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Erik Carlson for the degree of Master of Science in Chemistry presented on
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Title: Development of Organocatalyzed, Intramolecular Heteroatom
        Michael Addition and Application Towards Alkaloid Synthesis

Abstract approved:

____________________________________

Rich G. Carter

Effective methods for the enantiopure formation of substituted
piperidine rings are significantly important due to their presence in alkaloid
products. A valuable method to form these ring systems would be via an
intramolecular heteroatom Michael addition from the corresponding enone
or enal. Described herein is a methodology that has been developed in
order to form piperidine, pyrrolidine and indoline ring systems using
organocatalysis. These ring systems have been prepared with yields of 50-87% and ee as high as 95%. This methodology has been utilized in the synthesis of three natural products: homopipeolic acid, homoproline, and pelletierine. Homopipeolic acid was synthesized in 7 steps and 28% yield from commercially available 1-bromo-5-hexene. Homoproline was synthesized in 7 steps and 10% overall yield from commercially available 1-bromo-4-heptene. Pelletierine was synthesized in 8 steps and 26% overall yield from commercially available 1-bromo-5-hexene.

Synthetic efforts toward cermizine D are also disclosed. This synthesis involves the use of our organocatalytic methodology in order to form the initial piperidine ring. Using the Boc protected amine for this reaction gave the desired piperidine ring in 86% yield and 92% ee. One key step is the Ti(O-Pr)_4 mediated coupling to produce the core carbon structure in 68% yield and 1:1 dr. This reaction is has not yet been optimized. Another key step is the use of RCM in order to form the second ring in the system with a 94% yield.
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Development of Organocatalyzed, Intramolecular Heteroatom Michael
Addition and Application Towards Alkaloid Synthesis

by

Erik Carlson

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APPROVED:

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Major Professor, representing Chemistry

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Chair of the Department of Chemistry

________________________________________
Dean of the Graduate School

I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

________________________________________
Erik Carlson, Author
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Development of Organocatalyzed, Intramolecular Heteroatom Michael Addition and Application Towards Alkaloid Synthesis

Chapter I. Introduction into organocatalyzed heteroatom Michael additions and other piperidine forming reactions

1.1 Introduction

Pyrrolidine and piperidine-based ring systems are ubiquitous in natural products. Consequently, construction of these heterocyclic ring systems in an enantioenriched fashion has been a subject of considerable synthetic attention. A variety of groups have showcased the ability to asymmetrically deprotonate N-protected pyrrolidines and piperidines, for example one can look at work by Beak,¹ Hoppe,² and others.³ In addition, Comins has developed an asymmetric pyridinium salt reaction for the synthesis of enantioenriched piperidines.⁴ More recently, dipolar cycloadditions⁵ have been exploited for the construction of these heterocyclic ring systems; however, there are limited examples in the use of organocatalysts for the construction of these ring systems.⁶,⁷ This, combined with our general interest in alkaloid total synthesis, caused us to investigate this valuable transformation.
1.2 Previous Studies

1.2.1 Organocatalytic Asymmetric Aza-Michael Reactions

1.2.1.1 Miller’s Asymmetric Azidation

First, here is an example of an organocatalytic asymmetric aza-Michael reaction reported by Miller in 2002. Miller demonstrated that the use of a chiral tripeptide 1.4 was effective in the conjugate addition of TMS azide to α,β-unsaturated imides. It was found in optimizing the reaction that is was key to have the intramolecular hydrogen bonding to lock the peptide secondary structure to allow for high enantioselectivities (Scheme 1.1).

Scheme 1.1. Asymmetric Azidation Using Miller’s Method

A key challenge that existed with the general scope of this transformation was with moderating reactivity. Both the catalyst and the nucleophile are amine-containing species; therefore, the chiral secondary amine chosen as the catalyst must not undergo a conjugate addition. At the same time the amine reagent must not produce an iminium ion, as this would lead to the production of a racemic product.
1.2.1.2 MacMillan’s Amine Conjugate Addition

In 2006, MacMillan and co-workers reported an enantioselective organocatalytic amine conjugate addition using a N-silyloxy carbamate as the nitrogen nucleophile. These reagents have an enhanced nucleophilicity due to the presence of the silyloxy moiety, the α-effect. In addition to the increased nucleophilicity of the nitrogen reagent, it also contained a carbamate functionality that muted the reversibility of the reaction. MacMillan and co-workers tested out a variety of catalysts for this reaction starting with proline and eventually finding that the use of imidazolidinone 1.7 as its pTSA salt gave excellent selectivity (Scheme 1.2).

**Scheme 1.2. Amine Conjugate Addition Using MacMillan’s Method**

![Scheme 1.2](image)

1.2.1.3 Córdova’s Aziridination

Córdova and co-workers used a similar nucleophile for their addition, using a hydroxy amine with a carbamate-protecting group. The use of this substrate only differs in that there is no silyl group on the hydroxy group; however, this causes an interestingly different reaction to occur. Rather then just having the conjugate addition, in this case, the Michael product
undergoes an intramolecular hemiacetal formation to produce 5-hydroxyazolines (Scheme 1.3). Córdova changed the catalyst as well using a proline based catalyst in the TMS protected diphenyl prolinol 1.7. This catalyst system gave yield to the desired products with excellent yields and selectivity. Córdova also showed that replacement of the hydroxy amine substrate for a substrate with a suitable leaving group that aziridine formation occurs.\textsuperscript{10}

**Scheme 1.3.** Enantioselective Aziridination Catalyzed by a Chiral Pyrrolidine

1.2.1.4 Wang’s Michael and Aldol Additions

Wang and co-workers reported a method for a Michael addition using $N$-heterocycles to nitroolefins.\textsuperscript{11} The process used a cinchona alkaloid derivative as the organocatalyst. It was shown that the process could be carried out using a wide variety of substituents on the nitroolefin and a benzotriazole as the nucleophilic nitrogen (Scheme 1.4). He also demonstrated that the alternate $N$-heterocycle nucleophile such as 1\textit{H}-...
[1,2,3] triazole or 5-phenyl-1H-tetrazole could be used.

**Scheme 1.4. Michael Addition Reaction by Wang**

\[
\begin{align*}
&\text{N} \quad \text{N} \\
&\text{1.11} \quad \text{R: aryl or alkyl} \\
&\text{1.12} \\
&\text{10 mol% catalyst} \\
&\text{-25 °C, DCM} \\
&\text{up to 94% ee} \\
&\text{64-90% yield} \\
&\text{1.13} \\
&\text{1.14}
\end{align*}
\]

In a later report, Wang and co-workers also developed a conjugate addition-aldol-dehydration reaction between \(\alpha,\beta\)-unsaturated aldehydes with 2-\(\text{N}\)-protected amino benzaldehydes. The organocatalyst used for this transformation was \((S)\)-diphenylprolinol TES ether and the process gave 1,2-dihydroquinolines in high enantioselectivity with good yields (Scheme 1.5). \(^{12}\)

**Scheme 1.5. Cascade Conjugate Addition-Aldol-Dehydration Reaction by Wang**

\[
\begin{align*}
&\text{R: aryl or alkyl} \\
&\text{1.15} \\
&\text{1.16} \\
&\text{NaOAc (0.5 equiv)} \\
&\text{4 A MS} \\
&\text{Cl\(\text{CH}_2\text{CH}_2\text{Cl}\)} \\
&\text{up to 98% yield and 96% ee} \\
&\text{1.17}
\end{align*}
\]

In this case, it was key that the product from the conjugate addition reaction underwent an intermolecular aldol reaction and dehydration. This cascade process was required in order to push the equilibrium in the catalytic conjugate addition toward the final product. The proposed
mechanism for this process is shown in Scheme 1.6.

**Scheme 1.6. Cascade Organocatalytic Enantioselective Conjugate Addition-Aldol-Dehydration Reactions**

1.2.1.5 Jørgensen’s contributions

Jørgensen and co-workers reported an organocatalyzed asymmetric aza-Michael addition using hydrazones to cyclic eneones. This process used a cinchona alkaloid as the catalyst to yield the addition product in good yield and stereoselectivity (Scheme 1.7). A study was conducted to determine the influence that the structure of the enone had on the stereoselectivity giving products with up to 77% ee that could be recrystallized to give nearly enantiopure products.
Scheme 1.7. Jørgensen’s Aza-Michael Reaction with Hydrazones

In a later report, Jørgensen and co-workers disclosed a process in which a variety of nitrogen heterocycles were used as the nucleophiles employed in enantioselective organocatalytic conjugate additions to α,β-unsaturated aldehydes. For this process, the catalyst used was 2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine. This process was shown to be successful using a variety of nitrogen heterocycles such as 1,2,4-triazoles (Scheme 1.8), 5-phenyl-1H-tetrazoles, benzotriazoles and 1,2,3-triazoles.13

Scheme 1.8. Conjugate Addition of N Heterocycles

1.2.1.6 Fustero’s Intramolecular Aza-Michael Reaction

Independently and concurrent to our work Fustero and co-workers reported on an organocatalytic intramolecular aza-Michael reaction.14 This work was similar to ours in that it was forming pyrrolidine and piperidine
ring systems even using the same catalyst (Scheme 1.9). They reported the effectiveness of this reaction on a range of substrates with generally high levels of enantioselectivity; however, there are some general advantages to our methodology over this report. Specifically, the reaction temperatures for these transformations are low (typically starting at -50°C) and require a slow warming over long periods of time (such as -50°C to -30°C over a period of 48 h). Additionally, the use of benzoic acid as an additive was used in order to have the reaction proceed at a suitable rate. This additive may not be advantageous for acid-sensitive substrates.

**Scheme 1.9. Organocatalytic Intramolecular Aza-Michael Reaction**

1.2.2 Asymmetric Deprotonation of \( N \)-Protected Pyrrolidines and Piperidines.

1.2.2.1 Asymmetric Deprotonation of \( N \)-Boc-Pyrrolidine

Beak and co-workers reported a variety of asymmetric lithiations. Included in these was the asymmetric deprotonation lithiation of \( N \)-Boc-pyrrolidines shown in Scheme 1.10.\(^{15} \) In this report Beak discusses the rate of this reaction and how it precedes via the prelithiation complex 1.33
that is the rate limiting step with the complex being highly favored in the equilibrium. It was also reported that the addition of a variety of electrophiles following the lithiation led to an enantioenriched product.

**Scheme 1.10.** The deprotonation of N-Boc-pyrrolidine via prelithiation complex

1.2.2.2 Substrate-Directed Deprotonation

Hoppe and co-workers also reported a variety of asymmetric lithiations. Shown in scheme 1.11 is the substrate-directed deprotonation of the prolinol carbamate 1.36.\(^\text{16}\) Hoppe reported that even with out the use of sparteine similar stereoselectivity was obtained. Due to this observation he concluded that the less shielded amino function intervenes in the deprotonation step in an intra- or intermolecular way.

**Scheme 1.11.** Diastereoselective deprotonation of the prolinol carbamate 1.36

---

1.2.3 Asymmetric Pyridinium Salt Reactions

Comins and co-workers reported in 1994 the use of pyridinium salts formed with chiral acids to produce 2-alkyl(aryl)-2,3-dihydro-4-pyridones via Grignard addition (Scheme 1.12). After optimization the pyridinium salt formed using (-)-8-phenylmenthyl as the homochiral chloroformate gave the best results. In addition to using the (-)-8-phenylmenthyl salt it was reported that either the (-)- or (+)-trans-(α-cumyl)cyclohexanol (TCC) could be used in order to obtain both enantiomers. Further optimization was done with the substitution at the C-3 position of the starting pyidine. This was necessary because the pyridinium salt is susceptible to nucleophilic attack at either α-position if there is not some sort of substituent to assist in directing the nucleophile. It was decided that a bulky substituent such as a tri-substituted silyl group would help in the directing; the tri-isopropyl silyl group was found to give the best results.

Scheme 1.12. Comins use of pyridinium salts
1.2.4 Dipolar Cycloadditions

1.2.4.1 Chelation-Controlled 1,3-Dipolar Cycloaddition

Confalone and co-workers reported the synthesis of isoxazolidines via a MgBr$_2$-induced chelation-controlled 1,3-Dipolar Cycloaddition (Scheme 1.13).\textsuperscript{17} $N$-hydroxyphenylglycinol was used as a chiral auxiliary and diastereomeric ratios up to 94% were obtained. A variety of these isoxazolidines were formed and depending on the linking atoms between the aldehyde and alkene they were able to obtain pyrrolidines, tetrahydrofurans, and cyclopentane ring systems following hydrogenation of the isoxazolidine.

**Scheme 1.13.** Chelation-Controlled 1,3-Dipolar Cycloaddition

1.2.4.2 Ag$^+$-Catalyzed Asymmetric [C+NC+CC] Reaction

Garner and co-workers reported selective Ag$^+$-catalyzed asymmetric [C+NC+CC] coupling process in order to synthesize highly functionalized pyrrolidines in a single chemical step (Scheme 1.14).\textsuperscript{18} Oppolzer’s camphorsultam was the chiral auxiliary that enables the desired cascade reaction and provides a reliable method to control the stereochemistry of the products. AgOAc was used as the Ag$^+$ catalyst in order to coordinate with the imine formed to facilitate the 1,3-dipolar cycloaddition.
**Scheme 1.14.** Ag⁺-Catalyzed Asymmetric [C+NC+CC] Synthesis of Pyrrolidines

The proposed step-wise process requires the rapid condensation of the starting amine and aldehyde to form the resulting imine intermediate. The imine intermediate then coordinates with the silver catalyst forming the reactive azomethine ylide 1.54. This intermediate will then react with the alkene present in a 1,3-dipolar cycloaddition to produce the final highly functionalized pyrrolidine product (Scheme 1.15).

**Scheme 1.15.** Ag⁺-Catalyzed Asymmetric [C+NC+CC] Coupling Reaction Cascade

1.2.4.3 Organocatalytic [C+NC+CC] Reaction

Córdova and co-workers later altered the [C+NC+CC] reaction such that a proline derivative could be used in an organocatalytic fashion to achieve similar results (Scheme 1.16). Using α,β-unsaturated aldehydes
to form iminium intermediates with a proline derivative they were able to accomplish the same 1,3-dipolar cycloaddition with an azomethine ylide. The TMS ether of diphenyl prolinol was found to be the optimal catalyst for the reaction. The step-wise mechanism proceeds in a similar fashion where the azomethine ylide is formed invoking a hydrogen bonding intermediate with which the alkene can react.

**Scheme 1.16.** Organocatalytic [C+NC+CC] Synthesis of Pyrrolidines

In recent years, there has been a wealth of research in the field of organocatalytic aza-Michael reactions. Despite these advances there have only been a few examples of intramolecular aza-Michael reaction for the formation of piperidine ring systems. There has been a variety of research done on the optimization of catalyst systems for this type of reaction as well as a general scope of reactivity. Our plans to advance this field of chemistry involve the use of an intramolecular aza-Michael in order to form piperidine and pyrrolidine ring systems to be used as building blocks in the synthesis of alkaloids.
Chapter 2. Intramolecular Organocatalyzed Heteroatom

Michael Addition

2.1 Introduction

With a strong interest in the synthesis of alkaloids, there was use for an effective method for the enantiopure formation of substituted piperidine rings. A valuable method to form these ring systems would be via an intramolecular heteroatom Michael addition from the corresponding enone or enal. This transformation is ideally suited for the use of organocatalysis. It was envisioned that a general transformation as shown in Scheme 2.1 could not only be useful for the rapid construction of piperidine rings but possibly pyrrolidine and hexahydroazapine ring systems as well. Also shown in Scheme 2.1 is an ideal starting material for this reaction in the enal or alkyl enone. In order to reduce the reactivity of the amine and to help minimize the background reaction of a spontaneous Michael reaction, it was felt that a carbamate-protecting group such as Boc and Cbz was necessary.

Scheme 2.1. General Transformation for Development
2.2 Optimization of Reaction

We chose to first explore the cyclization of the piperidine precursor 2.7. The synthesis of this known enal\(^\text{14}\) was readily prepared in four steps from commercially available 6-bromo-hexene (Scheme 2.2). Displacement of the bromide with sodium azide followed by Staudinger reduction and Cbz protection of the resulting amine gave 2.4 in 78% yield over 3 steps. Cross metathesis of the mono-substituted alkene (2.4) with crotonaldehyde (2.5) using 2\(^{\text{nd}}\) generation Grubbs catalyst (2.6) gave the desired enal 2.7 in 78% yield and only the Z isomer was observed.

**Scheme 2.2. Synthesis of Starting Enal**

It is worth noting that in these reactions the use of acrolein in place of crotonaldehyde gave consistently lower yields as was shown by research preformed by a fellow graduate student. The intramolecular organocatalytic heteroatom Michael addition along with the three catalysts used is shown in Scheme 2.3. The enantioselectivity of the reaction was determined using chiral HPLC. The aldehyde product from the cyclization was unstable on the chiral HPLC column so it was reduced at the end of
each reaction with NaBH₄ to provide the more stable alcohol.

**Scheme 2.3. Optimization of Heteroatom Michael Addition**

The optimization of this reaction is shown in Table 1. Initial use of proline as the catalyst (20 mol%) with ethanol as the solvent gave the desired product, however, with a modest 9% ee (Entry 1). Scanning the number of possible organocatalysts, the TMS diphenylprolinol catalyst had been observed to give increased control in enantioselectivity. Using this catalyst gave an improved 59% ee when using a 20 mol% catalyst loading and still using ethanol as the solvent (Entry 2). Further optimization with Jørgensen’s trifluoromethyl derivative 1.27²⁰ led to an additional improvement in enantioselectivity (Entry 3). While the enantioselectivity had continued to increase, the yields for the transformation remained unacceptably low. Changing to a mixed solvent system with CHCl₃ led to a dramatic increase in the yield to 62% with a gain in the enantioselectivity (Entry 4). Use of 1,2-dichloroethane (DCE) improved the yield to 80% (Entry 5). Changing ethanol for the more polar methanol accelerated the
rate of the reaction and gave a modest improvement in enantioselectivity (Entry 6). Final optimization required the reaction to be cooled to -25 °C (typically by placing the flask un stirred in the freezer until complete by TLC) to give the product 2.9 in 70% yield along with excellent enantioselectivity (95% ee) (Entry 7).

**Table 1. Optimization of Heteroatom Michael Addition**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>% ee (%)</th>
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<tr>
<td>1</td>
<td>2.10</td>
<td>EtOH, rt</td>
<td>9% ee</td>
<td>(40%)</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>EtOH, rt</td>
<td>59% ee</td>
<td>(41%)</td>
</tr>
<tr>
<td>3</td>
<td>1.27</td>
<td>EtOH, rt</td>
<td>71% ee</td>
<td>(29%)</td>
</tr>
<tr>
<td>4</td>
<td>1.27</td>
<td>EtOH / CHCl₂</td>
<td>80% ee</td>
<td>(62%)</td>
</tr>
<tr>
<td>5</td>
<td>1.27</td>
<td>EtOH / DCE</td>
<td>78% ee</td>
<td>(80%)</td>
</tr>
<tr>
<td>6</td>
<td>1.27</td>
<td>MeOH / DCE</td>
<td>83% ee</td>
<td>(78%)</td>
</tr>
<tr>
<td>7</td>
<td>1.27</td>
<td>MeOH / DCE</td>
<td>95% ee</td>
<td>(70%)</td>
</tr>
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A possible mechanistic model to address the stereochemical outcome of the reaction is put forth in Scheme 2.4. After imine formation with the aldehyde the conformation can be set such that the molecule sits in a chair-type intermediate where the large side chain of the prolinol derivative is blocking attack from the back face. This allows for cyclization to occur with high enantioselectivity.
Scheme 2.4. Possible Mechanistic Model for Observed Stereocchemical Outcome

2.3 Scope of Reaction

With a working catalyst system, we next began to explore the scope of the transformation. We set out to study the effect of ring size (five versus six versus seven) as well as the effect of substitution. First, we chose to explore the effect of different ring sizes. The 5-membered and 7-membered precursors were made in a similar fashion as the previous enal (Scheme 2.5). Displacement of the respective starting bromides with sodium azide followed by Staudinger reduction, and Cbz protection gave the desired starting Cbz protected amines. It should be mentioned that the yield for the five- and seven-membered substrates was considerably lower; 41% and 30% yields respectively over the same 3 steps.

Scheme 2.5. Synthesis of Starting Cbz Protected Amines
Interestingly, the use of the previously discussed 2nd generation Grubbs conditions (crotonaldehyde, CH$_2$Cl$_2$, 45°C) on the five membered series gave inconsistent results (Scheme 2.6). These inconsistencies appeared to depend solely on the bottle of Grubbs catalyst that was used. With older bottles, clean conversion was observed, however, with newer bottles of Grubbs catalyst, a complex mixture of compounds was observed in the metathesis reaction. After considerable experimentation, it was discovered that an “aging” of the commercial catalyst was required to obtain reproducible results. The catalyst was removed from the sealed bottle and allowed to sit on the bench top or in a desiccator exposed to air for a period of 3 days. This “aging” process has proven critical to the success of any cross metathesis where the Cbz nitrogen is located 5 atoms away from the internal alkene carbon (alkenes 2.13, 2.21, and 2.28). While we are unsure as to the exact nature of this “aging” process careful inspection of the aged 2nd generation Grubbs catalyst by ¹H NMR spectrum reveals some subtle changes in the splitting pattern in the aromatic region. It should be noted that a somewhat related observation has been reported by Belchert.$^{21}$
**Scheme 2.6. Metathesis of the 5- and 7-Membered Precursors**

![Scheme 2.6](image)

In addition to the different ring sizes we were interested in exploring the effect of substitution on the chain. We prepared the precursors for both the 5-membered and 6-membered ring systems with dimethyl substitution in the α position and the β position relative to the Cbz nitrogen. Substitution at the α position was accomplished by a Curtis rearrangement following other known procedures\(^2\) followed by Cbz protection of the free amine giving the α-dimethyl substrates in 44% and 42% yields for the five and six membered systems respectively over the 4 steps (Scheme 2.7). The subsequent enals were formed by metathesis with crotonaldehyde using 2\(^{nd}\) generation Grubb’s catalyst. For the 5-membered system the “aged” Grubb’s was used to give consistent results. The resulting enals were obtained in 65% and 75% yields for the five and six membered systems respectively.
Scheme 2.7. Synthesis of α-dimethyl substrates

The β-substituted enals were constructed from alkylation of the starting nitrile 2.25 followed by reduction with LiAlH₄ to give the β-dimethyl amine (Scheme 2.7). Cbz protection of these substrates gave higher yields using CbzOnSu rather than the CbzCl previously used. The Cbz protected amines were isolated in 50% and 65% over 3 steps for the five and six membered systems respectively. Metathesis with crotonaldehyde using 2nd generation Grubbs’s catalyst under the same conditions used in earlier substrates gave the desired enals in 72% and 81% for the five and six membered systems respectively.

Scheme 2.7. Synthesis of β-dimethyl substrates
With the required precursors in hand, we studied their reactivity using the optimized reaction conditions (Scheme 2.8). The parent non-substituted pyrrolidine was constructed from the corresponding enal in 67% with 90% ee. Substitution on the carbon backbone yielded some interesting results. In general, dimethyl substitution in the α position led to a reduced reactivity, presumably on steric grounds. The α-dimethyl pyrrolidine required extended reaction time to go to completion and led to a reduced level of enantioselectivity. Formation of the piperidine analogue was not reliable even under extended reaction times and increased amounts of catalyst. Conversely, dimethyl substitution β to the amino group yielded increased reactivity with good levels of enantiomeric excess. The increased reaction rate is likely due to the reduced level of conformational flexibility for the backbone - in accord with Thorpe and Ingold’s observations.\textsuperscript{24} We were unable to obtain a cyclized product from the 7-membered system. In the formation of 2.33 and 2.35 the alcohols contained a minor impurity that could be removed after hydrogenation of the Cbz protecting group (87-90% yields). We were unable to determine the ee for alcohols 2.33, 2.35, and 2.36 due to lack of separation on the HPLC. Therefore, the (S) Mosher ester of these alcohols were made in order to obtain sufficient separation on HPLC to determine ee.
Scheme 2.8. Exploration of Scope for Organocatalyzed Intramolecular Heteroatom Michael Addition

We were also interested in exploring the possibility of accessing indoline ring systems in an enantioselective manner (Scheme 2.9). The precursor was accessed from its corresponding known o-allyl aniline 2.37. Cbz protection gave aniline 2.38 followed by Grubbs cross metathesis using the “aged” catalyst provided the desired enal 2.39. Not surprisingly, this compound was unstable and had to be immediately submitted into the cyclization reaction upon formation. Despite this instability, the level of enantioselectivity in the cyclization to form indoline 2.40 was still quite good at 92% ee with a reasonable 63% yield.
**Scheme 2.9.** Enantioselective Construction of Indoline Ring System

We also looked into using the $p$-chloro substituted precursor for the cyclization. Following the same conditions to obtain the Cbz protected amine in 83% yield worked well, however, metathesis using the “aged” catalyst provided the enal in a poor 30% yield (Scheme 2.10). The low yield of the metathesis was contributed to the lack of stability of the resulting enal. In addition to the metathesis giving a poor yield the construction of the indoline ring under typical conditions was not observed nor was the enal ever recovered; this is likely due to the instability of the enal.

**Scheme 2.10.** Construction of the $p$-Chloro Indoline

In conclusion, an organocatalyzed, intramolecular heteroatom
Michael addition protocol has been developed for the asymmetric synthesis of pyrrolidine, indoline, and piperidine derivatives. The protocol takes advantage of simple reaction conditions along with the absence of any additives. The catalyst is commercially available or is readily prepared in 4 steps from either enantiomer of proline. The scope of this transformation has been explored on a series of enal precursors, highlighting differences in reactivity involving ring size and substitution. In general, this methodology is useful in the asymmetric synthesis of a variety of nitrogen ring systems and can be used in alkaloid synthesis.
2.4. Experimental

**General.** Infrared spectra were recorded neat unless otherwise indicated and are reported in cm$^{-1}$. $^1$H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. $^{13}$C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by a bunsen flame, then cooled under argon. Solvents and commercial reagents were purified in accord with literature procedures or used without further purification.
**Aldehyde 2.7:** To a pressure vessel containing known 1-carbobenzyloxyamino-5-hexene (2.4) (200 mg, 0.86 mmol) and CH$_2$Cl$_2$ (20 mL) was added 2.5 (300 mg, 4.29 mmol, 0.35 mL) and 2$^{nd}$ generation Grubbs catalyst (36 mg, 0.042 mmol, 5 mol%). The vessel was sealed and heated to 45°C. After 48 h the mixture was then cooled to rt, concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-25% EtOAc/Hexanes to give 2.7 (175 mg, 0.67 mmol, 78%) as a brownish oil. IR (neat) 3348, 3032, 2932, 2862, 2731, 1684, 1635, 1240 $^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (d, $J = 7.8$ Hz, 1H), 7.25-7.32 (m, 5H), 6.77 (dt, $J = 15.6$, 6.4 Hz, 1H), 6.06 (dd, $J = 7.6$, 15.2 Hz, 1H), 5.34 (bs, NH), 5.06 (s, 2H), 3.15-3.18 (m, 2H), 2.28-2.30 (m, 2H), 1.45-1.55 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 194.2, 158.4, 156.6, 136.7, 133.0, 128.5, 128.04, 127.99, 66.5, 40.6, 32.2, 29.4, 24.9; HRMS (EI+) calc. For C$_{15}$H$_{19}$NO$_3$ (M+) 261.1365, found 261.1360.

**General Procedure of Organocatalyzed Heteroatom Michael Addition with in situ NaBH$_4$ reduction:** To a solution of aldehyde (1 equiv.) and MeOH (0.2 M) was added a solution of the catalyst 1.27 (20 mol %) in DCE (0.04 M in catalyst 1.27) via syringe at -25°C. The reaction was placed in the freezer (-25°C). After judged to be complete by TLC, the
solution was warmed to 0°C and NaBH₄ (3 equiv.) was added. The solution was then allowed to warm to rt. After 2 h, the reaction was quenched with HCl (2 ml per mmol of aldehyde, 10% aq.), diluted with H₂O (50 mL per mmol aldehyde) and extracted with Et₂O (3 X 100 mL per mmol aldehyde). The combined organic layers were washed with sat. aq. NaCl (300 mL per mmol aldehyde) and the dried extract (MgSO₄) was concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with EtOAc/Hexanes to give the alcohol (60-71%).

**General Procedure of Racemic Heteroatom Michael Addition**

**with in situ NaBH₄ reduction:** To a solution of aldehyde (1 equiv.) and CH₂CN (0.2 M) was added BF₃·Et₂O (2 equiv.) at rt. The solution was allowed to stir at rt. for 1 h. The reaction was then quenched with aqueous sodium bicarbonate, then extracted with Et₂O (3 X 100 mL per mmol of aldehyde) and the combined organic layers were washed with sat. aq. NaCl, dried over MgSO₄, and concentrated in vacuo. The crude mixture was then dissolved in MeOH (0.1 M), cooled to 0°C and 20 mg of NaBH₄ was added. The solution was then allowed to warm to rt and stir for 2 h. The reaction was quenched with 10% HCl, extracted with Et₂O (3 X 100 mL per mmol of aldehyde) and the combined organic layers were dried over MgSO₄, and concentrated in vacuo. The crude product was purified by
chromatography over silica gel, eluting with 100% hexanes up to 30% EtOAc/Hexanes to give the desired cyclized alcohols with yields ranging from 59-71%.

Alcohol (R)-2.9: Purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give the known alcohol 2.9\textsuperscript{14} (17.7 mg, 0.067 mmol, 70%) as a pale yellow oil. [a]$_D$ +14.2 (c = 0.8, CHCl$_3$), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.42 (m, 5H), 5.17 (s, 2H), 4.50-4.60 (m, 1H), 4.05-4.12 (m, 1H), 3.55-3.65 (m, 1H), 3.35-3.50 (m, 1H), 2.79 (t, $J = 12.8$ Hz, 1H), 1.98 (t, $J = 13.6$ Hz, 1H), 1.52-1.70 (m, 5H), 1.40-1.52 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.8, 136.7, 128.6, 128.1, 127.9, 67.4, 58.7, 47.0, 39.5, 32.6, 29.2, 25.5, 19.1; HRMS (EI) calcd. For C$_{15}$H$_{21}$NO$_3$ (M$^+$) 263.1522, found 263.1522.

Aldehyde 2.16: To a pressure vessel containing a solution of known 1-carbobenzyloxyamino-4-pentene (2.13)$^{14}$ (100 mg, 0.457 mmol) in CH$_2$Cl$_2$ (10 mL) was added sequentially aldehyde 2.5 (159.7 mg, 0.186 mL, 2.28 mmol) and aged\textsuperscript{27} 2$^{nd}$ generation Grubbs catalyst (19.4 mg, 0.023 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the
solution was cooled to rt and concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 10%-30% EtOAc/Hexanes to yield known 2.16 (76 mg, 0.306 mmol, 67%) as a brownish oil. IR (neat) 3338, 3070, 2940, 1684, 1532, 1247 'H NMR (300 MHz, CDCl₃) δ 9.51 (d, J = 7.5 Hz, 1H), 7.30-7.38 (m, 5H), 6.81-6.88 (m, 1H), 6.15 (dd, J = 8.1, 15.6 Hz, 1H), 5.12 (s, 2H), 4.80 (bs, 1H), 3.25-3.30 (m, 2H), 2.37-2.44 (m, 2H), 1.71-1.81 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 194.0, 157.4, 156.5, 136.5, 133.2, 128.53, 128.14, 128.07, 66.6, 40.4, 29.8, 28.3; HRMS (El+) calcd. For C₁₄H₁₇NO₃ (M+) 247.1209, found 247.1213.

\[
\begin{align*}
\text{Aldehyde } 2.17: & \text{ To a pressure vessel containing a solution of known } \\
& \text{1-carbobenzoyloxyamino-6-heptene (2.15) (100 mg, 0.358 mmol) in } \\
& \text{CH₂Cl₂ (10 mL) was added sequentially aldehyde 2.5 (125.5 mg, 1.79} \\
& \text{mmol, 0.146 mL) and aged 2nd generation Grubbs catalyst (19.4 mg,} \\
& \text{0.023 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48} \\
& \text{h, the solution was cooled to rt and concentrated in vacuo. The crude} \\
& \text{product was purified by chromatography over silica gel, eluting with 10%-} \\
& \text{30% EtOAc/Hexanes to yield known 2.17 (86 mg, 0.265 mmol, 75%) as a} \\
& \text{brownish oil. IR (neat) peaks 3340, 3062, 2934, 1683, 1532, 1249 'H NMR}
\end{align*}
\]
(300 MHz, CD$_3$Cl) $\delta$ peaks 9.53-9.51 (d, J = 7.8, 1H), 7.38-7.30 (m, 5H), 6.89-6.79 (m, 1H), 6.17-6.09 (m, 1H), 5.12 (s, 2H), 4.75 (bs, 1H), 3.23-3.21 (m, 2H), 2.37-2.34 (m, 2H), 1.58-1.50 (m, 4H), 1.50-1.35 (m, 2H); $^{13}$C NMR (300 MHz, CD$_3$Cl) $\delta$ peaks 194.1, 158.5, 156.5, 136.6, 133.1, 128.5, 128.1, 66.6, 40.8, 32.5, 29.7, 27.4, 26.2 HRMS (FAB+) calcd. For C$_{16}$H$_{21}$O$_2$N (M+) 275.3389, found 276.16061.

![Chemical Structure](image)

**Carbamate 2.21:** To a stirred solution of the known amine 2.19 (8.6 mmol) in acetone (10 mL) and H$_2$O (10 mL) at rt was added sequentially K$_2$CO$_3$ (1.14 g, 8.60 mmol) and CbzCl (2.93 g, 2.45 mL, 17.2 mmol). After 30 min, the reaction was quenched with H$_2$O (15 mL) and extracted with CH$_2$Cl$_2$ (3 X 25 mL). The combined organic layers were washed with sat. aq. NaCl (25 mL) and the dried extract (MgSO$_4$) was concentrated *in vacuo*. The crude product was purified by chromatography over silica gel, eluting with 0-20% EtOAc/Hexanes to yield 2.21 (936 mg, 3.784 mmol, 44% over 4 steps) as a light yellow oil. IR (neat) 3419, 3349, 3070, 3032, 2973, 1776, 1715, 1638, 1506; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.43 (m, 5H), 5.80-5.90 (m, 1H), 5.10 (s, 2H), 4.98-5.04 (m, 2H), 4.82 (bs, 1H), 2.06-2.12 (m, 2H), 1.78-1.82 (m, 2H), 1.34 (s, 6H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 154.6, 138.6, 136.9, 128.9, 128.5, 128.0, 114.5, 73.5, 66.0,
52.7, 39.5, 28.6, 27.1; HRMS (El+) calcd. For C_{15}H_{21}NO_2 (M+) 247.1572, found 247.1573.

**Carbamate 2.22:** To a stirred solution of the known amine 2.20 (8.6 mL) in acetone (10 mL) and H_2O (10 mL) at rt was added sequentially K_2CO_3 (1.14 g, 8.60 mmol) and CbzCl (2.93 g, 2.45 mL, 17.2 mmol). After 30 min, the reaction was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 25mL). The combined organic layers were washed with sat. aq. NaCl (25 mL) and the dried extract (MgSO_4) was concentrated *in vacuo*. The crude product was purified by chromatography over silica gel, eluting with 0-20% EtOAc/Hexanes to yield 2.22 (943 mg, 3.612 mmol, 42% over 4 steps) as a light yellow oil. IR (neat) 3350, 3062, 3023, 2940, 2864, 1715, 1640, 1506; ^1^H NMR (400 MHz, CDCl_3) δ 7.30-7.41 (m, 5H), 5.78-5.90 (m, 1H), 4.98-5.21 (m, 4H), 4.69 (bs, 1H), 2.07-2.09 (m, 2H), 1.66-1.71 (m, 2H), 1.34 (s, 6H); ^13^C NMR (400 MHz, CDCl_3) δ 154.6, 138.7, 136.8, 128.6, 128.5, 128.3, 114.7, 66.0, 52.8, 40.4, 34.0, 27.8, 27.0, 23.7 HRMS (El+) calcd. For C_{15}H_{23}NO_2 (M+) 261.1729, found 261.17389.
**Aldehyde 2.24:** To a pressure vessel containing a solution of alkene 2.21 (200 mg, 0.796 mmol) in CH₂Cl₂ (20 mL) was added sequentially aldehyde 2.5 (279 mg, 3.98 mmol, 0.324 mL) and aged 2nd generation Grubbs catalyst (33.8 mg, 0.040 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the solution was cooled to rt and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to yield 2.24 (144 mg, 0.516 mmol, 65%) as a brownish oil. IR (neat) 3341, 2968, 1688, 1526, 1454 ¹H NMR (300 MHz, CDCl₃) δ 9.47 (d, J = 7.8 Hz, 1H), 7.30-7.38 (m, 5H), 6.83 (dt, J = 15.6, 6.0 Hz, 1H), 6.12 (dd, J = 7.5, 15.6 Hz, 1H), 5.07 (s, 2H), 4.66 (bs, 1H), 2.29-2.37 (m, 2H), 1.91-1.96 (m, 2H), 1.33 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 193.9, 158.4, 154.7, 136.6, 133.0, 128.6, 128.20, 128.16, 66.3, 52.6, 37.6, 27.9, 27.4; HRMS (EI⁺) calcd. For C₁₆H₂₁NO₃ (M⁺) 275.1521, found 275.1522.

**Aldehyde 2.24:** To a pressure vessel containing a solution of alkene 2.22 (200 mg, 0.796 mmol) in CH₂Cl₂ (20 mL) was added sequentially aldehyde 2.5 (279 mg, 3.98 mmol, 0.324 mL) and 2nd
generation Grubbs catalyst (33.8 mg, 0.040 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the solution was cooled to rt and concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to yield 2.24 (166 mg, 0.573 mmol, 72%) as a brownish oil. IR (neat) 3345, 3027, 2944, 1690, 1525, 1455 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (d, J = 7.8 Hz, 1H), 7.30-7.37 (m, 5H), 6.83 (dt, J = 15.6, 6.6 Hz, 1H), 6.13 (dd, J = 7.8, 15. 6 Hz, 1H), 5.07 (s, 2H), 4.64 (bs, 1H), 2.33-2.38 (m, 2H), 1.73-1.78 (m, 2H), 1.50-1.57 (m, 2H), 1.31 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 194.1, 158.3, 154.6, 136.7, 133.1, 128.5, 128.0, 66.1, 52.7, 39.5, 27.3, 22.5; HRMS (EI+) calcd. For C₁₇H₂₃NO₃ (M+1) 290.1756, found 290.1755.

**Carbamate 2.28:** To a stirred solution of the known amine 2.26 (3.62 mmol) in THF (6 mL) and H₂O (6 mL) was added sequentially NaHCO₃ (304 mg, 3.62 mmol), NaOH (2 mL, 10% aq.) and Cbz-OnSu (902 mg, 3.62 mmol). After 16 h, the organic solvent was removed in vacuo and the residual aqueous solution was extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with sat. aq. NaCl (30 mL) and the dried extract (MgSO₄) was concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-20%
EtOAc/Hexanes to yield 2.28 (444.5 mg, 1.81 mmol, 50% over 3 steps) as a light yellow oil. IR (neat) 3343, 3071, 3033, 2960, 1698, 1639; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.33-7.39\) (m, 5H), 5.74-5.90 (m, 1H), 5.13 (s, 2H), 5.03-5.10 (m, 2H), 4.87 (bs, 1H), 3.05 (d, \(J = 6.6\) Hz, 2H), 2.00 (d, \(J = 7.5\) Hz, 2H), 0.90 (s, 6H); \(^13\)C NMR (300 MHz, CDCl\(_3\)) \(\delta 156.7, 136.7, 134.7, 128.5, 128.4, 128.2, 117.6, 66.7, 50.9, 44.3, 34.8, 24.7\); HRMS (EI+) calcd.

For \(\text{C}_{15}\text{H}_{21}\text{O}_{2}\text{N}\) (M+) 247.1572, found 247.1580.

Carbamate 2.29: To a stirred solution of the known amine 2.27\(^{30}\) (7.24 mmol) in THF (12 mL) and \(\text{H}_2\text{O}\) (12 mL) was added sequentially NaHCO\(_3\) (563 mg, 7.24 mmol), NaOH (3 mL, 10% aq.) and Cbz-OnSu (1.67 mg, 7.24 mmol). After 16 h, the organic solvent was removed \textit{in vacuo} and the residual aqueous solution was extracted with Et\(_2\)O (3 X 30 mL). The combined organic layers were washed with sat. aq. NaCl (30 mL) and the dried extract (MgSO\(_4\)) was concentrated \textit{in vacuo}. The crude product was purified by chromatography over silica gel, eluting with 0-20% EtOAc/Hexanes to yield 2.29 (1.22 g (4.69 mmol, 65% over 3 steps) as a light yellow oil. IR (neat) 3432, 3341, 3062, 2959, 2916, 1733, 1533; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.33-7.39\) (m, 5H), 5.76-5.83 (m, 1H), 5.13 (s, 2H), 4.94-5.05 (m, 2H), 4.79 (bs, 1H), 3.06 (d, \(J = 6.6\) Hz, 2H), 2.03-2.06 (m, 2H), 1.28-1.40 (m, 4H), 0.90 (s, 6H); \(^13\)C NMR (300 MHz, CDCl\(_3\)) \(\delta \)}
156.7, 139.2, 128.6, 128.4, 128.2, 114.2, 69.7, 66.7, 51.0, 38.8, 34.3, 28.3, 24.7; HRMS (EI+) calcd. For C₁₆H₂₃NO₂ (M+) 261.1729, found 261.1732.

**Aldehyde 2.30:** To a pressure vessel containing a solution of **2.28** (200 mg, 0.796 mmol) in CH₂Cl₂ (20 mL) was added sequentially aldehyde **2.5** (279 mg, 3.98 mmol, 0.324 mL) and aged²⁷ 2nd generation Grubbs catalyst (33.8 mg, 0.040 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the solution was cooled to rt and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to yield **2.30** (160 mg, 0.573 mmol, 72%) as a brownish oil. IR (neat) 3354, 2958, 2864, 2713, 1699, 1455, 1417, 1280; ¹H NMR (300 MHz, CDCl₃) δ 9.53 (d, J = 7.8 Hz, 1H), 7.30-7.38 (m, 5H), 6.90 (dt, J = 16.2, 6.9 Hz, 1H), 6.13 (dd, J = 7.8, 15.3 Hz, 1H), 5.12 (s, 2H), 4.93 (bs, NH), 3.10 (d, J = 6.6 Hz, 2H), 2.26 (d, J = 7.8 Hz, 2H), 1.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 193.7, 156.7, 154.7, 136.4, 135.5, 128.6, 128.2, 66.9, 50.9, 42.7, 35.8, 24.9; HRMS (EI+) calcd. For C₁₆H₁₂NO₃ (M+) 275.1522, found 275.1513.
Aldehyde 2.31: To a pressure vessel containing a solution of 2.29 (100 mg, 0.383 mmol) in CH₂Cl₂ (10 mL) was added sequentially aldehyde 2.5 (134 mg, 0.32 mL, 1.92 mmol) and aged²⁷ 2nd generation Grubbs catalyst (16 mg, 0.019 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the solution was cooled to rt and concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to yield 2.31 (89.8 mg, 0.310 mmol, 81%) as a brownish oil. IR (neat) 3344, 2959, 2864, 2722, 1689, 1653, 1539, 1455, 1242 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.49 (d, J = 8.1 Hz, 1H), 7.30-7.30 (m, 5H), 6.82 (dt, J = 15.6, 6.7 Hz, 1H), 6.12 (dd, J = 8.4, 15.6 Hz, 1H), 5.11 (s, 2H), 4.80-4.90 (m, 1H), 3.06 (d, J = 6.6 Hz, 2H), 2.30-2.30 (m, 2H), 1.36-1.42 (m, 2H), 0.92 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 194.1, 159.0, 156.7, 136.5, 132.7, 128.6, 128.2, 66.8, 50.6, 37.2, 34.5, 27.5, 24.7; HRMS (El+) calcd. For C₁₇H₂₃NO₃ (M+) 289.1678, found 289.1688.

Alcohol 2.32: The reaction time was 48 h at -25°C. The crude product was purified by chromatography over silica gel, eluting with 10-
30% EtOAc/Hexanes to give the known alcohol $2.32^{14}$ (15 mg, 0.060 mmol, 67%) as a pale yellow oil. Enantiomeric excess was determined by chiral HPLC [4.6 X 250 mm Diacel OD column, 95:5 hexanes/iPrOH, retention times 16.03 (major) and 17.24 min (minor)] to be 95% ee. $[\alpha]_D = +7.2$ (c = 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30-7.41 (m, 5H), 5.18 (d, $J = 3.6$ Hz, 1H), 5.13 (d, $J = 3.6$ Hz, 1H), 4.75 (bs, OH), 4.20-4.30 (m, 1H), 4.05-4.13 (m, 1H), 3.60-3.70 (m, 2H), 3.40-3.50 (m, 1H), 3.15-3.25 (m, 1H), 1.90-2.10 (m, 1H), 1.65-1.80 (m, 1H), 1.50-1.70 (m, 2H), 1.30-1.47 (m, 2H); $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 156.7, 136.7, 128.5, 128.0, 127.8, 67.1, 59.1, 54.3, 46.3, 38.2, 31.1, 23.6; HRMS (El+) calc. for C$_{14}$H$_{19}$NO$_3$ (M+) 249.1142, found 249.1355.

Alcohol $2.33$: The reaction time was 96 h at -25°C. The crude product was purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give the alcohol $2.33$ (15 mg, 0.054 mmol, 60%) as a pale yellow oil. A minor inseparable impurity was present in this product that could be readily removed by hydrogenation. Alternatively, enantiomeric excess was determined by chiral HPLC of Mosher ester derivative$^{31}$ [4.6 X 250 mm Diacel OD column, 98:2 hexanes/iPrOH,
retention times 17.78 (major) and 16.96 min (minor)) to be 79% ee. IR (neat) 3449, 2962, 1691; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.8-7.39 (m, 5H), 5.12-5.23 (m, 2H), 4.30 (bs, 1H), 4.10 (bs, 1H), 3.50-3.58 (m, 2H), 1.90-2.15 (m, 3H), 1.50-1.85 (m, 5H), 1.43 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.6, 136.6, 128.5, 128.0, 67.3, 61.4, 59.0, 56.6, 40.7, 39.0, 29.3, 28.2, 26.3; HRMS (EI+) calc. for C$_{16}$H$_{23}$NO$_3$ (M+) 277.1678, found 277.1670.

**Alcohol 2.45:** To a solution of 2.33 (11.0 mg, 0.0389 mmol) in MeOH (0.5 mL) was added Pd/C (2 mg, 10% Pd), and then the reaction flask was flushed and filled with hydrogen gas. The reaction was done under 1 atm of hydrogen gas and was stirred for 16 h. The reaction mixture was filtered over celite to remove the Pd/C and was concentrated *in vacuo* to give 2.45 (5.0 mg, 0.350 mmol, 90%) as a pale yellow waxy oil. $[\alpha]_D$ 13.2 (c = 0.65, CHCl$_3$); IR (neat) 3391, 2959, 1683; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.92-3.87 (m, 1H), 3.80-3.74 (m, 1H), 3.57-3.54 (m, 1H), 3.27 (bs, 1H), 2.03-1.99 (m, 1H), 1.82-1.78 (m, 1H), 1.76-1.63 (m, 4H), 1.23 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 62.0, 59.6, 58.4, 39.4, 36.6, 31.5, 30.3, 29.2; HRMS (Cl+) calcd. For C$_8$H$_{16}$NO (M+H) 144.1388, found 144.1383.
**Alcohol 2.35:** The reaction time was 48 h at -25°C. The crude product was purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give the alcohol **2.35** (16 mg, 0.058 mmol, 64%) as a pale yellow oil. A minor inseparable impurity was present in this product that could be readily removed by hydrogenation. Alternatively, enantiomeric excess was determined by chiral HPLC of Mosher ester derivative$^{31}$ [4.6 X 250 mm Diacel OD column, 95:5 hexanes/iPrOH, retention times 13.92 (major) and 10.58 min (minor)] to be 85% ee. $[\alpha]_D = -3.4$ (c = 0.35, CHCl$_3$); IR (neat) 3450, 2956, 1702; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37-7.30 (m, 5H), 5.16 (s, 2H), 4.25 (m, 1H), 3.65-3.3 (m, 3H), 2.00-1.94 (m, 1H), 1.9-1.5 (m, 5H), 1.11 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.8, 136.7, 128.5, 128.1, 128.1, 67.3, 61.4, 59.0, 56.6, 40.7, 39.0, 29.3, 28.2, 26.3; HRMS (El+) calcd. For C$_{16}$H$_{23}$NO$_3$ (M+) 277.1678, found 277.1671.
**Alcohol 2.46:** To a solution of 2.35 (8.0 mg, .028 mmol) in MeOH (0.5 mL) was added Pd/C (2 mg, 10% Pd), and then the reaction flask was flushed and filled with hydrogen gas. The reaction was done under 1 atm of hydrogen gas and was stirred for 16 h. The reaction mixture was filtered over celite to remove the Pd/C and was concentrated *in vacuo* to give 2.46 (3.5 mg, 0.0280 mmol, 87%) as a pale yellow waxy oil. $[\alpha]_D$ 36 (c = 0.1, CHCl$_3$); IR (neat) 3370, 2959, 1692; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.93-3.87 (m, 1H), 3.80-3.75 (m, 1H), 3.57-3.53 (m, 1H), 2.05-1.98 (m, 1H), 1.83-1.76 (m, 1H), 1.75-1.56 (m, 4H), 1.24 (s, 3H), 1.20 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 62.0, 59.7, 58.5, 39.3, 36.6; 31.4, 30.2, 29.1; HRMS (Cl+) calcd. For C$_8$H$_{18}$NO (M+H) 144.1388, found 144.1391.

**Alcohol 2.36:** The reaction time was 48 h at -25°C. The crude product was purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give the alcohol 2.36 (15.7 mg, 0.054 mmol, 63%) as a pale yellow oil. Enantiomeric excess was determined by chiral HPLC of Mosher ester derivative$^{31}$ [4.6 X 250 mm Diacel OD column, 97:3 hexanes/iPrOH, retention times 11.25 (major) and 10.12 min (minor)] to be
95% ee. [α]_D -9.2 (c = 0.25, CHCl₃); IR (neat) 3470, 2927, 1692; ^1^H NMR (300 MHz, CDCl₃) δ 7.30-7.40 (m, 5H), 5.17 (s, 2H), 4.50-4.60 (m, 1H), 3.30-3.70 (m, 3H), 2.54 (d, J = 13.2 Hz, 1H), 1.85-2.05 (m, 2H), 1.30-1.60 (m, 5H), 0.94 (s, 3H), 0.92 (s, 3H); ^13^C NMR (75 MHz, CDCl₃) δ 157.2, 136.7, 128.5, 128.0, 127.7, 67.4, 58.5, 50.0, 46.3, 32.7, 32.0, 30.5, 28.9, 25.2, 22.9; HRMS (El+) calcd. For C₁₇H₂₅NO₃ (M+) 291.1835 found 291.1828.

![Chemical Structure](image)

**Carbamate 2.38**: To a stirred solution of the known amine 2.37^32 (500 mg, 3.00 mmol) in acetone (16 mL) and H₂O (16 mL) at rt was added sequentially K₂CO₃ (414 mg, 3.00 mmol) and CbzCl (608 mg, 0.64 mL, 4.5 mmol). After 30 min, the reaction was quenched with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (30 mL) and the dried extract (MgSO₄) was concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-20% EtOAc/Hexanes to yield the known 2.38^33 (750 mg, 2.49 mmol, 83%) as a flaky while solid. Mp 57-60°C; IR (neat) 3283, 3030, 1692, 1533, 1244, 744; ^1^H NMR (300 MHz, CDCl₃) δ 7.86-7.83 (d, J = 7.2, 1H), 7.45-7.38 (m, 5H), 7.29-7.25 (m, 1H), 7.19-7.17
(m, 1H), 7.13-7.08 (m, 1H), 6.68 (bs, 1H), 6.02-5.91 (m, 1H), 5.23 (s, 2H), 5.19 (dd, $J = 0.9$, 9.6 Hz, 1H), 5.04 (dd, $J = 0.9$, 17.1 Hz, 1H), 3.35 (d, $J = 6.0$ Hz, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 153.8, 136.2, 136.0, 135.7, 130.2, 128.6, 128.3, 127.5, 124.5, 122.2, 116.8, 67.0, 36.5; HRMS (El+) calcd. For C$_{17}$H$_{17}$O$_2$N (M+) 267.1259, found 267.1250.

**Aldehyde 2.39:** To a pressure vessel containing a solution of 2.38 (100 mg, 0.374 mmol) in CH$_2$Cl$_2$ (10 mL) was added sequentially aldehyde 2.5 (131 mg, 0.15 mL, 1.87 mmol) and aged$^{27}$ 2$^{nd}$ generation Grubbs catalyst (16 mg, 0.019 mmol, 5 mol %). The vessel was sealed and heated to 45°C. After 48 h, the solution was cooled to rt and concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to yield 2.39 (57.4 mg, 0.194 mmol, 52%) as a brownish oil. IR (neat) 3378, 2944, 1672, 1500$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 7.8$ Hz, 1H), 7.65-7.70 (m, 1H), 7.30-7.45 (m, 5H), 7.15-7.30 (m, 2H), 6.90-7.00 (m, 21H), 6.45 (bs, 1H), 6.04 (dd, $J = 7.8$, 15.6 Hz, 1H), 5.20 (s, 2H), 3.63 (dd, $J = 1.2$, 6.0 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.4, 154.7, 154.1, 135.9, 135.4, 133.7, 130.2, 128.7,
128.4, 128.3, 125.8, 124.4, 67.3, 34.9; HRMS (EI+) calcd. For C₁₈H₁₇NO₃ (M+) 295.1209, found 295.1209.

Alcohol 2.40: The reaction time was 48 h at -25°C. The crude product was purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give the alcohol 2.40 (15.7 mg, 0.053 mmol, 63%) as a pale yellow oil. Enantiomeric excess was determined by chiral HPLC [4.6 X 250 mm Diacel OD column, 95:5 hexanes/iPrOH, retention times 22.34 (major) and 26.92 min (minor)] to be 92% ee. [α]₀ +7.4 (c = 1.0, CHCl₃); IR (neat) 3422, 2915, 1704, 1599, 1485; ¹H NMR (400 MHz, DMSO-d₆ at 80°C) δ 7.63 (d, J = 8 Hz, 1H), 7.50-7.30 (m, 5H) 7.22 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 6.8 Hz, 1H), 5.28 (s, 2H), 4.61-4.56 (m, 1H), 4.24 (bs, 1H), 3.50 (t, J = 6.4 Hz, 2H), 3.32 (dd, J = 9.6, 16.4 Hz, 1H), 2.90 (dd, J = 2.4, 16.4 Hz, 1H), 1.98-1.92 (m, 1H), 1.69-1.63 (m, 1H); ¹³C NMR (100 MHz, DMSO-d₆ at 80°C) δ 152.9, 142.0, 137.0, 131.2, 128.9, 128.4, 128.2, 127.5, 125.5, 123.2, 115.3, 67.0, 58.0, 37.9, 33.7; HRMS (EI+) calcd. For C₁₈H₁₉NO₃ (M+) 297.1365 found 297.1364.
Chapter 3. Application of Intramolecular Organocatalyzed Heteroatom Michael Addition

3.1 Introduction

With a working catalyst system, we next sought to demonstrate the utility of the route for the construction of selected alkaloids and cyclic β-amino acid derivatives. In addition to demonstrating the utility of this cyclization we did not currently know the absolute configuration of the cyclization, and needed to synthesize a known compound with which to compare the optical rotation. The three compounds chosen were known compounds with some significance to them, as well as being of similar structure to our previously synthesized piperidine and pyrrolidine rings. These compounds were β-amino acid derivatives homopipeolic acid, homoproline, and the alkaloid pelleterine.

3.2 Synthesis of Homopipeolic Acid

First, the cyclic β-amino acid, homopipeolic acid, was selected as an initial target for the application of this methodology. The cyclization to the β-amino aldehyde was accomplished using our methodology to achieve the piperidine ring. The aldehyde was then oxidized to the corresponding acid via the Pinnick oxidation, which proceeded smoothly to give the acid in 76% isolated yield. The final step was the Cbz deprotection that afforded
the desired β-amino acid in near quantitative yield and rapid fashion (Scheme 3.1). Comparison of the observed optical rotation for the synthetic homopipercolic acid \{[\alpha]_D = -23.6^\circ (c = 0.11, \text{H}_2\text{O})\} with the literature value \{(S)-isomer lit.\}^{35} \{[\alpha]_D = +24^\circ (c = 0.87, \text{H}_2\text{O})\} also allowed us to establish the \(R\) absolute configuration of synthetic homopipercolic acid 3.2, which in turn confirms the absolute configuration of the cyclization to give the \(R\) enantiomer as the major product.

**Scheme 3.1. Synthesis of Homopipecolic Acid**

![Scheme 3.1. Synthesis of Homopipecolic Acid](image)

### 3.3 Synthesis of Homoproline

Homoproline has attracted considerable attention for its use in medicinal chemistry as well as organocatalysis.\(^{36}\) As anticipated, homoproline was synthesized following the same sequence of steps used in the synthesis of homopipecolic acid. Starting from the enal, the cyclization proceeded well to give the 5-membered pyrrolidine ring system. The aldehyde was oxidized to the acid using the Pinnick oxidation and final deprotection of the amine using \(\text{H}_2\) (g) and \(\text{Pd/C}\) yielded the desired product, homoproline, in 54% over the 3 steps (Scheme 3.2). Again, the synthesized material matched the literature values for this compound,\(^{35}\) confirming the absolute configuration of the 5-membered ring systems as
well. It should be noted that the oxidation of the cyclized β-amino aldehyde 2.32 needed to be conducted immediately after its formation; use of purified aldehyde 2.32 led to considerable erosion in enantioselectivity. The synthesis of homoproline demonstrates the usefulness of this methodology in the rapid and efficient synthesis of both 5 and 6-membered cyclic β-amino acids.

**Scheme 3.2. Synthesis of Homoproline**

3.4 Synthesis of Pelletierine

Next we set out to synthesize pelletierine; an alkaloid with an interesting history in natural products. Tanert first isolated pelletierine in 1878; however, debate swirled in the chemical community for years as to the exact structure of this natural product – in part due to chemists’ inability to synthesize it. Gilman and Marion finally resolved the issue through NMR studies 83 years after it was originally isolated. Further confirmation came through synthesis by Beyerman and Maat in 1963. This natural product was synthesized starting from the 6-membered cyclized β-amino aldehyde. Grignard addition yielded the secondary alcohol as an inconsequential 3:1 ratio of diastereomers which was oxidized using Dess-Martin’s periodinane to give methyl ketone 3.6 in 71% yield over 2 steps.
Finally, hydrogenation of the Cbz protection group revealed (-)-pelletierine in 99% yield (Scheme 3.3). The observed optical rotation for synthetic pelletierine $\{[\alpha]_D = -18.0^\circ \ (c = 0.5, \ \text{EtOH})\}$ matched nicely with the literature value.\textsuperscript{41}

**Scheme 3.3. Synthesis of Pelletierine**

The application of this methodology to the synthesis of homoproline, homopipeolic acid, and pelletierine demonstrates its usefulness in total synthesis. Along with the high enantioselectivity obtained, it gives access to the rapid construction of a variety of $N$ cyclic ring systems, which are valuable for the synthesis of alkaloids. Further utilization of this methodology is shown in the synthetic progress towards cermizine D.
3.5 Experimental

**Aldehyde 2.8:** To a solution of 2.7 (150 mg, 0.574 mmol), and MeOH (3 mL) was added a solution of the catalyst 1.27 (68.5 mg, 0.115 mmol) in DCE (2.75 mL) via syringe and placed in the freezer unstirred (-25°C). After 3 d, the solution was concentrated *in vacuo*. The crude product was purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to give known 2.8¹⁴ (103.5 mg, 0.40 mmol, 69%) as a pale yellow oil. [α]_D 25.3 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.73 (s, 1H), 7.30-7.38 (m, 5H), 5.13 (s, 2H), 4.90-5.00 (m, 1H), 4.05-4.15 (m, 1H), 2.88 (t, J = 12.4 Hz, 1H) 2.72-2.80 (m, 1H), 2.58-2.66 (m, 1H), 1.58-1.78 (m, 4H), 1.45-1.55 (m, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 200.5, 155.2, 136.7, 128.5, 128.0, 127.9, 67.2, 46.2, 44.5, 39.6, 28.7, 25.2, 18.8.

**Acid 3.1:** To a solution of 2.8 (63 mg, 0.241 mmol), t-BuOH (3 mL) water (3 mL) and 2-methyl-2-butene (0.6 mL, 5.6mmol) was added Na₃PO₄ (332.6 mg, 2.41 mmol) followed by NaClO₂ (98.4 mg, 1.085 mmol). The reaction was stirred at rt for 1 h before quenching it with 15 mL of saturated NaCl. Then the solution was extracted with Et₂O (3 X 15 mL),
the combined organic layers were dried over MgSO₄, and concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with 0-40% EtOAc/Hexanes to give known 3.1⁴² (51 mg, 0.183 mmol, 76%) as a colorless oil. [α]_D⁻18 (c = 0.5, CHCl₃); IR (neat): 3060, 3033, 2934, 1732, 1703; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.39 (m, 5H), 5.16 (s, 2H), 4.84 (bs, 1H), 4.11 (d, J = 13.2 Hz, 1H), 2.90 (t, J = 12.4 Hz, 1H), 2.65-2.69 (m, 2H), 1.62-1.70 (m, 4H), 1.00-1.60 (m, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 176.6, 155.8, 136.8, 128.5, 128.0, 127.8, 67.3, 48.0, 39.7, 35.1, 28.2, 25.2, 18.8.

(R)-Homopipercolic Acid (3.2): To a solution of 3.1 (51 mg, 0.183 mmol) in MeOH (1.5 mL) was added Pd/C (5 mg, 10% Pd), and then the reaction flask was flushed and filled with hydrogen gas. The reaction was done under 1 atm of hydrogen gas and was stirred for 16 h. The reaction mixture was filtered over Celite⁵ to remove the Pd/C and was concentrated in vacuo to give 3.2 (26 mg, 0.183 mmol, 99%) as a pale yellow waxy oil. [α]_D⁻23.6 (c = 0.11, H₂O), lit. Value⁴³ (S)-3.2: [α]_D¹ +24.0 (c = 0.87, H₂O); ¹H NMR (400 MHz, MeOD) δ 5.00 (bs, 1H), 3.44 (d, J = 12.0 Hz, 1H), 3.30-3.38 (m, 1H), 3.00 (t, J = 12.8 Hz, 1H), 2.40-2.52 (m, 2H), 1.88-1.93 (m, 3H), 1.55-1.72 (m, 3H); ¹³C NMR (100 MHz, MeOD) δ 176.0, 54.6, 44.0,
39.2, 28.3, 22.3, 21.8; HRMS (EI+) calcd. For C_{7}H_{13}NO_{2} (M+) 143.1852, found 143.0950.

(R)-Homoproline (3.4): To a solution of 2.16 (54 mg, 0.217 mmol) in MeOH (2 mL) cooled to -25°C was added a cooled solution of 1.27 (22.5 mg, 0.038 mmol) in DCE (4.75 mL), the reaction mixture was kept at -25°C for 48 h. The solution was then concentrated in vacuo. The crude and unstable aldehyde 2.32 was carried on without further purification.

To a solution of crude aldehyde 2.32 (0.217 mmol), t-BuOH (2 mL), water (2 mL), and 1.0 mL (9.32mmol) of 2-methyl-2-butene was added NaH_{2}PO_{4} (299 mg, 2.17 mmol) followed by NaClO_{2} (88.6 mg, 0.98 mmol) of was added. The reaction was stirred at rt for 1 h before quenching it with 30 mL of saturated NaCl. Then the solution was extracted with Et_{2}O (3 X 10 mL), the combined organic layers were dried over MgSO_{4}, and concentrated in vacuo. The crude acid 3.3 was dissolved in 10 mL of Et_{2}O, extracted into a 20% NaOH (10 mL) aqueous layer washed with Et_{2}O (1 X 10 mL), and then reacidified with 10% HCl (25 mL) and extracted with Et_{2}O (3 X 20 mL), the combined organic layers were dried over MgSO_{4}, and
concentrated in vacuo. The crude acid 3.3 was carried on without further purification.

To a solution of crude acid 3.3 (0.217 mmol) and MeOH (1.0 mL) was added Pd/C (5 mg, 10% Pd). Then the reaction flask was flushed with hydrogen gas. The reaction was done under 1 atm of hydrogen gas and was stirred for 16 h. The reaction mixture was filtered over Celite® to remove the Pd/C and was concentrated in vacuo to yield the desired amino acid 3.4 (17 mg, 0.117 mmol, 54% over 3 steps) as a waxy oil. \([\alpha]_D -3.25 (c = 0.4, \text{H}_2\text{O})\) lit. value\(^{43}\) (S)-3.4: \([\alpha]_D +3.4 (c = 1.0, \text{H}_2\text{O})\); \(^1\text{H} NMR\) (400 MHz, \text{D}_2\text{O}) \(\delta\) 3.60-3.80 (m, 1H), 3.20-3.30 (m, 2H), 2.50-2.60 (m, 2H), 2.10-2.20 (m, 1H), 1.95-2.10 (m, 2H), 1.55-1.65 (m, 1H); \(^{13}\text{C} NMR\) (100 MHz, \text{CDCl}_3) \(\delta\) 171.9, 57.6, 45.0, 38.3, 29.3, 23.0.

**Ketone 3.6:** To a solution of 2.8 (130 mg, 0.498 mmol) in THF (5 mL) at -78°C was slowly added a solution of MeMgBr (0.3 mL, 1.0 mmol, 3.0 M in Et₂O). The mixture was allowed to stir at -78°C for 30 min. Then the solution was warmed to rt and stirring for 4 h. The reaction was quenched with water (2 mL). Then the solution was extracted with Et₂O (3 X 15 mL), the combined organic layers were dried over MgSO₄, and
concentrated *in vacuo*. To a solution of crude 3.5 (0.498 mmol) in CH$_2$Cl$_2$ (6 mL) was added sodium bicarbonate (209 mg, 2.49 mmol) followed by Dess Martin’s reagent (268 mg, 0.62 mmol). The mixture was allowed to stir for 4 h before the reaction was quenched with 10% aqueous sodium bicarbonate (2 mL). Then the solution was extracted with Et$_2$O (3 X 15 mL), the combined organic layers were dried over MgSO$_4$, concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to give known 3.6$^{44}$ (97 mg, 0.353 mmol, 71% over 2 steps) as a colorless oil. [α]$_D$ +10.1 (c = 0.9, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30-7.41 (m, 5H), 5.16 (d, J = 12.8 Hz, 1H), 5.13 (d, J = 12.8 Hz, 1H), 4.84 (s, 1H), 4.07 (bs, 1H), 2.88 (t, J = 12.4 Hz, 1H), 2.70-2.75 (m, 2H), 2.17 (s, 3H), 1.60-1.80 (m, 4H), 1.40-1.55 (m, 2H); $^{13}$C NMR (400 MHz, CDCl$_3$) δ 206.9, 155.3, 136.8, 128.5, 128.0, 127.9, 67.1, 47.5, 44.3, 39.8, 30.1, 28.3, 25.3, 18.8.

(R)-Pelletierine (3.7): To a solution of 3.6 (25 mg, 0.091 mmol) in EtOAc (1 mL) was added Pd/C (3 mg, 10% Pd). The flask was flushed and filled with hydrogen gas. The mixture was stirred under 1 atm of hydrogen for 2 h. The solution was filtered over Celite® to remove the carbon then conc. HCl (0.1 mL) was added to form the hydrochloride salt. The solution
was concentrated *in vacuo* to give 3.7 (16 mg, 0.09 mmol, >99%) as a white granular solid. mp 218-219°C; \([\alpha]_D\) -18.0 (c = 0.5, EtOH), lit. Value44 (R)-3.7: \([\alpha]_D\) -18.1 (c = 8.18, EtOH); mp 218-220°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.65 (bs, 1H), 9.22 (bs, 1H), 3.51 (bs, 2H), 3.36 (d, \(J = 16.0\) Hz, 1H), 2.90-3.05 (m, 2H), 2.24 (s, 3H), 1.90-2.10 (m, 2H), 1.80-1.90 (m, 2H), 1.70-1.80 (m, 1H), 1.50-1.65 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 205.1, 53.2, 45.9, 45.1, 30.6, 28.4, 22.3, 22.2.
Chapter 4. Application Toward the Synthesis of Cermizine D

4.1 Introduction

Plants of the *Lycopodium* species have been known to produce a number of structurally diverse and complex alkaloids. Many of these compounds continue to have interesting biogenetic\(^4\) and biological\(^5\) points of view as well as serving for challenging targets for total synthesis. Cernuine (4.1) and lycocernuine (4.2) are a few of the cernuane-type *Lycopodium* alkaloids that contain a fused tetracyclic ring system containing an aminal moiety (Figure 4.1). Cermizine D (4.3) also falls into the cernuane-type *Lycopodium* alkaloids - despite not having either a tetracyclic ring system or the aminal moiety. Cermizine D is considered to have a N-C\(_5\) seco-cernuane skeleton as the N-C\(_9\) bond that would form the tetracyclic core is missing. In addition to the lack of the N-C\(_9\) there is also no carbonyl group to make the aminal moiety that is generally seen in this type of alkaloids (Scheme 4.1). The total synthesis of various types of *Lycopodium* alkaloids have been reported,\(^6\) however, there has only been one report on the synthesis of cernuane-type alkaloids in 2008 by Takayama and co-workers.\(^7\)
Scheme 4.1. Cernuane-type *Lycopodium* alkaloids isolated from *Lycopodium cernuum*

4.2 Isolation and Bioactivity of Cermizine D

In 2004, Kobayashi and co-workers reported the isolation of cermizine D from the club moss *lycopodium cernuum*. It was also reported that cermizine exhibited cytotoxicity against murine lymphoma L1210 cells with an IC$_{50}$ of 7.5 $\mu$g/mL.$^{49}$ Although the structure of cermizine D was proposed by Kobayashi based on spectroscopic methods, the relative stereochemistry was deduced from cross-peaks observed in the phase sensitive NOESY spectrum the absolute configuration has not been confirmed. In addition to the absolute configuration not being clear, the counteranion of the natural product has not been reported so far. To date, there has been only one total synthesis of cermizine D by Takayama in 2008.$^{50}$

4.3 Other Synthetic Studies Towards Cermizine D

In 2008, Takayama and co-workers reported the first asymmetric total syntheses of cernuine and cermizine D. They accomplished these syntheses by going through the advanced intermediate 4.4 and starting
from (+)-citronellal. The synthesis involved organocatalytic α-amination to
give the oxazolidinone, followed by diastereoselective allylation and
asymmetric transfer aminoallylation as key steps. The retrosynthesis of
cermizine D is outlined in Scheme 4.2. Construction of the final ring in
cermizine D would be accomplished using RCM. The aminolactam 4.4
was the common intermediate used for the synthesis of both cermizine D
and cernuine. Homoallylamine 4.4 was prepared by a stereoselective
installation of both the allyl and amino groups onto aldehyde 4.5 which
came from Wittig homologation of 4.6. The quinolizidine moiety in 4.6 was
obtained from diastereoselective allylation to aminoacetal 4.7 followed by
RCM. Oxazolidinone 4.8 was constructed from organocatalytic α-
amination of the known aldehyde 4.9.

**Scheme 4.2. Retrosynthetic Analysis of Cermizine D**

Started with (+)-citronellal 4.10, the oxazolidinone was formed by
protecting the aldehyde as an acetal, followed by oxidative cleavage of the
alkene to give the aldehyde (Scheme 4.3). The amination was carried out using dibenzyl azodicarboxylate in the presence of catalytic 1.7 in CH₂Cl₂ at room temperature, followed by in situ reduction. The resulting mixture was then converted to the oxazolidinone using K₂CO₃ in toluene to give the desired product 4.8 in 94% yield and 84% de.

**Scheme 4.3. Organocatalytic Oxazolidinone Synthesis**

Sequential reduction of the Cbz group followed by hydrogenation of the resulting hydrazine gave oxazolidinone 4.11 (Scheme 4.4). Treatment of 4.11 with a catalytic amount of ρ-TsOH in refluxing MeOH caused cyclization to occur and gave the aminoacetal 4.7. Upon reaction of the aminoacetal with allyltrimethylsilane in the presence of TiCl₄, oxazolidinone 4.13 was formed as a single isomer. Hydrolysis of the oxazolidinone followed by acryloylation of the resulting amine gave acrylamide 4.14 as a single diastereomer in 56% over 6 steps. The quinolizidinone 4.6 was formed in 99% by RCM using Grubbs’ first-generation catalyst followed by hydrogenation of the resulting alkene.
Scheme 4.4. Synthesis of Key Intermediate 4.6

In Scheme 4.5, the synthesis of the homoallylamine is shown. The alcohol in 4.6 was oxidized with IBX in DMSO to the aldehyde which was then homologated to 4.15 using the Wittig reaction with Ph₃PCH₂(OH)Cl and KHMDS in THF followed by mild acid hydrolysis to give aldehyde 4.5 in 62% over three steps. Next, the installation of an alkyl chain and an amine function was accomplished simultaneously and stereoselectively by aminoallylation developed by Kobayashi et al.⁵⁴ Using 4.16 derived from (1R)-camphor quinone, the homoallylamine 4.4 was obtained in 92% with 94% de.
The completion of cermizine D is shown in Scheme 4.6. The homoallylamine 4.4, was converted into piperidone 4.20 in three steps using an acryloylation, RCM and hydrogenation to obtain the final lactam ring in 78%. Complete reduction of the bisamide in 4.20 was achieved using LiAlH₄ in THF to give the target compound 4.3 in 60% yield; however, the ¹H NMR data of the synthetic 4.3 was not identical to that reported for the natural cermizine D. Based off of the reported isolation of the compound, they chose to form the TFA salt. The ¹H and ¹³C NMR data from the TFA salt of the synthetic 4.3 did match the reported data of the isolated compound. While the NMR spectra matched, the optical rotation showed a significantly different value and opposite sign to that of the natural product: synthetic TFA salt, [α]²⁰ D +24.2 (c 0.50, MeOH); natural,
[α]$_D^{25}$ -33 (c 0.6, MeOH). Due to this discrepancy, the absolute configuration of natural cermizine D remains a question.

**Scheme 4.6. Completion of Synthesis of Cermizine D**

Overall, Takayama and co-workers have completed the first asymmetric total synthesis of (+)-cermizine D in 20 steps with a 12% overall yield. Highlights in this synthesis include the organocatalytic α-amination to construct the oxazolidinone, which was then used for the diastereoselective allylation. Other key steps include the synthesis of the homoallylamine by asymmetric transfer aminoallylation and the stereoselective construction of the aminal ring system. In addition to these highlights the general and scalable process in which the quinolizidine ring system was synthesized allows for the rapid construction of other quinolizidine-type alkaloids.

**4.4 Our Approach to Cermizine D**

We were interested in using our recently developed methodology in
the synthesis of cermizine D. We envisioned using our cyclized piperidine as a common intermediate that could be used for making both the A and C rings (Scheme 4.7). The retrosynthetic analysis would have the B ring being formed from a Grubbs’ RCM followed by hydrogenation taking us to intermediate 4.21. Iridium-mediated coupling of the amine 4.23 and allyl carbonate 4.22 using a ligand developed by Hartwig\textsuperscript{55} could give the desired coupling. While this catalyst system has generated considerable attention in recent years,\textsuperscript{56} to our knowledge no application to natural product synthesis. The two coupling fragments could both be derived from a common intermediate, which had been previously made. The A ring fragment could come from methyl Grignard addition, followed by functional group manipulations. The C ring fragment could come from a Wittig reaction to the ester, reduction, and conversion to the allyl carbonate. Overall, this strategy would provide us with a rapid and convergent synthesis of the desired target.

**Scheme 4.7.** Retrosynthesis of Cermizine D

4.5 Synthesis of Key Iridium Coupling Precursors

The first step was to synthesize the two fragments for the coupling
reaction (Scheme 4.8). Using the cyclized aldehyde 2.8, which had been made previously, as a common intermediate we carried it along two paths to obtain both the A and C ring fragments for the key coupling. To get to the allyl carbonate fragment, the starting aldehyde was reacted with the methyl ester Wittig reagent to give the allyl ester in 87%. The methyl ester was then reduced using Dibal-H to give the corresponding alcohol 4.26 in 90%. The alcohol was then reacted with methyl chloroformate to give the desired allyl carbonate 4.27 in 79% yield. In order to get ring fragment A, we used the same procedure to get to the methyl ketone as was used in the synthesis of pelletierine. Methyl Grignard addition to the aldehyde gave the corresponding alcohol as a mixture of diastereomers which was oxidized to the methyl ketone using Dess-Martin’s periodinane in 71% over both steps. Methylenation using the methyl Wittig reagent at 0 °C preceded well giving the methylene product in 84%. Attempts to deprotect the Cbz using sodium naphthalene proved to be problematic as the free base was volatile and could not be isolated. Further attempts to form the HCl salt in situ using TMSCl and sodium iodide was also plagued with low yields and a variety of impurities that could not be separated. Due to the problems in removing the Cbz protecting group, we chose to change to the Boc group.
Scheme 4.8. Synthesis of the Cbz protected A and C ring fragments

Instead of deprotecting and reprotecting at an advanced intermediate, we chose to go back to the initial protecting step and change to the Boc group at that point (Scheme 4.9). The protection proceeded well as did the Grubbs' metathesis to provide the desired Boc protected enal 4.29 in 71% yield over 2 steps. The desired stereocenter in cermizine D had the S configuration, thus the S version of the catalyst was needed. In addition, we were able to reduce catalyst loading to 10 mol% by increasing concentration and reaction time. The Boc protected amine cyclized as expected to give the desired aldehyde 4.31 in 86% yield and 92% ee.

Scheme 4.9. Final Optimization of Cyclization with N-Boc Protecting Group
With the cyclized Boc protected aldehyde 4.31 in hand, efforts shifted to constructing key A and C-ring fragments. Following the same procedures used with the Cbz substrate, the Boc protected substrate reacted similarly. The methyl Grignard addition followed by DMP oxidation to the methyl ketone proceeded in 73% yield. The methylenation worked in 78% yield and now the deprotection of the Boc protecting group worked nicely using TFA to form the TFA salt in situ. Synthesis of the C-ring fragment from the starting aldehyde proceeded similarly to the Cbz protected substrate yielding the allyl carbonate in 60% over 3 steps (Scheme 4.10). With both ring fragments synthesized, we moved on to the iridium coupling system.

**Scheme 4.10.** Synthesis of the Boc protected A and C ring fragments

Based on literature precedent, the $(R, R, R)$ ligand 4.38 was prepared in order to obtain the desired $S$ stereocenter from the reaction (Scheme 4.11). The ligand, which is air sensitive, was prepared following a literature procedure. The product was identified using $^{31}$P NMR,
however, the product was air sensitive and needed to be purified under a nitrogen atmosphere as the phosphorus was readily oxidized which was observed using $^{31}$P NMR.

**Scheme 4.11.** Synthesis of the Iridium ligand

\[
\text{Ph}^-\text{NH}^-\text{Ph} + \text{PCl}_3 \xrightarrow{n\text{-BuLi}, -78 \, ^\circ\text{C}, \text{THF}} \, \begin{array}{c}
\text{Et}_3\text{N}, (R)-\text{BINOL} \\
75\% 
\end{array} \xrightarrow{\text{then}} \text{4.38}
\]

### 4.6 Studies on the Iridium Coupling

With our components in hand, we were ready to test out the desired iridium coupling (Scheme 4.12). The key coupling on the actual substrates, however, gave no reaction and only the starting allyl carbonate was recovered. The free amine was volatile and thus was never recovered from any reactions where it was used. First, we needed to insure that our ligand and catalyst system were working as intended. To test our reaction conditions, the known allyl carbonate 4.39 was prepared following Hartwig’s protocol, and was reacted with pyrrolidine using the same conditions reported by Hartwig. Using these substrates, the reaction worked as reported giving us the desired product with a yield to that of what was reported.
Scheme 4.12. Initial Iridium couplings.

Based on these results, we suspected the problem was one of our substrates. Consequently, we designed a few model systems to test this prediction out (Scheme 4.13). One model system had the known allyl carbonate reacting with our amine substrate. The other model had our allyl carbonate reacting with a known amine, pyrrolidine. These model systems gave way to some interesting results. From the reaction between our allyl carbonate and pyrrolidine, we obtained almost entirely the undesired linear product 4.42 in a mixture of 19:1. The linear product had been reported as a second product from many of these reactions previously, however, never was it the major product, and typically only obtained as a small by-product. Based off of earlier reports, we believed that this is due to the steric bulk of our piperidine ring off of the allyl carbonate. The second model system reaction was between our substituted piperidine 4.33 and the known allyl carbonate. This reaction proceeded to give a 3:2 mixture of isomers favoring the desired branched product 4.44 based off of crude $^1$H NMR. Unfortunately, the mixture was unstable on silica and could not be purified.
These two model systems helped to demonstrate that it was our likely the allyl carbonate substrate that was problematic in the iridium coupling. One final model system was performed using our allyl carbonate with a primary activated amine, benzyl amine. This final reaction was much slower to react, however, only the internal substituted product was observed in a 25% yield. These results helped to demonstrate some of the limitations to this reaction. In the end, it was decided to use an alternative route to couple the two fragments.

**Scheme 4.13. Results from Iridium Model System Couplings**

![Scheme 4.13](image)

### 4.7 Alternate Synthetic Strategies for the Synthesis of Cermizine D

After the variety of iridium coupling model systems, we decided to devise an alternative synthesis for cermizine D. One possibility would be the direct coupling of the two fragments through a substitution process. We chose to carry out the direct substitution on an activated version of the
allylic alcohol. Vinyl Grignard addition gave a mixture of diastereomers in 68% yield that were separated. We chose to use a model system with piperidine as the amine to test out the reaction conditions (Scheme 4.14). Directly coupling the two fragments using an activated allylic alcohol as the leaving group proved to be problematic as once the allylic alcohol was activated, as its mesylate, internal carbamate formation with the Boc carbamate occurred to give the bicycle 4.49 as a single isomer in a 66% yield. While the newly formed stereocenter was not confirmed, it is likely that the reaction proceeded with inversion at this stereocenter.

**Scheme 4.14.** Self-cyclization resulting from direct coupling route

A revised retrosynthesis is proposed in Scheme 4.15. In this approach, we chose to alter the second coupling fragment to an open chain with a primary amine (Scheme 4.15), while leaving the synthesis of the first piperidine ring the same using our heteroatom Michael reaction. There were two possible options with this approach. The first option was to generate an imine with the cyclized aldehyde followed by addition of the vinyl Grignard leading us to a similar intermediate as we had in our original retrosynthesis. Alternatively, reductive amination with a α,β-unsaturated ketone and the amine 4.53 followed by RCM and reduction would yield
compound 4.50. Both of these alternative syntheses would first involve the synthesis of the chiral amine 4.53.

**Scheme 4.15. Revised Retrosynthesis for Cermizine D**

4.7.1 Synthesis of Chiral Amine 4.53

We envisioned synthesizing the chiral amine 4.53 from the known benzyl protected aldehyde\(^5\) 4.56 following chemistry developed by Ellman and co-workers using the chiral \(\text{tert}\)-butanesulfonamide 4.57 (Scheme 4.16).\(^6\) Monoprotection of the 1,5-pentanediol with benzyl bromide followed by Swern oxidation yielded the aldehyde 4.56. This aldehyde was then condensed with the \(\text{S \, tert}\)-butylsulfonamide using Cs\(_2\)CO\(_3\) in refluxing CH\(_2\)Cl\(_2\) to give the sulfimide 4.58 in 90%. The sulfimide was then reacted with the desired Grignard reagent to produce the sulfamide with a 9:1 dr as determined by \(^1\)H NMR. Cleavage of the sulfamide under acid hydrolysis yielded the chiral \(\alpha\)-substituted amine 4.53. With our amine in hand, we
next focused on the two potential strategies for fragment coupling.

**Scheme 4.16. Synthesis of Chiral Amine 4.53**

\[
\text{HO} \xrightarrow{\text{1) \text{BrBr, NaH, Bu}_3\text{N}^+\text{I}}} \text{BnO} \xrightarrow{\text{2) \text{DMSO, (COCl)}_2, Et}_3\text{N, CH}_2\text{Cl}_2, -78^\circ\text{C} \rightarrow 0^\circ\text{C}}} \text{4.56} \xrightarrow{\text{H}_2\text{N}^+} \text{4.57} \xrightarrow{\text{C}_2\text{CO}_3, \text{DCM, reflux, 90%}}} \text{4.58}
\]

4.7.2 Imine Formation Route

We first selected to explore Route A (Scheme 4.17). Unfortunately, under a wide variety of conditions we were unable to generate the desired imine 4.52. Selected conditions explored included: (a) \text{Cs}_2\text{CO}_3, \text{CH}_2\text{Cl}_2\text{ reflux; (b) PhMe, mol sieves; (c) Na}_2\text{SO}_4, \text{THF. Each of these conditions resulted in similar complex mixtures with multiple distinct spots via TLC analysis. Any attempts to purify these mixtures using silica gel chromatography resulted in further decomposition - this is possibly due to the amine being α-branched and hindered. The crude }^1\text{H showed some indications of imine formation and the original aldehyde signal was absent.}

We then considered using a one-pot system where the imine would be formed and without purification the vinyl Grignard would be added. This would allow us to react any of the imine formed without allowing for further decomposition (Scheme 4.17). Using one of our imine forming conditions, (\text{Na}_2\text{SO}_4, \text{THF}) to form the imine the vinyl Grignard was added \textit{in situ,}
however, we were unable to form any of the desired amine and obtained a complex mixture of compounds that further decomposed on silica.

**Scheme 4.17. Attempts at imine formation**

![Scheme 4.17. Atoms at imine formation](image)

To test out the stability and the reactivity of our substrates, we ran a series of model systems to determine if the imine formation was problematic (Scheme 4.18). The imine formation on these systems proved to be much cleaner - crude NMR analysis showed the formation of a single product. The key $^1$H NMR signals were observed in the crude mixture 4.62 (the loss of the aldehyde peak at 10.0 ppm and the presence of a new singlet peak at 8.19 ppm), 4.64 (the loss of the aldehyde peak at 9.75 ppm and the presence of a new triplet peak at 7.59 ppm), 4.66 (the loss of the aldehyde peak at 9.75 ppm and the presence of a new triplet at 7.78 ppm). While the crude NMR analysis showed that the imines were formed, they were unstable on silica gel and could not be purified. Based on these results, it was determined that Route B was likely to prove more promising.
Scheme 4.18. Model systems to determine imine stability

4.7.3 Reductive Amination Route

Given the problems with forming a stable aldehyde-derived imine substrate, we shifted our focus to Route B, which would employ a α,β-unsaturated ketone-derived imine substrate. This imine should be better behaved and reductive amination would yield access to the key amine function. It should be noted that typically methods, such as NaBH(OAc)₃ and AcOH, for reductive amination often do not work well on α,β-unsaturated ketones.⁶¹ An alternative method for reductive amination is a stepwise process using Ti(OiPr)₄, followed by reduction of the titanium intermediate with NaBH₄. It has been shown that this reaction works on phenyl substituted α,β-unsaturated ketones,⁶² while we were unaware of any precedence for the use of these conditions on the methyl substituted α,β-unsaturated or vinyl ketones. We chose to investigate the reactivity of all three versions of the α,β-unsaturated ketone (Scheme 4.19). All three
were synthesized using the same conditions - only varying the Grignard reagent concentration (Table 2).

**Scheme 4.19.** Grignard addition, oxidation, reductive amination sequence

![Scheme 4.19]

**Table 2.** Results for three-step sequence

<table>
<thead>
<tr>
<th>R</th>
<th>Grignard Conc.</th>
<th>Ketone Yield</th>
<th>Reductive Amination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>2.0 M in THF</td>
<td>48% over 2 steps</td>
<td>68% 1:1 dr at rt</td>
</tr>
<tr>
<td>Me</td>
<td>0.5 M in THF</td>
<td>54% over 2 steps</td>
<td>Recovered alcohol</td>
</tr>
<tr>
<td>H</td>
<td>1.0 M in THF</td>
<td>73% over 2 steps</td>
<td>Recovered alcohol</td>
</tr>
</tbody>
</table>

The phenyl substituted α,β-unsaturated ketone was synthesized in the lowest yield of the three with only 48% yield over the two steps. The vinyl ketone was the highest yielding substrate with a 73% yield and the methyl substituted α,β-unsaturated ketone was obtained in 54% over the same two steps. When the three α,β-unsaturated ketones were submitted to the reductive amination conditions, only the phenyl substituted α,β-unsaturated ketone gave the desired product, while the other two gave only reduced alcohol. This is believed to be due to the increased reactivity that phenyl ring gives to the ketone through conjugation. It is worth noting that the reduction is performed at rt with short (5 min) reaction times; extended
reduction times resulted in lower yields as over reduction of the alkene was observed. While the coupled product was obtained in a reasonable 68% yield, the diastereoselectivity was a disappointing 1:1 mixture. No attempts to improve this level of selectivity have been made to date. We believe that the diastereoselectivity may increase if the reduction is carried out at reduced temperature.

With the coupled amine in hand, the next step was to close the ring using RCM (Scheme 4.20). The alkene system is a 1,2 di-substituted alkene being coupled with a 1,1 di-substituted alkene which represents a challenging RCM to do despite forming a six membered ring. A variety of conditions were used in order to close the ring: 2.6 (5 mol%), CH₂Cl₂, rt and 45 °C; 2.6 (10 mol%), PhMe, 80 °C; 4.70 (5 mol%), CH₂Cl₂, 45 °C; 4.70 (5 mol%), PhMe, 80 °C; 4.70 (5 mol%), PhMe, CH₂CH₂, 80 °C; 4.70 (10 mol%), CH₂Cl₂, CH₂CH₂, 45 °C; 4.70 (25 mol%), PhMe, CH₂CH₂, 80 °C; none of these conditions gave the desired RCM product.
Scheme 4.20. RCM reactions

Table 3. RCM conditions

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2.6</td>
<td>10 mol%, PhMe, 80 °C</td>
<td>NR</td>
</tr>
<tr>
<td>H</td>
<td>4.70</td>
<td>5 mol%, PhMe 80 °C</td>
<td>NR</td>
</tr>
<tr>
<td>Cbz</td>
<td>4.70</td>
<td>10 mol%, PhMe, 80 °C</td>
<td>NR</td>
</tr>
<tr>
<td>Cbz</td>
<td>2.6</td>
<td>30 mol% slow addition PhMe, reflux</td>
<td>94%</td>
</tr>
</tbody>
</table>

With the RCM proving to be problematic, we then considered the presence of the free amine proton to be a possible problem for the RCM, and chose to protect the amine. Due to positioning of the amine, Cbz protection using bases such as K₂CO₃, or Et₃N did not work. Using a stronger base such as NaH, however, did allow for Cbz protection yielding 4.69 in 77% yield.

Initial attempts at RCM on the Cbz protected amine continued to be unsuccessful. A set of forcing conditions reported by Gennari has been shown to facilitate some RCM reactions that would not take place
otherwise. The conditions reported were slow addition via syringe pump of a 30 mol % catalyst solution of Grubbs’ 2nd Generation catalyst in toluene over 2 h to a solution of the alkene in refluxing toluene, did give the RCM product (4.71) in an excellent 94% yield.

With the second ring closed, large advancements in the total synthesis of cermizine D had been achieved. The final few remaining steps include a global hydrogenation, activation of the resulting alcohol that is expected to spontaneously cyclize with the free amine and one final deprotection of the remaining Boc group. We are uncertain of the diastereoselectivity on the alkene reduction at this time. The remaining key optimization is to improve the diastereoselectivity of the titanium mediated reductive amination.
4.8 Experimental

**Alkene 4.25**: To a solution of 3.6 (53 mg, 0.193 mmol) in THF (1 mL) was added a pre-made solution of methyl triphenylphosphonium bromide (136.5 mg, 0.382 mmol) with n-BuLi (145 µL, 0.363 mmol, 2.5 M in hexanes) in THF (0.7 mL) at 0 °C. After 2 h, the yellow reaction mixture was quenched with water (1 mL), extracted with EtOAc (3 x 5 mL). Then dried over MgSO₄, and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to give 4.25 (44 mg, 0.161 mmol, 84%) as a pale yellow oil. [α]₀ -30.4 (c = 1.15, CHCl₃); IR (neat) 3069, 3027, 2937, 2857, 1699, 1421, 1343, 1259, 1166; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.43 (m, 5H), 5.16 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 4.74 (d, J = 19.2 Hz, 2H), 4.49 (bs, 1H), 4.07 (d, J = 11.2 Hz, 1H), 2.90 (t, J = 14.8 Hz, 1H), 2.36-2.41 (m, 1H), 2.19-2.26 (m, 1H), 1.60-1.80 (m, 6H), 1.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 142.7, 137.0, 128.4, 127.9, 112.8, 66.9, 48.8, 39.3, 38.2, 29.7, 27.5, 25.5, 22.0, 18.7; HRMS (EI+) calcd. For C₁₇H₂₅NO₂ (M⁺) 273.17288, found 273.17317.
Ester 4.72: To a solution of 2.8 (385 mg, 1.45 mmol) in CH$_2$Cl$_2$ was added Ph$_3$P=CHCO$_2$Me (510 mg, 2.9 mmol) at rt. After 16 h, the reaction was concentrated in vacuo then suspended in a 3:1 mixture of hexanes/ether (60 mL) and filtered over Celite®, then rinsed with a 3:1 mixture of hexanes/ether (30 mL). The resulting solution was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give 4.72 (400 mg, 1.26 mmol, 87%) as a colorless oil. [α]$_D$ +24.25 (c = 4.0, CHCl$_3$); IR (neat) 2945, 2857, 1724, 1697, 1421, 1258; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.30-7.41 (m, 5H), 6.90 (dt, $J$ = 15.3 Hz, $J$ = 7.8 Hz, 1H), 5.87 (d, $J$ = 15.6 Hz, 1H), 5.13 (s, 2H), 4.48 (bs, 1H), 4.09 (d, $J$ = 12 Hz, 1H), 3.73 (s, 3H), 2.86 (t, $J$ = 12.9 Hz, 1H), 2.54-2.61 (m, 1H), 2.40-2.45 (m, 1H), 1.60-1.80 (m, 4H), 1.40-1.56 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.6, 155.4, 145.5, 136.8, 128.5, 127.9, 127.8, 123.0, 67.1, 51.4, 49.9, 39.3, 32.8, 27.9, 25.3, 18.7; HRMS (EI+) calcd. For C$_{18}$H$_{23}$NO$_4$ (M+) 318.17053, found 318.17130.
**Alcohol 4.26:** To a solution of 4.72 (73.5 mg, 0.232 mmol) in CH$_2$Cl$_2$ (1.5 mL) at -78 °C was added DIBAL-H (695 μL, 0.695 mmol, 1.0 M in CH$_2$Cl$_2$) at -78 °C. After 2 h, and then it was warmed to room temp. and quenched with sat. aq. sodium tartrate (30 mL). After vigorous stirring for 1 h the mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL) and washed with brine (30 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel eluting with 20-40% EtOAc/Hexanes to give 4.26 (60 mg, 0.207 mmol, 90%) as a colorless oil. 

$[\alpha]_D$ -34.5 (c = 2.0, CHCl$_3$); IR (neat) 3432, 2937, 2861, 1694, 1424, 1353, 1257; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30-7.41 (m, 5H), 5.5-5.7 (m, 2H), 5.16 (d, $J = 12.4$ Hz, 1H), 5.12 (d, $J = 12.4$ Hz, 1H) 4.37 (bs, 1H), 3.99-4.08 (m, 3H), 2.86 (t, $J = 12.8$ Hz, 1H), 2.42-2.51 (m, 1H), 2.18-2.25 (m, 1H), 1.50-1.70 (m, 5H), 1.40-1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.8, 137.0, 131.7, 128.8, 128.5, 128.0, 127.9, 66.9, 63.3, 62.6, 51.0, 50.6, 39.3, 32.8, 27.9, 25.4, 18.8; HRMS (EI+) calcd. For C$_{17}$H$_{23}$NNaO$_3$ (M+) 312.1576, found 312.1583.
**Carbonate 4.27:** To a solution of 4.26 (60 mg, 0.207 mmol) in CH₂Cl₂ (2.5 mL) at 0 °C was added pyridine (49 mg, 50 μL, 0.622 mmol), followed by dropwise addition of ClCO₂Me (21.5 mg, 18 μL, 0.228 mmol) at 0 °C. After 1 h, the solution was then diluted with water (5 mL), and sequentially extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and sat. aq. NH₄Cl (10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel eluting with 10-25% EtOAc/Hexanes to give 4.27 (57 mg, 0.164 mmol, 79%) as a colorless oil. [α]D -32.3 (c = 2.85, CHCl₃); IR (neat) 2939, 2859, 1749, 1695, 1444, 1422, 1262; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.41 (m, 5H), 5.65-5.8 (m, 1H), 5.56-5.64 (m, 1H), 5.15 (d, J = 12.4 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H) 4.51 (d, J = 5.2 Hz, 2H), 4.38 (bs, 1H), 4.06 (d, J = 12.4 Hz, 1H), 3.78 (s, 3H), 2.84 (t, J = 12.8 Hz, 1H), 2.41-2.49 (m, 1H), 2.20-2.30 (m, 1H), 1.50-1.70 (m, 5H), 1.40-1.50 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 137.0, 133.2, 128.5, 127.9, 127.8, 125.7, 68.2, 66.9, 54.7, 50.3, 39.3, 32.8, 27.7, 25.4, 18.8; HRMS (EI+) calcd. For C₁₉H₂₆NO₅ (M+) 348.18109, found 348.18175.
**Aldehyde 4.31:** To a solution of 4.29 (970 mg, 4.25 mmol), and MeOH (12 mL) was added a solution of the catalyst 4.30 (254 mg, 0.425 mmol) in DCE (12 mL) via syringe and placed in the freezer un stirred (-25°C). After 7 d, the solution was concentrated in vacuo. The crude product was purified by chromatography over silica gel eluting with 0-25% EtOAc/Hexanes to give known 4.31 (820 mg, 3.57 mmol, 84%) as a colorless oil. [\(\alpha\)]\(_D\) = -36.4 (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.66 (d, \(J = 2.8\) Hz, 1H), 4.76 (bs, 1H), 3.92 (d, \(J = 11.2\) Hz, 1H), 2.63-2.74 (m, 2H), 2.44-2.50 (m, 1H), 1.50-1.70 (m, 5H), 1.34-1.50 (m, 2H), 1.38 (s, 9H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 200.7, 154.6, 79.8, 45.8, 44.5, 39.2, 28.8, 28.3, 25.2, 18.8. (b6p29)

**Ketone 4.32:** To a solution of 4.31 (410 mg, 1.80 mmol) in Et\(_2\)O (15 mL) at rt was slowly added a solution of MeMgBr (1.8 mL, 5.4 mmol, 3.0 M in Et\(_2\)O). The mixture was allowed to stir at rt for 2 h. The reaction was quenched with saturated aqueous NH\(_4\)Cl (5 mL). Then the solution was
extracted with Et₂O (3 X 30 mL), the combined organic layers were dried over MgSO₄, and concentrated *in vacuo*.

To a solution of crude **4.73** (1.8 mmol) in CH₂Cl₂ (20 mL) was added sodium bicarbonate (756 mg, 9 mmol) followed by Dess Martin’s reagent (1.56 g, 3.6 mmol). After 2 h the reaction was quenched with 10% aqueous sodium bicarbonate (10 mL), and extracted with Et₂O (3 X 30 mL). The combined organic layers were dried over MgSO₄, concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to give known **4.32** (315 mg, 1.3 mmol, 73% over 2 steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.74 (d, J = 4.5 Hz, 1H), 3.98 (d, J = 12, 1H), 2.79 (t, J = 12.9 Hz, 1H), 2.66 (dd, J = 7.8, 1.8 Hz, 2H), 2.20 (s, 3H), 1.50-1.75 (m, 5H), 1.40-1.55 (m, 2H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 207.1, 154.7, 79.6, 47.3, 44.3, 39.4, 30.1, 29.7, 28.4, 25.3, 18.9. (b6p24/b6p27)

![Chemical Structure](image)

**Alkene 4.74:** To a solution of **4.32** (315 mg, 1.3 mmol) in THF (8 mL) was added a pre made solution of methyl triphenylphosphonium bromide (932.7 mg, 2.61 mmol) with n-BuLi (1.55 mL, 2.48 mmol, 1.6 M in hexanes) in THF (5 mL) at 0 °C. After 2 h, the reaction was quenched with water (5 mL), extracted with EtOAc (3 x 25 mL), the combined organic
layers were dried over MgSO₄, and concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to give \textbf{4.74} (242 mg, 1.01 mmol, 78%) as a colorless oil. [α]₀ -26.1 (c = 1.0, CHCl₃); IR (neat) 3073, 2974, 2934, 2856, 1693, 1413, 1364, 1266, 1161; \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 4.74 (d, J = 15.9 Hz, 2H), 4.38 (bs, 1H), 3.98 (d, J = 11.1 Hz, 1H), 2.81 (t, J = 12.9 Hz, 1H), 2.30-2.37 (m, 1H), 2.18-2.26 (m, 1H), 1.79 (s, 3H), 1.50-1.66 (m, 5H), 1.47 (s, 9H), 1.25-1.50 (m, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 155.0, 142.8, 112.6, 79.0, 48.5, 38.8, 38.1, 28.2, 27.3, 25.5, 22.1, 18.8; HRMS (EI+) calcd. for C₁₄H₂₅NO₂ (M+) 238.1807, found 238.1830. (b6p28)

\[ \text{Alkene 4.33: To a solution of 4.74 (120 mg, .50 mmol) in CH}_2\text{Cl}_2 (2.3 mL) was added TFA (2.3 mL). The solution was allowed to stir for 2 h. The solution was concentrated in vacuo to give 4.33 (127 mg, 0.5 mmol, >99%) as a colorless glassy solid. [α]₀ -9.8 (c = 1.0, CHCl₃); IR (neat) 2950, 2865, 2545, 1780, 1674, 1437, 1202; \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 8.46 (bs, 1H), 4.84 (d, J = 36.8 Hz, 2H), 3.39 (bs, 1H), 3.12 (bs, 1H), 2.90 (bs, 1H), 2.43 (bs, 1H), 2.26 (m, 1H), 1.70-1.90 (m, 3H), 1.60-1.70 (m, 4H), 1.40-1.55 (m, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 138.9, 115.5, 55.2, 45.1, 38.8, 38.1, 28.2, 27.3, 25.5, 22.1, 18.8; HRMS (EI+) calcd. for C₁₄H₂₅NO₂ (M+) 238.1807, found 238.1830. (b6p28) \]
42.0, 28.4, 22.2, 21.7; HRMS (EI+) calcd. for C_{18}H_{18}F_{3}NO_{2} (M+) 253.1290, found 253.1287. (b6p30)

**Ester 4.75:** To a solution of 4.31 (450 mg, 1.97 mmol) in CH_{2}Cl_{2} was added Ph_{3}P=CHCO_{2}Me (522 mg, 2.96 mmol). After 16 h, the resulting solution was concentrated *in vacuo* then suspended in a 3:1 mixture of hexanes/ether (60 mL) and filtered over Celite®, then rinsed with a 3:1 mixture of hexanes/ether (30 mL). The resulting solution was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to give 4.74 (445 mg, 1.58 mmol, 80%) as a colorless oil. [α]_{D} -16.5 (c = 1.0, CHCl_{3}); IR (neat) 2975, 2936, 2858, 1725, 1689, 1412, 1272; ^{1}H NMR (400 MHz, CDCl_{3}) δ 6.86 (dt, J = 15.6 Hz, J = 7.6 Hz, 1H), 5.80 (d, J = 15.6, 1H), 4.34 (bs, 1H), 3.96 (d, J = 12 Hz, 1H), 3.66 (s, 3H), 2.71 (t, J = 12.9 Hz, 1H), 2.52-2.61 (m, 1H), 2.25-2.32 (m, 1H), 1.50-1.70 (m, 5H), 1.30-1.46 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl_{3}) δ 166.6, 154.8, 146.0, 122.6, 79.4, 51.3, 49.6, 38.7, 32.9, 28.3, 25.3, 18.8; HRMS (EI+) calcd. For C_{15}H_{28}NO_{4} (M+) 284.1862, found 284.1868. (b6p25)
Alcohol 4.34: To a solution of 4.75 (356 mg, 1.258 mmol) in CH₂Cl₂ (12 mL) at -78 °C was added DIBAL-H (3.77 mL, 3.77 mmol, 1.0 M in CH₂Cl₂). After 2 h, the mixture was warmed to room temp and quenched with sat. aq. sodium tartrate (150 mL). After vigorous stirring for 1 h, the mixture was extracted with CH₂Cl₂ (3 x 50 mL) and washed with brine (30 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel eluting with 20-40% EtOAc/Hexanes to give 4.34 (298 mg, 1.17 mmol, 93%) as a colorless oil. [α]₀ -33.3 (c = 2.0, CHCl₃); IR (neat) 3446, 2933, 2859, 1685, 1418, 1364, 1162; ¹H NMR (400 MHz, CDCl₃) δ 5.54-5.66 (m, 2H), 4.22 (bs, 1H), 3.99-4.02 (m, 2H), 3.91 (d, J = 12.4 Hz, 1H), 2.72 (t, J = 12.8 Hz, 1H), 2.40 (bs, 1H), 2.33-2.38 (m, 1H), 2.12-2.19 (m, 1H), 1.50-1.70 (m, 5H), 1.40-1.50 (m, 1H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.2, 131.4, 129.0, 79.2, 63.2, 50.2, 38.9, 32.8, 28.4, 27.7, 25.4, 18.8; HRMS (EI+) calcd. For C₁₄H₂₆NO₃ (M⁺) 256.1913, found 256.1918. (b6p26)
Carbonate 4.35: To a solution of 4.34 (158 mg, 0.62 mmol) in CH$_2$Cl$_2$ (10.0 mL) at 0 °C was added sequentially pyridine (147 mg, 0.150 mL, 1.86 mmol) and ClCO$_2$Me (64.4 mg, 0.054 mL, 0.68 mmol). After 1 h, the solution was then diluted with water (15 mL) and sequentially extracted with EtOAc (3 x 20 mL). The combined organic layers were washed sequentially with brine (20 mL) and sat. aq. NH$_4$Cl (20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel eluting with 10-25% EtOAc/Hexanes to give 4.35 (158 mg, 0.502 mmol, 81%) as a colorless oil. [α]$_D$ -27.4 (c = 1.0, CHCl$_3$); IR (neat) 2934, 2857, 1750, 1688, 1266; $^1$H NMR (300 MHz, CDCl$_3$) 5.69-5.76 (m, 1H), 5.60-5.68 (m, 1H), 4.56 (d, J = 6 Hz, 2H), 4.28 (bs, 1H), 3.95 (d, J = 12.4 Hz, 1H), 3.78 (s, 3H), 2.75 (t, J = 12.8 Hz, 1H), 2.41-2.49 (m, 1H), 2.20-2.30 (m, 1H), 1.50-1.70 (m, 5H), 1.40-1.50 (m, 1H), 1.39 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.6, 155.0, 133.6, 125.3, 79.2, 68.3, 54.7, 49.9, 38.9, 32.9, 28.4, 27.7, 25.4, 18.8; HRMS (ESI) calcd. For C$_{16}$H$_{28}$NO$_5$ (M+) 314.1967, found 314.1961. (b6p37)
Phosphoramidite 4.38: To a solution of 4.36 (143 mg, 0.546 mmol) in THF (9 mL) at -78 °C was added n-BuLi (0.375 mL, 0.6 mmol, 1.6 M in hexanes). After 30 min, a solution of 4.37 (75 mg, 48 μL, 0.546 mmol) in THF (1 mL) was added. The mixture was slowly warmed to 0 °C. After 3 h, Et₃N (275.7 mg, 0.38 mL, 2.73 mmol) was added to the solution followed by a solution of R-BINOL (148.5 mg, 0.546 mmol) in THF (6 mL). After 18 h, the mixture was concentrated in vacuo and purified by chromatography over silica gel, under N₂, eluting with 4:1 CH₂Cl₂/PE to give known 4.38 (221 mg, 0.41 mmol, 75%) as a fine white powder. m.p. 87-89 °C, ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 9 Hz, 1H), 7.94 (d, J = 9 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.30-7.45 (m, 4H), 7.10-7.25 (m, 13H), 4.47 (dq, J = 10.8 Hz, 6.9 Hz, 2H), 1.70 (d, J = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 150.5, 149.8, 143.1, 132.8, 131.4, 130.4, 129.6, 128.3, 128.1, 128.0, 127.8, 127.3, 127.2, 126.7, 126.0, 125.8, 124.8, 124.3, 122.5, 122.4, 121.2, 54.5 (d, J = 10 Hz), 23.0 (d, J = 12 Hz); ³¹P NMR (121 MHz, CDCl₃) 150.5.
Amine 4.41: To a solution of 4.39 (50 mg, 0.26 mmol) in THF (0.1 mL) was added sequentially a pre-made solution (0.1 mL) of [Ir(COD)Cl]_2 (14 mg 0.026 mmol) and 4.38 (8.8 mg, 0.013 mmol) in THF (1 mL) and piperidine 4.40 (24 mg, 28 μL, 0.338 mmol). After 18 h, the reaction was concentrated in vacuo and purified by chromatography over silica gel eluting with 5-20% EtOAc/Hexanes to give known 4.41 (31.5 mg, 0.17 mmol, 65%) as a colorless oil. [α]_D -69.7 (c = 1.55, CHCl_3); 'H NMR (300 MHz, CDCl_3) δ 7.28-7.37 (m, 4H), 7.20-7.25 (m, 1H), 6.0-6.12 (m, 1H), 5.20 (dd, J = 17.2, 1.2 Hz, 1H), 5.00 (dd, J = 10.0, 1.2 Hz, 1H), 3.58 (d, J = 8.8 Hz, 1H), 2.45-2.54 (m, 2H), 2.33-2.42 (m, 2H), 1.76 (m, 4H); ^13C NMR (100 MHz, CDCl_3) δ 142.7, 141.0, 128.5, 127.6, 127.1, 115.1, 75.2, 53.0, 23.3.

Amines 4.42/4.43: To a solution of 4.35 (25 mg, 0.08 mmol) and 4.40 (7.4 mg, 0.10 mmol) in THF (0.5 mL) was added a pre-made solution of 4.38 (2.7 mg, 0.004 mmol) and [Ir(COD)Cl]_2 (4.3 mg, 0.008 mmol) in THF (0.25 mL) at rt. After 16h, the solution was concentrated in vacuo and
purified by chromatography over basic alumina eluting 10-30% EtOAc/Hexanes to give a 19:1 mixture of **4.42** (19 mg, 0.064 mmol, 80%) and **4.43** (1 mg, 0.003 mmol, 4%) as colorless oils. \([\alpha]_D -28.5, (c = 0.85, \text{CHCl}_3)\); IR (neat) 2930, 2850, 2778, 1694, 1164; \(^1\text{H} \text{NMR (300 MHz, CDCl}_3\) 5.48-5.68 (m, 2H), 4.25 (bs, 1H), 3.95 (d, \(J = 12.4 \text{ Hz, 1H}), 3.01 (d, J = 6 \text{ Hz, 2H}), 2.75 (t, J = 12.8 \text{ Hz, 1H}), 2.48 (s, 3H), 2.20-2.45 (m, 2H), 1.77 (s, 4H), 1.50-1.60 (m, 6H), 1.44 (s, 9H); \(^13\text{C} \text{NMR (100 MHz, CDCl}_3\) \(\delta\) 155.0, 129.8, 79.0, 58.2, 53.9, 39.0, 33.0, 30.3, 29.7, 28.5, 27.5, 25.5, 23.4, 18.8; HRMS (El+) calcd. For \(\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_2 \) (M+) 308.4589, found 309.2543. (b6p44)

![Chemical Reaction Diagram]

**Amine 4.47:** To a solution of **4.35** (23 mg, 0.073 mmol) and **4.46** (11.8 mg, 0.11 mmol) in THF (0.45 mL) was added a pre-made solution of **4.38** (4.0 mg, 0.007 mmol) and [Ir(COD)Cl]\(_2\) (2.5 mg, 0.0035 mmol) in THF (0.25 mL) at rt. After 16 h, the solution was then concentrated in vacuo and purified by chromatography over silica gel eluting with 20-60% EtOAc/Hexanes to obtain **4.47** (6.3 mg, 0.0018 mmol, 25%) as a colorless oil. \([\alpha]_D -22.0, (c = 0.7, \text{CHCl}_3)\); IR (neat) 3307, 2928, 2853, 1684, 1167; \(^1\text{H} \text{NMR (300 MHz, CDCl}_3\) \(\delta\) 7.22-7.36 (m, 5H), 5.63-5.75 (m, 1H), 5.13-5.21 (m, 2H), 4.36 (bs, 1H) 3.95 (bs, 1H), 3.84 (d, \(J = 13.2 \text{ Hz, 1H}), 3.64 (d, J =
12.9 Hz, 1H), 3.00-3.10 (m, 1H), 2.72-2.88 (m, 1H), 1.82-1.98 (m, 1H), 1.77 (s, 4H), 1.50-1.60 (m, 6H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 140.6, 128.4, 128.2, 126.8, 116.4, 79.3, 58.7, 51.2, 36.5, 30.3, 29.7, 29.3, 29.0, 28.5, 25.6, 22.7, 19.1; HRMS (EI) calcd. For C₂₁H₃₂N₂O₂ (M⁺) 344.2464, found 344.2470. (b6p52)

**Carbonate 4.49:** To a stirred solution of 4.31 (100 mg, 0.439 mmol) in THF (4 mL) was added vinyl magnesium bromide (1.3 mL, 1.316 mmol, 1.0 M in THF) at rt. After 2 h, the reaction was quenched with sat. aq. NH₄Cl (1 mL) and extracted with Et₂O (5 mL x 3). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel eluting 10-40% EtOAc/Hexanes to give 4.76 (76 mg, 0.298 mmol, 68%) as a colorless oil and a 1:1 mixture of diastereomers that were carried on without further purification.

To a stirred solution of 4.76 (30 mg, 0.117 mmol) in CH₂CL₂ (1.1 mL) at -10 °C was added sequentially Et₃N (15.5 mg, 21 µL, 0.153 mmol) and MsCl (15.5 mg, 10.5 µL, 0.135 mmol) dropwise. After 30 min. the reaction was cooled to -30 °C and piperidine (15 mg, 17.5 µL, 0.176 mmol) was added. The resulting mixture was allowed to warm to -15 °C and after 16 h, the reaction was quenched with sat. aq. NaHCO₃ (1 mL) and
extracted with CH$_2$Cl$_2$ (5 mL x 3). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel eluting 10-40\% EtOAc/Hexanes to give 4.49 (14 mg, 0.077 mmol, 66\%) as a white waxy oil. [\(\alpha\)]$_D$ -6.3, (c = 0.75, CHCl$_3$); IR (neat) 3322, 2941, 2859, 1681, 1456, 1119, 748; $^1$H NMR (400 MHz, CDCl$_3$) \(\delta\) 5.84-5.93 (m, 1H), 5.38 (d, \(J = 17.2\) Hz, 1H), 5.25 (d, \(J = 10.8\) Hz, 1H), 4.61-4.66 (m, 1H), 4.49 (d, \(J = 11.2\) Hz, 1H), 3.32-3.37 (m, 1H), 2.66 (t, \(J = 13.2\) Hz, 1H), 2.12-2.18 (m, 1H), 1.86 (d, \(J = 10.4\) Hz, 2H), 1.61-1.69 (m, 3H), 1.40-1.52 (m, 3H), 1.19-1.41 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) \(\delta\) 153.3, 135.3, 117.1, 75.2, 53.9, 44.7, 36.0, 33.5, 24.9, 23.6; HRMS (EI+) calcd. For C$_{10}$H$_{15}$NO$_2$ (M$^+$) 181.1103, found 181.1110. (b6p58)

Alcohol 4.77: To a suspension of NaH (384 mg, 9.6 mmol, 60 \% in mineral oil) in DMF (20 mL) was added 4.55 (1000 mg, 9.6 mmol) at 0°C. After 30 min, the solution was recooled to 0°C and BnBr (1,641 mg, 1.148 mL, 9.6 mmol) was added slowly followed by TBAI (176.8 mg, 0.48 mmol). Next, the mixture was allowed to warm to rt. After 16h, the reaction was quenched with sat. NH$_4$Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel eluting with 20-50\% EtOAc/Hexanes to obtain known 4.77 (1.01 g, 5.184 mmol, 54\%) as a colorless oil. $^1$H NMR
(300 MHz, CDCl₃) 7.25-7.40 (m, 5H), 4.52 (s, 2H), 3.63 (t, J = 6.6 Hz, 2H), 3.50 (t, J = 6.3 Hz, 2H), 1.88 (bs, 1H), 1.55-1.70 (m, 4H), 1.42-1.51 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 128.4, 127.7, 127.6, 72.9, 70.3, 62.7, 32.5, 29.5, 22.4. (b6p71)

**Aldehyde 4.56:** To a solution of oxalyl chloride (980.7 mg, 0.663 mL, 7.726 mmol) in CH₂Cl₂ (15 mL) at -78°C was added a solution of DMSO (644 mg, 0.585 mL, 8.24 mmol) in CH₂Cl₂ (4 mL). After 10 min, 4.77 (1000 mg, 5.15 mmol) in CH₂Cl₂ (5 mL) was added at -78°C dropwise. After 1.5 h, Et₃N (2,343 mg, 3.23 mL, 23.18 mmol) was added and the mixture was warmed to 0°C. Once the mixture reached 0°C, the reaction was quenched with water (25 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and the dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel eluting with 10-25% EtOAc/Hexanes to obtain 4.56 (760 mg, 3.9 mmol, 77%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) 9.78 (s, 1H), 7.25-7.40 (m, 5H), 4.52 (s, 2H), 3.51 (t, J = 6.3 Hz, 2H), 2.45-2.54 (m, 2H), 1.55-1.80 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 202.5, 138.5, 128.4, 127.7, 72.9, 69.7, 43.6, 29.2, 19.0. (b6p72)
Sulfonimine 4.58: To a solution of 4.56 (740 mg, 3.85 mmol) and 4.57 (389 mg, 3.21 mmol) in CH₂Cl₂ (15 mL) was added Cs₂CO₃ (1254 mg, 3.85 mmol) and the mixture was heated to reflux. After 18 h, the mixture was cooled to rt and filtered through a pad of Celite®. Then washed with CH₂Cl₂ (3 x 15 mL), the combined filtrates were dried (MgSO₄), concentrated in vacuo and purified by chromatography over silica gel eluting with 10-25% EtOAc/Hexanes to obtain known 4.58 (856 mg, 2.89 mmol, 90%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 8.08 (t, J = 6 Hz, 1H), 7.25-7.40 (m, 5H), 4.51 (s, 2H), 3.50 (t, J = 6.3 Hz, 2H), 2.45-2.54 (m, 2H), 1.70-1.85 (m, 4H), 1.20 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 138.5, 128.4, 127.6, 72.9, 69.7, 56.5, 35.8, 29.3, 22.3. (b6p73)

Sulfonamide 4.78: To a solution of 4.58 (700 mg, 2.37 mmol) in PhMe (12 mL) at -78°C was added a premade solution of 4.59 (7.11 mL, 3.55 mmol, 0.2 M in THF) slowly. After 2 h the reaction mixture was quenched with aq. sat. Na₂SO₄ (15 mL) and warmed to rt. The dried (MgSO₄) mixture was filtered through Celite®, concentrated in vacuo, and purified by chromatography over silica gel eluting with 20-50% EtOAc/Hexanes to obtain 4.78 (708 mg, 2.01 mmol, 85%) as a colorless
oil. \([\alpha]_D \text{ -66.3 (c = 1.00, CHCl}_3\text{); IR (neat) 3268, 3225, 3069, 3030, 2937, 2861, 1652, 1455, 1363, 1069; }^1\text{H NMR (400 MHz, CDCl}_3\text{) }\delta \text{ 7.25-7.40 (m, 5H), 4.84 (d, } J = \text{ 28.4 Hz, 2H), 4.50 (s, 2H), 3.49 (t, } J = \text{ 6.3 Hz, 2H), 3.36-3.48 (m, 1H), 3.25 (s, 1H), 2.32-2.45 (m, 1H), 2.22-2.32 (m, 1H), 1.75 (s, 3H), 1.60-1.71 (m, 2H), 1.45-1.60 (m, 4H), 1.20 (s, 9H); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) }\delta \text{ 142.4, 138.6, 130.1, 128.4, 127.6, 114.2, 72.9, 69.9, 56.5, 51.5, 44.4, 35.1, 29.5, 22.6, 21.7. HRMS (El+) calcd. For C}_{20}\text{H}_{34}\text{O}_2\text{NS (M+) 352.2310, found 352.2304. (b6p77)}

\[
\begin{align*}
\text{Amine 4.53: To a solution of 4.78 (190 mg, 0.54 mmol) in MeOH (3.5 mL) was added conc. HCl (0.084 mL, 1.08 mmol, 12.8 M). The resulting solution was allowed to stir for 1h before being concentrated in vacuo, and purified by chromatography over silica gel eluting with 50% EtOAc/Hexanes to 10% MeOH/CH}_2\text{Cl}_2\text{ to obtain 4.53 (155 mg, 0.54 mmol, >99%) as the HCl salt which was then dissolved in aq. sat. Na}_2\text{CO}_3\text{ (15 mL), and extracted with CH}_2\text{Cl}_2\text{ (3 x 15 mL) to obtain 4.53 as the free amine. } [\alpha]_D \text{ -0.57 (c = 1.15, CHCl}_3\text{); IR (neat) 3069, 3030, 2933, 2856, 1646, 1455, 1102; }^1\text{H NMR (300 MHz, CDCl}_3\text{) }\delta \text{ 7.25-7.40 (m, 5H), 4.80 (d, } J = \text{ 23.4 Hz, 2H), 4.52 (s, 2H), 3.50 (t, } J = \text{ 6.3 Hz, 2H), 2.90 (bs, 1H), 2.15-2.21 (m, 1H), 1.86-1.98 (m, 1H), 1.74 (s, 3H), 1.60-1.71 (m, 2H), 1.35-1.60}
\end{align*}
\]
(m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.3, 138.6, 128.3, 127.6, 127.5, 112.7, 72.9, 70.3, 48.4, 46.9, 37.7, 29.8, 22.9, 22.3. HRMS (EI+) calcd. For C$_{16}$H$_{25}$NO (M+) 248.2014, found 248.2012. (b6p80)

![Chemical Reaction Diagram]

**Ketone 5.5:** To a solution of 4.31 (530 mg, 2.09 mmol) in THF (15 mL) was added a premade solution of 4.39 (8 mL, 4.0 mmol, 0.2 M in THF) at rt. After 2 h the reaction was quenched with saturated (aq) NH$_4$Cl (5 mL), extracted with Et$_2$O (3 x 30 mL) and washed with brine (15 mL). The dried (MgSO$_4$) extract was concentrated in vacuo to provide crude 4.80 that was carried on without purification. To a solution of crude 4.80 (2.09 mmol) in CH$_2$Cl$_2$ (45 mL) was added sodium bicarbonate (877.8 mg, 10.45 mmol) followed by Dess Martin’s reagent (1.77 g, 4.18 mmol) at rt. After 3 h the reaction was quenched with saturated aq. sodium bicarbonate (15 mL). Then the solution was extracted with Et$_2$O (3 x 30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-20% EtOAc/Hexanes to give 5.5 (327 mg, 1.0 mmol, 48% over 2 steps) as a pale yellow oil. [α]$_D$ +28.3 (c = 0.8, CHCl$_3$); IR (neat) 2975, 2934, 2861, 1685, 1163 'H NMR (400 MHz, CDCl$_3$) δ 7.53-7.63 (m, 2H), 7.38-7.41 (m, 2H), 7.31-7.36 (m, 1H), 6.86 (d, J = 12.8 Hz, 1H of the minor isomer), 6.79 (d, J = 16 Hz, 1H of
major isomer), 6.24 (d, \( J = 12.8 \) Hz, 1H or minor isomer), 4.81 (bs, 1H), 4.05 (bs, 1H), 2.81-2.96 (m, 2H), 2.68 (d, \( J = 7.6 \) Hz, 1H of major isomer), 1.50-1.80 (m, 5H), 1.48 (s, 11H); \(^{13}\text{C} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 200.9, 198.4, 154.8, 154.7, 143.0, 140.2, 135.2, 134.5, 133.1, 130.5, 129.2, 128.9, 128.6, 128.4, 128.3, 126.7, 126.1, 79.6, 47.9, 44.2, 41.6, 39.4, 28.4, 28.2, 25.3, 18.9. HRMS (EI\(^{+}\)) calcd. For \( \text{C}_{20}\text{H}_{28}\text{NO}_{3} \) (M\(^{+}\)) 330.2069, found 330.2074. (b7p63/64)

**Amine 4.68:** To a neat mixture of **5.5** (320 mg, 0.966 mmol) and **4.53** (263 mg, 1.06 mmol) was added Ti(O-i-Pr)\(_4\) (439 mg, 0.47 mL, 1.545 mmol) at rt. After 3 h, MeOH (4.5 mL) was added followed by NaBH\(_4\) (58.5 mg, 1.55 mmol). After 5 min, the reaction was quenched with 1 M NaOH (1 mL, 1 mmol). The mixture was diluted with Et\(_2\)O (10 mL) and filtered through Celite\(^{\circledR}\), washed with Et\(_2\)O (15 mL), and extracted with Et\(_2\)O (15 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo}, and purified by chromatography over silica eluting with 10-50% EtOAc/Hexanes to obtain **4.68** (276 mg, 0.492 mmol, 51%) as a colorless 1:1 mixture of diastereomers. IR (neat) 2932, 2855, 1686, 1165; \(^{1}\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.23-7.40 (m, 20H, mixed isomers), 6.49 (d, \( J = 15.6 \) Hz, 1H, single isomer), 6.38 (d, \( J = 15.6 \) Hz, 1H, single isomer), 5.99 (dd, \( J = 16, \)
8.4 Hz, 1H, single isomer), 5.86 (m, 1H, single isomer), 4.82 (d, J = 15.6 Hz, 2H, single isomer), 4.76 (d, J = 14.8 Hz, 2H, single isomer), 4.52 (s, 2H, single isomer), 4.46 (s, 2H, single isomer), 4.34 (bs, 2H, mixed isomers), 3.98 (bs, 2H, mixed isomers), 3.50 (t, J = 6.4 Hz, 2H, single isomer), 3.43 (t, J = 6.4 Hz, 2H, single isomer), 3.25-3.35 (m, 1H, single isomer), 3.17-3.25 (m, 1H, single isomer), 2.70-2.90 (m, 4H, mixed isomers), 2.20-2.30 (m, 2H, mixed isomers), 1.90-2.10 (m, 4H, mixed isomers), 1.78 (s, 3H, single isomer), 1.63 (s, 3H, single isomer), 1.30-1.65 (m, 26H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.9, 143.7, 143.5, 138.7, 137.2, 136.9, 133.7, 132.5, 131.2, 130.9, 128.5, 128.4, 128.3, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.3, 113.3, 112.7, 79.2, 72.9, 72.8, 70.43, 70.38, 56.5, 55.6, 52.5, 50.6, 48.0, 43.8, 43.5, 39.4, 37.2, 36.5, 35.1, 34.2, 30.2, 29.9, 29.7, 29.1, 28.5, 27.6, 25.6, 22.7, 22.5, 22.2, 22.0; HRMS (EI) calcd. For C\(_{36}\)H\(_{52}\)N\(_2\)O\(_3\) (M+) 560.3978, found 561.4636. (b7p66)

**Alkene 4.69:** To a stirred solution of 4.68 (56 mg, 0.10 mmol) in THF (1.5 mL) was added NaH (5 mg, 0.125 mmol, 60 % in mineral oil) at rt. After 30 min, CbzCl (43 mg, 36 \(\mu\)L, 0.25 mmol) was added. After 2 h, the reaction was quenched with sat. aq. NaHCO\(_3\) (1 mL). The mixture was diluted with H\(_2\)O (5 mL) and extracted with Et\(_2\)O (5 mL x 3). The dried
(MgSO₄) filtered was concentrated *in vacuo* and purified by chromatography over silica eluting with 10-50% EtOAc/Hexanes to obtain **4.69** (52 mg, 0.077 mmol, 77%) as a colorless oil and a mixture of 2 diastereomers. H NMR (400 MHz, CDCl₃) δ 725-7.42 (m, 15H), 6.69 (bs, 1H), 6.37 (bs, 1H), 5.3 (bs, 1H), 5.15 (s, 2H), 4.60-4.85 (m, 3H), 4.50 (s, 2H), 4.25-4.35 (m, 2H), 4.15-4.25 (m, 1H), 3.85-4.05 (bs, 1H), 3.78 (t, J = 6.8 Hz, 1H), 3.4-3.55 (m, 2H), 3.20-3.30 (m, 1H), 2.60-2.95 (m, 2H), 2.20-2.45 (m, 2H), 1.88 (t, J = 3.6 Hz, 1H), 1.30-1.70 (m, 22H); H NMR (400 MHz, DMSO) δ 7.20-7.37 (m, 15H), 6.50 (bs, 2H), 5.10 (m, 2H), 4.76 (d, J = 17.6 Hz, 1H), 4.63 (d, J = 28 Hz, 1H), 4.44 (s, 1H), 4.27 (s, 1H), 4.16 (bs, 1H), 3.70-3.95 (m, 2H), 3.41 (s, 1H), 3.19 (s, 1H), 2.65-2.80 (m, 1H), 2.15-2.45 (m, 2H), 2.03 (m, 1H), 1.20-1.80 (m, 24H); C NMR (100 MHz, DMSO) δ 154.7, 154.4, 143.3, 142.7, 139.2, 139.1, 137.4, 137.2, 131.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 127.6, 113.0, 79.1, 78.8, 72.3, 72.1, 70.1, 70.0, 66.5, 55.3, 48.9, 42.0, 32.5, 30.2, 29.6, 29.4, 28.5, 28.4, 27.4, 25.8, 25.5, 23.9, 23.2, 22.6, 19.3, 19.0; HRMS (El+) calcd. For C₄₆H₅₈N₂O₅ (M+) 694.4346, found 694.6009.

(b7p68)

**Alkene 4.71**: To a refluxing stirred solution of **4.69** (55 mg, 0.81
mmol) in PhMe (5 mL) was added via syringe pump over 2 h a solution of Grubb’s 2nd generation catalyst (20.6 mg, 0.024 mmol, 30 mol % of catalyst) in PhMe (10 mL). After 2 h, the addition was complete. The mixture was then cooled to rt, concentrated in vacuo, and purified by chromatography over silica eluting with 10-35% EtOAc/Hexanes to obtain **4.71** (45 mg, 0.076 mmol, 94%) as a light brown oil and a mixture of diastereomers. ¹H NMR (400 MHz, DMSO) δ 7.28-7.37 (m, 10H), 5.79 (bs, 1H), 5.15 (d, J =12.4 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.42 (s, 2H), 3.91 (bs 1H), 3.80-3.94 (m, 2H), 3.71 (bs, 1H), 3.37 (t, J = 4 Hz, 2H) 2.78 (bs, 1H), 2.42 (bs, 1H), 2.30 (d, J = 14.4 Hz, 1H), 1.97 (d, J = 16 Hz, 1H), 1.73 (s, 3H), 1.2-1.6 (m, 20H); ¹³C NMR (100 MHz, DMSO) δ 155.3, 154.4, 139.2, 137.2, 132.9, 128.8, 128.6, 128.5, 128.4, 127.8, 127.7, 122.8, 78.9, 72.3, 69.9, 66.6, 52.3, 50.2, 35.8, 33.5, 31.9, 29.6, 28.6, 25.6, 24.2, 23.6, 19.1; HRMS (EI+) calcd. For C₃₆H₅₁N₂O₅ (M+) 591.3798, found 591.3794. (b7p74)
Chapter 5. Future Plans and Conclusion

The work highlighted in this dissertation has illustrated the advances that our research group has made in the area organocatalysis for heteroatom Michael additions and the application of this methodology to synthesize multiple natural products. The process of this work started with the development and optimization of the organocatalyzed heteroatom Michael addition (Scheme 5.1). A general scope for the synthesis of piperidine, pyrrolidine and indoline ring systems has been explored.

Scheme 5.1. Organocatalyzed Heteroatom Michael Addition

The methodology was applied to the synthesis of several natural products. Using this methodology we were able to use a similar intermediate for the rapid synthesis of homoproline, homopipeolic acid and pelleterine (Scheme 5.2). This highlights some of the advantages of the methodology in the ability to access a variety of products starting from similar simple materials.
Scheme 5.2. Synthesis of natural products

We have also applied this methodology toward the total synthesis of cermizine D (Scheme 5.3). Our original approach accessed the A and C rings of cermizine D via our organocatalyzed Micheal reaction. Unfortunately, subsequent Hartwig style amination proved problematic.

Scheme 5.3. Original Synthetic Plan for Cermizine D

Our revised approach continued to exploit the organocatalyzed Micheal addition (Scheme 5.4). Reductive amination using Ti(OiPr)$_4$ was now used to couple the two fragments successfully. The following ring closing metathesis on the Cbz protected amine has been accomplished to form the ring.
The synthesis of cermizine is well on its way with two of the rings formed and all of the carbons present in the current advanced intermediate 4.71. The remaining work on the total synthesis of cermizine D includes the optimization of the reductive amination in order to improve the diastereoselectivity of the product. It is possible that just by reducing the temperature at which the reduction takes place that the selectivity may increase. Following the RCM, global hydrogenation should remove both the Cbz and the benzyl protecting groups as well as reduce the alkene in the newly formed ring. We are uncertain of the diastereoselectivity on the alkene reduction. Activation of the alcohol with mesyl chloride should allow for spontaneous cyclization with the amine to close the third and final ring and complete the carbon structure of cermizine D. Final deprotection of the Boc protecting group and formation of a salt, most likely the TFA salt formed from in the same step will complete the total synthesis of cermizine
D (Scheme 5.5).

**Scheme 5.5. Proposed Completion of Cermizine D.**
REFERENCES


7 It is important to note that enantioselective, intermolecular Michael addition of nitrogen-based nucleophiles have been previously disclosed through metal-catalyzed and organocatalyzed processes. Metal-catalyzed:


2006, 45, 1747-1749.

27. An “aged” catalyst is defined as exposure of 2\textsuperscript{nd} Generation Grubbs catalyst purchased from Sigma-Aldrich Corporation (Cat# 569747) to air \textit{via} an unsealed (open) vial. After 72 h, the vial was resealed that catalyst was ready for use.

28. An “aged” catalyst is defined as exposure of 2\textsuperscript{nd} Generation Grubbs catalyst purchased from Sigma-Aldrich Corporation (Cat# 569747) to air \textit{via} an unsealed (open) vial. After 72 h, the vial was resealed that catalyst was ready for use.


31. **Procedure for Preparation of Mosher ester derivative:** To a stirred solution of the starting alcohol (2-3 mg) in CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) was added 4-DMAP (10 equiv.) followed by (R)-Mosher’s acid chloride (5 equiv.) at rt. After 2 h, the reaction was quenched by the addition of H\textsubscript{2}O (10 mL) and the solution extracted with Et\textsubscript{2}O (3 X 10 mL). The combined dried (MgSO\textsubscript{4}) organic layer was concentrated \textit{in vacuo} and purified by chromatography
over silica gel, eluting with 0-15% EtOAc/Hexanes to give 3-5 mg (75-92%) of the desired ester as a colorless oil.


(a) Tanret, C. Compt. Rend. 1878, 86, 1270. (b) Tanret, C. Compt. Rend. 1880, 90, 695.


3020 – 3021


52 (a) Wijdeven, M. A.; Botman, P.N.M.; Wijmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. Org. Lett. 2005, 7, 4005-4007. (b)


