrrolidine 19. This structure now contained everything needed to make the bicyclic structure. Dehydrogenation of 19 removed the benzyl protecting group and initiated the desired intramolecular cyclization yielding the major diastereomer 20 in a 5:1 ratio after chromatographic separation. The diastereomer 20 was then further deprotected to remove the silyl group from the alcohol group at the end of the seven-carbon chain. This alcohol group was then converted to a bromide on reaction with CBr₄ and PPh₃ giving an alkyl bromide 23. Finally, to produce the desired alkyne, 23 was reacted with a lithium acetylide-ethylendiamine complex in DMSO. Based on 2D NMR NOESY experiments and computation predictions the relative configuration of the major diastereomer 24 matched that of 275A.
Scheme 37: Total synthesis of 275A from a pyrrolidine.

Reagents and conditions:  (a) (i) but-3-enylmagnesium bromide, CuBr-Me2S, BF3·Et2O, THF dry, -78°C to rt, 84%, (ii) 30% TFA in CH2Cl2, 0°C to rt, (iii) chromatographic separation, 74% (overall); (b) Cbz-Cl, TEA, CH2Cl2, 96%; (c) LiBH4 2M in THF, 0°C, 84%; (d) p-TsCl, TEA, DMAP, CH2Cl2, 0°C to rt, 97%; (e) 25, t-BuLi 1.7M in pentane, Cul, Et2O/hexane, -78°C to -5°C, 81%; (f) methyl vinyl ketone, Ru-cat. Hoveyda-Grubbs, toluene, 40°C, 90%; (g) (i)H2, Pd/C 10%, MeOH, rt, (ii) chromatographic separation, 76% (overall); (h) TBAF, THF, 0°C to rt, 62%; (i) CBr₄, PPh₃, CH2Cl2, 0°C to rt, 93%; (j) lithium acetylide ethylenediamine complex, DMSO, rt, 45%.

3.2.5. Application of Iridium catalyzed “borrowing hydrogen” methodology for the synthesis of natural products.

Our group has long had an interest in the synthesis of bicyclic amphibian alkaloids. Structures like these are of interest both because they may be of pharmaceutical importance and because developing a general method for the synthesis of the base ring structure could then allow for access to other more complex structures. Our focus recently has been the use of an Iridium catalyst and borrowing hydrogen methodology in the synthesis of natural products. This
methodology\textsuperscript{10} has proved efficacious in the both the enantioselective synthesis of Noranabasamine\textsuperscript{11} and in the synthesis of nicotine and anabasine derivatives.\textsuperscript{12} The total synthesis of noranabasamine as reported by our group is illustrated below in Scheme 38. The construction of the three-ring system uses a combination of methodology developed in our lab\textsuperscript{13} for the synthesis of the diol and the N-heterocyclization conditions optimized by Fujita et al.\textsuperscript{10} A commercially available pyridine 25 was combined with n-butyllithium and δ-valerolactone to give ketone 26 which was subsequently reduced to provide the diol 27. The diol and (R)-1-phenylethylamine were then combined in toluene with the iridium catalyst ([Cp*IrCl\textsubscript{2}]) and heated at 110°C in a sealed pressure tube. This reaction gave the two diastereomers of the 2-substituted piperidine 28\textsubscript{a} and 28\textsubscript{b} with a diastereomeric ratio of 28\textsubscript{a}:28\textsubscript{b} 95:5. This reaction was repeated using (S)-1-phenylethylamine and the resulting diastereomers 29\textsubscript{a} and 29\textsubscript{b} were obtained with a diastereomeric ratio of 29\textsubscript{a}:29\textsubscript{b} 95:5. The piperidine ring system underwent hydrogenation to remove the N-substitution and then was subjected to treatment with phosphoryl trichloride which gave the chlorinated analogues 30 and 31. Finally to obtain both enantiomers of noranabasamine, Fu and coworkers’ Suzuki-Miyaura coupling condition\textsuperscript{14} were applied to 30 and 31.
Scheme 38: Iridium catalyzed synthesis of Noranabasamine.

Reagents and conditions: (a) (i) n-BuLi, Et₂O, -78°C; (ii) δ-valerolactone, 98%; (b) BH₃·SMe₂, toluene, 40°C, 88%; (c) (i) (R)-1-phenethylamine, KOAc, [Cp*IrCl₂]₂, toluene, 110°C, (ii) chromatographic separation, 72%, dr = 95:5; (d) (i) (S)-1-phenethylamine, KOAc, [Cp*IrCl₂]₂, toluene, 110°C, (ii) chromatographic separation, 69%, dr = 95:5; (e) (i) H₂, Pd/C, EtOH, 55°C; (ii) POCl₃, 120°C; (f) 3-pyridineboronic acid, Pd₂(dba)₃, PCy₃, K₃PO₄, dioxane/H₂O, 100°C, 18h
In addition to using the \([\text{Cp}^*\text{IrCl}_2]_2\) catalyst for the N-heterocyclization step of the synthesis of noranabasamine our group has also used it in the development of an environmentally friendly synthesis of nicotine and anabasine derivatives.\(^\text{12}\) The synthesis of 2-substituted pyrrolidines and 2-substituted piperidines from 1,4-butanediols and 1,5-pentanediols was performed in the microwave and optimized using sodium bicarbonate as a base under aqueous conditions. The preparation of the diol employed methodology developed in our laboratory and is illustrated below in Scheme 39.\(^\text{12}\) The 3-bromopyridine (33a) or 5-bromo-2-methoxypyridine (33b) was dissolved in diethyl ether at -78°C and treated with n-butyllithium. γ-Butyrolactone or δ-valerolactone were subsequently added to the reaction mixture to produce the hydroxy ketones. The hydroxy ketones were then subjected to reduction with sodium borohydride in methanol affording the desired diols. The N-heterocyclization process was conducted by the addition of the diol to a stirred solution of \([\text{Cp}^*\text{IrCl}_2]_2\), Na\(_2\)CO\(_3\), and water in a microwave reactor tube. This solution was treated with an amine and then irradiated at 110°C for 2 hours thus affording the final products in good yields.

Scheme 39: Synthesis of nicotine and anabasine derivatives
3.3. Results and Discussion

3.3.1. Retrosynthesis approach and synthetic strategies.

We have recently demonstrated the usefulness of the iridium catalyzed N-heterocyclization for the synthesis of novel substituted pyrrolidine and piperidine structures from diols. Fujita and coworkers have also demonstrated the utility of this method in the synthesis of unsubstituted azepanes from 1,6-hexanediols. Given our interest in the amphibian alkaloids it was a natural progression of our work to apply this methodology to the lehmizidine ring structure.

Our retrosynthetic approach for the construction of the bicyclic ring system is mapped out in Figure 13. We thought to introduce the acetylene group last using the chemistry employed by Lesma, Sacchetti, and Silvani in their total synthesis of lehmizidine 275A. This would follow the creation of the five-member ring of the lehmizidine through removal of the protecting group from the azepane nitrogen and subsequent intramolecular reductive amination. It is envisioned that the scaffold for the five-member ring could be introduced by Grignard addition at the nitrile group of the 7-member ring. The 7-member ring structure could be accessed through iridium-catalyzed borrowing hydrogen chemistry and an appropriate diol and amine.

As diols of this type were not available for purchase it was also necessary to devise a synthetic strategy for their synthesis. We chose 5-acetylvaleric acid as the starting material as it
contained the basic skeletal structure we desired and functional groups that we could manipulate independently of each other. There were other commercially available compounds that would have required less manipulation on our part to obtain the diol however the cost per gram of these compounds made their use economically unreasonable.\textsuperscript{20,21} We developed two synthetic strategies for the synthesis of the diol, both of which share a common starting point and only deviate after the synthesis of the protected ester (42) as laid out in Scheme 40. The commercially available 5-acetylvaleric acid will be converted to a keto-ester (40) which allows for the reduction of the ketone and subsequent protection of the newly formed alcohol group to form (42).

\begin{center}
\includegraphics[width=\textwidth]{scheme40.png}
\end{center}

\textbf{Scheme 40:} Common starting point-the synthesis of a protected ester.

With the protected ester (42) in hand we can continue down one of two paths. The first strategy is outlined below in Scheme 41 and employs the use of a Weinreb amide (43) to Weinreb ketone conversion\textsuperscript{22,23} as one of the major building steps. This reaction was chosen as it is considered very reliable and does not lead to over addition as can sometimes be the case with Grignard reactions. After the vinyl ketone is added it can be reduced and then the entire compound would be deprotected to produce the desired vinyl diol (46).
Scheme 41: Strategy one-synthesis of diol from protected ester.

Strategy two reduces the protected ester (42) to a primary alcohol (47), then oxidizes it to an aldehyde (48) and converts it to a secondary vinyl alcohol (45) through a Grignard reaction followed by a final deprotection step to give the vinyl diol (46) (Scheme 42).

3.3.2. Synthesis of the Protected Ester

With our synthetic strategies in hand we set out to convert 5-acetylvaleric acid into the protected ester. As illustrated in Scheme 43 5-acetylvaleric acid was refluxed with methanol and a catalytic amount of concentrated sulfuric acid. This provided the keto-ester (40) in a
quantitative yield. The ketone on 40 was then treated with sodium borohydride in methanol at 0°C to afford the corresponding secondary alcohol (41) in excellent yield (90%).

Scheme 43: Conversion of 5-acetylvaleric acid functional groups.

Several sets of reaction conditions were explored before finding one that gave the protected ester (42) in excellent yield. These are shown below in Table 7. It was found that the combination of imidazole and tert-butyldimethylsilyl chloride (TBDMS-Cl) in anhydrous dichloromethane (DCM) at room temperature for 12 hours provided 42 in 74% yield after chromatographic purification.

Table 7: Optimization of TBDMS-Cl addition reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>TBDMS-Cl (eq)</th>
<th>Base used (eq.)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Run time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>DIPEA (4.5)</td>
<td>DCM</td>
<td>35</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>DIPEA (4.5)</td>
<td>THF</td>
<td>35</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>Imidazole (2.5)</td>
<td>THF</td>
<td>25</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Imidazole (3.5)</td>
<td>DCM</td>
<td>25</td>
<td>12</td>
<td>74</td>
</tr>
</tbody>
</table>

3.3.3. Attempted synthesis of the vinyl diol – Strategy One

With the protected ester in hand we opted to employ Strategy One and attempted to synthesize the Weinreb vinyl ketone as laid out in Scheme 41. Using the chemistry put forth by Weinreb and Nahm we attempted to convert the protected ester to the Weinreb amide. The protected ester (42) was dissolved in anhydrous tetrahydrofuran (THF) and added to a slurry of
N-methoxy-N-methylamine hydrochloride and isopropyl magnesium bromide at -5°C. The solution was stirred until TLC showed an absence of 42. The reaction was then quenched and subjected to chromatographic purification.

After several unsuccessful attempts in which only starting material was recovered we went back into the literature and found an article by Williams et al24 in which they noted that the order of reagent addition can be significant. They suggested that it was important to combine the N-methoxy-N-methylamine hydrochloride with the ester before adding the isopropyl magnesium bromide. It was thought that combining the N-methoxy-N-methylamine hydrochloride with the isopropylmagnesium bromide first led either to degradation or a reaction with the organomagnesium reagent.24 With this in mind 42 was combined with N-methoxy-N-methylamine hydrochloride and dissolved with anhydrous THF. This solution was then treated with isopropyl magnesium bromide at -5°C. The solution was stirred until TLC showed an absence of the protected ester (42). The reaction was then quenched and subjected to chromatographic purification giving the Weinreb amide (43) in good yield (62%) (Scheme 44).

Scheme 44: Conversion of TBDMS-protected ester (42) to Weinreb amide (43)

<table>
<thead>
<tr>
<th>Reagents and conditions:</th>
<th>(a) (i) N,O-dimethylhydroxylamine, dry THF, -5°C, iPrMgBr; (ii) 42, dry THF; (iii) chromatographic separation, 0%</th>
<th>(b) (i) N,O-dimethylhydroxylamine, dry THF, 42, -5°C; (ii) iPrMgBr, warm to rt; (iii) chromatographic separation, 62%</th>
</tr>
</thead>
</table>

Having successfully obtained the Weinreb amide (43) we now set about converting it to the Weinreb vinyl ketone (44).22,23 The amide was treated with vinylmagnesium bromide in anhydrous THF at -5°C and then the reaction solution was slowly warmed to room temperature and monitored until TLC showed an absence of 43. The reaction was then quenched and subjected to chromatographic purification. Unfortunately, this set of reaction conditions did not
yield any of 44. We again reviewed the literature and found a method suggested by Prosser and Liotta\textsuperscript{25} for synthesizing the vinyl ketone from the ester in a one-pot sequence. Their process saw the Weinreb amide formed in situ using isopropylmagnesium chloride and then converting to the corresponding ketone by adding a slight excess of the appropriate nucleophilic Grignard. Using this new procedure we combined 42 with N-methoxy-N-methylamine hydrochloride and anhydrous THF. This solution was then treated with isopropyl magnesium bromide at -5°C and stirred until TLC showed an absence of the protected ester. Vinylmagnesium bromide was then added to the solution and reaction monitoring was continued by small aliquot workup. While these aliquots showed both 43 and 44 on TLC when the reaction was quenched and the crude product analyzed by NMR 44 was only present in very trace amounts. Extending the length of the reaction time did not appreciably increase the amount of 44. Based on these results it was decided that our chosen substrate was just not conducive to this conversion using this reaction; we therefore changed our strategy (Scheme 45).

![Scheme 45: Attempted synthesis of the Weinreb ketone 32.](image)

3.3.4. Synthesis of vinyl diol – Strategy Two

The first two steps of Strategy Two are the conversion of the ester to an aldehyde. While there are reagents available for the selective reduction of esters to aldehydes the use of these are notoriously tricky and with their use exists the potential for over reduction.\textsuperscript{26} Given the difficulty we had encountered with the Weinreb amide to ketone synthesis we therefore opted for a route that afforded us more synthetic control over the desired product. The protected ester (42) was treated with lithium aluminum hydride in anhydrous THF under an argon atmosphere to reduce it to the primary alcohol (47) in quantitative yield (Scheme 46)

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We then explored a variety of reagent conditions for oxidizing the primary alcohol back to an aldehyde. This optimization is outlined below in Table 8. It was found that the quality and age of the Dess-Martin Periodinane reagent used had a marked effect on both the reaction times and yields. The reagent was found to vary from vendor to vendor and the presence of a distinct “vinegary” odor was indicative of the reagent’s degradation. We obtained the best yields using new Dess-martin periodinane reagent from Oakwood Chemicals and tert-butyl alcohol as a co-reagent.

Table 8: Optimization of reaction conditions for aldehyde synthesis.

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Co-reagent</th>
<th>Temperature (°C)</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridinium dichromate (2eq)</td>
<td>3Å molecular sieves</td>
<td>0 - 25</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>Pyridinium dichromate (2eq)</td>
<td>3Å molecular sieves</td>
<td>0</td>
<td>4</td>
<td>31 (37 S.M.)</td>
</tr>
<tr>
<td>Dess-Martin Periodinane (1.2eq)</td>
<td></td>
<td>0</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>Dess-Martin Periodinane (2eq)</td>
<td>NaHCO₃ (5eq)</td>
<td>0 - 25</td>
<td>24</td>
<td>0 (85 S.M.)</td>
</tr>
<tr>
<td>Dess-Martin Periodinane (1.5eq)</td>
<td>NaHCO₃ (5eq), t-butyl alcohol (1.5eq)</td>
<td>0 - 25</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Dess-Martin Periodinane (1.5eq)</td>
<td>t-butyl alcohol (2eq)</td>
<td>0 - 25</td>
<td>1.5</td>
<td>71</td>
</tr>
<tr>
<td>Dess-Martin Periodinane (2eq)</td>
<td>t-butyl alcohol (2eq)</td>
<td>0 - 25</td>
<td>1.5</td>
<td>88</td>
</tr>
</tbody>
</table>

After obtaining the desired aldehyde (48) it was treated with vinylmagnesium bromide at -5°C and stirred until TLC showed an absence of the aldehyde. The solution was quenched and subjected to chromatographic purification giving a moderate yield (63% cr). It was noted at this point that two very similar products (31% and 32%) were being formed on the basis of TLC analysis. Their similarity made them difficult to purify chromatographically. It was posited that silyl migration might be occurring in situ, which would explain the very structurally similar products being formed. If that were the case, subjecting both products to deprotection should then afford the same vinyl diol product. To that end the mixture of similar products (45cr) were
dissolved in THF with an excess of tetra-n-butylammonium fluoride. This reaction was allowed to run for four days at which point it was stopped due to the appearance of possible degradation products. After purification, the vinyl diol (46) was successfully obtained in 18% yield (Scheme 47).

Scheme 47: Initial attempted synthesis of vinyl diol (46).

3.3.5. Synthesis of vinyl diol – Revised Strategy Two

Having successfully obtained the vinyl diol we turned our attention to increasing our yields by refining our strategy. Since we thought that migration of the silyl group might be an issue we opted to exchange the tert-butyldimethylsilyl chloride group for the more stable tert-butyldiphenylsilyl chloride group. With this change we then set about building our molecule as laid out in Scheme 48.
We obtained each of the intermediates in excellent yields until the conversion from the aldehyde (51) to the vinyl alcohol (46) step was reached. At this point we examined two methods for the deprotection step and the synthesis of the diol (46) (Scheme 49). The first method involved removing the protecting group with 3% methanolic HCl without first isolating the intermediate vinyl alcohol (52). This led to a much shorter reaction time and an increased diol yield. However, during the vinyl Grignard addition step we still observed what we presumed to be silyl migration while monitoring the reaction. With the change in protecting group these compounds were now clearly distinguishable from each other on TLC. The intermediate vinyl alcohol (52) was isolated and purified by chromatographic separation. Upon doing so we discovered that the two compounds we were observing were the desired vinyl alcohol (52) and the primary alcohol (50). While some reduction of the aldehyde was not ideal the ability to isolate and reuse 50 was a positive. With the isolated 52 (39% yield) in hand the second method of deprotection was explored. For this method, 52 was treated with an excess of tetra-N-butyl ammonium fluoride (TBAF) and monitored by TLC until the reaction was complete. The reaction was then quenched and stirred with an ion exchange resin and calcium.
carbonate to remove most of the TBAF from solution. After purification, 46 was successfully obtained in 95% yield (37% yield over two steps).

![Chemical structure](image.png)

**Scheme 49**: Synthesis of vinyl diol; deprotection performed using either a one-pot system or over two steps.

3.3.6. **Synthesis of mono- and di-substituted hexane diols for iridium catalyzed N-heterocyclization.**

With our process for the construction of the vinyl diol in hand we undertook the synthesis of several other diols. Using the established seven step method we were able to obtain these diols in good yields overall as laid out in Table 9. The only diol not synthesized using this method was the heptane-1,6-diol (entry 1); it was obtained through the reduction of 5-acetylvaleric acid with lithium aluminum hydride in one step.
3.3.7. Attempted iridium catalyzed N-heterocyclization of 1,6- and 2,6-heptane-diols.

Having established an efficient route for the preparation of these novel diols we turned our attention to the construction of the azepane ring needed for the bicyclic ring structure of lehmizidine 275A. Using 2,5-hexanediol as a model substrate for comparative purposes and the method established by Fujita et al\textsuperscript{10} for the N-heterocyclization of diols from primary amines we attempted the synthesis of the mono-substituted azepane ring. The low yields obtained for the azepane ring to led to an examination of the reaction conditions (Table 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diol</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image of diol 1]</td>
<td>62*</td>
</tr>
<tr>
<td>2</td>
<td>![Image of diol 2]</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>![Image of diol 3]</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>![Image of diol 4]</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 9: Overall yields of synthesized diols.
Initially, we thought that the poor yields were due to the use of reactions conditions specialized for the 2,5-hexanediol but switching to the more generalized reaction conditions only improved the yields of the N-benzyl-2,5-dimethylpyrrolidine. Because the diols were extremely viscous and not very soluble in toluene we also tried running the reaction under aqueous conditions in the microwave positing that our groups previous success with 1,4-butanediols and 1,5-pentanediols might apply in this case. Unfortunately, these reaction conditions also did not give improved yields when compared to the original method.

It was noted that upon addition of the benzylamine to the reaction solution containing the diol, catalyst and base a precipitate formed. The speed of the formation seemed to be dependent on the concentration of the diol in the solution, as at lower concentrations there was less precipitate and it did not form until the solution was stirred. This contrasted with the higher concentrations where it formed as the benzylamine was being added. In all cases, the precipitate would dissolve into solution when heated. An analysis of the material remaining after isolation of the 1-benzyl-2-methylazepane product showed that polymerization was occurring rather than the desired cyclization (Figure 14).
Figure 14: Proposed polymeric structures.

The peaks at 310 and 634 correspond to what we believe to be a monomer and dimer respectively. The peak at 961 corresponds to the proposed polymeric structure which consists of five benzyl amines daisy chained together by the diols. The remaining significant peaks correspond to the loss of a benzyl group from the various fragments. For example, removing a benzyl group from the fragment represented by peak 310 would generate peak 219 (Figure 15).
**Figure 15:** Direct injection Electrospray Ionization mass spectrum of residue from heptane-1,6-diol N-heterocyclization.
In an attempt to prevent polymerization, we continued to decrease the amount of diol present in solution; we found that at a concentration of 0.2M we had significantly increased the yields of the mono-substituted azepane ring and so we moved forward with our attempts at cyclization of the di-substituted azepane rings from the synthesized diols. Unfortunately, in these cases we saw no formation of the azepane product while monitoring the reaction by TLC and mass spectrometry analysis of the compounds obtained confirmed that polymerization had occurred.

3.4. Conclusions

We have devised a strategy for the synthesis of several economically unviable and/or commercially unavailable diols and were successful in our goal in synthesizing these diols in good overall yields. We have also demonstrated a method for the formation of a mono-substituted azepane ring using iridium-catalyzed N-heterocyclization. Further work for improving the reaction conditions for the synthesis of the di-substituted azepane ring systems is needed to overcome polymerization issues.
3.5. Experimental Section

General Methods

Chemicals were purchased from Alfa Aesar, Oakwood Chemicals, Acros Organics, TCI Chemicals, and Sigma Aldrich unless otherwise noted. Toluene, tetrahydrofuran (THF), dichloromethane (DCM), and methanol (MeOH) were purchased from Fisher Scientific and distilled before use. All solvents were used under argon or nitrogen unless otherwise noted. Thin layer chromatography (TLC) 20 x 20 cm glass plates precoated with 250 μm silica gel were purchased from Sorbent Technologies and used to monitor reactions via visualization with shortwave UV light, iodine, potassium permanganate, phosphomolybdic acid (PMA), 2,4-dinitrophenyl hydrazine (2,4-DNPH), or p-anisaldehyde stains. Chromatography is in reference to flash column chromatography on silica gel (Silica Gel 60, 230-400 mesh). Proton and carbon NMR were recorded on a variety of Varian 300MHz, 400MHz, 500MHz, and 600MHz nuclear magnetic resonance spectrometers as well as a Bruker 300MHz nuclear magnetic resonance spectrometer. All spectra were obtained at ambient temperature in deuterated chloroform (CDCl₃) from Cambridge Isotope Laboratories, Inc. ¹H NMR chemical shifts are reported in δ values (ppm) relative to chloroform-d (7.26 ppm). ¹³C NMR chemical shifts are reported in δ values (ppm) relative to chloroform-d (77.0 ppm).
**Methyl 6-oxoheptanoate (40):** 5-acetylvaleric acid (5.109 g, 35.44 mmol) was dissolved in methanol (50 mL). Concentrated sulfuric acid (55 drops) was added to the reaction mixture and the mixture was refluxed using a Dean-Stark trap. The reaction progression was monitored by TLC using a 2,4-dinitrophenylhydrazine stain until all the starting material was consumed. The crude mixture was concentrated under reduced pressure. The residue was diluted with saturated NaHCO₃ (100 mL) and extracted with DCM (75 mL x 3). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 40 (5.534 g, 99%) as a clear, watery liquid.

**¹H NMR (300 MHz, Chloroform-d):** δ 3.55 (s, 3H), 2.35 (t, J = 7.0 Hz, 2H), 2.21 (t, J = 7.1 Hz, 2H), 2.03 (s, 3H), 1.53 – 1.46 (m, 4H)

**¹³C NMR (75 MHz, Chloroform-d):** δ 208.3, 173.6, 51.4, 43.0, 33.6, 29.7, 24.2, 23.0

**Methyl 6-hydroxyheptanoate (41):** To a solution of 40 (3.450 g, 21.81 mmol) in methanol (25 mL) at 0°C was added powdered NaBH₄ (0.906 g, 23.9 mmol). The reaction was stirred on ice and the reaction progression was monitored by TLC using a p-anisaldehyde stain until all the starting material was consumed. The crude mixture was concentrated under reduced pressure. The residue was diluted with DI water (100 mL) and extracted with EtOAc (75 mL x 3). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford crude 41 (3.193 g, 92%) as a white oil.

**¹H NMR (400 MHz, Chloroform-d):** δ 3.71 – 3.63 (m, 1H), 3.56 (s, 3H), 2.52 (s, 1H), 2.22 (t, J = 7.5 Hz, 2H), 1.60 – 1.48 (m, 2H), 1.42 – 1.21 (m, 4H), 1.07 (d, J = 6.2 Hz, 3H)

**¹³C NMR (100 MHz, Chloroform-d):** δ 174.4, 67.6, 51.6, 38.8, 34.1, 25.3, 24.9, 23.5.
Methyl 6-((tert-butyldimethylsilyl)oxy)heptanoate (42): Imidazole (6.919 g, 0.102 mol) and 41 (4.652 g, 0.0290 mol) were placed in a clean, dry flask and solvated with anhydrous DCM (40 mL) under a blanket of nitrogen. Tert-butyldimethylsilyl chloride (TBDMS-Cl) (8.977 g, 0.0596 mol) was solvated with anhydrous DCM (15 mL) under a blanket of argon in a separate flask. This solution was added drop-wise to the reaction flask containing the stirred solution of imidazole and 41. On addition of the TBDMS-Cl solution a white precipitate formed. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with DCM (50 mL) and extracted with DI water (1 x 150 mL). Organic fraction was set aside and the aqueous fraction was extracted with t-butyl methyl ether (2 x 150 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:49 DCM/hexane) to yield 42 (5.899 g, 74%) as a pale-yellow oil.

¹H NMR (400 MHz, Chloroform-d): δ 3.77 (h, J = 6.1 Hz, 1H), 3.65 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.48 – 1.22 (m, 4H), 1.10 (d, J = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (d, J = 2.3 Hz, 6H)

¹³C NMR (100 MHz, Chloroform-d): δ 174.4, 68.5, 51.6, 39.4, 26.1, 25.5, 25.2, 23.9, -4.2, -4.5

6-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylheptanamide (43) (method a): N,O-dimethylhydroxylamine hydrochloride (757 mg, 7.12 mmol) was solvated in anhydrous THF (5 mL) under a blanket of nitrogen. The slurry was cooled to -5°C and a solution of isopropylmagnesium bromide (1M in THF, 14.4 mL) was added dropwise to the reaction flask. On addition the remaining solid N,O-dimethylhydroxylamine hydrochloride dissolved into solution. 42 (1.194 g, 4.75 mmol) was solvated with anhydrous THF (1.5 mL) under a blanket of nitrogen in a separate flask. This solution was also added drop-wise to the
reaction flask containing the stirred solution of N,O-dimethylhydroxylamine hydrochloride and isopropyl magnesium bromide. This addition was accompanied by a color change (from yellow to pale brown). The reaction was stirred on ice and progression was monitored by TLC using a p-anisaldehyde stain. The reaction was quenched with saturated NH₄Cl (50 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic fractions were washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. An NMR analysis of the crude material showed only S.M. present. (0g, 0%

(method b): N,O-dimethylhydroxylamine hydrochloride (967 mg, 9.75 mmol) and 42 (1.787 g, 6.504 mmol) were solvated in anhydrous THF (20.0 mL) under a blanket of argon. The slurry was cooled to -5°C and a cold solution of isopropylmagnesium bromide (3M in THF, 6.6 mL) was added dropwise to the reaction flask. On addition the remaining solid N,O-dimethylhydroxylamine hydrochloride dissolved into solution. The reaction was warmed to room temperature and progression was monitored by TLC using a p-anisaldehyde stain. The reaction was quenched with 20% NH₄Cl (30 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with CHCl₃ (50 mL x 3). The combined organic fractions were washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:4 EtOAc:Hexanes) to yield 43 (1.214 g, 62%) as a pale yellow oil.

¹HNMR (400 MHz, Chloroform-d): δ 3.75 – 3.66 (m, 1H), 3.60 (s, 3H), 3.09 (s, 3H), 2.33 (t, J = 7.6 Hz, 2H), 1.61 – 1.48 (m, 2H), 1.41 – 1.19 (m, 4H), 1.03 (d, J = 6.1 Hz, 3H), 0.80 (s, 9H), -0.04 (s, 6H)

¹³CNMR (100 MHz, Chloroform-d): δ 68.5, 61.2, 39.5, 26.0, 25.6, 24.8, 23.6, -4.3, -4.6
Attempted Synthesis of 8-((tert-butyldimethylsilyl)oxy)non-1-en-3-one (44)

(method a): The Weinreb amide (43) (1.256 g, 4.137 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon and the reaction solution was cooled to -5°C. A cold solution of vinylmagnesium bromide (1M in THF, 8.2 mL) was added dropwise to the reaction flask. The reaction was warmed to room temperature and progression was monitored by p-anisaldehyde and KMnO₄ stains. When 43 appeared to be fully converted the reaction was quenched with saturated NH₄Cl (40 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic fractions were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:4 EtOAc:Hexanes). No product was obtained, (0 g, 0%)

(method b): N,O-dimethylhydroxylamine hydrochloride (122 mg, 1.25 mmol) and 42 (280 mg, 1.02 mmol) were solvated in anhydrous THF (20.0 mL) under a blanket of argon. The slurry was cooled to -5°C and a cold solution of isopropylmagnesium bromide (3M in THF, 3.0 mL) was added dropwise to the reaction flask. On addition the remaining solid N,O-dimethylhydroxylamine hydrochloride dissolved into solution. The reaction mixture was stirred at -5°C and progression was monitored by TLC using a p-anisaldehyde stain. When monitoring (TLC) indicated that 42 had been converted to 43 a cold solution of vinylmagnesium bromide (1M in THF, 1.5 mL) was added dropwise to the reaction flask. When monitoring showed the disappearance of 43 the reaction was quenched with saturated NH₄Cl (30 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. An NMR analysis of the crude material showed no product present (0g, 0%).
6-((tert-butyldimethylsilyloxy)heptan-1-ol (47): The protected ester (42) (557 mg, 2.03 mmol) was solvated with anhydrous THF under a blanket of argon and cooled to -5°C. A solution of lithium aluminum hydride (0.96 M in THF, 2.2 mL) was added dropwise to the reaction flask. The reaction stirred at -5°C and progression was monitored by TLC using a p-anisaldehyde stain until all of 42 was consumed. The reaction was quenched with Glauber’s salt and diluted with EtOAc (15 mL). The solid precipitate was filtered and washed copiously with EtOAc; the combined washings were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford 47 (0.495 g, 99%) as a white oil.

1H NMR (600 MHz, Chloroform-d): δ 3.77 – 3.71 (m, 1H), 3.57 (t, J = 6.7 Hz, 2H), 2.35 (s, 1H), 1.52 (p, J = 6.9 Hz, 2H), 1.44 – 1.20 (m, 6H), 1.07 (d, J = 6.1 Hz, 3H), 0.84 (d, 3H), 0.00 (s, 6H)

13C NMR (100 MHz, Chloroform-d): δ 68.5, 62.7, 39.6, 32.7, 25.9, 25.5, 23.7, 18.1, -4.44, -4.75

6-((tert-butyldimethylsilyloxy)heptanal (48): The protected primary alcohol (47) (515 mg, 2.09 mmol) was solvated with anhydrous DCM (15 mL) under a blanket of argon and the solution was cooled to 0°C. The reaction flask septum was removed and solid Dess-martin periodinane (DMP) (1.068 g, 2.518 mmol) was quickly added to the reaction solution. The septum was replaced, the argon blanket refreshed and any DMP residue on the sides of the flask rinsed down with anhydrous DCM (15 mL). The reaction slurry was warmed to room temperature and monitored by TLC. When all the starting material was consumed (TLC) the solution was cooled to 0°C and a solution of saturated NaHCO₃ with sodium thiosulfate (Na₂S₂O₃) (20 mL:2 mg) was added to quench the reaction. The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (30 mL x 2). The combined
organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO$_2$, 1:4 EtOAc:Hexanes) affording 48 as a pale yellow oil (379 mg, 74%).

$^1$H NMR (300 MHz, Chloroform-d): $\delta$ 10.43 (s, 1H), 3.79 (q, $J = 5.8$ Hz, 1H), 2.36 (t, $J = 7.5$ Hz, 2H), 1.92 – 1.82 (m, 2H), 1.74 – 1.55 (m, 2H), 1.49 – 1.22 (m, 2H), 1.12 (d, $J = 6.0$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H)

$^{13}$C NMR (75 MHz, Chloroform-d): $\delta$ 180.0, 68.3, 39.2, 34.1, 31.6, 25.8, 25.2, 24.7, 23.7, -4.4, -4.8.

8-((tert-butyldimethylsilyl)oxy)non-1-en-3-ol (45): The protected aldehyde (48) (346 mg, 1.14 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon. This solution was cooled to -5°C and a cold solution of vinylmagnesium bromide (1M in THF, 2.1 mL) was added dropwise to the reaction flask. The reaction solution was stirred on ice until none of 48 was observed by TLC. The reaction was quenched by the slow addition of 20% NH$_4$Cl (25 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with t-butyilmethyl ether (25 mL x 2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO$_2$, 1:4 EtOAc:Hexanes) affording 45cr as an off white oil (240 mg, 62%).

8-((tert-butyldimethylsilyl)oxy)non-1-en-3-ol (45): The protected aldehyde (48) (346 mg, 1.14 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon. This solution was cooled to -5°C and a cold solution of vinylmagnesium bromide (1M in THF, 2.1 mL) was added dropwise to the reaction flask. The reaction solution was stirred on ice until none of 48 was observed by TLC. The reaction was quenched by the slow addition of 20% NH$_4$Cl (25 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with t-butyilmethyl ether (25 mL x 2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO$_2$, 1:4 EtOAc:Hexanes) affording 45cr as an off white oil (240 mg, 62%).

non-8-ene-2,7-diol (46): The crude protected vinyl alcohol 45cr (223 mg, 0.819 mmol) was solvated with anhydrous THF (5 mL) under a blanket of argon. A cold solution of tetra-N-butyrammonium fluoride (TBAF) (1M in THF, 1.6 mL) was added to the reaction flask. The reaction progress was monitored by TLC and additional TBAF (1 mL x 2) was added at ~24hour intervals in an attempt to push the reaction to completion. The reaction was stopped...
when TLC monitoring indicated the presence of possible degradation products after four days; the reaction mixture was purified by flash chromatography (SiO₂, 1:5:94 NH₄OH:MeOH:EtOAc) followed by (SiO₂, 1:99 NH₄OH:EtOAc) to afford 46 (23 mg, 18%).

\[ ^1\text{H NMR} (300 \text{ MHz, Chloroform-}d): \delta 5.92 - 5.77 (m, 1H), 5.26 - 5.05 (m, 2H), 4.09 (h, 1H), 3.79 (h, \( J = 7.1, 6.3 \text{ Hz, 1H} \)), 2.47 - 2.37 (m, 2H), 1.58 - 1.22 (m, 4H), 1.18 (d, \( J = 6.1 \text{ Hz, 3H} \)), 0.91 (t, \( J = 7.2 \text{ Hz, 4H} \)) \]

\[ ^{13}\text{C NMR} (75 \text{ MHz, Chloroform-}d): \delta 141.3, 114.5, 73.0, 67.9, 53.7, 39.2, 36.9, 28.7, 25.6, 25.3, 25.3, 23.5, 20.8, 14.1 \]

methyl 6-((tert-butyldiphenylsilyl)oxy)heptanoate (37): Imidazole (2.777 g, 0.04080 mol) and 41 (1.865 g, 0.01164 mol) were solvated with anhydrous DCM (25 mL) under a blanket of argon. Tert-butyldiphenylsilyl chloride (TBDPS-Cl) (6.0 mL, 0.023 mol) was added dropwise to the reaction flask, on addition a white precipitate formed. The reaction mixture was stirred at room temperature until 41 was observed no longer observed by TLC. The reaction mixture was diluted with t-butyl methyl ether (50mL) and DI water (75 mL) and the organic and aqueous layers separated. The organic fraction was set aside and the aqueous fraction was extracted with t-butyl methyl ether (75 mL x 3). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:19 EtOAc:hexane) to yield 49 (3.712 g, 80%) as a whitish, pale yellow oil.

\[ ^1\text{H NMR} (300 \text{ MHz, Chloroform-}d): \delta = 7.76 - 7.33 (m, 10H), 3.87 (h, \( J = 5.3 \text{ Hz, 1H} \)), 3.68 (s, 3H), 2.26 (t, \( J = 7.4 \text{ Hz, 2H} \)), 1.62 - 1.25 (m, 9H), 1.08 (s, 9H). \]
6-((tert-butyl diphenylsilyl)oxy)heptan-1-ol (50): The protected ester (49) (1.475 g, 3.700 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon and cooled to 0°C. A solution of lithium aluminum hydride (0.96M in THF, 4.8 mL) was added dropwise to the reaction flask. The reaction solution was stirred on ice until 49 was no longer observed by TLC. The reaction was quenched by the slow addition of Glauber’s salt until hydrogen gas stopped evolving. The resultant mixture was filtered and rinsed copiously with EtOAc. The filtrate was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford 50 (1.287 g, 94%) as a cloudy, white oil.

$^1$H NMR (300 MHz, Chloroform-d): δ 7.77 – 7.34 (m, 10H), 3.87 (h, $J = 5.9$ Hz, 1H), 3.59 (t, $J = 6.6$ Hz, 2H), 1.64 (s, 1H), 1.58 – 1.20 (m, 8H), 1.10 (d, $J = 5.3$ Hz, 12H)

$^{13}$C NMR (75 MHz, Chloroform-d): δ 135.9, 129.5, 127.4, 69.5, 62.9, 39.4, 32.7, 27.1, 25.7, 25.0, 23.3, 19.3.

6-((tert-butyl diphenylsilyl)oxy)heptanal (51): Dess-Martin periodinane (4.073 g, 9.603 mmol) was solvated with anhydrous DCM (60 mL) under a blanket of argon and cooled to 0°C. In a separate flask, 50 (1.789 g, 4.827 mmol) and $t$-butyl alcohol (1.0 mL, 9.6 mmol) were solvated with anhydrous DCM (15 mL) under a blanket of argon. The solution containing 50 and the $t$-butyl alcohol was transferred to the flask with the Dess-Martin periodinane and the reaction mixture was warmed to room temperature. When all the starting material was consumed (TLC) the solution was cooled to 0°C and a solution of saturated NaHCO$_3$:Na$_2$S$_2$O$_3$ (150 mL:15 mg) was added to quench the reaction. The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (150 mL x 2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was then
purified by flash chromatography (SiO$_2$, 1:4 EtOAc:Hexanes) affording 51 as a pale yellow oil (1.577 g, 89%).

$^1$H NMR (300 MHz, Chloroform-$d$): $\delta$ 9.72 (t, $J$ = 1.8 Hz, 1H), 7.75 – 7.35 (m, 10H), 3.88 (h, $J$ = 6.0 Hz, 1H), 2.34 (td, $J$ = 7.3, 1.8 Hz, 2H), 1.60 – 1.25 (m, 6H), 1.10 (d, $J$ = 7.4 Hz, 12H)

$^{13}$C NMR (75 MHz, Chloroform-$d$): $\delta$ 202.6, 135.9, 129.5, 127.4, 69.2, 43.8, 39.0, 27.1, 24.7, 23.2, 22.1, 19.1

**non-8-ene-2,7-diol (46):** The protected aldehyde (51) (371 mg, 1.01 mmol) was solvated in anhydrous THF (5 mL) under a blanket of argon and cooled to -5°C. A solution of vinylmagnesium bromide (1M in THF, 2.0 mL) was added to the reaction flask dropwise. The reaction solution was stirred at -5°C until 51 was no longer observed by TLC. The reaction was quenched by the slow addition of ice cold 3% methanolic HCl (33 mL) and stirred on ice for an additional 2 hours. The reaction solution was concentrated under reduced pressure and the residue diluted with water (60 mL) and extracted with t-butyl methyl ether (60 mL x 3). The combined organic fractions were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO$_2$, EtOAc) to yield 34 (0.062 g, 39%) as a clear oil.

$^1$H NMR (300 MHz, Chloroform-$d$): $\delta$ 5.91 – 5.75 (m, 1H), 5.18 (d, $J$ = 17.1 Hz, 1H), 5.06 (d, $J$ = 10.3 Hz, 1H), 4.06 (q, $J$ = 6.5 Hz, 1H), 3.76 (q, $J$ = 5.8 Hz, 1H), 2.46 (s, 2H), 1.58 – 1.20 (m, 8H), 1.15 (d, $J$ = 6.0 Hz, 3H)
8-((tert-butyldiphenylsilyl)oxy)non-1-en-3-ol (52): The protected aldehyde (51) (550 mg, 1.49 mmol) was solvated in THF (10 mL) under a blanket of argon and cooled to -78°C in a bath of dry ice and acetone. A solution of vinylmagnesium bromide (1M in THF, 10.6 mL) was added to the reaction flask dropwise. The reaction solution was stirred at -78°C until 51 was no longer observed by TLC. The reaction was quenched at -78°C by the slow addition of 20% NH₄Cl (20 mL) and diethyl ether (20 mL) and then warmed to room temperature. When the mixture had warmed, it was further diluted with DI water (20 mL) and diethyl ether (20 mL) and the organic and aqueous layers were separated. The organic fraction was set aside and the aqueous fraction was extracted with EtOAc (50 mL x 2). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:4 EtOAc:hexane) to yield 52 (0.233 g, 39%) as a pale yellow oil.

**¹H NMR (300 MHz, Chloroform-d):** δ 7.80 – 7.74 (m, 4H), 7.54 – 7.36 (m, 6H), 5.98 – 5.78 (m, 1H), 5.25 (dq, J = 17.2, 1.4 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 3.93 (h, J = 5.9 Hz, 1H), 2.06 (s, 2H), 1.66 – 1.22 (m, 8H), 1.15 (s, 9H), 1.14 (d, J = 6.1 Hz, 3H)

**¹³C NMR (75 MHz, Chloroform-d):** δ 141.4, 135.9, 134.9, 134.6, 129.5, 129.5, 127.6, 127.5, 114.5, 73.1, 69.5, 39.4, 37.0, 27.2, 25.4, 25.4, 25.3, 25.2, 23.4, 23.3, 19.4

**non-8-ene-2,7-diol (46):** Protected secondary alcohol (52) (0.462 g, 1.16 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon and cooled to 0°C. A cold solution of TBAF (1M in THF, 4.8 mL) was added dropwise to the reaction flask and the solution was warmed to room temperature. When all the starting material was consumed (TLC) the septum was removed and the solution was diluted with methanol (25 mL). CaCO₃ (8.010 g, 80.03 mmol) and Dowex 50WX8-400 ion exchange resin (24.126 g) were added and the resultant slurry was stirred for one hour at room temperature. The slurry was then filtered...
through a celite pad and rinsed with methanol (10 mL x 3). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (SiO₂, EtOAc) to yield 46 (0.176 g, 95%) as a clear oil.

**¹H NMR (300 MHz, Chloroform-d):** δ 5.75 (ddd, J = 16.9, 10.4, 6.2 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.98 (d, J = 10.4 Hz, 1H), 3.97 (q, J = 5.8 Hz, 1H), 3.67 (q, J = 6.1, 5.4 Hz, 1H), 3.19 (s, 2H), 1.54 – 1.21 (m, 8H), 1.07 (d, J = 6.2 Hz, 3H)

**¹³C NMR (75 MHz, Chloroform-d):** δ 141.3, 114.2, 72.8, 67.6, 39.0, 36.9, 25.6, 25.5, 25.3, 25.2, 23.3

7-((tert-butyl diphenylsilyl)oxy)octan-2-ol (53): The protected aldehyde (51) (553 mg, 1.50 mmol) was solvated in THF (10 mL) under a blanket of argon and cooled to -78°C in a bath of dry ice and acetone. A solution of methylmagnesium bromide (3M in diethyl ether, 4.6 mL) was added to the reaction flask dropwise. The reaction solution was stirred at -78°C until 51 was no longer observed by TLC. The reaction was quenched at -78°C by the slow addition of a saturated solution of NH₄Cl (12 mL) and then warmed to room temperature. When the mixture had warmed, it was further diluted with DI water (30 mL) and diethyl ether (40 mL) and the organic and aqueous layers were separated. The organic fraction was set aside and the aqueous fraction was extracted with EtOAc (50 mL x 2). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:4 EtOAc:hexane) to yield 53 (0.336 g, 58%) as a pale yellow oil.

**¹H NMR (300 MHz, Chloroform-d):** δ 7.73 – 7.66 (m, 4H), 7.47 – 7.33 (m, 6H), 3.85 (h, J = 6.0 Hz, 1H), 3.78 – 3.67 (m, 1H), 2.06 (s, 1H), 1.58 – 1.20 (m, 8H), 1.16 (d, J = 6.2 Hz, 3H), 1.07 (d, J = 5.7 Hz, 12H)

**¹³C NMR (75 MHz, Chloroform-d):** δ 135.9, 134.9, 134.6, 129.4, 129.4, 127.5, 127.4, 69.5, 68.1, 39.5, 39.3, 27.0, 25.7, 25.2, 23.4, 23.2, 19.3
octane-2,7-diol (55): Protected secondary alcohol (53) (0.454 g, 1.181 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon and cooled to 0°C. A cold solution of TBAF (1M in THF, 4.8 mL) was added dropwise to the reaction flask and the solution was warmed to room temperature. When all the starting material was consumed (TLC) the septum was removed and the solution was diluted with methanol (25 mL). CaCO$_3$ (8.205 g, 81.98 mmol) and Dowex 50WX8-400 ion exchange resin (24.156 g) were added and the resultant slurry was stirred for one hour at room temperature. The slurry was then filtered through a celite pad and rinsed with methanol (10 mL x 3). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (SiO$_2$, EtOAc) to yield 55 (0.158 g, 91%) as a clear oil.

$^1$H NMR (300 MHz, Chloroform-d): δ 3.75 – 3.61 (m, 2H), 3.12 (s, 2H), 1.47 – 1.21 (m, 8H), 1.08 (d, $J = 6.2$ Hz, 6H)

$^{13}$C NMR (75 MHz Chloroform-d): δ 67.6, 67.5, 39.1, 25.7, 25.6, 23.3

9-((tert-butyldiphenylsilyl)oxy)dec-1-en-4-ol (54): The protected aldehyde (51) (1.012 g, 2.75 mmol) was solvated in THF (15 mL) under a blanket of argon and cooled to -78°C in a bath of dry ice and acetone. A solution of allylmagnesium bromide (1M in diethyl ether, 20 mL) was added to the reaction flask dropwise. The reaction solution was stirred at -78°C for 90 minutes. The reaction was halted at this point due to the appearance of side products in addition to the desired product (TLC). The reaction was quenched at -78°C by the slow addition of 20% NH$_4$Cl (40 mL) and diethyl ether (20 mL) and then warmed to room temperature. When the mixture had warmed, it was further diluted with DI water (40 mL) and diethyl ether (40 mL) and the organic and aqueous layers separated. The organic fraction was set aside and the aqueous fraction was extracted with EtOAc (100 mL x 2). The combined organic fractions were dried
over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂, 1:9 EtOAc:hexane) to yield 54 (0.277 g, 25%) as a pale yellow oil.

**¹H NMR (300 MHz, Chloroform-d):** δ 7.78 – 7.70 (m, 4H), 7.49 – 7.33 (m, 6H), 6.00 – 5.77 (m, 1H), 5.21 – 5.16 (m, 1H), 5.15 – 5.11 (m, 1H), 3.91 (h, J = 6.0 Hz, 1H), 3.68 – 3.57 (m, 1H), 2.36 – 2.24 (m, 1H), 2.23 – 2.09 (m, 1H), 2.01 (s, 1H), 1.66 – 1.28 (m, 8H), 1.13 (d, J = 6.1 Hz, 3H), 1.12 (s, 9H)

**¹³C NMR (75 MHz, Chloroform-d):** δ 135.9, 134.9, 134.6, 129.5, 129.4, 127.5, 127.4, 117.8, 70.6, 70.6, 69.5, 41.9, 39.4, 39.4, 36.8, 36.7, 27.1, 25.7, 25.6, 25.3, 25.2, 23.3, 23.3, 19.3

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dec-9-ene-2,7-diol (56): Protected secondary alcohol (54) (0.269 g, 0.656 mmol) was solvated with anhydrous THF (5 mL) under a blanket of argon and cooled to 0°C. A cold solution of TBAF (1M in THF, 3.2 mL) was added dropwise to the reaction flask and the solution was warmed to room temperature. When all the starting material was consumed (TLC) the septum was removed and the solution was diluted with methanol (20 mL). CaCO₃ (5.172 g, 51.68 mmol) and Dowex 50WX8-400 ion exchange resin (15.383 g) were added and the resultant slurry was stirred for one hour at room temperature. The slurry was then filtered through Celite pad and rinsed with methanol (10 mL x 3). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (SiO₂, EtOAc) to yield 44 (0.0986 g, 87%) as a clear oil.

**¹H NMR (300 MHz, Chloroform-d):** δ 5.84 – 5.68 (m, 1H), 5.10 – 4.99 (m, 2H), 3.76 – 3.64 (m, 1H), 3.63 – 3.51 (m, 1H), 2.68 (s, 2H), 2.36 – 1.92 (m, 2H), 1.51 – 1.22 (m, 8H), 1.10 (d, J = 6.2 Hz, 3H)

**¹³C NMR (75 MHz Chloroform-d):** δ 135.0, 134.9, 134.9, 117.6, 117.6, 117.7, 70.6, 70.5, 67.7, 67.6, 41.9, 39.1, 36.6, 25.7, 25.6, 25.6, 25.5, 23.4
heptane-1,6-diol (57): Solid lithium aluminum hydride (1.503 g, 39.60 mmol) was added to a clean, dry round bottom flask and solvated with anhydrous THF (55 mL) under a blanket of argon. The mixture was stirred vigorously for four hours to bring the solid LiAlH₄ into solution and then cooled to 0°C. In a separate flask, 5-acetylvaleric acid (0.754 g, 5.23 mmol) was solvated with anhydrous THF (10 mL) under a blanket of argon. This solution was added drop-wise to the reaction flask containing the stirred solution of LiAlH₄ and the reaction mixture was brought slowly back to room temperature. After the starting material had been consumed (TLC) the solution was cooled to 0°C and the reaction quenched by the slow addition of Glauber’s salt until hydrogen gas stopped evolving. The resultant mixture was filtered and rinsed copiously with EtOAc (15 mL x 5). The filtrate was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure and the residue was purified by flash chromatography (SiO₂, EtOAc) to yield 57 (0.432 g, 62%) as a clear oil.

¹H NMR (300 MHz, Chloroform-d): δ 3.84 – 3.69 (m, 1H), 3.57 (t, J = 6.6 Hz, 2H), 3.05 (s, 2H), 1.60 – 1.27 (m, 8H), 1.14 (d, J = 6.2 Hz, 3H)

¹³C NMR (75 MHz Chloroform-d): δ 67.7, 62.4, 39.1, 32.5, 25.7, 25.4, 23.4.

General method for the N-heterocyclization of diols:
The catalyst [Cp*IrCl₂] (5 mol %) and NaHCO₃ (5 mol %) were added to a heavy-walled pressure reactor. A solution (0.2M) of the diol (1 equiv.) and anhydrous toluene was prepared in a separate vial and transferred to the pressure reactor. The solution containing diol, catalyst, and base was stirred vigorously. Benzylamine (1.5 equiv.) was added to the stirring solution, the reactor was flushed with argon and sealed. The solution was heated to 110°C for 17 hours. The mixture was then concentrated under reduced pressure and purified by flash chromatography to afford the cyclic amine.
1-benzyl-2,5-dimethylpyrrolidine: Prepared from hexane-2,5-diol (0.25 mL, 2.0 mmol), [Cp*IrCl₂] (41 mg, 0.051 mmol), NaHCO₃ (9.6 mg, 0.11 mmol), and benzylamine (0.33 mL, 3.0 mmol) in toluene (3 mL). Purification by flash chromatography (SiO₂, EtOAc) afforded a pale yellow oil 58 (0.361 g, 95%, cis/trans 71:29). Spectroscopic data was consistent with those previously reported for this compound.¹⁰

¹H NMR (300 MHz, Chloroform-d) δ 7.65 – 7.20 (m, 5H), 3.95 (d, J = 13.8 Hz, 1H), 3.85 (s, 1H), 3.62 (d, J = 13.8 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.78 – 2.61 (m, 1H), 2.18 – 2.07 (m, 1H), 1.95 – 1.83 (m, 1H), 1.55 – 1.42 (m, 1H), 1.18 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H)

¹³C NMR (75 MHz, Chloroform-d) δ 139.6, 129.3, 128.6, 128.5, 128.2, 127.9, 127.0, 126.7, 126.5, 59.8, 55.4, 55.4, 55.0, 53.3, 51.8, 31.4, 31.1, 20.8, 17.2

1-benzyl-2-methyazepane: Prepared from 57 (150 mg, 1.13 mmol), [Cp*IrCl₂] (36 mg, 0.045 mmol), NaHCO₃ (10 mg, 0.12 mmol), and benzylamine (0.17 mL, 1.6 mmol) in toluene (5 mL). Purification by flash chromatography (Al₂O₃, 1:19 EtOAc:Hexanes) afforded 59 (0.053 g, 23%) as a pale yellow oil

¹H NMR (300 MHz, Chloroform-d): δ 7.52 – 7.26 (m, 5H), 3.81 (s, 2H), 3.09 – 2.96 (m, 1H), 2.92 – 2.81 (m, 1H), 2.70 – 2.59 (m, 1H), 1.98 – 1.46 (m, 8H), 1.18 (d, J = 6.4 Hz, 3H).

¹³C NMR (75 MHz, Chloroform-d): δ 141.4, 128.7, 128.1, 128.1, 126.6, 57.3, 56.9, 49.0, 36.1, 29.1, 28.5, 25.4, 19.2.

MS: (ESI) m/z 961.2 (M₂ + K), 630.1 (M₁ + H), 310.7 (M)
1-benzyl-2,7-dimethylazepane: Prepared from 43 (173 mg, 1.18 mmol), [Cp*IrCl₂] (25 mg, 0.031 mmol), NaHCO₃ (6.4 mg, 0.076 mmol), and benzylamine (0.22 mL, 2.0 mmol) in toluene (6.5 mL). TLC analysis of the crude product showed no formation of the azepane ring system. Purification by flash chromatography (SiO₂, 50:50 EtOAc:Hexanes to pure EtOAc) afforded no product (0 g, 0%).

1-benzyl-2-methyl-7-vinylazepane: Prepared from 46 (167 mg, 1.11 mmol), [Cp*IrCl₂] (25 mg, 0.031 mmol), NaHCO₃ (6.2 mg, 0.074 mmol), and benzylamine (0.19 mL, 1.7 mmol) in toluene (5.5 mL). TLC analysis of the crude product showed no formation of the azepane ring system (61). Purification by flash chromatography (Al₂O₃, gradient column from 100% hexanes to 100% ethyl acetate) afforded no product (61) (0 g, 0%).

MS: (ESI) m/z 247.7 (M)

2-allyl-1-benzyl-7-methylazepane: Prepared from 56 (98 mg, 0.55 mmol), [Cp*IrCl₂] (11 mg, 0.013 mmol), NaHCO₃ (2.5 mg, 0.030 mmol), and benzylamine (0.09 mL, 0.82 mmol) in toluene (2.8 mL). TLC analysis of the crude product showed no formation of the azepane ring system (62), (0 g, 0%).

MS: (ESI) m/z 539.03 (M + K)
3.6. References

(1) Pubchem. cocaine | C17H21NO4 - PubChem

(2) Pubchem. nicotine | C10H14N2 - PubChem

(3) Pubchem. morphine | C17H19NO3 - PubChem


(21)  Methyl 6-oxoheptanoate...|Ark Pharm, Inc.


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