2018

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Sarah Elizabeth Cleary

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FRAGMENTATION, REARRANGEMENT, AND C-H INSERTION: REACTIONS OF VINYL CATIONS DERIVED FROM DIAZO CARBONYLS

A Dissertation Presented

by

Sarah Elizabeth Cleary

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy
Specializing in Chemistry

October, 2018

Defense Date: June 21, 2018
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ABSTRACT

Many commercialized medicinal compounds are analogs of chemicals isolated from sources found in nature (also called natural products). However, the natural sources of these chemicals, such as plants, fungi, or insects, only offer small quantities of these bioactive agents. Thus, it is typically desirable to find ways to synthesize these products and their analogs in large quantities using cost-effective methods that also minimize the impact on the environment. It is also important to develop strategies that expedite the process of modifying the natural products, which allows medicinal chemists to determine which functional groups are enhancing or deleterious to the bioactivity. In the Brewer lab, I have investigated organic reactions and methodologies with this aim - to find ways to efficiently break and form carbon-carbon bonds, and to utilize these reactions in the total synthesis of structurally related natural products.

The total synthesis of natural products is often used to showcase a methodology’s utility by applying it in a more complex structure. The Lewis acid-promoted fragmentation of γ-silyloxy-β-hydroxy-α-diazo esters to provide tethered aldehyde ynoates was discovered and developed in the Brewer lab. This methodology was extended to bicyclic systems, in which the ring-fusion bond fragmented as a way to afford 10-membered ring ynoles and ynolides, which are traditionally challenging to synthesize. This work will exhibit how the fragmentation reaction that provided 10-membered ynolides has the potential to lend itself to the synthesis of several structurally related, bioactive natural products via a divergent total synthesis strategy.

In addition, this dissertation will describe our discovery that modifying the diazo carbonyl precursor to a β-hydroxy-α-diazo ketone changes the course of the Lewis acid-promoted reaction. Rather than a fragmentation sequence, the compound is converted to a vinyl cation, which undergoes a rearrangement then a C-H insertion of a second vinyl cation intermediate. This transition metal-free rearrangement/C-H insertion reaction provided cyclopentenone products. The migratory aptitudes of non-equivalent substituents in the cationic rearrangement step will also be discussed. Finally, the disparate reactivities of vinyl cations derived from diazo ketone, diazo ester, and diazo amide precursors will be detailed from an experimental and computational perspective. The results underscore the fact that this rearrangement and C-H insertion reaction may eventually be an effective way to prepare complex cyclopentyl-containing structures, which are common motifs in biologically active natural products.
CITATIONS

Material from this dissertation has been published in the following form:

ACKNOWLEDGEMENTS

There are many amazing people who made this thesis possible. First I would like to give an enthusiastic thanks to my advisor, Professor Matthias Brewer. From him, I have seen what it means to be both an intuitive and inquisitive chemist, as well as an outstandingly supportive mentor who pushes a healthy balance of challenge and encouragement, which helps us become our best and brightest selves. I feel very privileged to have studied under his advisement, and like to think I have come out a confident researcher ready to test the boundaries of chemistry thanks to him!

I would like to thank my committee members, Professor José Madalengoitia and Professor Matthew Liptak, for their interest, suggestions, and support with my research over the years. Their additional perspectives have broadened the way I think about chemistry, which has been essential in moving forward with project ideas. And a very gracious thank you to my chairperson, Professor Teresa Ruiz, who has given me vital advice about this dissertation and my defense, as well as what it is like to post-doc abroad. I could not have obtained crucial data without the help of Dr. Monika Ivancic and Bruce O’Rourke, both of whom I thank for their kindness and support. I would also like to thank Angie Gatesy, who provided us with numerous pieces of glassware (in particular, a diazomethane-generating apparatus, which reduced our changes of blowing up the lab)!

I could never have completed my degree without the camaraderie of my fellow group mates. I have never met a group who I can laugh so hard with, and who tolerate my particular brand of insane so gracefully. Dr. Geoffrey Giampa, Ramya Srinivasan, Nicolas Dodge, Jian Fang, Magenta Hensinger, and Evan Howard, what would I have
done without you? I would like to give a special thank you to Magenta for working closely with me on the vinyl cation project, and sharing both the ups and downs throughout the process. And I can genuinely say I would not have gotten through graduate school in one piece without Ramya Srinivasan or Nicolas Dodge. They are the kindest, sassiest, most brilliant people I have ever worked with and their friendships have kept me sane.

To my fellow graduate students: our extracurricular excursions gave me something outside of chemistry to look forward to over the years! Be it Duff hour, hiking, the annual Christmas party, hanging out at the beach, or really finding any excuse to kick back with you all was truly a pleasure. To my year: Christine, Michelle, Jonathan, Matt, Nick, Teruki, and Mona, you stellar human beings! I will always fondly remember our Secret Santa/Cunning Cupid gift exchanges and Restaurant Week feasts, and could not have asked for a better crew to go through grad school with!

Finally I need to thank my family. Words really cannot express my gratitude to them. Their support has been unwavering over the years. Jack and Shelia Cleary, I would not be here without you (literally!). I have tried to embody your work ethic, strength, and ambition. Still trying! Hope it works out. And to Meghan/Meg/meggles – you keep me silly and ridiculous, and I would not have gotten through the difficult times without your help lightening the mood.

This dissertation was financially supported by Award GM092870 from NIGM (a component of the NIH) and the NSF under CHE-1665113.
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LIST OF ABBREVIATIONS

9-BBN 9-Borabicyclo[3.3.1]nonane
AcOH Acetic acid
aq Aqueous
Ar Aryl
AuCl(PPh₃) Chloro(triphenylphosphine)gold(I)
BCF Tris(pentafluorophenyl)borane
R-Binol R-(+)-1,1’-Binaphthol
BF₃·OEt₂ Boron trifluoride diethyl etherate
Boc tert-Butyloxy carbonyl
b.r.s.m. Based on recovered starting material
Bu₂CuLi Lithium dibutylcopper
CF₃Ph α,α,α-Trifluorotoluene
CSA Camphorsulfonic acid
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC N,N'-Dicyclohexyl carbodiimide
DCE 1,2-Dichloroethane
DCM Dichloromethane
DEAD Diethyl azodicarboxylate
DIAD Diisopropyl azodicarboxylate
DIBAL-H Diisobutylaluminum hydride
DMAP 4-(Dimethylamino)pyridine
DME 1,2-Dimethoxyethane
DMF Dimethylformamide
DMP Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)
DMSO Dimethyl sulfoxide
dr Diastereomeric ratio
Dy(OTf)₃ Dysprosium(III) trifluoromethanesulfonate
EDA Ethyl diazoacetate
ee Enantiomeric excess
Et Ethyl
Et₂N Triethylamine
Et₂O Diethyl ether
EtOAc Ethyl acetate
EtOH Ethanol
Et₂SiH Triethylsilane
Eu(fod)₃ Europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)
EWG Electron withdrawing group
Fe(II)(TPP) Iron(II) meso-tetraphenylporphyrin
GABA Gamma-Aminobutyric acid
GC-MS Gas chromatography–mass spectrometry
Grubbs I  Bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride, or Grubb’s Catalyst™ 1st Generation
Grubbs II  Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium or Grubbs Catalyst™ 2nd Generation
HAT  Hydrogen-atom transfer
HMPA  Hexamethylphosphoramide
HOtBu  tert-Butyl alcohol
HWE  Horner–Wadsworth-Emmons (olefination)
IBX  2-Iodoxybenzoic acid
In(OTf)₃  Indium(III) trifluoromethanesulfonate
iPr  iso-Propyl
iPr₂NEt  N,N-Diisopropylethylamine
KOrBu  Potassium tert-butoxide
L.A.  Lewis acid
LDA  Lithium diisopropylamide
LiHMDS  Hexamethylidisilazane lithium salt
m-CPBA  meta-Chloroperoxybenzoic acid
Mg(OTf)₂  Magnesium(II) trifluoromethanesulfonate
Me  Methyl
MeCN  Acetonitrile
MeLi  Methylolithium
MeMgBr  Methylmagnesium bromide
Me₂NH  Dimethylamine
MeOH  Methanol
MeONa  Sodium methoxide
Mg(OTf)₂  Magnesium trifluoromethanesulfonate
MsCl  Methanesulfonyl chloride
MsN₃  Methanesulfonyl azide
MsOH  Methanesulfonic acid
μW  Microwave
NaOAc  Sodium acetate
n-BuLi  n-Butyllithium
NBS  N-Bromosuccinimide
NHAc  Acetamide
Nu  Nucleophile
NMR  Nuclear magnetic resonance
p-ABSA  para-Acetamidobenzenesulfonyl azide
nPr  n-Propyl
Pb(OAc)₄  Lead(IV) acetate
PBu₃  Tributylphosphine
Pd(dppf)Cl₂  [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd(OAc)₂  Palladium(II) acetate
Ph  Phenyl
Phl(OAc)₂  (Diacetoxyiodo)benzene
CHAPTER 1 : A GENERAL BACKGROUND ON α-DIAZO CARABONYLS, 5- AND 10-MEMBERED RINGS, CATIONIC REARRANGEMENTS, AND COMPUTATIONAL ORGANIC CHEMISTRY

My work in the Brewer group has focused on reaction methodology development for the synthesis of small organic molecules. As a group, we are particularly interested in probing reaction mechanisms, as well as the application of these new methods in bioactive and natural product syntheses. For example, the Brewer group previously discovered and developed new ways of breaking carbon-carbon bonds and applied this fragmentation in a number of natural product total syntheses. More recently, I led the discovery of a new way of forming carbon-carbon bonds, which is currently under further development within the group.

The content in this dissertation covers both bond-breaking and bond-forming reactions. Chapter 2 is an account of the application of a carbon-carbon bond fragmentation reaction that has provided a key intermediate that will be further functionalized to prepare naturally occurring bioactive compounds. Specifically, this reaction proceeds via the cleavage of the Cβ-Cγ bond of a γ-silyloxy-β-hydroxy-α-diazo lactone to provide a 10-membered cyclic ymolide product. The second subject is a detailed look into a new rearrangement/carbon-carbon bond-forming reaction. This reaction begins with β-hydroxy-α-diazo carbonyls, which are precursors to highly reactive vinyl cations. These vinyl cations undergo a bond migration followed by an intramolecular C-H insertion to form 5-membered rings. This dissertation details the discovery and optimization of this novel reaction, the scope and limitations of the
rearrangement step, and an elucidation of how the vinyl cation intermediates dictate the fate of the C-H insertion reaction.

1.1. α-Diazo carbonyl compounds

There has been an ongoing interest in α-diazo carbonyls, both in their use in classical organic methods as well as the pursuit of new applications in synthesis.\(^1\) The reasons for this interest lie in the versatility of the functional group’s preparation and reactivity, as well as the fact that transformations involving this group are often mild and green.\(^1\) That is, decomposition of diazo species releases nitrogen gas, which is a green alternative to many other leaving groups (i.e. halogens).\(^2\) The irreversible liberation of \(\text{N}_2\) is also the driving force behind diazo carbonyl reactivity.

1.1.1. Properties of α-diazo carbonyl compounds

Diazo compounds are characterized as a terminal functional group that consists of two linked nitrogen atoms with a general chemical formula of \(\text{R}_2\text{C}≡\text{N}_2\). When the R group(s) consists of aliphatic functionality, the diazo compound tends to be explosive and unstable. However, α-diazo carbonyl compounds (when the R group(s) consists of carbonyl functionality) are resonance stabilized therefore safer to handle (Figure 1.1).

\(\text{R}_1\text{O}\text{N}^+\text{R}_2\)
\(\text{R}_1\text{O}\text{N}^+\text{R}_2\)
\(\text{R}_1\text{O}\text{N}^+\text{R}_2\)

1.1 1.2 1.3

Figure 1.1 Resonance forms of α-diazo carbonyls

α-Diazo carbonyls are synthetically significant because, while stabilized, they are reactive. They are ambiphilic, having both electrophilic and nucleophilic properties (compare 1.1 to 1.2 and 1.3).\(^3\) Over the years, extensive work has gone into both
developing methods to synthesize these useful compounds, and to discover chemical transformations starting with \( \alpha \)-diazo carboxyls.

### 1.1.2. Synthesis of \( \alpha \)-diazo carboxyl compounds

There exists numerous methods for the synthesis of diazo carboxyl compounds (Scheme 1.1). Classic examples include diazotization of primary amines (a, summarized in section 1.1.2.1), dehydrogenation of hydrazones (b), acylation of alkyl diazo compounds (c, summarized in section 1.1.2.2), and diazo transfer of azides to carboxyls (d, summarized in section 1.1.2.3) No significant work has been done to further develop the first two examples, though both are still frequently employed.\(^1\) However, safety remains a top concern with many of these methods, especially c and d which utilize explosive and/or acutely toxic starting materials. Summarized below are techniques that are generally used in the Brewer lab for the preparation of \( \alpha \)-diazo carboxyls.

![Scheme 1.1 Common methods for the synthesis of \( \alpha \)-diazo carboxyls](image)

\(^1\)
1.1.2.1. Diazotization reactions

Diazotization has been the method of choice for the conversion of amino acids and their derivatives to diazo carbonyls.\textsuperscript{4} For example, ethyl diazoacetate (EDA, 1.5) has traditionally been prepared from glycine ethyl ester (1.4) using sodium nitrite (Scheme 1.2a).\textsuperscript{5} Recent reports have expanded this methodology for use in flow, which has the capability of directly linking the \textit{in situ} generation of ethyl 2-diazoacetate (1.5) with further useful reactions.\textsuperscript{6}

![Scheme 1.2 Diazotization methods for synthesis of $\alpha$-diazo esters](image)

More complicated amino acid derivatives, including alanine, phenylalanine, isoleucine, and methionine, have been converted to diazo esters using an improved diazotization method. This preparation utilized isoamyl nitrite and acetic acid (AcOH) in place of nitric acid, which reduced the formation of side products (Scheme 1.2b).\textsuperscript{7} This also improved the yield of $\alpha$-substituted $\alpha$-diazo esters ($R^2$) compared to their preparation from HNO$_2$.

1.1.2.2. Acylation of diazomethane

The acylation of diazomethane is one of the most widely used routes to $\alpha$-diazo ketones. Efforts to improve the safe generation of diazomethane \textit{in situ} have gained interest over time due to the toxicity and explosiveness of the chemical. The standard
modern-day method for the preparation of diazomethane is via the decomposition of Diazald® under basic conditions, with simultaneous codistillation with an organic solvent (typically Et₂O). The distillate is then acylated without the need for further purification, thereby reducing the users’ exposure to the chemical (Scheme 1.3).

Scheme 1.3 Modern approach to acylation of diazomethane

One potential drawback to the acylation step of the reaction is the necessity for a base (i.e. Et₃N) or superstoichiometric amounts of diazomethane to trap the hydrogen chloride byproduct. The use of a tertiary amine base has the potential unintended consequence of generating a ketene from the acid halide, which could affect the acylation of diazomethane (Scheme 1.4, top). In 2010, De Kimpe and coworkers reported the replacement of Et₃N with CaO as a hydrohalic acid scavenger in the Arndt-Eistert reaction (Scheme 1.4). This reagent was inert toward deprotonation of enolizable acyl halides, which afforded several diazo ketones in near-quantitative yields.

Scheme 1.4 CaO as hydrogen bromide scavenger in acylation of diazomethane
1.1.2.3. **Diazo transfer reactions**

Diazo transfer reactions are typically carried out on $\alpha$-methylene-containing carbonyls using sulfonyl azides and base. In many examples, the diazo transfer occurs at a site in between two electron-withdrawing groups (Scheme 1.5).¹

![Diazo transfer reaction](image)

Scheme 1.5 Diazocarbonyls from diazo transfer reactions

Diazo transfer reactions offer a pathway to diazo ketones that are not always possible via acylation of diazomethane. For example, $\alpha,\beta$-unsaturated acid chlorides (1.8) are not suitable in the Arndt-Eistert reaction since they undergo dipolar cycloadditions with diazomethane to form pyrazolines (1.9, Scheme 1.6a).¹⁰ Fortunately $\alpha,\beta$-unsaturated ketones are amenable to diazo transfer. Danheiser and coworkers developed a methodology for the synthesis of $\alpha$-diazo ketones via trifluoroacetyl ketones (1.10, Scheme 1.6b).¹¹ This method took advantage of the facile deformylation of the trifluoroacetyl group. Avoiding the use of diazomethane provided new access to $\alpha',\beta'$-unsaturated $\alpha$-diazo ketones (1.11) in high yields. This procedure is also compatible with cyclic $\alpha$-diazo carbonyl compounds that are not accessible through the use of acid chlorides.
Work has gone into developing safer alternatives to traditional azide transfer reagents such as tosyl azide (TsN$_3$). While there has been a lot of progress in this field, there are few examples of alternative azides that are shelf stable and are not shock or impact sensitive. Even more desirable, from a practical standpoint, is the availability of commercial reagents, which would circumvent the experimenter’s need to use NaN$_3$, thereby preventing exposure to another reagent that comes with a severe health risk warning. One such azide reagent that has been commercialized is para-acetamidobenzenesulfonyl azide (p-ABSA) which has become a widely utilized diazo transfer reagent, not least of all due to its lack of special safety or storage instructions (Figure 1.2). For two examples of the synthetic utility of this reagent in this work, see sections 2.3.3 and 5.3.2.

![Scheme 1.6 Detrifluoroacetylation and diazo transfer](image)

**Figure 1.2 Comparison of common diazo transfer reagents**
1.1.2.4. Other preparations of α-diazo carbonyls

The direct conversion of alcohols to α-diazo esters can be achieved via the decomposition of tosyl hydrazones derived from glycine (Scheme 1.7a). House and coworkers reported the conversion of 2-oxoacetic acid (1.12) to (tosylhydrazono)acetyl chloride (1.13), which then reacted with alcohols and Et₃N to convert to various α-diazo esters (1.14). A more recent iteration of this reaction, reported by Toma et al., proceeded via bromoacetyl bromide (1.15, Scheme 1.7b). In this case, the alcohol was esterified prior to diazo formation, and the conversion of bromide 1.16 to diazo ester 1.14 by substitution and double-elimination of the tosyl groups was promoted by DBU. See section 2.3.2 for a specific example of the Toma method toward α-diazo esters.

a. Three-step synthesis of α-diazo esters from alcohols

\[
\begin{align*}
\text{HOC} &= \text{HCl} \\
\text{TsNHNH}_2 &\rightarrow \text{TsHN} \quad \text{Et}_3\text{N} (2 \text{ equiv}) \\
\text{O} &= \text{N}_2 \\
\text{O} &= \text{R}
\end{align*}
\]

b. Two-step synthesis of α-diazo esters from alcohols

\[
\begin{align*}
\text{BrBCl} &= \text{NaHCO}_3 \\
\text{BrBH} &= \text{TsHNHN} \quad \text{DBU} (5 \text{ equiv}) \\
\text{N}_2 &= \text{R}
\end{align*}
\]

Scheme 1.7 Synthetic methods toward α-diazo esters from alcohols

1.1.3. Reactivity of α-diazo carbonyl compounds

Diazo compounds are often desired as reaction precursors due to their ability to release nitrogen gas – a process which entropically drives reactions. α-Diazo carbonyls are useful in a variety of differing reactions: thermal, photochemical, acid-promoted, or
in metal catalyzed reactions. There is a growing assortment of enantioselective reactions that use diazo carbonyl starting materials, as well as diazo carbonyls in organocatalytic reactions. Summarized below is a selection of reactions that use diazo carbonyls under conditions similar to those used in our lab, or use the diazo compounds as precursors to products that are similar to those reported in Chapters 2, 3, 4, and 5.

1.1.3.1. Reactions with Brønsted and Lewis Acids

Diazo carbonyls have been identified as useful precursors to epoxides and aziridines via Darzens and aza-Darzens reactions. The Darzens reaction proceeds by reacting a diazo carbonyl with an aldehyde or imine, which undergoes an epoxidation or aziridination from displacement of N₂ by the anionic heteroatom (see Scheme 1.8 for the mechanism).

Gong et al. recently reported an asymmetric Darzens reaction between aldehydes and diazoacetamides. When 1.17 and 1.18 were treated with Ti(OiPr)₄ and R-binol, the diazo carbonyl carbon added into the aldehyde, then the oxy anion (1.19) displaced N₂ in an epoxidation step. This exhibited a method to prepared optically pure epoxides which have the potential to be further derivatized to amino acids, among many other useful motifs.

Scheme 1.8 Darzens reaction that leads to optically pure epoxides
Treatment of ethyl diazoacetate (EDA, 1.5) and imine 1.21 with triflic acid (TfOH) provided aziridine 1.23 in high diastereoselectivity (Scheme 1.9). As with the Darzen epoxidation mechanism, the aza-variation proceeded through an aldol-type addition of the nucleophilic EDA into the protonated iminine to provide intermediate 1.22, and N₂ acted as the leaving group in the cyclization of the nitrogen step.

![Scheme 1.9 Aza-Darzens reaction](attachment:image)

Using very similar starting materials to the aza-Darzens reaction, Hashimoto and Maruoka reported an asymmetric Mannich reaction between N-Boc imines (1.24) and diazo esters or diazo phosphonates (1.25, Scheme 1.10). By replacing triflic acid for a chiral dicarboxylic acid catalyst, diazo-retaining chiral Mannich products (1.26) were isolated rather than aziridines.

![Scheme 1.10 Mannich reaction between imines and diazo compounds](attachment:image)
Doyle and coworkers demonstrated that diazo carbonyls could react with nitrile compounds under Lewis acid conditions, which behaved differently compared with the Darzens or Mannich reactions (above). In this case, instead of promoting an aldol-type addition (which would provide isoxazoles \( 1.30 \), Scheme 1.11a), the Lewis acid (“LA”) coordinated to the nitrile nitrogen which facilitated the nucleophilic attack of the oxygen of the diazo carbonyl to form vinyl diazonium intermediate \( 1.31 \) (Scheme 1.11b).\(^{20}\) The nitrogen lone pair displaced \( N_2 \) to afford the oxazole products \( 1.32 \). This example is a reminder of how diazo carbonyls have nucleophilic sites at both the \( \alpha \)-carbon and the oxygen.

![Scheme 1.11 Possible pathways of the Lewis acid-promoted reaction between \( \alpha \)-diazo carbonyls and nitriles](image)

As exemplified above, diazo carbonyls can react with a number of electrophiles under acidic conditions, which produce intermediates that either liberate nitrogen from a diazonium formed \textit{in situ}, or retain the diazo functional group.

\subsection{1.1.3.2. Reactions with metal catalysts}

Many reactions that involve diazo carbonyls and metal catalysts proceed through a metal carbene intermediate. The diazo group \( 1.33 \) donates electrons to the metal center to form zwitterionic intermediate \( 1.34 \), which then liberates \( N_2 \) to generate the
metal carbene 1.35 (Scheme 1.12). These metal carbenes have useful reactivities that depend on other functional groups present either within the diazo molecule, or on other reactants.

$$\begin{array}{c}
\text{N} = \text{N} & \text{M}^{(n+)} & \text{M}^{(n-1)+} & \text{[M]} \\
\text{R} & \text{R} & \text{R} & \text{R}
\end{array}$$

Scheme 1.12 Generation of metal carbenes from diazo precursors

One of the most widely reported reactions that proceed through metal carbene intermediates generated from diazo carbonyls are sp$^3$ C-H insertion reactions. This will be discussed in more detail in Section 1.4. However, when certain functional groups other than saturated hydrocarbons are present in the reaction mixture, the metal carbene has the opportunity to react in other modes beyond C-H insertion.

When alkenes (1.37) are present in the reaction mixture, metal carbenes (1.38) generated from diazo compounds (1.36) can react to form cyclopropanes (1.39, Scheme 1.13). The ambiphilic nature of the metal carbene drives it to react with the alkene as both an electron acceptor and an electron donor. Stereoselectivity was a challenge early on in this transformation’s development, however continued investigations showed that metal catalyst, ligand, and diazo ester selection can improve both enantio- and diastereoselectivity.$^{21,22}$

$$\begin{array}{c}
\text{O} & \text{Z} & \text{N}_2 \\
\text{R}^1 & \text{R}^2 & \text{R}^3
\end{array} \quad \text{1.36} \quad \text{1.37} \quad \text{1.38} \quad \text{1.39}

\text{Scheme 1.13 Proposed general mechanism for metal carbene cyclopropanation of alkenes}

Vinylogous Wolff rearrangements, which have been studied extensively by Amos Smith III and coworkers,$^{23-25}$ involve the reaction of unconjugated, unsaturated diazo
ketones with metal catalysts (Scheme 1.14). Studies showed that cyclopropanation occurs, followed by a retro-[2+2] cycloaddition to provide a ketene intermediate, which ultimately was trapped by an alcohol.

\[
\text{Scheme 1.14 Vinylogous Wolff rearrangement}
\]

The ketenes generated in the vinylogous Wolff rearrangement can also be trapped intramolecularly. Seki and Georg prepared mono-, bi-, and tricyclic piperidone compounds (1.42) from a vinylogous Wolff rearrangement (Scheme 1.15).26 Pendant enamine-diazo ketones (1.40) were treated with silver(I) benzoate to generate ketene 1.41 via a Wolff rearrangement, which then underwent a 6-exo-dig cyclization to provide the cyclic enamineones (1.42).

\[
\text{Scheme 1.15 Cyclic enamineones via vinylogous Wolff rearrangement/cyclization}
\]

Diazo carbonyls have been employed as olefination reaction partners to aldehydes and ketones in Wittig-type reactions. Distinct from the traditional Wittig reaction, olefination with diazo carbonyls use metal catalysts, and neutral reaction conditions are favored to alkaline conditions.27 The initial report of an organometallic diazo carbonyl olefination was in 1989 by Lu et al. where a molybdenum catalyst was used in the presence of triphenylphosphine to decompose ethyl diazoacetate (EDA), which then reacted with the carbonyl to form the olefin (Scheme 1.16A).28
Other metal catalysts have been used in this olefination chemistry, including rhenium, copper (B), rhodium, ruthenium, cobalt, iridium, and iron (C, Scheme 1.16).\textsuperscript{27} In general, these olefination reactions were $E$-selective.

Diazo carbonyls have proven utility as partners in transition metal cross-coupling reactions. For example, Wang and coworkers developed a Pd(0)-catalyzed coupling between $\beta$-hydroxy-$\alpha$-diazo esters and aryl iodides to prepare $\alpha$-aryl enoates (1.48, Scheme 1.17).\textsuperscript{29} This reaction exhibited a dual reactivity with palladium, which underwent oxidative addition with aryl iodides ("ArI"), then reacted with the diazo species to form metal carbene complexes. Specifically, the arylpalladium(II) species ("ArPdI") decomposed the diazo to generate Pd-carbene 1.44, which was a confirmed intermediate due to the observation of 1,2-alkyl shift product 1.45. The aryl palladium could also undergo migratory insertion to form 1.46, which could either rearrange to 1.47 (not observed) or go through $\beta$-OH elimination to generate IPdOH and 1.48. This was a rare example of $\beta$-OH elimination, and the demonstration of this termination step
effectively expands the synthetic utility of palladium methodology, creating the opportunity to use these precursors instead of those which would end with β-hydride elimination.

\[
\text{HO-N=N}_2\text{N}_2\text{O}\text{CO_2Et} + \text{I-Pd(I)-aryl iodides} \rightarrow \text{CO_2Et-R^3-R^2}
\]

59-86% yield

Scheme 1.17  Pd-catalyzed coupling of β-hydroxy-α-diazo esters and aryl iodides

In addition to forming metal carbenoids, diazo carbonyls are also known to react with transition metal intermediates in other ways. For example, Chen and Wang developed the reaction of diazo carbonyls (1.50) as nucleophiles with π-allyl palladium complexes (i.e. 1.49, Scheme 1.18).\textsuperscript{30} Diazo carbonyls are considered “soft” carbon centered nucleophiles, which suggests that they are more likely to attack the allyl ligand as opposed to the metal center.\textsuperscript{30} This makes diazo carbonyls ideal for the formation of a new C-C bond to generate diazonium 1.51. After nucleophilic attack, deprotonation leads to elimination of nitrogen to afford 1,3-dienes (1.52).
1.1.3.3. Aldol-type reactivity with ketones and aldehydes

Diazo carbonyls are known to act as the nucleophile in aldol-type reactions under Lewis or Brønsted acidic conditions (see section 1.1.3.1). Additionally, diazo carbonyls can participate in aldol-type additions under basic conditions. For example, DBU can catalyze the addition of diazo carbonyls with aldehydes or imines to afford β-hydroxy- or β-amino-α-diazo carbonyls (Scheme 1.19).³¹

Building upon these aldol-type addition methods, asymmetric variants have been reported. One strategy for asymmetric aldol-type addition of ethyl diazoacetate (EDA) to aldehydes is through the use of Lewis acid catalysts with chiral ligands (Scheme 1.20). For example, Wang and coworkers prepared chiral β-hydroxy-α-diazo esters from a Zr(OrBu)₄/(S)-6,6’-BINOL catalyzed reaction with EDA and aldehydes.³² The products were isolated in fair yields (47-82%), however the enantioselectivity of the products left room for improvement (57-87% ee).
A few years after, Trost and coworkers improved upon Wang’s chiral Lewis acid strategy by using a Mg-(S,S)-ProPhenol system with cis-1,2-cyclopentanediol as an additive. This catalytic system could reduce catalyst and ligand loading (from 20% Zr to 10% Mg) and improved yields and enantioselectivity (87-97% ee).33

Stereoselective aldol-type additions of diazo carbonyls have also been achieved by tethering the α-diazo carbonyl to chiral auxiliaries.3 These reactions were mediated by achiral acids (i.e. TfOH)34 or bases (i.e. LDA or LiHMDS).35 Zhao et al. effected a diastereoselective aldol-type addition of an α-diazo carbonyl (1.53, containing Evan’s auxiliary) with tosylimines in high yield (Scheme 1.21).36 The chiral auxiliary was smoothly converted to the corresponding methyl ester upon treatment with LiOMe.

1.2. Heterolytic carbon-carbon bond fragmentation reactions

Heterolytic bond cleavage occurs when the electrons from the bond that is fragmented are unevenly distributed between the products, often producing at least one ion (Figure 1.3a). This is in contrast with a homolytic bond cleavage, in which the bonding electron pair is evenly distributed between products (i.e. homolysis of bromine, Figure 1.3b). A classic example of heterolytic bond cleavage is the disassociation of a
leaving group to give a carbocation in E1 (elimination) reactions. In Figure 1.3a, the leaving group (Br\(^-\)) gains the electrons from the cleaved bond, leaving the carbocation without electrons from the fragmented bond.

![Chemical structure](image)

**Figure 1.3 Heterolytic (a) and homolytic (b) bond cleavage**

### 1.2.1. Grob-type fragmentations

Molecules can undergo a regulated heterolytic cleavage into three fragments when the parent molecule contains certain combinations of heteroatoms (Scheme 1.22). In the mechanism defined by Grob, the electrophuge “a-b” fragment leaves without the bonding electron pair (between b–c) which instead becomes the unsaturated fragment “c=d”. The nucleofuge group “X” leaves with the bonding electron pair (between d–X) to become the :X fragment.

![Chemical structure](image)

**Scheme 1.22 Grob fragmentation mechanism**

As with an E2 elimination, the concerted Grob fragmentation requires the fragmenting bonds to be in an antiperiplanar orientation in order to donate into the antibonding orbitals. For example, trans-1,10-diolmonotosylate (1.55) productively fragmented to form 5-cyclodecenone (1.56), whereas base treatment of cis-1,10-dionmonotosylate (1.57) did not effect the Grob fragmentation and only elimination products were observed (Scheme 1.23).
There are other forms of Grob-type fragmentations that use different combinations of electrofuges and nucleofuges. The Eschenmoser-Tanabe fragmentation begins with the condensation of $\alpha,\beta$-epoxyketone $1.58$ with a sulfonylhydrazine to form a hydrazone ($1.59$) that rearranges to open the epoxide, and ultimately the Grob-type fragmentation occurs to form ketone $1.62$, alkyne $1.61$, and $N_2$ (Scheme 1.24). In the fragmentation step, the oxygen and carbon act as the electrofuge to form ketone $1.61$, while the $N=N-SO_2Ar$ is the nucleofuge, which liberates $N_2$ and the sulfonyl.

The Brewer group has developed a C-C fragmentation reaction that proceeds via similar electrofuge and nucleofuge to the Eschenmoser-Tanabe fragmentation, though
differs in fragmentation precursor. Specifically, \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo carbonyls (1.63) were treated with SnCl\(_4\), which promoted the elimination of the tertiary alcohol and generated vinyl diazonium 1.65 (Scheme 1.25). The Grob-type fragmentation occurred by lone pair donation from the silyloxy group, which caused C-C fragmentation to form an alkyne and release N\(_2\). Oxonium intermediate 1.66 was then desilylated to provide tethered aldehyde ynoate or ynone 1.67.\(^{40,41}\)

![Scheme 1.25 Fragmentation of \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo carbonyls to provide tethered aldehyde ynoates](image)

Similar to the Eschenmoser-Tanabe fragmentation, an oxygen and carbon form a carbonyl thus act as the electrofuge, and N\(_2\) acts as the nucleofuge. This reaction builds upon the Eschenmoser-Tanabe in that it avoids the use of a sulfonyl activating group, improving the atom economy going from reactant to product. The synthetic utility of the product was also favorable, as the nucleofuge and electrofuge remained tethered and could be further functionalized into natural products.\(^{42-45}\)

### 1.3. Medium-sized rings

Medium-sized rings are cyclic structures that consist of 8-11 atoms. The synthesis of this class of ring-sizes is accompanied by a unique set of challenges. Similar
to macrocycles (≥12-membered rings), medium-size rings can be prepared by intramolecular cyclization. However, compared to their 5- and 6-membered ring counterparts, these larger rings experience an entropic disadvantage during cyclization. This disadvantage arises from a slower rate of cyclization (or the rate of the two ends meeting to form a new bond), which must outcompete the rate of dimerization.

Enthalpic challenges are also encountered in the synthesis of medium-sized rings. With 8-11 membered rings, transannular strain is inherent to the cyclization transition state and the ring product. This can make the cyclization event difficult to achieve from an energetic perspective.

Common ways to overcome these challenges in medium-sized ring synthesis have been the use of high dilution to minimize competing dimerization/polymerization processes, and high temperature conditions in order to overcome the kinetic barriers that might exist during the cyclization event. Efforts have gone toward reducing or eliminating these practical limitations, including work accomplished in the Brewer group. Below is a summary of the importance of medium-sized lactones from a biological perspective, as well as traditional and modern methods for their synthesis.

1.3.1. Medium-size lactone natural products and their properties

10-Membered macrolides, or medium-sized lactone natural products, are continually sought after by both biologists and chemists due to their biological activity and scarce availability. For example, those which exhibit phytotoxic activity can be used as herbicides or as analogs in the discovery of new herbicides. Some of these compounds are also sought after for their medicinal activities. Overall, the subgroup of
10-membered lactones does not appear to present a general pattern of biological activity, which in turn makes them an interesting class of compounds.\textsuperscript{50}

![(-)-Pinolidoxin](image)

Some members of the pinolidoxin family, a class of 10-membered lactones isolated from \textit{Ascochyta pinodes}, were found to be responsible for the legions found in diseased peas and bean leaves (Figure 1.4).\textsuperscript{51} Further experiments showed that epipinolidoxin was active in a shrimp brine assay (a cytotoxicity assay) at a concentration of 50 $\mu$g/ml. Herbarumin I and II (Figure 1.5) were isolated from a culture of \textit{Phoma herbarum} fungus and are structurally related to (+)-pinolidoxin and other phytotoxic 10-membered lactones isolated from fungi.\textsuperscript{52}

![Herbarumin I and II](image)

Diplodialides A, B, and C were isolated from \textit{Diplodia pinea}, a fungus that causes sphaeropsis blight (a disease that disfigures pine trees, Figure 1.6).\textsuperscript{53} Diplodialide A was found to inhibit 11$\alpha$-hydroxylase of progesterone in \textit{Rhizopus stolonifer} cell cultures (black mold).
As discussed above, the preparation of medium-sized rings comes with challenges and limitations. The traditional method proceeds via macrolactonization, and modern-day cyclization reactions have been applied to the synthesis of medium-sized rings (i.e. ring closing metathesis). These methods and their inherent benefits and limitations are summarized below.

**1.3.2. Synthesis of medium-size lactones**

Despite recent progress in C-C bond forming reactions for cyclization reactions (i.e. intramolecular RCM, cross-coupling reactions, etc), macrolactonization remains the most popular method for producing macrocyclic frameworks. Activation of a carboxylic moiety (1.68, typically formed from a carboxylic acid via a Mukaiyama redox condensation) often enhances intramolecular esterification between carbonyl and alcohol (Scheme 1.26). One such activated carboxyl derivative is the Corey-Nicolaou S-pyridyl ester (1.69, when R = pyridine). This, and its numerous iterations and improvements (see Figure 1.7), are “the most famous” and most utilized activated esters in macrolactonization methods. These modified esters induce a double-activation of both carbonyl and alcohol. An internal proton transfer from the hydroxyl group to the heteroaryl atom (1.69) renders intermediate 1.70 that undergoes an electrostatically driven esterification. These methods have proven success with rings 12-members and
over, but rarely have shown high yields for 8-11 membered lactones. One example of the use of the Corey-Nicolaou macrolactonization in natural product synthesis will be summarized in section 2.2.2.1.

![Scheme 1.26 Macrolactonization via activated carboxyl group](image)

Other activators have been developed for macrolactonization (Figure 1.7). For example, the Corey-Brunelle imidazoyl thioester was discovered after the Corey-Nicolaou pyridinyl thioester, and reacted to afford macrolactones under comparatively milder conditions and in higher yields.

![Figure 1.7 Thioesters as carboxyl activators in macrolactonization](image)

While these reagents were overall good promoters for macrolactonizations, preparation of 10-membered rings remains a challenge, high dilution conditions are usually needed, and thioester selection is not general. For an example of a survey of macrolactonization methods applied toward natural product synthesis, see section 2.2.1.1.

### 1.3.2.2. Ring-closing metathesis

Ring-closing metathesis (RCM) is a cyclization method in which non-conjugated dienes are converted to cycloalkenes in the presence of metal carbene complexes. Like macrolactonization methods, RCM used for the preparation of medium-size rings is not
always productive, and intermolecular dimerization or oligomerization can become more favorable when the cyclization is slow.  

The first reported synthesis of a 10-membered ring by RCM was that of Fürstner and coworkers in their total synthesis of Jasmine ketolactone (1.73) and its $E$-isomer (1.74, Scheme 1.27). Treatment of diene 1.72 with Grubbs catalyst under high dilution conditions afforded the 10-membered lactones in high yield, but in a mix of alkene isomers.

![Scheme 1.27 RCM approach to total synthesis of jasmine ketolactone](image)

RCM was also the key step in the synthesis of the 10-membered lactone 1.76, which is a potential intermediate in the total synthesis of epothilone A (Scheme 1.28). In this case, diene 1.75 was converted to 1.76, and the double-bond was achieved in a higher ratio of the desired isomer (in this case, $E$) compared with that of jasmine ketolactone (1.73).

![Scheme 1.28 10-Membered lactone intermediate via RCM](image)
1.3.2.3. **Fragmentation approach toward medium size lactones**

Researchers have employed various fragmentation approaches to prepare medium-size rings, where the bond that is cleaved is that which fuses two rings together. Examples include Grob-type (see Scheme 1.23, section 1.2.1 for an example), redox-mediated, and ring expansion by side-chain insertion fragmentations.\(^{65}\)

A recent (2015) example of a redox-mediated, retro-Claisen cleavage that resulted in medium-size lactones was reported by Rodriguez and coworkers.\(^{66}\) The fragmentation precursor (1.78) was generated from the NaBH\(_4\)-reduction and rearrangement of bicyclic hemiacetal 1.77. The hemiacetal intermediate (1.78) then underwent a base-promoted Claisen fragmentation in refluxing dioxane, which provided a library of 9-, 10-, and 11-membered lactones (1.79, Scheme 1.29).

![Scheme 1.29 Medium-size lactones via retro-Claisen cleavage of hemiacetals](image)

Around this time, the Brewer group reported the Grob-type fragmentation of bicyclic \(\gamma\)-silyloxy-\(\beta\)-hydroxy-\(\alpha\)-diazo lactones, which provided medium-size ynomides (Scheme 1.30).\(^{67}\) Similar to the fragmentation reaction developed by the Brewer group that was discussed in section 1.2.1, this ring cleavage was promoted by SnCl\(_4\), and proceeded by the donation of electrons from the silyloxy electrophile and culminated in the release of N\(_2\). An application of this reaction is featured in this dissertation, and will be discussed further in Chapter 2.
1.4. C-H insertion reactions

The need to form C-C bonds is ubiquitous for synthetic chemists from a range of scientific branches. Traditionally, these bonds have been formed through the reaction of two complimentary functional groups. For example, the Grignard reaction couples an organometallic group (RMgX) with a carbonyl group. However, in the case of C-H insertion reactions, one or both of those functional groups is a C-H bond, which is normally considered inert. This strategy minimizes the number of functional groups required to form the desired C-C bond. Reducing the need for additional functional groups within a synthetic plan can be advantageous from a time, cost, and resource perspective, and C-H insertions are intrinsically step and atom economic.

sp³ C-H insertion reactions are frequently exemplified by insertion of a metal carbene into a C-H bond. Rhodium carbenes, generated from diazo carbonyl precursors, are particularly effective in this regard and have been developed into highly useful methods. Transition metal-free C-H insertions also have attracted attention. Both classifications of C-H insertion are discussed below.
1.4.1. Metal carbene insertion

The ability to form carbenes in the presence of a transition metal was initially reported by Greuter et al. in 1958. In this work, a diazo ketone (1.83) was treated with copper oxide to afford cyclopentanone 1.84, which was the result of a carbene C-H insertion (Scheme 1.31).

This exciting discovery was followed by a number of examples, but synthetic utility and generality of metal carbone insertions were not achieved until the Teyssie group discovered that ethyl diazoacetate, treated with a dirhodium catalyst, gave intermolecular C-H insertion products with alkanes, which exhibited different regioselectivity compared with free, photochemically promoted carbene C-H insertion. For example, intramolecular dirhodium-catalyzed C-H insertion occurs by the formation of 5-membered rings are favored regardless of substitution at the site of insertion, and regardless of the presence of competing methine sites (i.e. Table 1.1, entry 2). Recent advances in intramolecular metal-carbene C-H insertion have accomplished chemo-, regio-, enantio-, and diastereoselectivity through the adjustments of ligand and/or substitution adjacent to the diazo group.
Table 1.1 Rh-catalyzed intramolecular C-H insertion reaction

\[
\begin{align*}
\text{Entry} & & \text{Starting Diazo Ester} & & \text{Product} & & \text{Yield} \\
1 & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{N}_2 \\
\text{C}_7\text{H}_{15}
\end{array} & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{C}_7\text{H}_{15}
\end{array} & & 68 \\
2 & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{N}_2 \\
\text{H}
\end{array} & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{-}
\end{array} & & 55 \\
3 & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{N}_2 \\
\text{H}
\end{array} & & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & & \begin{array}{c}
\text{H}
\end{array} & & 64
\end{align*}
\]

**1.4.2. Transition metal-free C-H insertion**

Transition metal catalysis in chemical synthesis has become ubiquitous due to its high atom economy. Agrochemical and pharmaceutical industries utilize metal-catalyzed reactions despite the costly processes required to remove the residual catalysts in order to comply with the regulations set forth by international bodies. Semiconducting organic polymers are also often synthesized using transition metal catalysts, however the presence of residual metals has a negative impact on the performance of these devices. For these reasons, transition metal-free bond formations are sought after in order to reduce the need for costly purifications.
Davies et al. recently reported a metal-free C-H functionalization of alkanes using carbenes that were thermally generated from aryldiazoacetates (Scheme 1.32).\textsuperscript{77} This was a novel example of a metal-free carbene insertion, though diastereoselectivity was lower compared with its metal-catalyzed counterparts when the reaction could produce diastereomers.\textsuperscript{78}

\[
\begin{align*}
\text{CO}_2\text{R}^2 & \quad \text{N}_2 \\
\text{R}_1 & \quad \text{X} & \quad \text{n} \\
\text{80 °C, 24-48 h} & \quad \text{CO}_2\text{R}^2
\end{align*}
\]

\textit{Scheme 1.32 Metal-free C-H insertion of carbenes}

Maulide, Alfonso, \textit{et al.} discovered a diazo- and transition metal-free insertion reaction that makes use of iodonium ylides (1.86) as carbene precursors (1.87) in place of diazo functional groups (Scheme 1.33).\textsuperscript{79} β-Ketoamides (1.85) were treated with NaH and PhI(OAc)\textsubscript{2} to directly afford a variety of β-lactams (1.88) in good yields.

\[
\begin{align*}
\text{R}_1 & \quad \text{O} & \quad \text{N} & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 & \quad \text{NaH, PhI(OAc)}\textsubscript{2} & \quad \text{THF, 0 °C to rt} \\
\text{1.85} & \quad \text{1.86} & \quad \text{1.87} & \quad \text{1.88}
\end{align*}
\]

\textit{Scheme 1.33 Diazoo- and metal-free carbene C-H insertion}

These examples represent two of many useful C-H insertion reactions that proceed without the need of a transition metal catalyst. We have discovered and
developed another such reaction, which will be described in detail in Chapters 3, 4, and 5.

1.5. Cationic rearrangements

The cationic rearrangements discussed below involve a 1,2 bond shift to a partial positive or fully cationic atom. These sections will survey cationic rearrangements that involve partial-positive oxygen and nitrogen, and carbocations. We recently reported a new rearrangement of carbocations (see Chapters 3, 4, and 5) that exhibit similar rearrangement behavior to known cationic rearrangements such as those described below.

1.5.1. Baeyer-Villiger (1,2-shift onto an oxygen cation)

A variety of ketones can be oxidized to esters (or lactones) in the presence of peroxo acids. The rearrangement proceeds after the peracid adds to the carbonyl to form the peroxy-hemiacetal or “Criegee” intermediate (1.90, Scheme 1.34). The Criegee intermediate undergoes a bond migration with rupture of the O-O bond to provide the ester product (1.91). The bond migration is under stereoelectronic control, called the “primary effect,” which dictates that the migrating group (in this case, R^2) must be antiperiplanar to the O-O bond that is fragmented during the concerted migration step. Typically, free-rotation of the C-OO bond makes it possible for either R^1 or R^2 to migrate. The relative ease that a substituent migrates in these cationic rearrangements is known as “migratory aptitude,” a concept that will be further discussed in section 4.2. The known relative migratory aptitudes of various substituents in the Baeyer-Villiger oxidation has been an inspiration to our efforts in defining relative migratory aptitudes with our cationic rearrangement (discussed in greater detail in Chapter 4).
1.5.2. Beckmann and Stieglitz rearrangements (nitrogen cation)

The Beckmann rearrangement is one of the most common transformations of oximes utilized in organic synthesis.\(^\text{84}\) It is a cationic rearrangement in which the partial-positive charge is generated on a nitrogen atom. Specifically, under acidic conditions the oxime (1.92) is protonated and, upon dehydration, undergoes a concerted 1,2-shift that forms a nitrilium cation intermediate (1.95). Hydration of the nitrilium and tautomerization provides an amide or lactam (1.96, Scheme 1.35). Unlike the Baeyer-Villiger rearrangement, the substituent that migrates in the Beckmann rearrangement 1,2-shift step is predetermined by the stereochemistry of the oxime (1.92) due to the lack of free-rotation about the N=C bond. The bond that is anti- to the N-OH bond will migrate exclusively, unless there is a unique feature to the oxime that causes the 1,2-shift to occur step-wise (for an example, see Scheme 4.8 in section 4.3.5).\(^\text{85}\)
It was widely assumed that the rate-limiting step of the Beckmann rearrangement was the 1,2-shift step (1.94 $\rightarrow$ 1.95), though there remained a lack of experimental evidence to confirm this. A theoretical study by Nguyen et al. postulated that the $N$-protonated isomer (1.93) was more stable and therefore the initially protonated species. The rate-determining step predicted by their calculations was the 1,2-shift of the hydrogen to the oxygen, rather than the previously postulated 1,2-alkyl shift. It was also found that solvent had a strong influence on this step, and the solvent was likely acting as a carrier for the proton during the 1,2-shift.

A different cationic rearrangement onto nitrogen is the Stieglitz rearrangement, in which hydroxylamines are used in place of oximes (Scheme 1.36). Traditionally, this rearrangement was promoted by PCl$_5$, but other modifications used Pb(OAc)$_4$, and Phl(OAc)$_2$ with NaCNBH$_3$ (to afford amine rather than imine).
Unlike the Beckmann rearrangement, the migratory step of the Stieglitz reaction is not predefined according to the hydroxylamine precursor. Therefore, each of the substituents has the potential to migrate. However, nonequivalent substituents might migrate at different rates, or have different migratory aptitudes. For example, Hay and coworkers subjected triarylmethyl amines (1.97) to PCl$_5$ and analyzed the imine products (1.98) of each reaction to determine the migratory ratios (accounting for there being two unsubstituted phenyl rings, Scheme 1.37). When the aryl ring had an electron-withdrawing group (i.e. $X = \text{NO}_2$ or Cl) the product of the unsubstituted phenyl group migration (1.98b) was comparatively higher than the product of the substituted aryl group migration (1.98a). Conversely, when the aryl group had an electron-donating group (i.e. $X = \text{OMe}$), 1.98a was isolated as the major product and 1.98b was minor. Therefore the migratory aptitude of the aryl groups changed depending on electronic substitution.

![Scheme 1.37 Migratory aptitude study of aryl groups in the Stieglitz rearrangement](image)

**1.5.3. Carbocation rearrangements**

In our work we explored vinyl cation reactivity, specifically vinyl cations that undergo a 1,2-rearrangement. Other carbocation rearrangements have been studied extensively.

Pinacol reactions are classified as rearrangements where the cation is generated on a carbon atom prior to the rearrangement step. When a 1,2-diol (i.e. 1.99) is treated
with acid, it is converted to a carbonyl (1.103) via a carbocation that is generated by E1 elimination of water, followed by 1,2-alkyl shift (1.101 \rightarrow 1.102, Scheme 1.38). These rearrangements were an early study of the reactivity of carbocations.

The Tiffeneau-Demjanov ring expansion is a similar rearrangement that proceeds via a carbonium intermediate (i.e. 1.106, Scheme 1.39). The amine moiety of amino alcohols are oxidized by nitrous acid (HNO$_2$) to give diazonium 1.105. The reaction mechanism is often drawn in a concerted fashion in order to bypass an unstable primary cation intermediate (1.106). However, small variations in the reaction conditions change the outcome in terms of product distribution, so it may be that the concerted versus step-wise nature of the migration step is dependent on reaction conditions.
The β-hydroxy-α-diazonium Tiffeneau-Demjanov precursors (1.113, Scheme 1.40) can also be prepared by reacting α-diazoacetates with ketones (1.112) under Lewis acidic conditions, which undergo an in situ ring expansion to provide β-ketoesters (1.114). In this case, the diazo functional group could be prepared ahead of time, which meant that functional groups sensitive to oxidation conditions (i.e. thioether, X = S) were tolerated.
1,2-Migrations of vinyl cations are reasonably well-studied, and are discussed in more detail in section 1.6. Similar to the rearrangements discussed above, the 1,2-shifts are typically associated with forming a more stable cationic intermediate. Similar to the Beckmann rearrangement, vinyl cations (or cations generated from vinyl cations) are tend to be captured intermolecularly. The other rearrangements summarized above culminated in deprotonation of the cation to from the carbonyl or imine products.

### 1.6. Vinyl cations

Vinyl cations are known species in organic synthesis, though previously were rejected as possible intermediates due to a lack of experimental evidence. This empirical deficiency was likely due to the difficulties in generating vinyl cations (Figure 1.8). Vinyl cations were traditionally generated through electrophilic addition to alkynes (A), electrophilic addition to allenes (B), or solvolysis of vinyl halides (C, Figure 1.8). However, it was not until vinyl triflates were used in solvolysis that there was substantial proof of the vinyl cation intermediate. This is thanks to the good leaving group character, but weak nucleophilicity of triflate ions. When vinyl halides were used, it was possible that the halogen ion was recapturing the vinyl cation, thus not providing products that would be indicative of the vinyl cation intermediates.
Figure 1.8 Traditional methods to generate vinyl cations

An early experiment that provided evidence for the existence of vinyl cation intermediates came from the reaction of 3-hexyne with trifluoroacetic acid (Scheme 1.41). If the reaction proceeded by direct addition of activated alkyne 1.116, the trifluoroacetate ion would react to exclusively form (Z)-1.115. However, a mix of E and Z isomers were isolated, which would result from trifluoroacetate reacting with vinyl cation 1.117 from either side.

Schegolev and coworkers reported several examples of vinyl cations that result from the acylation of alkynes (Scheme 1.42). The vinyl cations could rearrange to
form other cations (such as a tertiary cation), or react with functional groups pendant to the vinyl cation, such as C-H insertion (further discussed in section 3.3).

![Scheme 1.42 Acylation of alkynes forms vinyl cations]

Diazonium ions can be vinyl cation precursors. This was first observed after the treatment of 1.118 with nitrosyl chloride (NOCl) resulted in deaminated products 1.122, (E)-1.123, and (Z)-1.123 (Scheme 1.43). The proposed sequence for the formation of vinyl cations shows that the release of nitrogen from diazonium 1.119 drove the vinyl cation formation, followed by a 1,2-phenyl shift, which provided a vinyl cation that could either be deprotonated to form 1.122, or be captured by chloride to form the two isomers of 1.123.

![Scheme 1.43 Vinyl cations generated from deamination of diphenylvinylamine]

More recently, the Padwa and Pellicciari groups have demonstrated that vinyl cations can be generated by subjecting β-hydroxy-α-diazo esters to Lewis acids (Scheme 1.44). They propose that the Lewis acid promotes the elimination of the tertiary alcohol to for the vinyl diazonium 1.125, which then releases nitrogen to form vinyl cation 1.126. That cation was captured in solution, but could also undergo a
rearrangement to provide more stable cations which further reacted to from a variety of products. This strategy to generate vinyl cations avoided oxidation conditions for the generation of the diazonium, and afforded functionally useful products. This reaction will be further discussed in section 3.2, and it in part inspired the Brewer group’s fragmentation reaction (section 1.2.1, 1.3.2.3, 2.1) and our recently discovered rearrangement/C-H insertion reaction (Chapters 3, 4, and 5).

Scheme 1.44 Vinyl diazonium and vinyl cations generated from β-hydroxy-α-diazo esters

Vinyl cations can undergo rearrangements in order to form a more stable vinyl cation or carbocation of another class. Of the examples of vinyl cation rearrangements discussed above, those reported by Schegolev and Pellicciari, in fact, could undergo a number of rearrangements following the formation of the initial vinyl cation, which is not uncommon for cationic intermediates.97

Figure 1.9 Migration across vinyl cation

Hydride, methyl, alkyl, aryl, and heteroatoms can shift across the double bond of a vinyl cation (Figure 1.9).97 Our discovery and development of the rearrangement/C-H insertion of vinyl cations included a study into the relative ease of methyl, alkyl, and aryl
groups to migrate across vinyl cations that were generated from diazo ketone precursors (results discussed in Chapter 4).

1.7. Cyclopentenones

Enones are powerful synthons in total synthesis due to the diversity of ways to further functionalize them. These include 1,2-addition, 1,4-addition, allylic functionalization, and carbonyl functionalization. Cyclopentenones are present in several important biologically active molecules (Figure 1.10). Monocyclic cyclopentenones are key motifs in prostaglandin and prostanoid compounds (i.e. PGB₂, Figure 1.10), while bicyclic and polycyclic cyclopentenones are common motifs found in other products isolated from nature (i.e. didemnenones and ianostanoid).

![Figure 1.10 Sample of biologically active cyclopentenone compounds](image)

The Pauson-Khand reaction is a powerful method for the synthesis of cyclopentenones (1.132 and 1.133). The reaction proceeds through a formal [2+2+1] cycloaddition of an alkyne (1.130), alkene (1.131), and CO (Scheme 1.45). Originally, a stoichiometric quantity of Co₂(CO)₈ was used, but recent advances have employed catalytic quantities of metal catalyst under an atmosphere of CO. The transformation is functional group tolerant, an assortment of metal catalysts are suitable (including
palladium\textsuperscript{106} nickel, iridium\textsuperscript{107} rhodium\textsuperscript{108} etc.) and enantioselective variations have been reported\textsuperscript{105, 108, 109}.

\[
\text{Scheme 1.45 Pauson-Khand method for the synthesis of cyclopentenones}
\]

1,6-Enynes (1.134) are precursors to intramolecular Pauson-Khand reactions that produce bicyclic cyclopentenones (1.135), where the rings are fused at the $\beta,\gamma$-bond (Figure 1.11). When chiral ligands are used with the metal catalyst, this reaction can proceed enantioselectively\textsuperscript{108}.

\[
\text{Scheme 1.46 Bicyclic cyclopentenone not accessible by Pauson-Khand}
\]

One pitfall of the Pauson-Khand reaction is the need for alkyne precursors, which can preclude some target substrates. For example, if the target bicyclic cyclopentenone had $\alpha,\beta$-unsaturation where the two rings were fused, the alkyne precursor would need to be a cyclic alkyne, which are either unstable reagents, or do not exist (Scheme 1.46).
Lewis acid, which results in a mixture of clockwise and counterclockwise rotation and (depending of substituents) a mixture of deprotonation regioisomers (1.139 and 1.140, Scheme 1.47).

Scheme 1.47 Acid-catalyzed Nazarov cyclization

Recent developments with the Nazarov cyclization have included the use of catalytic quantities of promoters, enhanced regioselectivity of alkene formation by adjusting substitution of the divinyl ketone precursor, and improvements to enantioselectivity through the use of chiral promoters. For example, a β-silyl group can direct the alkene formation once cation 1.143 is generated if conditions promote desilylation faster than deprotonation (Scheme 1.48). Other β-substituents, such as an ester, can make the geminal β-proton more acidic to promote a regioselective alkene formation.
The general improvements to catalytic and asymmetric organic chemistry has contributed to improvements to the Nazarov cyclization. For example, a chiral copper-NHC complex catalyzed the regio-, diastereo- and enantioselective Nazarov cyclization of indole β-ketoesters (1.146) to provide tricyclic products in high yields (1.147, Scheme 1.49).110

One drawback of the Nazarov cyclization is that, due to the unsaturation of the divinyl precursors, α,α-disubstituted cyclopentenones cannot be prepared directly (i.e. where R1 and R2 are geminal, Scheme 1.50).
Our work on the rearrangement and C-H insertion of vinyl cations prepares cyclopentenones that are not directly accessible by Pauson-Khand or Nazarov cyclization (see Scheme 1.46 and Scheme 1.50). See Chapters 3 and 4 for substrate scope and proposed mechanism.

1.8. γ-Lactones

γ-Lactone, lactones made up of a 5-membered ring, are abundant motifs in bioactive compounds found in nature (Figure 1.12). γ-Butyrolactone, structurally the simplest γ-lactone, is a prodrug for the neurotransmitter and psychoactive γ-hydroxybutyric acid.\(^{111,112}\) L-Ascorbic acid, or vitamin C, is an essential nutrient in the human diet and acts as an enzyme cofactor and an antioxidant.\(^{113}\) Spironolactone, which is structurally related to 17α-hydroxyprogesterone and aldosterone, has aldosterone-blocking activity, therefore can be used to treat high blood pressure and edema, and is used in feminizing hormone therapy for transgender women. The presence of the γ-lactone moiety in place of a hydroxyl group at C17 increases the oral bioavailability and potency of spironolactone compared with hydroxyprogesterone.\(^{114}\)
A particularly potent sensitizer found in plants is the class of α-methylene-γ-butyrolactones (i.e. alantolactone, Figure 1.12). These natural products act as Michael acceptors to 1,4-attack from –SH or –NH₂ groups present in proteins (i.e. cysteine and lysine).¹¹⁵ In effect, alantolactone forms a covalent hapten-protein complex when reacted with a nucleophilic amino acid residue. This elicits the allergic sensitivity. Beyond their allergenic capabilities, α-methylene-γ-butyrolactone-containing compounds have exhibited antitumoral, cytotoxic, antimicrobial, and phytotoxic activities.¹¹⁶

1.8.1. Synthesis of γ-lactones

One obvious way to synthesize γ-lactones is via intramolecular O-acylation of γ-hydroxyl carboxylic acids (i.e. γ-butyrolactone from γ-hydroxybutyric acid, Figure 1.13). In order to increase complexity of possible γ-lactones that can be synthesized, new approaches have been developed.

Due to their potential to enhance pharmacological activity, and their diverse bioactivities, the synthesis of γ-lactones has been pursued by chemists and biologists alike. There is a truly numerous and diverse array of existing methods for the synthesis of γ-lactones. Thus, this section will focus on the summary of prior synthetic methods that prepared bicyclic γ-lactones intramolecularly.

Many of the modern methods for the synthesis of γ-lactones actually targeted the highly prevalent α-methylene-β-butyrolactones (i.e. alantolactone, Figure 1.12 and 1.151, Scheme 1.51).¹¹⁷ For example, Taylor and coworkers have developed a one-pot Michael
addition/Horner-Wadsworth-Emmons (HWE) olefination method for the preparation of bicyclic $\alpha$-methylene-$\beta$-butyrolactones.\textsuperscript{118} Deprotonation of the phosphonoacetate 1.148 initiated the intramolecular Michael addition to afford adduct 1.149, which underwent proton transfer to provide phosphonate anion 1.150. Addition of an aldehyde initiated the HWE olefination to provide the methylene lactones (1.151).

![Scheme 1.51 α-Methylene-β-butyrolactones via Michael addition/HWE](image)

Nicolaou and coworkers developed a phenylselenolactonization method which provided a number of bicyclic $\gamma$-lactones in good yields (Scheme 1.52).\textsuperscript{119} The reactive phenylselenium ion (1.153) was generated from the reaction of alkene 1.152 with PhSeCl, which the tethered carboxylic acid opened via nucleophilic substitution to form bicycle 1.154. Oxidation and elimination of the phenylselenium provided $\alpha,\beta$-unsaturated lactone 1.155 in 79% yield over two steps.
Finally, bicyclic \( \gamma \)-lactones can be prepared by rhodium carbene C-H insertion. For example, Shie and coworkers reported the diastereoselective formation of bicyclic lactone 1.157 from the treatment of \( \alpha \)-phosphoryl-\( \alpha \)-diazoacetate precursor 1.156 with rhodium dimer (Scheme 1.53).\(^\text{120}\) A number of other bicyclic lactones were also prepared, though none in high yield.

\[ \begin{align*}
\text{Scheme 1.53 Bicyclic } \gamma \text{-lactones via rhodium carbene insertion}
\end{align*} \]

\[ \begin{align*}
\text{1.156} & \quad \text{Rh}_2(OAc)_4 \quad (5 \text{ mol\%}) \quad 40\% \text{ yield} \quad 91:9 \ X/X' \\
\text{1.157} & \quad \text{1.157}'
\end{align*} \]

\[ \begin{align*}
\gamma \text{-Lactams}
\end{align*} \]

\( \gamma \)-Lactams are core structures in a large number of natural and unnatural biologically active compounds. These 2-pyrrolidinone products are derived from \( \gamma \)-amino acids, the most simple of which is \textit{gamma} -aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the mammalian central nervous system (Figure 1.14).\(^\text{121}\)
Many γ-lactams isolated from nature exhibit additional neurological activities. For example, erysothramidine 2 demonstrates anticonvulsive, sedative, and hypnotic properties in addition to acting as a neuromuscular blocking agent. (−)-Clausenamide has shown the ability to enhance synaptic transmission, which improved memory and learning capacities in amnesia animal models (Figure 1.15). It is also an antidementia candidate for this reason. Only the (−)-enantiomer is biologically active, but clausenamide is isolated as a racemic mixture from its plant source, which highlights the importance of finding enantioselective methods to synthesize these γ-lactam motifs.

γ-Lactam compounds have found pharmacological use outside of the neurological field. Other known activities include antimalarial, cytotoxic, chemotherapeutic, vasoconstriction/vasodilation, anti-inflammatory, and antifungal. One of the most essential uses of γ-lactam products are as antibiotics.

1.9.1. γ-Lactams as β-lactam antibiotic alternatives

Particular interest in γ-lactam products began with the observation of a increase in bacterial resistance toward traditional β-lactam antibiotics (Figure 1.16). Derivatives
of β-lactam antibiotics have proven broad spectrum activities which has contributed to their extended use over the years. However, prolonged exposure to β-lactam antimicrobials has the consequence of hyperproduction of β-lactamases within the targeted bacterial species, which renders the 4-membered lactam antibiotic ineffective.\textsuperscript{126-128} Carbapenems, a class of β-lactam antibiotics that are reserved for suspected multidrug-resistant bacteria, are more robust to common mechanisms of antibiotic resistance.\textsuperscript{129} However, in the last decade, a new metallo-β-lactamase has emerged in bacteria, which has caused a drug resistance to carbapenem antibiotics.\textsuperscript{130}

![Diagram of β-lactam antibiotics](image)

**Figure 1.16 Classic examples of β-lactam antibiotics**

Because the primary mechanism for multidrug resistance hinges on the hydrolysis of the 4-membered ring drug core via a β-lactamase, γ-lactams have recently been targeted as alternatives to classical antibiotics. γ-Lactam antibiotics were designated as a possible solution to overcoming the β-lactamase problem because the essential source of biological activity of β-lactam antibiotics comes from the activated amide bond, not the 4-membered ring.\textsuperscript{125} For this reason, there is a growing interest in developing new methods for the synthesis of γ-lactams.

### 1.9.2. Existing methods for intramolecular γ-lactam synthesis

The literature offers an array of methods for the synthesis of γ-lactams. These include intramolecular N-alkylation of amides (i.e. Scheme 1.54), intramolecular
cyclization via amide bond formation, intramolecular hydroamination,\textsuperscript{131} intramolecular reductive amination,\textsuperscript{133} [4+1] or [3+2] annulation reaction, and oxidation of pyrrolidines (i.e. Scheme 1.55).\textsuperscript{134} The methods summarized below cover both classical and modern techniques, and are only a small glimpse into the numerous efforts that have gone into preparing $\gamma$-lactams.

Nicolaou has developed an IBX-mediated cyclization of aryl carbamoyl alkenes (1.158) that leads to lactams.\textsuperscript{131} This mechanism was also extended to the synthesis of fused and bridged bicyclic $\gamma$-lactams (i.e. 1.159, Scheme 1.54).

An example of the synthesis of a spirocyclic $\gamma$-lactam was implemented by Shu et al. in which homopropargyl amide 1.160 was treated with a gold catalyst followed by $m$-CPBA to provide bicycle 1.161 (Scheme 1.55).\textsuperscript{134}

Alcaide and coworkers have developed a stereoselective, ring expansion method for the synthesis of highly functionalized mono- and bicyclic $\gamma$-lactams. Azide 1.163 was synthesized diastereospecifically from known $\beta$-lactam 1.162 in three steps (Scheme 1.56).\textsuperscript{135,136} The azide was then treated with PPh$_3$ under Staudinger-like conditions, but
rather than isolating amine 1.164, the *in situ*-generated iminophosphorane 1.165 acted as a nucleophile to the methyl ester to form \( \gamma \)-lactam 1.166, which upon hydrolysis gave \( \gamma \)-lactam 1.167. Typical yields of the ring expansion step were 51-60%.

The literature is rich with examples of the use of diazo amides as precursors to metal carbene intermediates, which can lead to \( \gamma \)-lactams after intramolecular C-H insertion (1.166, Scheme 1.57). However, existing examples were not general in their selectivity for \( \gamma \)-lactam formation (1.167 and 1.168) over \( \beta \)-lactams (1.169), and required optimization of the rhodium catalysts in order to increase selectivity. Additionally, many examples required that an electron withdrawing group be alpha- to the diazo (\( X = \text{EWG} \)) to promote reactivity, further reducing the generality of this reaction. Chapter 5 summarizes our effort to prepare bicyclic \( \gamma \)-lactams using diazo amide precursors, which we proposed would overcome the \( \beta \)-lactam selectivity issue.
1.10. **Computational organic chemistry**

Progress in speed and capacity of computers has allowed computational chemists to develop increasingly accurate solutions to the Schrödinger equation, which explains why computational chemistry has interacted with nearly every other division of chemistry.\(^{141}\) Recently, experimental and theoretical chemists have frequently formed complementary partnerships in order to gain a more complete picture of chemical problems that otherwise might not have been solved.\(^{142}\) A common example of this is the teaming up of synthetic organic chemists with computational organic chemists, who together have provided detailed insight into reaction mechanisms that were previously obscure.

The caveat remains that computational data can, at times, fail to explain experimental data. In these cases, the computational chemist must reexamine and/or adjust the methods used for the predictions.\(^{143,144}\) Therefore, these partnerships are often not only complimentary, but also necessarily cooperative. Since computational modeling may not always provide the full picture of what happens empirically, it is vital to pair the two approaches for the sake of accuracy.

**1.10.1. Reaction mechanism elucidation**

Reaction mechanisms that proceed via a single step can often be elucidated using experimental data (i.e. solvent effects, substituent effects, kinetic isotope effects, etc.).
For more complicated reaction mechanisms, such as those that proceed through multiple steps, experimental data might only provide insight into the rate-limiting step. Fortunately, computational methods have enabled chemists to model reaction mechanisms in great detail.

In terms of defining a reaction mechanism, it is typically the job of the organic chemist to propose hypothetical intermediates and transition state structures that best fit the experimental results. Computational chemists can then enter the molecular structures of the intermediates and transition states into a program (i.e. Gaussian, Schrödinger, etc) which will run optimization (minimization) calculations on each structure using an indicated functional and basis set. After each compound structure is optimized to the minimized conformation, the single-point energies are calculated for each and compared. The first structure is typically set to (a relative) 0.0 kcal/mol, and the following intermediates and transition states are compared relative to that. Analysis of the single point energies can help elucidate what factors might influence a reaction fate.

1.10.1.1. Consideration of computational results and product ratios

There are many ways to marry experimental and computational organic chemistry in order to elucidate reaction mechanisms. Experiments are sometimes designed in order to verify computational data, but computational methods are often employed after empirical results raise questions.

For example, our group has previously partnered with computational chemistry groups in order to answer mechanistic questions that arose from examination of the products isolated from reactions. Specifically, cationic 1-aza-2-azoniaallene salts \textbf{1.170} and \textbf{1.173} react intramolecularly via distinct mechanistic pathways that lead to two
classes of N-containing heterocycles (1.172 and 1.174, Scheme 1.58). The variation of the alkene ring size resulted in differing products upon treatment with AlCl₃.

\[ \text{Allylic C-H insertion} \]

\[
\begin{align*}
\text{Ph}_2N=\text{N} & \quad \text{Cl} \\
\text{1.170} & \\
\text{i) } & \text{AlCl₃} \quad -60°C \\
\text{ii)} & \text{warm to rt} \\
\text{iii)} & \text{Et₃N} \\
& \text{69% yield}
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_2N & \quad \text{N} \\
\text{N} & \quad \text{Cl} \\
\text{1.171} & \\
\text{1.172}
\end{align*}
\]

\[ \text{Alkene chloroamination} \]

\[
\begin{align*}
\text{Ph}_2N=\text{N} & \quad \text{Cl} \\
\text{1.173} & \\
\text{i) } & \text{AlCl₃} \quad -60°C \\
\text{ii)} & \text{warm to rt} \\
\text{iii)} & \text{Et₃N} \\
& \text{84% yield}
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_2N & \quad \text{N} \\
\text{N} & \quad \text{Cl} \\
\text{1.174} & \\
\text{1.175}
\end{align*}
\]

Scheme 1.58 Chemoselectivity of intramolecular reactions of 1-aza-2-azoniaallenes

Computationally predicted activation enthalpies and free energies helped explain how ring size affected the difference in products. The calculations indicated that the cyclopentene derivate (1.171) formed the product of allylic C-H insertion (1.172 via 1.176) through a transition state (TS 1.1) that had a free energy of 0.9 kcal/mol less than the transition state of the competing pathway (TS 1.2, Figure 1.17 top). The lower TS energy of TS 1.1 was due to distortion in the system caused by the 5-membered ring.
Figure 1.17 Gibb’s free energy barriers of C-H insertion versus chloroamination pathways

Conversely, the cyclohexene derivative (1.174) underwent the chloroamination pathway more readily because the insertion transition state (TS 1.4) was 4.0 kcal/mol less in energy compared with the transition state (TS 1.3) did not benefit from distortion and was thus higher in energy (Figure 1.17 bottom). In this example, the use of
computational methods provided a rational for the disparate reactivity and helped verify the nitrenium-like character of the 1-aza-2-azoniaallene salts. This is exhibited in the (2+1) sequence that leads to aziridinium 1.179 in the chloroamination pathway.
CHAPTER 2 : PROGRESS TOWARD THE DIVERGENT SYNTHESIS OF
MEDIUM-SIZE RING NATURAL PRODUCTS VIA A RING
FRAGMENTATION METHOD

2.1. Introduction

Small molecule natural products and their analogs are often targeted as therapeutic agents (i.e. Taxol®, rapamycin, and Zocor®). The natural products themselves are not always the optimal structure to produce a biological activity, therefore they are often modified to both enhance the inherent structural features that produce the effect and remove moieties that are unnecessary (or even deleterious). One way researchers can expedite the process of synthesizing a library of analogs for testing is through the use of “diversity-oriented synthesis” or divergent synthesis, which puts together simple building blocks to form an advanced “common” intermediate that is then further derivatized in differing ways depending on the target analogs (Figure 2.1).

![Figure 2.1 Divergent total synthesis or “diversity-oriented synthesis”](image)

During his time in the Brewer group, Ali Bayir developed a new ring fragmentation method for the synthesis of medium-sized ynolides (2.2) using bicyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo lactone precursors (2.1, Scheme 2.1 top). We set out to expand upon Ali’s work by applying this ring fragmentation approach to the divergent
synthesis of a set of structurally similar, 10-membered lactone natural products that are related to each other by the placement of a methyl group at the C5 position. In addition, we targeted a 10-carbon chain fatty acid natural product that could result from the hydrolysis of an analog of the lactone natural products.

### Previous work

![Chemical structure 2.1](image)

**Scheme 2.1** Ring fragmentation approach to 10-membered ynolides

### 2.2. Background information on the target compounds

Our target compounds can be differentiated by the oxidation state at the β-position, where phoracantholide I, fusanolide A, and ieodomycin D are hydrocarbons, while diplodialides A and C and curvularin contain a third oxygen (Scheme 2.2). Despite their structural differences, we proposed that these natural products could be prepared from a common ynolide intermediate (2.6, Scheme 2.2). We envisioned that the alkyne functional group could be hydrogenated to provide phoracantholide I, or isomerized to provide fusanolide A and a precursor for ieodomycin D. We also proposed that oxidation
of the alkyne to provide ketone 2.7 would complete the formal synthesis of curvularin and diplodialide A.\textsuperscript{152, 153} Finally, reduction of ketone 2.7 would afford diplodialide C.

There are various examples of prior methods used to synthesize these natural products, many of which rely on a macrolactonization method (see Chapter 1.3.2.1 for discussion). However, this number of products have not been prepared from the derivatization of one common intermediate prior to this work, perhaps because prior syntheses were target-oriented syntheses.

The placement of the alkyne group in our proposed common intermediate 2.6 is the key in our divergent strategy. It unlocks the possibility of oxidation to a ketone (2.7), which is a known intermediate in prior syntheses of some of the products.\textsuperscript{152, 153} Considering the bioactivities of these compounds, and the fact that divergent total...
synthesis has emerged as a way to streamline the construction of a library of compounds, I set out to prepare the structurally-related natural products from ynolide 2.6.

2.2.1. (±)-Phoracantholide I

Phoracantholide I was first isolated from a secretion by the Australian insect named *Phoracantha synonyma*. While the biological or medicinal activity of this product has not been reported, it has been synthesized at least 74 times according to a Reaxys. The appeal for chemists to synthesize the product likely stems from its structural simplicity, and the challenging nature of preparing 10-membered rings. Selected examples of prior syntheses of phoracantholide I are provided below, the majority of which utilized a macrolactonization as the key step.

2.2.1.1. (±)-Phoracantholide I via lactonization

Bartra and Vilarrasa used carboxylic acid 2.8 as a model substrate in their investigation into the optimal lactonization conditions for synthesis of phoracantholide I in which they surveyed common lactonization conditions at that time. Table 2.1 shows that of the conditions screened when \( X = \text{OH} \), Gerlach’s modification of the Corey-Nicolaou approach (entry 1) prevailed over the Corey-Brunelle (entry 3), Steglich (entry 4), and Mitsunobu (entry 5) methods. They also explored the use of \( S_N2 \)-type esterification (entries 6-7). Alkylbromides in DMSO were ideal, as they were highly reactive toward the substitution reaction without promoting the competing elimination reaction. The authors propose that the irreversible nature of these reactions are favorable compared with entries 1-5 which proceed via a reversible attack of the hydroxyl to the activated carbonyl.
Table 2.1 Optimization of phoracantholide I via intramolecular lactonization

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Activation Reagent</th>
<th>Additive</th>
<th>Yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>PySSPy/PPh₃</td>
<td>AgClO₄</td>
<td>50 (25)</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>PySSPy/PPh₃</td>
<td>DMAP</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>ImSSIm/PPh₃</td>
<td>- -</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>DCC</td>
<td>DMAP/TFA</td>
<td>10 (15)</td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td>PPh₃/DEAD</td>
<td>- -</td>
<td>0 (0)</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>- -</td>
<td>Cs₂CO₃</td>
<td>40 (5)</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>- -</td>
<td>K₂CO₃</td>
<td>55 (10)</td>
</tr>
</tbody>
</table>

Recently, (−)- and (+)-phoracantholide I were each synthesized from the same carboxylic acid precursor (2.9) using the Yamaguchi and Mitsunobu esterifications to prepare 2.10 and 2.11, respectively (Scheme 2.3).¹⁵⁵ Hydrogenation provided both enantiomers of phoracantholide I in good yields. This is an example of a synthetic strategy that provided both enantiomers of a natural product from a common, late stage intermediate. In the general sense, similar to divergent total synthesis, it is useful to prepare both enantiomers from a common intermediate in order to streamline testing in biological assays.

Scheme 2.3 Divergent syntheses of (−)- and (+)-phoracantholide I via esterification methods
It is worth noting that each of the conditions summarized in Table 2.1 and Scheme 2.3 required high dilution (up to 155 mL/mmole) to suppress formation of dimer side products, which is a common limitation to classic lactonization methods.

### 2.2.1.2. Grob-type fragmentation approach to (−)-phoracantholide I

Sakai and coworkers reported a Grob fragmentation method for the stereocontrolled synthesis of (−)-phoracantholide I (Scheme 2.4).\textsuperscript{156} The chiral building block 2.12 was converted to acetal 2.13 over 5 steps, which upon treatment with mesyl chloride underwent the Grob-type fragmentation to provide the 10-membered ynone intermediate (2.15). Five additional steps to remove the alcohol and ethylidene provided (−)-phoracantholide I. The good yield in the key fragmentation step sets a promising precedence for applying our Grob-type fragmentation in the synthesis of phoracantholide I and similar natural products.

![Scheme 2.4 Grob fragmentation to access ynone intermediate 2.15](image)

### 2.2.1.3. Baeyer-Villiger oxidation to prepare (−)-phoracantholide I

One of the earliest methods for asymmetric synthesis of phoracantholide I was the use of a Baeyer-Villiger oxidation, as reported by the Enders group (Scheme 2.5).\textsuperscript{157} Cyclononone, prepared using an intricate photochemical method,\textsuperscript{158} was converted to a
chiral hydrazone, which allowed them to install the methyl group stereoselectively. The hydrazone was converted back to the ketone using ozone, which provided chiral ketone 2.16. Treatment with \textit{m}-CPBA provided (-)-phoracantholide I as the Baeyer-Villiger oxidation product in good yield.

Going from a 9- to a 10-membered ring, it seems likely that the entropic cost typically associated with forming medium-sized rings was already paid in the preparation of cyclononone (see 1.3 for discussion of medium-size ring preparation and challenges).

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (a) at (0,0) {\includegraphics[width=0.6\textwidth]{example.png}};
  \node[anchor=west] at (a.east) {\small Scheme 2.5 Baeyer-Villiger oxidation to prepare (-)-phoracantholide I};
\end{tikzpicture}
\end{center}

2.2.2. (±)-Diplodialides A and C

The isolation and bioactivities of diplodialies A and C are discussed in section 1.3.1. This class of 10-membered lactones has been prepared using a diverse range of methods, including macrolactonization. More recently, ring-closing metathesis (RCM) has been used for the preparation of diplodialides A and C, a method that was not available at the time of the products’ discovery. A sample of prior syntheses of diplodialides A and C are summarized below.

2.2.2.1. (±)-Diplodialide A via macrolactonization

Ishida and Wada reported the initial isolation\textsuperscript{53} and the first total synthesis of diplodialide A (Scheme 2.6).\textsuperscript{159} They began with a linear δ-keto ester 2.17 which was converted to thioester 2.18 in 8 steps. Refluxing 2.18 in xylene promoted the Corey-Nicolaou lactonization, where the alcohol attacked at the activated carbonyl, to afford
2.19 (see section 1.3.2.1 for more detail). The thioketal was converted back to a ketone using \(N\)-bromosuccinimide (NBS) in aqueous acetone, which subsequently was \(\gamma\)-selenated in 38% yield. Oxidation and elimination of phenylselenide 2.20 using sodium periodiate provided the desired \(\alpha,\beta\)-unsaturated natural product in 30% yield.

![Scheme 2.6 First reported total synthesis of (±)-diplodialide A](image)

The group later reported an improved method for the oxidation and elimination of the phenylselenide using 3% aq. \(\text{H}_2\text{O}_2\), which provided diplodialide A in 60% yield from 2.20. These initial total syntheses were not high yielding or concise, but considering the time it was published, the Wada group made good use of the methods available at that point.

2.2.2.2. Oxidative fragmentation access to (±)-phoracantholide, a precursor to (±)-diplodialides A and C

Wakamatsu and coworkers used phoracantholide I as a precursor to the synthesis of diplodialides A and C. They first prepared phoracantholide I by an oxidative fragmentation of bicyclic glycol 2.22 to afford \(\delta\)-keto ester 2.23 in a quantitative yield (Scheme 2.7). This yield is particularly impressive due to the fact that synthesis of
medium-size rings is not typically high yielding. The ketone was converted to a thio-ketal and subsequently desulfurized using Raney-nickel to provide phoracantholide I.

\[ \text{Phoracantholide I via oxidative fragmentation} \]

With phoracantholide I in hand, oxoselenium elimination was employed to afford \(\alpha,\beta\)-unsaturated lactone \(2.24\), which was epoxidized using \(m\)-CPBA and a catalytic amount of santonox\(^\circledR\) which provided a 2:1 mix of cis/trans diastereomers (Scheme 2.8). Each isomer was reduced using Birch conditions to afford diplodialide C and its epimer in acceptable yields.

\[ \text{Scheme 2.8 Diplodialide C and its epimer via oxidation of phoracantholide I} \]

Alkene \(2.24\) was also an important intermediate in the synthesis of diplodialide A (Scheme 2.9). Rather than isolating the epoxidation and reduction compounds, alkene
was carried forward to ketone 2.7 after the epoxidation, reduction, then Sarett oxidation. The oxidation of ketone 2.24 to diplodialide A was not trivial, but was accomplished after 6 transformations. Thus a divergent strategy was used for the synthesis of diplodialides A and C where phoracantholide I was the common intermediate and the building blocks were diol 2.22 and 3-hydroxy-1-iodobutane (Scheme 2.7).

![Scheme 2.9 Diplodialide A from β-ketolactone 2.7](image)

The synthesis of diplodialides C and A from common precursor 2.24 (prepared from phoracantholide I) follows the philosophy of divergent synthesis of natural products. In this case, the divergent synthesis began with simple building blocks (2.21 and 3-hydroxy-1-iodobutane) to form a key “common” intermediate (2.22) and subsequent derivatization provided the targeted products.

2.2.2.3. Formal synthesis of (+)-diplodialide A via ring-closing metathesis

Anand et al. implemented a RCM approach for the formal synthesis of (+)-diplodialide A (Scheme 2.10).\(^{161}\) Diene 2.26, which was prepared in 4 steps, was subjected to Grubb’s second generation catalyst (II) to give a 2:1 ratio of the cis/trans isomers of decanolide 2.27, which was subsequently hydrogenated. Deprotection of the ketal moiety was catalyzed by \(p\)-TsOH to give β-keto lactone 2.7. The synthesis of (+)-diplodialide A from 2.7 was reported by Wada (see above, Chapter 2.2.2)\(^{160}\) and Wakamatsu et al (Scheme 2.9).\(^{152}\)
2.2.2.4. Stereoselective synthesis of (+)-diplodialides B and C and formal synthesis of (+)-diplodialide A by RCM

Sharma and coworkers reported a ring-closing metathesis method for the synthesis of diplodialides A, B, and C. Their method differed from that which was reported by Anand et al. by the location of the resulting olefin after RCM, which directly provided (+)-diplodialide B. The methyl and hydroxyl stereocenters were set using known epoxides 2.28 and 2.30, which were further derivatized to alcohol 2.29 and carboxylic acid 2.31, respectively. Yamaguchi esterification using 2.29 and 2.31 followed by desilylation provided diene 2.32.

Scheme 2.10 Synthesis of (+)-diplodialide A via RCM

Scheme 2.11 Synthesis of diene precursor to RCM
The diene was treated with a stoichiometric quantity of Grubb’s first generation catalyst (I) under high dilution conditions to provide (+)-diplodialide B along with the cis-isomer (2.33, Scheme 2.12). (+)-Diplodialide B is a known precursor in the synthesis of (+)-diplodialide A, thus the formal total synthesis of A was complete.\(^{162}\) (+)-Diplodialide C was then prepared by hydrogenation of B.

![Scheme 2.12 Grubb’s RCM to provide (+)-diplodialides A, B, and C](image)

While this work required several steps, and the key cyclization step required high dilution and a stoichiometric quantity of the promoter, it was another example of a divergent-type synthetic strategy, where (+)-diplodialide B was a common intermediate in the synthesis of A and C.

### 2.2.3. (−)-Curvularin

First isolated from the mold *Penicillium gilmanii*, (−)-curvularin has exhibited a number of biological activities, namely antifungal and phytotoxic.\(^{163}\) While not a member of the 10-membered lactone class of natural products targeted in this work, (−)-
curvularin has been synthesized from a 10-membered lactone intermediate that we propose is accessible from our key intermediate 2.6 (see Scheme 2.14).

2.2.3.1. \((−)-\text{Curvularin via benzannulation of } (−)-\text{diploidialide C derivative}\)

Stoltz and coworkers previously developed a methodology that acyl-alkylated aryne intermediates (2.37) using \(\beta\)-ketoesters (2.35) to form bicyclic products (2.36, Scheme 2.13).\(^{164}\)

\[
\begin{align*}
\text{Scheme 2.13 Stoltz benzannulation of } \beta\text{-ketolactones} \\
2.34 + 2.35 & \xrightarrow{\text{CsF}} 2.36, \text{50-69\% yield} \\
\begin{bmatrix}
\text{2.37} + \text{2.38} & \xrightarrow{\text{Cs}^+} \text{2.39}
\end{bmatrix}
\end{align*}
\]

This methodology inspired the group to prepare \((−)\)-curvularin from 1,3-benzenediol 2.42 and ketone 2.7. The authors noted that \((−)\)-diploidialide C and its epimer (2.41) had the potential to be a precursor to ketone 2.7, and thus set out to prepare both natural products (Scheme 2.14).\(^{153}\)
Diene 2.40 was prepared in one step from known compounds, and was subjected to a one-pot silylation/RCM/desilylation using HMDS, Hoveyda-Grubb’s 3rd generation catalyst (H-G III) and HCl which provided (−)-dipodialide C and epi-(−)-dipodialide C (2.41). Both diastereomers were hydrogenated, and subjected to Dess-Martin oxidation conditions to afford ketone 2.7. The benzyne chemistry was then implemented using CsF to prepare the 12-membered lactone, which was then deprotected to give (−)-curvularin in 6 steps from known starting material.

2.2.4. Ieodomycin D

In 2011, Shin and coworkers isolated and characterized antimicrobial fatty acids from marine Bacillus species 09ID194, one of which was ieodomycin D. This fatty acid is composed of a 10-carbon chain, and the acid and alcohol are positioned such that we propose it can be synthesized from a 10-membered ynolide (i.e. 2.6) by saponification.
The existing total syntheses of this natural product, unlike the other examples discussed, do not suffer the drawbacks that accompany most medium-sized rings thanks to its acyclic structure. Ieodomycin D has never been synthesized via a macrocyclic intermediate, likely due to the challenges associated with synthesizing 10-membered rings. However, we were interested in including this product in our library of compounds targeted in our divergent synthetic strategy. Cyclic compounds tend to be better ligands in protein binding compared with their “floppy” linear counterparts. Therefore, from a biological assay perspective, it would be pertinent to have the capability of preparing a linear counterpart to our 10-membered ring natural products for a protein-binding comparison.

2.2.4.1. Total synthesis of ieodomycin D from alkyne zipper reaction/isomerization and by Suzuki cross coupling

The first reported total synthesis of this bioactive natural product was completed by Venkateswarlu et al. Their synthetic plan took advantage of the reactivity of terminal alkynes, and utilized the known isomerization of ynoates to diene esters (Scheme 2.15). They prepared alkyne 2.43 in two steps from racemic methyloxirane, and subjected the compound to base-mediated alkyne zipper conditions, which converted the internal alkyne to its terminal counterpart (2.44). Treatment of alkyne 2.44 with n-BuLi and methyl chloroformate provided ynoate 2.45, which was subjected to alkyne isomerization conditions to give diene ester 2.46. Finally, hydrolysis and deprotection with refluxing KOH provided ieodomycin D.
More recently, Vik and coworkers reported the stereoselective total synthesis of eodomycin D via a Suzuki-Miyaura cross-coupling between vinyl bromide 2.48 and boron compound 2.50. The preparation of vinyl bromide 2.48 began with the known conversion of pyridinium sulfonate to glutaconaldehyde potassium salt 2.47 (Scheme 2.16, top). The aldehyde 2.47 was converted to a methyl ester, and the hydroxy potassium salt to a vinyl bromide in 3 subsequent steps.

The boron coupling partner (2.50) was prepared by silylation of commercially available alcohol 2.49, then hydroboronation of the alkene using 9-BBN-H gave 2.50 (Scheme 2.16, bottom). The palladium-catalyzed Suzuki reaction was carried out between vinyl bromide 2.48 and alkylboron compound 2.50 to provide the 10-carbon chain intermediate (2.46), which was deprotected and hydrolyzed to afford eodomycin D in 7 sequential steps.
2.3. Synthesis of fragmentation precursor: bicyclic γ-silyloxy-β-hydroxy-α-diazo lactone 2.4

For the divergent total and formal syntheses of the 10-carbon-containing natural products, ynolide 2.6 was identified as a potential key “common” intermediate (Scheme 2.17).

The synthetic strategy for the synthesis of the construction of the 10-membered ring common intermediate, ynolide 2.6, was based on Bayir and Brewer’s synthesis of ynolides via ring fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazo lactones. We postulated that ynolide 2.6 could be obtained by the deoxygenation of ketone 2.5, which...
we predicted would be the major product of the fragmentation of bicyclic \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo lactone 2.4 (Scheme 2.17). Thus, I set out to prepare the corresponding bicyclic \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo lactone that could fragment to provide 2.5.

2.3.1. Synthesis of 2-((tert-Butyldimethylsilyl)oxy)-2-(1-hydroxyethyl)cyclohexanone

Our initial plan for the synthesis of bicyclic fragmentation precursor 2.4 was based on Ali’s synthesis of bicyclic \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo lactones (2.1, Scheme 2.18).\(^{67}\) Ali began with the bis-silylation of known \( \alpha \)-hydroxy-\( \beta \)-ketoester 2.51,\(^{171}\) which was then reduced by Dibal-H to the corresponding primary alcohol, and the silyl enol ether group was selectively deprotected under buffered CsF conditions to give 2.53.\(^{172}\) After screening various methods to prepare diazo lactone 2.1, Ali determined that acetylation of the alcohol to give bromoacetate 2.54 followed by treatment with \( N,N' \)-ditosylhydrazide and DBU afforded the \( cis \) and \( trans \) isomers of bicyclic diazo lactone 2.1 in the optimal yield.\(^{16}\) This method was convenient because both the conversion of bromoacetate to diazo ester and the cyclization to provide the \( \beta \)-hydroxy-\( \alpha \)-diazo lactone were promoted by DBU in a single step. I based my synthetic strategy around this one pot diazo conversion/cyclization step to afford bicyclic \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo lactone 2.4 (Scheme 2.19).
Each of the natural products that I targeted from key intermediate 2.5 contain a methyl group within the heterocycle (shown in bold, Scheme 2.19). I sought to install that methyl group prior to the ring fragmentation and thus designated ethyl ester 2.52 for conversion to methyl ketone 2.55, which could then be reduced to the corresponding secondary alcohol. From 2.55, my original plan mirrored Ali’s plan, where selective deprotection to afford 2.56 and acetylation/diazo lactonization could prepare 2.4.

I treated of ethyl ester 2.52 with MeLi and MeMgBr. Neither reagent led to the desired ketone (2.55), and starting material and the tertiary alcohol (not shown) were
obtained. We ultimately found that conversion of ethyl ester 2.52 to methyl ketone 2.55 could be achieved by treatment with ≥2 equivalents of TMSCH₂Li, followed by quench with MeOH in accordance with Demuth (Scheme 2.20).¹⁷³ In this mechanism, the first equivalent of TMSCH₂Li acted as a nucleophile to attack the ethyl ester, which gave α-silyl ketone 2.57. The presence of an α-silyl group renders the α-hydrogen more acidic, therefore the second equivalent of TMSCH₂Li to acted as a base to enolize the ketone, thereby preventing a second attack by the organometallic nucleophile. The MeOH desilylated and protonated enolate 2.58, which gave the desired methyl ketone in quantitative yield.

![Scheme 2.20 Conversion of ester to methyl ketone](image)

Methyl ketone 2.55 was then treated with NaBH₄ under cold conditions, which gave 84% yield of a single isolable diastereomer of the corresponding alcohol (2.59, Scheme 2.21). The silyl enol ether was selectively deprotected using CsF in AcOH to provide ketone 2.56 in 99% yield.¹⁷²
2.3.2. Initial route toward bicyclo [4.4.0] diazo lactone 2.4

With 2-((tert-butyldimethylsilyl)oxy)-2-(1-hydroxyethyl)cyclohexanone (2.56) in hand, I initially sought to synthesize bicyclic diazo lactone 2.4 using Ali’s method,\(^\text{67, 174}\) which was inspired by Toma et al.’s use of \(N,N’\)-ditosylhydrazine as a reagent to form diazo esters (Scheme 2.22).\(^\text{16, 67}\) Bromoacetylation of secondary alcohol 2.56 afforded bromoacetate 2.60 in 87% yield, however subsequent treatment with \(N,N’\)-ditosylhydrazine and DBU was not straightforward (Scheme 2.22 and Table 2.2). The desired bicyclic diazo lactone 2.4 was repeatedly isolated in addition to the corresponding diazo ester 2.61, and a compound that was determined to be silyl-transfer product 2.62.
Initial attempts to optimize the conversion to bicyclic diazo lactone 2.4 only resulted in a maximum of 31% yield (entry 2, Table 2.2). Therefore I took into consideration that diazo ester 2.61 could be cyclized to form diazo lactone 2.4 using LiHMDS under dilute conditions, so I attempted to optimize the conversion of bromoacetate 2.60 to the combination of diazos 2.61 and 2.4.

Extended reaction times led to an increased yield of undesired silyl transfer product 2.62 (entry 1). Abbreviated reaction times decreased the yield of the undesired side product 2.62, but did not generate either diazo ester 2.61 or lactone 2.4 in sufficient yields (entries 2-5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time</th>
<th>Temperature</th>
<th>Yield 2.4 (%)</th>
<th>Yield 2.61 (%)</th>
<th>Yield 2.62 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>Overnight</td>
<td>0 °C to rt</td>
<td>27%</td>
<td>trace</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>45 min</td>
<td>0 °C to rt</td>
<td>31%</td>
<td>4%</td>
<td>&gt;35%c</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>45 min</td>
<td>0 °C</td>
<td>21%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>15 min</td>
<td>0 °C</td>
<td>11%</td>
<td>26%</td>
<td>n.d.</td>
</tr>
<tr>
<td>5a</td>
<td>DBU</td>
<td>10 min</td>
<td>0 °C</td>
<td>11%</td>
<td>18%</td>
<td>trace</td>
</tr>
<tr>
<td>6a</td>
<td>LiHMDS</td>
<td>6.5 h</td>
<td>0 °C to rt</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>7a</td>
<td>Et3N</td>
<td>1 h</td>
<td>0 °C</td>
<td>n.d.</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>8a</td>
<td>K2CO3</td>
<td>Overnight</td>
<td>0 °C to rt</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*a*Recovered starting bromoacetate  
*b*Not detected  
*c*Did not isolate every fraction

Temperature appeared to have an impact on how productively the silyl-transfer product 2.62 formed. It is possible that silyl transfer was suppressed by keeping the reaction at 0 °C, therefore reactions that were kept cold tended to lead to better results (for example, compare entries 2 and 3). The use of LiHMDS, Et3N and K2CO3 in place of DBU (entries 6-8) did not efficiently promote the elimination of the sulfonyl groups from the hydrazide to generate the diazo functional group.
Overall, entry 3 represents the “optimal” conditions for the conversion of bromoacetate 2.60 to diazo esters 2.61 and 2.4. However, we were not satisfied with the yields following this route, therefore we sought an alternative method for the synthesis of the bicyclic diazo lactone fragmentation precursor 2.4.

### 2.3.3. Second and successful route toward bicyclo [4.4.0] diazo lactone 2.4

I planned an alternate method for synthesizing diazo lactone 2.4 starting from 2-((tert-butyldimethylsilyl)oxy)-2-(1-hydroxyethyl)cyclohexanone (2.56, Scheme 2.23). α-Diazo-β-keto esters (i.e. 2.63) can be prepared from β-keto esters (i.e. 2.64) upon treatment with a diazo-transfer reagent (see Chapter 1.1.2.3).¹ Davies et al. have reported the use of para-acetamidobenzenesulfonyl azide (p-ABSA) as a safer alternative to the traditional tosyl azide diazo-transfer reagent. In order to pursue this second generation route, I began by converting alcohol 2.56 to β-ketoester 2.64.

![Scheme 2.23 Revised retrosynthetic sequence for the preparation of bicycle 2.4 via diazo transfer](image)

The current literature provides a number of methods for converting an alcohol to a β-keto ester via Lewis acid-catalyzed transesterification reactions. I screened both BF₃·OEt₂¹⁷⁵ and I₂¹⁷⁶ as Lewis acids to catalyze the acetoacetylation of alcohol 2.56 using ethyl acetoacetate, but not reaction occurred (Scheme 2.24).

![Scheme 2.24 Traditional Lewis acid-promoted conversion of alcohol to β-keto ester](image)
An alternative to Lewis acid-promoted transesterification of ethyl acetoacetate is the use of ketene precursor 2,2,6-trimethyl-4H-1,3-diox-4-one (2.65). Upon heating, 2.65 rearranges to generate ketene 2.66 and release acetone in situ (see Scheme 2.25 for the mechanism). In my case, the ketene underwent nucleophilic attack by alcohol 2.56 which, upon tautomerization, afforded the β-ketoester 2.64 in 77% yield.\(^\text{177}\)

![Scheme 2.25 Acetoesterification of alcohol X via ketene precursor X](image)

β-Ketoester 2.64 was treated with p-ABSA and Et\(_3\)N to give α-diazo-β-ketoester 2.63 in 98% yield (Scheme 2.26). With α-diazo-β-ketoester 2.63 in hand, treatment with aqueous KOH was next prescribed.\(^\text{178}\) 5% Aqueous KOH with MeCN as a solvent was initially screened, and I was happy to find that α-diazo-β-keto ester had deacylated to intermediate 2.66 which cyclized to afford the bicyclic diazo lactone 2.4 in situ. However, under these conditions I always reobtained α-diazo-β-keto ester starting material. Optimization of this step was necessary in order to maximize the yield of bicyclic diazo lactone 2.4 (Table 2.3).
In an attempt to push the reaction to completion, I increased the volume of 5% aqueous KOH, however this resulted in a biphasic mixture, thus did not improve the yield (entries 2 and 3). Adjustment of the solvent to improve the solubility of the substrate helped the yield (entries 4-5). Specifically, a 1:1 mixture of MeCN and THF improved the reaction yield, but reversed the cis/trans diastereoselectivity (entry 4). A 2:3 mixture of MeCN and acetone further improved the yield to 78% and gave a 5:2 cis/trans ratio (entry 5). In an effort to reduce the volume of base used, increased concentration of KOH was tested, which did not improve the yield (entries 6-9). Switching to CsOH did not improve the yield, regardless of solvent (not shown). The conditions from entry 5 represent the optimized conditions for the formation of bicyclic diazo lactone 2.4.
Table 2.3 Optimization of conditions for the conversion of α-diazo-β-keto ester 2.63 to bicyclic diazo lactone 2.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Percent Aqueous KOH (w/w)</th>
<th>Volume Aqueous KOH/mmol Diazo</th>
<th>Solvent</th>
<th>Yield 2.4 (%)</th>
<th>Cis/Trans Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 %</td>
<td>3.3 ml/mmol</td>
<td>MeCN</td>
<td>58%</td>
<td>3 : 2</td>
</tr>
<tr>
<td>2</td>
<td>5%</td>
<td>6.6 ml/mmol</td>
<td>MeCN</td>
<td>52%</td>
<td>3 : 2</td>
</tr>
<tr>
<td>3</td>
<td>5%</td>
<td>10 ml/mmol</td>
<td>MeCN</td>
<td>n.r.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5%</td>
<td>10 ml/mmol</td>
<td>MeCN/THF (1 : 1)</td>
<td>63%</td>
<td>1 : 5</td>
</tr>
<tr>
<td>5</td>
<td>5%</td>
<td>10 ml/mmol</td>
<td>MeCN/Acetone (2 : 3)</td>
<td>78%</td>
<td>5 : 2</td>
</tr>
<tr>
<td>6</td>
<td>10%</td>
<td>4 ml/mmol</td>
<td>MeCN</td>
<td>44%</td>
<td>1 : 1</td>
</tr>
<tr>
<td>7</td>
<td>10%</td>
<td>7 ml/mmol</td>
<td>THF</td>
<td>n.r.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15%</td>
<td>3.7 ml/mmol</td>
<td>MeCN</td>
<td>53%</td>
<td>2 : 3</td>
</tr>
<tr>
<td>9</td>
<td>15%</td>
<td>3.3 ml/mmol</td>
<td>DMSO</td>
<td>59%</td>
<td>1 : 1</td>
</tr>
</tbody>
</table>

*aNo reaction

Compared with the initial route I perused (described in 2.3.2), this method that proceeds via α-diazo-β-ketoester 2.63 adds an additional step to the route, but the overall yield of the reaction from alcohol 2.56 to bicyclic diazo lactone 2.4 is improved from 31% to 50%.

2.4. Fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazo lactone and synthesis of key intermediate 2.6

As discussed, Ali Bayir developed a Lewis acid-promoted Grob-type fragmentation of bicyclic diazo lactones that led to medium-size rings.67,174 The proposed mechanism that leads to ynonlide 2.5 is depicted in Scheme 2.27 I: the bicyclic γ-silyloxy-β-hydroxy-α-diazo lactone reacts with a SnCl₄ (2.67) to eliminate the hydroxyl and provide vinyl diazonium 2.68, which then undergoes a Grob-type fragmentation initiated
by lone pair donation from the silyloxy moiety, and results in liberation of \( \text{N}_2 \). Desilylation of 2.69 then provides desired 10-membered ynlolide 2.5 (I, Scheme 2.27).

Unfortunately, there are side reactions that occurred in Ali’s system, where vinyl diazonium 2.68 can spontaneously liberate nitrogen to provide vinyl cation 2.70, which can further react in a number of ways (see Chapter 3 for more on vinyl cations generated from diazo carbonyls). For example, Ali isolated diene 2.72, which he proposed arose from a 1,3-hydrde shift to form allylic cation 2.71, which could be deprotonated to afford diene 2.72 (II, Scheme 2.27). Another isolated side product was epoxide 2.75 (III, Scheme 2.27). Ali proposed that this was a result of a side reaction that occurred by Lewis acid activation of the diazo moiety rather than the hydroxyl. This would promote intramolecular epoxidation to form 2.73, followed by liberation of nitrogen then proton transfer resulting in a second epoxide 2.74.

Scheme 2.27 Possible pathways to side products from of bicyclic diazo lactone 2.4
Ali discovered that treating bicyclic diazo lactone 2.1 with SnCl$_4$ in refluxing CH$_2$Cl$_2$, the yield of ymolide 2.5 was optimal and the amount of side product decreased. In the case of my substrate, when a mixture of cis and trans isomers of bicyclo [4.4.0] diazo lactone 2.4 (cis and trans) was subjected to SnCl$_4$ in refluxing CH$_2$Cl$_2$ for 10 min, the desired ymolide 2.5 was obtained in 31-48% yield, depending on the quality of the Lewis acid. When the isomers were reacted separately, cis-bicyclodiazo lactone 2.4-cis fragmented to give ymolide 2.5 in 58% yield, while the 2.4-trans isomer gave the ymolide in 29% yield (Scheme 2.28).

Since 2.4-cis fragmented in a significantly higher yield compared to 2.4-trans, I was investigated whether or not the trans isomer could isomerize to provide the cis isomer. I subjected 2.4-trans to the same conditions used to convert 2.63 to 2.4-cis and -trans, and was pleased to obtain 2.4-cis in 74% yield and recover 20% of 2.4-trans. From 2.63 to 2.5, this amounts to a 41% yield over 3 steps (summarized in Scheme 2.29).
With ymolide 2.5 in hand, the last step for obtaining key intermediate 2.6 was to deoxygenate the ketone. The Wolff-Kishner reduction was ruled out as an option since it proceeds via a free radical pathway, which we worried might react intramolecularly with the ynoate functional group.

We therefore proposed to deoxygenate the ketone via a Mozingo reduction. Conversion of ketone 2.5 to thioketal 2.76 had to be optimized, as sterically hindered ketones are slow to react with 1,2-ethanediethiol (Table 2.4). BF₃·OEt₂ was initially selected as the Lewis acid to catalyze the conversion. This reaction was sluggish, and provided the desired thioketal after stirring overnight in 54% yield (entry 1).¹⁸⁰ para-Toluenesulfonic acid (p-TsOH) in combination with silica gel¹⁸¹ did not provide thioketal 2.76 in a useful yield (entry 2).
Table 2.4 Optimization of thioketal formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Catalyst</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Reaction Time</th>
<th>Yield X (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃OEt₂</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>18 h</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>ρ-TsOH</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>26 h</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>Amberlyst® 15</td>
<td>CHCl₃</td>
<td>reflux</td>
<td>25 h</td>
<td>64%</td>
</tr>
<tr>
<td>4</td>
<td>FeCl₃•SiO₂</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>10 min</td>
<td>32%</td>
</tr>
</tbody>
</table>

Amberlyst® 15 has emerged as a convenient catalyst for the conversion of aldehydes and ketones to thiolanes. I subjected ketone 2.5 to the prescribed conditions and found that, with an elevated catalyst loading and extended reaction time, I was able to isolate thioketal 2.76 in 64% yield with no side products detected (entry 3).

In an attempt to reduce reaction time, iron(III) chloride dispersed on silica gel was selected as a Lewis acid catalyst, which is known to convert ketones to thioketals in under one minute. Interestingly, subjecting ketone 2.5 to freshly prepared FeCl₃•SiO₂ and 1,2-ethanedithiol gave a mixture of desired thioketal 2.76 in 32% yield, as well as an unidentified side product with the same mass in 28% yield. Overall, Amberlyst® 15 was selected as the optimal Lewis acid to catalyze this conversion.

Subjecting thioketal 2.76 to Raney-Ni in MeOH under an atmosphere of H₂ resulted in a mixture of desired alkyne 2.6 and side products, as well as the recovery of
starting material (entry 1, Table 2.5). Switching to THF as the solvent cleanly returned desulfurized ynolide 2.6 in 77% yield (entry 2).

Table 2.5 Raney-Nickel-catalyzed reduction of thioketal 2.76

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield 2.6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>83%</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>100%</td>
<td>77%</td>
</tr>
</tbody>
</table>

2.5. Attempted hydrogenation of alkyne 2.6 to afford (±)-phoracantholide I

Key intermediate 2.6 is the diversification point in our divergent synthetic strategy. A number of methods were tested to reduce alkyne 2.76 to provide the natural product phoracantholide I (results summarized in Table 2.6). The success of each entry was judged on the ability to form a new doublet that appeared at 1.3 ppm in 1H NMR, which could coincide with phoracantholide I.\textsuperscript{155} This metric was used due to the fact that none of the reduction conditions tested thus far completely converted the alkyne (2.6).

Hydrogenation using Pd/C did not result in productive formation of phoracantholide I, though other side products were detected when THF was used as solvent (entries 1-2). Adam’s catalyst (PtO\textsubscript{2}) under an atmosphere of H\textsubscript{2} successfully converted a small amount of the alkyne to a new product that could be phoracantholide or alkene 2.24 (entries 4-5). The warmer temperature seemed to increase the formation of the new doublet (entry 5). I was concerned that trace sulfur (leftover from the previous
reaction) could poison the Pd or Pt hydrogenation catalysts, so Raney-nickel was next used at warmer temperatures. Under an atmosphere of H₂ at 65 °C, Raney-Ni converted a small percent of the starting material such that the new doublet at 1.3 ppm was detected (entry 6). Microwave conditions were then used using Raney-Ni to attempt to increase the reaction rate, however only side products absent of a doublet resulted (entry 7).

**Table 2.6 Reduction conditions to prepare phoracantholide**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>New doublet at 1.3 ppm?</th>
<th>% Conversion&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd/C, H₂</td>
<td>THF</td>
<td>rt</td>
<td>no</td>
<td>23%</td>
</tr>
<tr>
<td>2</td>
<td>Pd/C, H₂</td>
<td>THF/H₂O</td>
<td>rt</td>
<td>no</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>Pd/C, H₂</td>
<td>MeOH</td>
<td>rt</td>
<td>no</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>PtO₂, H₂</td>
<td>MeOH</td>
<td>rt</td>
<td>yes</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>PtO₂, H₂</td>
<td>MeOH</td>
<td>50 °C</td>
<td>yes</td>
<td>34%</td>
</tr>
<tr>
<td>6</td>
<td>Raney-Ni, H₂</td>
<td>MeOH/H₂O</td>
<td>65 °C</td>
<td>yes</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Raney-Ni</td>
<td>MeOH</td>
<td>120 °C (μW)</td>
<td>no</td>
<td>29%</td>
</tr>
<tr>
<td>8</td>
<td>SmI₂ (excess)</td>
<td>THF/H₂O</td>
<td>rt</td>
<td>no</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on <sup>1</sup>H NMR of crude mixture  
<sup>b</sup>Not determined
Since hydrogenation methods were not successful, I next subjected alkyne 2.6 to a large excess of SmI$_2$ under conditions known to reduce ynoates to saturated esters.$^{184}$ Unfortunately, this also only lead to the recovery of starting material.

Since PtO$_2$ was the catalyst that showed the most promise in converting the alkyne to a new product, this catalyst should be used in a high-pressure hydrogenation since heat did not seem to improve the reaction.

2.6. **Attempted hydration of alkyne 2.76 to complete the synthesis of diplodialides A and C and curvularin**

I originally pursued the oxidation of the alkyne 2.76 with the thioketal intact in an attempt to avoid relying on volatile intermediates in the synthetic sequence (Table 2.7). The first method I used to attempt to convert 2.76 to ketone 2.77 was the tributylphosphine-catalyzed conjugate addition of methanol into the ynoate, which upon treatment with strong acid would provide ketone 2.77.$^{185}$ Unfortunately, this did not promote the reaction, possibly due to sluggish addition of the bulky Bu$_3$P catalyst (entry 1). PMe$_3$ has also been used to catalyze the conjugate addition of methanol into ynoates, which may be an option for this substrate going forward.
Conjugate addition of benzaldoxime anion to ynoates has been reported as a method to prepare β-ketoesters, however this was not suitable for cyclic ynoate 2.76 and only led to decomposition (entry 2).\textsuperscript{186} Finally, the combined acid-catalyzed hydrolysis\textsuperscript{187} of the alkyne did not lead to ketone 2.77 (entry 3).

Moving forward, it would be best to proceed with the conversion of alkyne 2.6 to ketone 2.7, where the thioketal has been desulfurized. It is a simpler substrate, structurally, therefore might cause less steric issues when it comes to the conjugate addition strategies.

### 2.7. Future Work

With the preparation of common intermediate 2.6 optimized, the divergent total syntheses of the natural products remains a challenge (Scheme 2.30). Traditional hydrogenation methods did not afford (±)-phoracantholide from the alkyne. Aside from hydrogenation, there are other reduction methods that have converted conjugated ynoates

---

**Table 2.7 Screening of conditions in attempt to prepare 2.77**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Reaction Time</th>
<th>Yield Thioketal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 i.</td>
<td>i. PBu₃ (10%), MeOH</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>1.5 h</td>
<td>no reaction</td>
</tr>
<tr>
<td></td>
<td>ii. pTsOH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Benzaldoxime, NaH</td>
<td>Dioxane/DMF</td>
<td>r.t.</td>
<td>0.5 h</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOHH₂O</td>
<td>DCE</td>
<td>100 °C</td>
<td>20 h</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>AcOH</td>
<td>(sealed tube)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O

O

O

S

S

O

2.76

conditions

2.77

Conjugate addition of benzaldoxime anion to ynoates has been reported as a method to prepare β-ketoesters, however this was not suitable for cyclic ynoate 2.76 and only led to decomposition (entry 2).\textsuperscript{186} Finally, the combined acid-catalyzed hydrolysis\textsuperscript{187} of the alkyne did not lead to ketone 2.77 (entry 3).

Moving forward, it would be best to proceed with the conversion of alkyne 2.6 to ketone 2.7, where the thioketal has been desulfurized. It is a simpler substrate, structurally, therefore might cause less steric issues when it comes to the conjugate addition strategies.

### 2.7. Future Work

With the preparation of common intermediate 2.6 optimized, the divergent total syntheses of the natural products remains a challenge (Scheme 2.30). Traditional hydrogenation methods did not afford (±)-phoracantholide from the alkyne. Aside from hydrogenation, there are other reduction methods that have converted conjugated ynoates
to saturated esters. For example, just last year Teichert and coworkers reported the use of ammonia borane as a transfer hydrogenation agent in a copper-catalyzed reduction.\textsuperscript{188} Similarly, Lipshutz \textit{et al.} reported a copper-catalyzed conjugate reduction, in which polymethylhydrosiloxane was the reductant.\textsuperscript{189} At this time, we cannot explain what is preventing the alkyne from hydrogenation or reduction, which makes it difficult to predict what conditions might be optimal. Considering that ynoates are typically excellent conjugate addition acceptors, it might be best to next explore that strategy.

\begin{center}
\textbf{Scheme 2.30 Synthetic plans for target natural products from common intermediate}
\end{center}

Another way to take advantage of the ynoate susceptibility to conjugate addition would be in the conversion to the ketone intermediate 2.6. Thus far, the phosphorous-promoted conjugate addition of methanol failed, but that was likely due to the bulky Bu\textsubscript{3}P. This could be alleviated by a smaller phosphine, such as PMe\textsubscript{3}. Another method that shows promise is the gold-catalyzed hydration of ynoates, which should prepare the β-keto ester (2.7) selectively.\textsuperscript{190}
It may also be possible to isomerize ynoate 2.6 to a diene ester. If the $E,Z$-diene results from isomerization, that would complete the synthesis of fusanolide A. The $Z,Z$-dienoate isomer might also be ring-opened by nucleophilic attack to provide either iedomonicin D or an intermediate that could be further functionalized to that natural product.

2.8. Conclusions

We have obtained the proposed common intermediate in the divergent total synthesis of six structurally related natural products through a ring fragmentation approach. The synthesis of the fragmentation precursor, bicyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo lactone 2.4, required an amendment to the initial route. The first route prepared the diazo lactone moiety from the conversion of a bromoacetate to diazo ester using $N,N'$-ditosylhydrazine and DBU, which was not a consistent or useful method. The second route converted a $\beta$-ketoester to $\alpha$-diazo ester using $p$-ABSA as a diazo transfer reagent, which formed the bicyclic diazo lactone under aqueous alkaline conditions in high yield.

The key step in the preparation of the key “common” intermediate was the fragmentation, which provided macrolide 2.5 in 58% yield from the $cis$-isomer of the bicyclic lactone, which was then deoxygenated using a Mozingo reduction in good yield.

Final steps in the synthetic route involve the divergent syntheses of the natural products, which is currently underway.
CHAPTER 3: CYCLOPENTENONES VIA C-H INSERTION INTO VINYL CATIONS

3.1. Introduction

The Brewer group has previously developed a Lewis acid-promoted ring fragmentation of γ-silyloxy-β-hydroxy-α-diazo esters, which was the basis of my natural product pursuit. The group proposed that this Grob-type fragmentation proceeded via a vinyl diazonium intermediate 3.1, which underwent a concerted fragmentation to provide tethered aldehyde ynoates 3.3 (Scheme 3.1). However, the concerted loss of nitrogen was never proven, and an alternative pathway including initial loss of N₂ to give a vinyl cation intermediate followed by fragmentation is plausible as well, and has precedence in the following section 3.2.

![Scheme 3.1 Lewis acid-mediated fragmentation of γ-silyloxy-β-hydroxy-α-diazo esters](image)

Chapter 1.6 discussed traditional methods and limitations for the generation of vinyl cations, and highlighted how the reactivity of such carbeniums is not well understood. Due to these limitations, we were interested in investigating new reactions that take advantage of the high reactivity of vinyl cations. We noted works by the Pellicciari and Padwa groups that investigated vinyl cations generated from β-hydroxy-α-diazo esters, which was an appealing way to access these highly reactive intermediates.
3.2. Diazo carbonyls as precursors to vinyl cations

Pelliciari\textsuperscript{104} and Padwa\textsuperscript{96} studied the reaction of β-hydroxy-α-diazo esters with Lewis acids (Scheme 3.2). Analysis of their isolated products over various reaction conditions led them to propose a vinyl cation intermediate. Specifically, they proposed that treating β-hydroxy-α-diazo ester with BF$_3$ generated vinyl cation via elimination of the hydroxyl to give diazonium that then looses N$_2$ (3.4 $\rightarrow$ 3.5 $\rightarrow$ 3.6, Scheme 3.2).

This initially formed exocyclic vinyl cation (3.6) could either be trapped by nucleophiles in solution to afford 3.7 (i.e. solvents such as MeCN and benzene, fluorine ion from BF$_3$, etc) or undergo a ring expansion to give a second vinyl cation 3.8 (see Chapter 1.5 for other examples of cationic rearrangements). A subsequent ring contraction of vinyl cation 3.8 would give allylic cation 3.9 which could either form lactone 3.10 or be trapped by nucleophiles to give 3.11. Compounds 3.7, 3.10, and 3.11 were all isolated in their studies.

![Scheme 3.2 Discovery of diazo esters as vinyl cation precursors](image)

Because the Pellicciari and Padwa groups had only investigated vinyl cations generated from ethyl diazoacetate derivatives, and because there are limited methods
available to generate vinyl cations thus limited studies of their reactivity, we were
interested to explore the possibility of other intramolecular reactions in similar cationic
systems. We began by searching the literature for potentially useful vinyl cation
reactivity that had been under-utilized due to limitations in vinyl cation preparative
methods. The results of our literature search are described in section 3.3.

3.3. C-H Insertion into vinyl cations

Smit and Schegolev studied the reactivity of vinyl cations that were generated by
the acylation of alkynes. The reactivity of one such cation (3.13, Scheme 3.3)
stood out to us. This proposed vinyl cation intermediate was formed by the reaction of
acylium 3.12 (generated from the reaction of pivaloyl chloride and AgBF₄) with 2-
butyne. Surprisingly, this reaction led to the formation of cyclopentenone 3.14 in 73%
yield, presumably via a 1,5-hydride shift and ring closure.

![Scheme 3.3 C-H insertion of vinyl cations generated from acylation of alkynes](image)

Similarly, Metzger and coworkers observed intramolecular C-H insertion of vinyl
cations generated from the alkylation of alkynes (Scheme 3.4). For example, they
treated isopropyl chloroformate with Et₃Al₂Cl₂ to generate carbocation 3.15 in situ after
the release of CO₂. The carbocation was attacked by 4-octyne to form vinyl cation 3.16,
which underwent a 1,5-hydride shift and cyclization to give tertiary cation 3.17, which
reacted with added hydride to provide cyclopentane 3.18 in 79% yield. The group was
curious if the 1,5-hydride shift and cyclization occurred in a concerted fashion, or as two
separate mechanistic steps. They used quantum mechanical calculations (MP2/6-311+G-(d,p)//MP/6-31G(d)+ZPVE) to predict a concerted C-H insertion of vinyl cation 3.16, which rules out the formation of a primary cation.

![Chemical structure](image)

Scheme 3.4 C-H insertion of vinyl cations generated from alkylation of alkynes

The acylation and alkylation of alkynes was a useful way to generate vinyl cations. However, the use of alkynes limits the product possibilities to monocyclic cyclopentenones. Yields were also the highest when the alkynes also were symmetric, otherwise a mixture regioisomers was obtained.

We noted that vinyl cations 3.13 (Scheme 3.3) and 3.16 (Scheme 3.4) were stationed in the same position relative to the carbonyl as vinyl cation 3.8 from Pellicciari’s work (Scheme 3.2). With precedence that vinyl cations can undergo C-H insertion to preferentially form 5-membered rings, we planned to generate vinyl cations using β-hydroxy-α-diazo ketones, and to test if those vinyl cations would undergo C-H insertion reactions. Since these vinyl cations could be generated intramolecularly, we expected to have good regiocontrol as well as the ability to prepare bicyclic systems which overcome some limitations seen with the acylation of alkynes.
3.4. Reaction of β-hydroxy-α-diazo ketones with Lewis acids to give bicyclic cyclopentenones

Our goal was to combine the concepts presented in the Pellicciari and Schegolev works in order to develop a practical method to make bicyclic cyclopentenones via a new rearrangement/C-H insertion reaction (summarized in Figure 3.1B). By exchanging diazo esters for diazo ketones, we envisioned that exocyclic vinyl cation 3.20 would be formed by the same mechanism as proposed by Pellicciari for the formation of 3.6. This cation would likely undergo ring expansion to generate a second cyclic vinyl cation 3.21, which has the potential to undergo a C-H insertion, as it is similar in structure to those which were prepared by Schegolev. This sequence would lead to bicyclic cyclopentenone products 3.22, the usefulness for which are described in Chapter 1.7.

I began this study by synthesizing β-hydroxy-α-diazo ketones 3.25 and 3.26 from cyclohexanone and lithiated 1-diazo-3,3-dimethylbutan-2-one 3.23 and 1-diazo-3-
methyl-butan-2-one \textbf{3.24}, respectively (Scheme 3.5). The Brewer group had previously optimized the fragmentation sequence and found that SnCl$_4$ was an optimal Lewis acid to promote $\beta$-hydroxyl elimination,\textsuperscript{41} so I began my study using SnCl$_4$. Upon treating \textbf{3.25} and \textbf{3.26} with SnCl$_4$, I was pleased to isolate the ring expansion/C-H insertion products \textbf{3.27} and \textbf{3.28} in 83\% and 70\% yield. With $\beta$-hydroxy-$\alpha$-diazo ketone \textbf{3.26}, I also isolated vinyl chloride \textbf{3.29} in a 10\% yield.

The isolation of these products led us to propose a reaction pathway that could account for both of the types of products observed (Scheme 3.6). SnCl$_4$-promoted elimination of tertiary hydroxide \textbf{3.26} would provide vinyl diazonium \textbf{3.30}, which upon loss of nitrogen would generate vinyl cation \textbf{3.31}. Vinyl chloride \textbf{3.29} would from by trapping this vinyl cation with chloride.
While carbonyl groups typically stabilize adjacent cations through resonance, the vacant p-orbital in vinyl cation \(3.31\) is orthogonal to the carbonyl \(\pi\)-system.\(^97\) In this case, we propose that the carbonyl destabilizes the cation by induction, which promotes a 1,2-shift giving a second vinyl cation \((3.32)\). This second vinyl cation is similar to that generated by Schegolev et al., which underwent C-H insertion at the \(\gamma\)-position to form a cyclopentenone.\(^101\) In our case, 1,5-hydride shift and cyclization would generate cation \(3.33\), which upon deprotonation would provide cyclopentenone \(3.28\).

### 3.4.1. Optimization of conditions for the transformation of \(\beta\)-hydroxy-\(\alpha\)-diazo ketones \(3.25\) and \(3.26\) to cyclopentenones \(3.27\) and \(3.28\)

At this point in the study, I tested other solvents and strong Lewis acids for their ability to promote the generation of the vinyl cation from \(\beta\)-hydroxy-\(\alpha\)-diazo ketone \(3.25\)
When the reaction was carried out in MeCN using SnCl₄, the yield dropped to 24% (entry 2). BF₃·OEt₂, In(OTf)₃, and Dy(OTf)₃ all gave inferior yields compared with SnCl₄ in CH₂Cl₂ (entries 3-5). When Dy(OTf)₃ was heated in MeCN, it gave an appreciable yield of 60%, possibly due to better solubility of the Lewis acid (entry 6). The optimal conditions were determined to be SnCl₄ in CH₂Cl₂.

The optimal conditions were determined to be SnCl₄ in CH₂Cl₂.

**Table 3.1 Screening of Lewis acids and solvents for the synthesis of 3.27**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield 3.27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>−20 °C</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>MeCN</td>
<td>−20 °C</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·OEt₂,</td>
<td>CH₂Cl₂</td>
<td>−20 °C</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>In(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>−20 °C</td>
<td>Minor</td>
</tr>
<tr>
<td>5</td>
<td>Dy(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>−20 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Dy(OTf)₃</td>
<td>MeCN</td>
<td>40 °C</td>
<td>60%</td>
</tr>
</tbody>
</table>

*1 equiv used, ²20 mL/mmol diazo

With the optimal Lewis acid and solvent known, I next screened how temperature effected the reaction. I had hoped that by adjusting this condition, I could suppress the competing intermolecular formation of vinyl chloride 3.29, therefore completed this portion of the conditions optimization using β-hydroxy-α-diazo ketone 3.26 which had formed vinyl chloride 3.29 in 10% using standard conditions. I first addressed the reaction temperature (results summarized in Table 3.2). At −35 °C, solubility became an issue where a white precipitate formed when the Lewis acid was added to the flask. We also suspect that the N₂ is slower to release at low temperatures, which was observable in this case. It may be for these reasons that the bicyclic cyclopentenone 3.28 was only isolated in 49% yield.
Table 3.2 Optimization of reaction temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yield 3.28 (%)</th>
<th>Yield 3.29 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−35 °C</td>
<td>49%</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>−20 °C</td>
<td>70%</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>76%</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>40 °C</td>
<td>71%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*aAll reaction carried on in 20 mL/mmol CH₂Cl₂

Overall, the other reaction temperatures tested did not seem to effect the ratio of 3.28 to 3.29 (entries 2-3) except for heating at reflux (entry 4). In a last effort to suppress the formation of vinyl chloride 3.29, I tested if more dilute conditions would enhance the intramolecular reaction to form 3.28, therefore reduce the product of intermolecular vinyl cation capture. Concentration was also varied, and did not have a noticeable effect on the product distribution.

3.4.2. Variation of ring size of β-hydroxy-α-diazo ketones

With the optimized reaction conditions determined, I focused my efforts on determining how varying the ring size affected the reaction. To do this, I synthesized a scope of β-hydroxy-α-diazo ketones by adding lithiated 1-diazo-3-methylbutan-2-one to cyclobutanone, cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone. These were then treated with SnCl₄ in CH₂Cl₂ to afford the corresponding bicyclic cyclopentenones (3.28 and 3.36 yields summarized in Table 3.3).*
Table 3.3 Effect of ring size on reaction fate of treatment of β-hydroxy-α-diazo ketones with SnCl₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Compound</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Compound</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Compound</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3.35a</td>
<td>75%</td>
<td>3.36a</td>
<td>&lt;5%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.37a</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3.35b</td>
<td>75%</td>
<td>3.36b</td>
<td>21%</td>
<td>3.37b</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.26</td>
<td>88%</td>
<td>3.28</td>
<td>70%</td>
<td>3.29</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3.35c</td>
<td>59%</td>
<td>3.36c</td>
<td>42%</td>
<td>3.37c</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3.35d</td>
<td>40%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.36d</td>
<td>Inseparable mixture</td>
<td>3.37d</td>
<td>Inseparable mixture</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield  <sup>b</sup>Determined by <sup>1</sup>H NMR  <sup>c</sup>Yield over 2 steps

The results summarized in Table 3.3 show that the cyclohexyl scaffold gives the best product yield. The lower yields obtained for other ring systems can be attributed to a less efficient rearrangement (ring expansion) step. For example, 4- and 5-membered rings gave low yields of the [3.3.0] and [4.3.0] bicyclic cyclopentenone products (3.36a and b). The reason for this may be explained by the ring strain associated with the vinyl cation formed after ring expansion (3.39 and 3.41, Scheme 3.7). When sp-hybridized bonds (such as those that make up vinyl cations) are in smaller cyclic systems, the bond angles might be forced to bend out of the optimal linear geometry (3.39b and 3.41b).<sup>98,193</sup>

In the case of the cyclobutyl and cyclopentyl derivatives, this likely made ring expansion less competitive compared to intermolecular capture of the exocyclic vinyl cations 3.38 and 3.40, and instead led to the corresponding vinyl chlorides (3.29 and 3.37) as the major products.
The cycloheptanone derivative (3.35c) also provided a lower yield of the corresponding [6.3.0] bicyclic cyclopentenone product (3.36c) compared with the cyclohexanone derivative. The fact that the vinyl chloride product 3.37c was isolated in 24% yield indicates that the ring expansion must be less effective. At this time, we are unsure why this would be the case. The cyclooctanone derivative (3.35d) gave a complex mixture of products when treated with SnCl\textsubscript{4}, and neither the bicyclic cyclopentenone product nor the vinyl chloride was isolated.

The stability of cyclooctyne (3.44, n = 1\textsuperscript{194}) and cyclononyne (3.44, n = 2\textsuperscript{195}) may allow the ring expanded vinyl cation 3.43 to fragment into an acylium (3.45) and alkyne products (3.44), which could make undesired pathways possible (Scheme 3.8). While these alkyne products were never isolated, it is possible that they reacted further once generated or were too volatile to isolate. For example, deprotonation of the α-hydrogen of 3.45 would lead to ketene intermediate 3.46, which can undergo a number of undesired side reactions (i.e. cycloaddition, dimerization, polymerization, nucleophilic attack, etc).\textsuperscript{196} These potential competing reactions may account for the inferior yields observed.
with cycloheptyl- and cyclooctyl-derived β-hydroxy-α-diazo ketone starting materials compared with the cyclohexyl-derived substrate.

Scheme 3.8 Possible alternate pathway to generate cyclooctyne/cyclononyne and ketene

Because we were isolating high yields of the undesired vinyl chloride products (3.37), we reexamined our Lewis acid options and sought a promoter that did not have the potential to release nucleophilic anions. Tris(pentafluorophenyl)borane ((C₆F₅)₃B or “BCF”) has been noted for its strong Lewis acidity (measuring as slightly weaker than BF₃ and stronger than SnCl₄)¹⁹⁷ and its unreactive B-C bonds.¹⁹⁸
I subjected the cyclohexyl-derived β-hydroxy-α-diazo ketone 3.26 to similar conditions that were found to be optimal with SnCl₄, with the adjustment that −15 °C was used in order to allow complete solvation of the Lewis acid (entry 1, Table 3.4). Switching to Et₂O led only to the formation of side products, and no bicyclic cyclopentenone 3.28 was observed (entry 2). Similar to SnCl₄, temperature did not have a strong influence on the yield of 3.28 until 40 °C (entries 3-5). Finally, it was noteworthy that the BCF could be used in a reduced quantity in the presence of MgSO₄. At 20 mol%, the BCF returned the cyclopentenone in only slightly diminished 67% yield, while 30 mol% provided the product in 80% yield which was near comparable to when a stoichiometric quantity of Lewis acid was used (entries 6-7).

After a solvent and temperature optimization, I subjected the substrates (3.26 and 3.35) to one equivalent of (C₆F₅)₃B in CH₂Cl₂ at −15 °C (results summarized in Table 3.5). I was pleased to see that in the absence of hydrolytic bonds within the Lewis acid, trapping of the vinyl cation by an anion was prevented and the yields of cyclopentyl,
cyclohexyl, and cycloheptyl substrates increased (3.36, entries 2-4). The results for the
cyclobutyl and cyclooctyl derivatives were not improved when treated with (C$_6$F$_5$)$_3$B
compared with SnCl$_4$, the latter which is in line with our prior results that did not show
trapping to be a competitive process.

Table 3.5 Effect of ring size on reaction fate of treatment of β-hydroxy-α-diazo ketones with (C$_6$F$_5$)$_3$B

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3.36a</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3.36b</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.28</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3.36c</td>
<td>66%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3.36d</td>
<td>Complex mix</td>
</tr>
</tbody>
</table>

3.4.3. Variation at the site of insertion

While I varied ring size to probe the scope of the ring expansion step of our
reaction, my coworker Magenta Hensinger varied the substitution and electronics at the
site of the C-H insertion. She varied substitution at the gamma-position of the diazo
ketone, comparing efficiency of insertion at a methyl (3.47), methylene (3.49), and
methine site (3.51, results summarized in Figure 3.2). Each substrate she prepared
contained one possible insertion site.
She observed the trend that C-H insertion occurred more efficiently in the order methyl > methylene > methine positions. Going from a methyl to a methylene position, there was a drop in yield from 70% to 55%. However, the fact that cyclopentenone formation occurred at all was impressive because the corresponding methylene substrates (3.54) tested by the Schegolev and coworkers in their work on the acylation of alkynes failed to cyclize (Scheme 3.9). Instead, they detected products that resulted from capturing cations 3.55 and 3.56 with halogens.
The expected product of C-H insertion at the methine position (3.52) was not observed, and instead diene 3.53 was isolated in 77% yield (Figure 3.2c). We propose that diene 3.53 forms through the same initial sequence of vinyl cation formation (3.58 to 3.59), but the subsequent 1,5-hydride shift then gives a less reactive tertiary cation (3.60) that does not ring close (Scheme 3.10). The cyclization to form bicycle 3.61 must be slower than deprotonation to form diene 3.53. This aligns with results observed by the Schegolev et al.\textsuperscript{191} They observed similar diene products after 1,5-hydride shift at a methine position, which did not go on to form cyclopentenones.
Interestingly, a diene product was not observed with the *n*-propyl substituent 3.49, indicating a more effective cyclization step compared with 3.60 to 3.61, possibly due to less steric or the less stable 2° cation. We do not have enough information based on these results to confirm a step-wise or concerted C-H insertion step, but it appears that each substitution type behaves differently. From the computational work completed by Metzger *et al.*, the C-H insertion/cyclization at a methyl position appeared to go through a concerted mechanism.\(^{192}\) A step-wise 1,5-hydride transfer from a methylene position would generate a secondary cation, which the Schegolev and coworkers provided experimental evidence for.\(^{191}\) In our case, we cannot be sure if the methyl or methylene C-H insertions were step-wise or concerted. Finally, the methine 1,5-hydride shift must have proceeded step-wise, as we did not observe any cyclization product. Computational studies are currently underway to address these issues.

We observed that having an increased number of insertion sites corresponded with an increased yield (Table 3.6). Specifically, we compared substrates with varying
numbers of methyl sites for C-H insertion. There was a near 10% decrease in yield as the number of methyl positions decreased by one. We originally proposed that this could be a reflection of the Thorpe-Ingold effect, which would promote the ring closure, but initial results from a computational study by the Hong group indicate that all three substrates have the same reaction path trend, which contradicts a gem-dimethyl effect.\(^{199}\)

### Table 3.6 Number of possible sites of insertion increases yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Cyclopentenone Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>3.27</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>3.26</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>3.47</td>
<td>70%</td>
</tr>
</tbody>
</table>

#### 3.4.4. Substituted cyclohexyl derivatives as vinyl cation precursors

We were curious to see if our ring expansion/C-H insertion reaction was amenable to substituted cyclic ketone precursors. We opted for cyclohexanone derivatives because that size ring gave the corresponding bicyclic cyclopentenone products in the highest yields.

We investigated substitution at the 4-position of the cyclohexanone, as these precursors would provide only one regioisomer of the bicyclic cyclopentenone product.\(^{80}\) Magenta and I proceeded to synthesize the 4,4-dimethylcyclohexanone and 4-\textit{tert}-butylcyclohexanone derivatives and subjected them to the BCF reaction conditions (results summarized in Table 3.7).\(^{80}\)
Table 3.7 Substitution at the 4-position

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Y</th>
<th>Compound</th>
<th>Yield (%)</th>
<th>Lewis acid</th>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>tBu</td>
<td>C</td>
<td>3.62</td>
<td>53%</td>
<td>(C₆F₅)₃B</td>
<td>3.63</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>C</td>
<td>3.64</td>
<td>86%</td>
<td>(C₆F₅)₃B</td>
<td>3.65</td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td>Ts</td>
<td></td>
<td>N</td>
<td>3.66</td>
<td>65%</td>
<td>Sc(OTf)₃</td>
<td>3.67</td>
<td>50%</td>
</tr>
</tbody>
</table>

*a* Isoalted yield of major diastereomer  
*b* From the reaction of major diastereomer  
*c* 1 equiv MgSO₄ used  
*d* Data provided by M. Hensinger

The 4-tert-butylcyclohexyl β-hydroxy-α-diazoketone derivative 3.62 was synthesized as a mixture of diastereomers (Table 3.7, entry 1). Reaction of the major diastereomer with (C₆F₅)₃B and one equivalent of MgSO₄ provided cyclopentenone 3.63 in 66% yield. MgSO₄ likely enhanced the yield by suppressing the formation of a side product that GC-MS indicated was likely formed by trapping the vinyl cation trapping with water.

Magenta synthesized 4,4-dimethylcyclohexyl derivative 3.64 and, upon treatment with (C₆F₅)₃B, isolated cyclopentenone 3.65 in high yield (Table 3.7, entry 2). This further demonstrates that substitution at the 4-position is well-tolerated.

In order to investigate if heteroatoms were tolerated within the ring of the β-hydroxy-α-diazoketone, I prepared the N-tosyl protected derivative 3.66. The deactivating p-toluenesulfonyl (“Ts”) protecting group was selected in order to reduce the competing Lewis basicity of nitrogen, since our mechanism depends on an interaction of the hydroxyl group with the Lewis acid. (C₆F₅)₃B did not effectively promote the
reaction, but treatment with the highly oxophilic Lewis acid Sc(OTf)$_3$ afforded complete conversion of the starting material, and heterocycle 3.67 was provided in an acceptable yield of 50% (entry 3, Table 3.7). Further optimization of protecting group and Lewis acid might further improve the yield of this useful derivative.

**3.5. Synthesis of monocyclic cyclopentenones via a 1,2-shift and remote C-H insertion reaction**

Having had success synthesizing bicyclic cyclopentenones by a ring expansion and C-H insertion sequence, I was interested to test if the reaction could be extended to the synthesis of monocyclic cyclopentenones. To test this, I prepared diazo ketones 3.68 and 3.70 from 4-heptanone and treated them with (C$_6$F$_5$)$_3$B. The corresponding cyclopentenones (3.69 and 3.71) were obtained in 33% and 63% yields respectively (summarized in Table 3.8).

**Table 3.8 Preparation of monocyclic cyclopentenone derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Compound</th>
<th>Yield (%)</th>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3.68</td>
<td>61%</td>
<td>3.69</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>3.70</td>
<td>35%</td>
<td>3.71</td>
<td>63%</td>
</tr>
</tbody>
</table>

Relative to the cyclic ketone derivatives discussed above, the 4-heptanone derivatives gave comparatively lower yields. This could be due to additional pathways that are possible in acyclic vinyl cations (Scheme 3.11). For example, vinyl cation 3.74 can decompose into acylium 3.75 and 4-heptyne, which could lead to additional reaction
pathways. In fact, when structure 3.74 was minimized in Gaussian, 3.75 and the 4-heptyne were provided as the favored structures over 3.74. As it is, this is not necessarily a detriment, as Schegolev demonstrated how vinyl cations can be generated from alkyne acylation (the reverse direction going from 4-heptyne and 3.75 to 3.74; for a specific example from their work see Scheme 3.3).

![Scheme 3.11 Possible diverging pathway of acyclic vinyl cation substrates](image)

Comparison the yields of monocyclic cyclopentenones 3.69 and 3.71 shows that the tert-butyl diazo precursor gave a more efficient reaction. We propose that acylium intermediate 3.75 becomes problematic when R = H, as deprotonation would lead to a ketene intermediate which has the potential to undergo additional undesired reactions (see Scheme 3.8 for acylium to ketene example). This could explain why the iPr derivative 3.68 reacted to give 33% yield compared to the more useful 63% yield with the tBu derivative 3.70.

### 3.6. Future work

The rearrangement and C-H insertion cascade of vinyl cations appears to be fairly general and could be developed in a number of useful directions. In terms of expanding
upon the reaction, I have already explored the migratory aptitude of a selection of functional groups in the rearrangement step of the vinyl cations (see Chapter 4) and determined the reactivity of vinyl cations generated from β-hydroxy-α-diazo amides (see Chapter 5).

We are now working toward probing the mechanism of the C-H insertion step to determine whether or not it is step-wise or concerted in nature. Experimental results and preliminary computational modeling by the Hong group suggests that this mechanism is highly depended on the substrate and the substitution at the site of insertion. Magenta Hensinger is currently working toward providing experimental evidence for the mechanism of C-H insertion at a methylene site by way of measuring the primary kinetic isotope effect on substrate 3.49-d (Scheme 3.12).

![Scheme 3.12 Probing the mechanism of C-H insertion at a methylene site](image)

A better understanding of the order of events that lead up to the formation of vinyl cation 3.78 would be beneficial (Scheme 3.13). We think that an initial elimination of the Lewis acid-coordinated β-hydroxyl group (3.76) gives diazonium 3.77, which liberates nitrogen gas in an irreversible step that drives the formation of the unstable vinyl cation 3.78. The Hong group has provided us with computational data that shows that the release of nitrogen to form vinyl cation 3.78 is the rate-limiting step. Experimentally, we have observed that nitrogen gas is not liberated until −40 °C. However, we do not have any data to show at what temperature the β-hydroxyl group eliminates, and we do not
have experimental nor computational evidence of the order of events leading up to that step.

![Scheme 3.13 Proposed sequence to generate vinyl cation X](image)

It may be possible to observe diazonium 3.77 by $^{13}$C NMR at reduced temperature (< −40 °C). If we are able to observe this intermediate by $^{13}$C, that may enable us to monitor at what temperature the tertiary hydroxyl is eliminated. The ability to control hydroxyl elimination to provide the normally transient diazonium species 3.77 in solution could enable us to explore the reactivity of the vinyl diazonium and possibility discover and develop new reactions.

Finally, Jian Fang and Nicholas Dodge have investigated the intramolecular trapping of the vinyl cation intermediate with pendant nucleophiles (Scheme 3.14). Jian has completed an aromatic diazo ketone substrate scope (3.79) which react with BCF to form vinyl cations that undergo electrophilic aromatic substitution reactions to form tricyclic products (3.80). Meanwhile, Nick has explored tethered alkenes as potential
nucleophiles that may react with vinyl cations generated from 3.81. Interestingly, the reactivity of his substrates showed a disparity depending on the R groups.

![Scheme 3.14 Capture of vinyl cations by pendant π-systems](image)

3.7. Conclusions

We have shown that β-hydroxy-α-diazo ketones are competent precursors to vinyl cations which can go through a cationic rearrangement and remote C-H insertion method to form monocyclic and bicyclic cyclopentenones. This reaction is promoted by transition metal-free Lewis acids, and the vinyl cations are generated under mild conditions that are relatively atom economical. We have the beginnings of a grasp on the reaction mechanism based on experimental observations, and are currently collaborating with the Hong group to gain a deeper insight to the C-H insertion step. Further work is underway or has been completed (discussed in Chapter 4 and Chapter 5) that expands the scope of reactivity of these diazo carbonyl-generated vinyl cations.
CHAPTER 4: MIGRATORY APTITUDE OF THE 1,2-SHIFT OF LINEAR VINYL CATIONS

4.1. Introduction

We recently reported a method to synthesize mono- and bicyclic cyclopentenones by the rearrangement and C-H insertion of vinyl cations (Chapter 3). We were curious to determine if the rearrangement step of the reaction sequence would proceed with selectively in unsymmetric substrates (i.e. \( R_1 \neq R_2 \), Scheme 4.1). In well-known cationic rearrangements (i.e. Baeyer-Villiger), the relative ease by which a substituent migrates is known as “migratory aptitude”.

The importance of this investigation stems from the fact that most naturally occurring cyclopentanone compounds have nonequivalent \( \alpha,\beta \)-substitution (for examples, see Figure 4.1). The ability to predict the migratory aptitude of substituents in the 1,2-shift of vinyl cations becomes essential if the reaction is to be applied in the synthesis of more structurally complex molecules. Thus, I set out to empirically determine if our rearrangement followed a trend in migratory aptitude.
4.2. Background

Most rearrangement reactions exhibit a migratory aptitude trend when the potential migrating groups are not equivalent. The rearrangement that we discovered (discussed in Chapter 3) proceeds via a reactive vinyl cation intermediate. The fact that other cationic rearrangements (i.e. Baeyer-Villiger, pinacol, etc) tend to follow migratory aptitude trends prompted us to investigate if the rearrangement we discovered also followed an observable trend.

4.2.1. Baeyer-Villiger oxidation migratory aptitude trend

Baeyer-Villiger oxidations are regularly applied reactions in organic synthesis. As discussed in section 1.5.1, the rearrangement occurs after a peroxy acid attacks an aldehyde or ketone to form the Criegee intermediate, which undergoes a 1,2-shift to form the ester or lactone product (see section 1.5.1 for details).

Figure 4.1 Selected examples of cyclopentane-containing bioactive compounds

![Figure 4.1 Selected examples of cyclopentane-containing bioactive compounds]

Figure 4.2 Criegee intermediate with free rotation can lead to migratory aptitude trends

![Figure 4.2 Criegee intermediate with free rotation can lead to migratory aptitude trends]
Most Criegee intermediates allow for free rotation around the C-O peroxy bond, which leaves $R^1$ and $R^2$ available as possible migratory groups (Figure 4.2). When this is the case, migratory aptitude trends have been experimentally defined for Baeyer-Villiger oxidations. The overall trend in aptitude is as follows:

$$methyl < cyclopropyl < 1^\circ alkyl < phenyl \sim benzyl < 2^\circ alkyl < 3^\circ alkyl$$

The $R$ group that can best stabilize the positive charge generated on the oxygen will more easily migrate, which is usually the more electron-dense $R$ group. For example, a methyl group is less electron dense compared with a $2^\circ$ alkyl group, therefore the $2^\circ$ group migrates in a higher ratio. The same overall trend has been observed in the pinacol and semi-pinacol rearrangements.\(^{201,202}\)

4.3. **Regioselectivity of 1,2-shift of vinyl cations generated from β-hydroxy-α-diazo ketones**

In order to determine if substituents acting in the rearrangement of vinyl cations had distinct migratory aptitudes, unsymmetric ketone precursors were used to prepare β-hydroxy-α-diazo ketones which would be treated with Lewis acids to generate the vinyl cations. The presence of two different potential migrating groups within the molecule provided us with the ability to directly compare their migratory aptitudes.

We previously found that the β-hydroxy-α-diazo ketone substrates that reacted most efficiently by 1,2-shift and C-H insertion were those derived from cyclohexanone (Chapter 3).\(^{80}\) With this in mind, I prepared substituted cyclohexyl-derived β-hydroxy-α-diazo ketones that would contain one $1^\circ$ alkyl migrating group, and another that was substituted with either electron-donating or electron-withdrawing groups. The analysis of the products allowed for the direct comparison of migratory aptitudes
4.3.1. Migratory preference of α-methylcyclohexyl-derived vinyl cation

I began with 2-methylcyclohexanone to test if a substituent at the 2-position would migrate more or less preferentially. β-Hydroxy-α-diazo ketone 4.4 was synthesized from lithiated 1-diazo-3,3-dimethylbutan-2-one and 2-methylcyclohexanone and was treated with SnCl₄ and (C₆F₅)₃B (summarized in Table 4.1).

Table 4.1 Effect of a γ-methyl group on reaction outcome

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>cyclopentenone a (% yield)</th>
<th>cyclopentenone b (% yield)</th>
<th>NMR ratio a : b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(C₆F₅)₃B</td>
<td>&gt;50%</td>
<td>inseparable mixture</td>
<td>n.d. b</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>39%</td>
<td>6%</td>
<td>6.5 : 1</td>
</tr>
</tbody>
</table>

*Based on ¹H NMR integrations of crude mixture  bNot determined

In both cases, the major regioisomer resulted from the migration of the more substituted side (4.5a, entries 1-2). This indicates that the migratory aptitude of 2° alkyl group is higher than the aptitude of 1° group, which aligns with migratory aptitudes defined in other cationic rearrangements.

(C₆F₅)₃B cleanly returned 4.5a in 50% yield, and more was detected in an inseparable mixture of products that included 4.5b (entry 1). In one trial, some starting material was recovered when (C₆F₅)₃B was used (not shown). It is possible that the hydroxyl group of 4.4 is sterically hindered from interaction with the bulky Lewis acid, preventing productive coordination (Scheme 3.6 illustrates why Lewis acid coordination
is essential to the reaction progress). While SnCl₄ gave a lower yield of the major regioisomer (entry 2), the ¹H NMR of the crude mixture was cleaner compared to the crude NMR taken after treating diazo ketone 4.4 with BCF (entry 1), therefore an NMR ratio could be calculated between the major and minor products 4.5a and 4.5b.

The two regioisomers emerge after the formation of vinyl cation 4.6 from β-hydroxy-α-diazo ketone 4.4 (Scheme 4.2). The more substituted alkyl group (which can best stabilize the positive charge) migrated in a higher ratio to form rearrangement product 4.7 (“path a”, Scheme 4.2). The minor product, resulting from “path b” (4.5b), was also observed, so there is some competitive migration of the 1° group versus the 2° group.

This result encouraged us to test if other unsymmetrical vinyl cation intermediates would rearrange regioselectively.

**4.3.2. Migratory preference of α-chlorocyclohexyl-derived vinyl cations**

The rearrangement of 2-methylcyclohexanone-derived vinyl cation (4.6) showed that a 2° alkyl group migrates in preference to a 1° alkyl group. I next synthesized α-chlorocyclohexanone derivative 4.13, in which either a 1° alkyl chain or a chloro-
substituted alkyl group could migrate. Chlorine is an inductively electron withdrawing group, which makes it’s attached carbon electropositive. This would reduce that carbon’s ability to stabilize the vinyl cation, and should affect the group’s migratory aptitude (Figure 4.3).

![Figure 4.3 Inductive effect of chlorine](image)

The α-halogen effect has been studied for the Baeyer-Villiger oxidation in terms of migratory aptitude and regioselectivity.\(^{203}\) α-Chloro ketones (i.e. 4.10) exhibited a strong preference for the migration of the non-substituted alkyl group, which resulted in α-chlorolactones (i.e. 4.11) as the major products (Scheme 4.3a). The only instances that this preference was not observed was when there was an intrinsic stereoelectronic bias that influenced the primary effect of the Criegee intermediate.\(^{83, 203, 204}\) These results indicate that α-chloro-substituents are not as effective at stabilizing a positive charge compared to an unsubstituted 1° alkyl group, which leads to a lower migratory aptitude for the substituted side. With this in mind, I hypothesized that when γ-chloro-β-hydroxy-α-diazo ketone 4.13 is treated with (C\(_6\)F\(_5\))\(_3\)B, the unsubstituted alkyl group would migrate to give bicyclic cyclopentenone 4.14 as the major product (Scheme 4.3b).
γ-Chloro-β-hydroxy-α-diazo ketone 4.13 was prepared from lithiated 1-diazo-3,3-dimethylbutan-2-one and 2-chlorocyclohexanone and was treated with BCF in CH₂Cl₂. To my surprise, I isolated dione 4.17 as the major product (Scheme 4.4) instead of the bicyclic cyclopentenones 4.14 or 4.15. This product forms by capture of vinyl cation 4.15 by water or hydroxide to afford enol 4.16, which tautomerizes to dione 4.17. Vinyl cation 4.15 might be stabilized by the adjacent chloride, which would explain why the trapping with –OH occurred in this case when it did not with other substrates.

The stabilization of intermediate 4.15 may also explain why the expected product of C-H insertion (4.14, Scheme 4.5) was not observed. In accord with our proposed
reaction sequence, the necessary C-H insertion into the vinyl cation is likely driven by the formation of a more stable tertiary cation (4.19) which leads to the cyclopentenone products (4.21, observed when $X = H$). If the positive charge was already stabilized by a substituent on the adjacent carbon (i.e. 4.15 when $X = Cl$), the difference in energy between 4.15 and 4.19 may not be such that insertion is favored.

While dione 4.17 was not a product we originally predicted, it is the result of migration of the non-halogenated alkyl group, which agrees with the migratory aptitude observed under Baeyer-Villiger oxidation conditions.

This result, combined with that discussed in section 4.3.1, is consistent with the idea that migratory aptitude of substituents in the 1,2-shift of vinyl cations depends the ability of the migrating group to stabilize the cation (summarized in Table 4.2). In the case of the $\gamma$-methyl group, the 2° alkyl had a higher migratory aptitude compared with the 1° in a ratio of 6.5 : 1 (4.5a and 4.5b, entry 1). Conversely, the major product formed from $\gamma$-chloro 4.13 indicated that the $\gamma$-chloro-substituted alkyl group did not have a significant aptitude for migration (entry 2). Both of these results reflect that the more electron-dense side has a higher migratory aptitude, presumably because it more effectively stabilizes the vinyl cation.
To further examine our theory that migratory aptitude in the 1,2-rearrangement of vinyl cations depended on the migrating group’s ability to stabilize the cation, I synthesized a variety of β-hydroxy-α-diazo ketone substrates from lithiated 1-diazo-3,3-dimethylbutan-2-one and a selection of acyclic ketones. The ketone precursors were selected in order to test if the tendency for migration preference would match the trend seen in the Baeyer-Villiger reaction (methyl < 1° alkyl < 2° alkyl < 3° alkyl) summarized in Table 4.3.\textsuperscript{205,206}

The β-hydroxy-α-diazo ketones were treated with BCF in CH$_2$Cl$_2$ at 0 °C, and the ratio of the cyclopentenone regioisomers were determined by $^1$H NMR and isolation. Calculating the crude $^1$H NMR ratios was useful in providing a more complete representation of the results, as isolation of monocyclic cyclopentenone products was not
always straightforward. The products were typically quite volatile and sometimes would coelute with side products.

Entry 1 shows that a 1° alkyl chain had a higher migratory aptitude than a methyl group, where the cyclopentenone products (4.23a and 4.23b) that result from the rearrangement were observed in a ratio of 1.7 : 1. The products obtained by reaction of diazo ketone 4.24, which was designed to compare methyl migration to 2° migration, were too volatile to obtain a reliable yield (entry 2). However, the cyclopentenone that results from 2° migration (4.25a) was observed in the crude mixture and enough was recovered to obtain compound characterization. The product of methyl migration (4.25b) was not isolated or observed in the crude mixture.
Table 4.3 Migratory aptitude comparison of 1°, 2°, and 3° alkyl versus Me

\[
\begin{array}{cccc}
\text{Entry} & \text{Lewis acid} & \alpha\text{-diazo ketone} & \text{Products (% yield)} & \text{NMR ratio}\text{a} \\
1 & (C_6F_5)_3B & 4.22 & 4.23a \text{21%, (39%)a} & 4.23b 23% \\
 & & & 1.7 : 1 \\
2 & (C_6F_5)_3B & 4.24 & 4.25a & 4.25b \\
 & & & 1 : 0 \text{too volatile to isolate} \\
3 & (C_6F_5)_3B & 4.26 & 4.27a \text{(66%)a} & 4.27b 19% \\
 & & & 3.5 : 1 \\
4 & (C_6F_5)_3B & 4.28 & \text{no reaction} & \\
5 & \text{SnCl}_4 & & & \\
6 & BF_3 \text{OEt}_2 & & & \\
\end{array}
\]

\text{a Based on crude 1H NMR integrations}

\[\beta\text{-Hydroxy-}\alpha\text{-diazo ketone 4.26, which would lead to less volatile products compared with 4.25a and b, was also prepared and subjected to the Lewis acid conditions. In this case a 3.5 : 1 ratio of cyclopentenone products (4.27a and 4.27b) was observed by NMR of the crude reaction mixture (entry 3). In this example, the 2° alkyl group exhibited a higher migratory aptitude than the methyl group, though isolation of the major product (4.27a) was problematic due to coelution with a side product.}\]
Interestingly, the analog that was designed to compare the migratory aptitudes of a $3^\circ$ alkyl group to methyl (4.28, derived from pinacolone) did not effectively react with (C$_6$F$_5$)$_3$B (entry 4). We attributed this to the sterically blocked $-\text{OH}$ reaction site. I tested less bulky Lewis acids (SnCl$_4$ and BF$_3$·OEt$_2$) which unfortunately also failed to promote the reaction (entries 5-6). Therefore, at present we cannot directly compare the migratory aptitudes of a methyl group to a $3^\circ$ alkyl group, but based on the trend established so far we expect the $3^\circ$ alkyl group to have a higher migratory aptitude compared to methyl.

As discussed in chapter 4.3.1, a methyl-substituted cyclohexanone derivative exhibits a preference for the migration of the $2^\circ$ alkyl group over the $1^\circ$ in a ratio of 6.5 : 1 (see Table 4.1). I was interested in probing the reactivity of a vinyl cation derived from 2,2-dimethylcyclohexanone (4.29, Scheme 4.6). Formation of the sterically hindered $\beta$-hydroxy-$\alpha$-diazo ketone 4.30 required optimization, and was only ever achieved in 19% yield by running the aldol-type addition in dry hexanes. When diazo ketone 4.30 was treated with (C$_6$F$_5$)$_3$B, I only recovered starting material, which is reminiscent of the challenges that the pinacolone derivative (4.28) presented. I hoped that by decreasing the Lewis acid size, the reaction might proceed more efficiently, however SnCl$_4$ and BF$_3$ did not afford an appreciable amount of 4.31a or 4.31b but rather a complex mixture of products.

![Scheme 4.6 Effect of $\gamma,\gamma$-dimethyl group on reaction outcome](image-url)
In summary, the experimental trend for migratory aptitude of alkyl substituents on a vinyl cation is *methyl < 1° < 2°*. This trend is in agreement with that which was observable in the Baeyer-Villiger oxidation, and the aptitude can be attributed to the ability of the migrating group to stabilize the vinyl cation.

### 4.3.4. Attempt to determine the migratory aptitude of aromatic substituents compared with methyl

I next set out to compare the migratory aptitude of aromatic groups to that of alkyl substituents. Aromatic groups can stabilize positive charge through resonance, which is likely the reason they have a higher migratory aptitude than methyl or 1° alkyl groups in known rearrangements.\(^{207}\) In cationic rearrangements, it is generally recognized that phenyl groups migrate via a phenonium ion intermediate.\(^{208}\) Migration of an aryl group across a vinyl cation would proceed via a cation similar to 4.32 (Figure 4.4). Spiroarene cation 4.32 was computationally studied by Hoffman *et al.* who confirmed it had a level of stability based on molecular orbital theory.\(^{209}\)

![Figure 4.4 Stable phenonium ion](image)

Thus, I set out to test our hypothesis that an aryl group would migrate in preference to methyl. I was also interested to see if a benzylic group would have a higher migratory aptitude than a methyl group. Accordingly, I prepared β-hydroxy-α-diazo ketones 4.33 and 4.35 from lithiated 1-diazo-3,3-dimethylbutan-2-one and acetophenone and phenylacetone, respectively (Table 4.4).
Table 4.4 Comparison of migratory aptitude of phenyl and benzylic substituent versus methyl

![Lewis acid (1 equiv) on HO\(\cdot\)N\(\cdot\)2CH\(_2\)Cl\(_2\) leading to 3-methyl- and 3-phenylcyclopentenones](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>(\alpha)-diazo ketone</th>
<th>Products (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((C_6F_5)_3B)</td>
<td>4.33</td>
<td>(4.34a) (15%)(^a) + (4.34b) (2%)(^a)</td>
</tr>
<tr>
<td>2</td>
<td>SnCl(_4)</td>
<td>4.33</td>
<td>(4.34a) (15%)(^a) + (4.34b) (2%)(^a)</td>
</tr>
<tr>
<td>3</td>
<td>((C_6F_5)_3B)</td>
<td>4.35</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

\(^a\)Yield determined by \(^1\)H NMR from SnCl\(_4\)

After subjecting \(\beta\)-hydroxy-\(\alpha\)-diazo ketones 4.33 and 4.35 to BCF, I was disappointed to observe complicated mixtures of products. It appeared that, unlike the various alkyl substituents we had previously explored, the phenyl and benzylic derivatives were not amenable for C-H insertion in good yields. In subjecting diazo ketone 4.33 to SnCl\(_4\) conditions, I was able to determine from the 15:2 NMR yields of cyclopentenones 4.34a and 4.34b that a phenyl group has a higher migratory aptitude compared with a methyl group (entry 1, Table 4.4).\(^{210}\) Unfortunately, there were numerous side products that I was not able to isolate or characterize. Diazo ketone 4.35 also gave a complex mixture of products upon reaction with BCF, none of which could be isolated for characterization (entry 3).
Tethering aromaticity to a vinyl cation might create the opportunity for new side reactions to occur. The aromatic groups may be capable of reacting directly with the vinyl cation via electrophilic aromatic substitution (S$_{E}$Ar), going on to form numerous products that we were unable to isolate or assign structures to. This type of intramolecular S$_{E}$Ar reactivity with vinyl cations is known for the formation of six-membered rings.\textsuperscript{211} Additionally, the Brewer group is currently investigating the reactivity of aromatic diazo ketones (4.36), which we propose react with Lewis acids to form vinyl cations 4.37 and 4.37 and undergo an S$_{E}$Ar (Scheme 4.7, top). Jian Fang has prepared numerous tricyclic cyclopentenones (4.39) using this method.

Known:

![Scheme 4.7 Possible reaction pathways of vinyl cations formed from aromatic precursors](image)

This work:

Because vinyl cations can react in S$_{E}$Ar reactions to provide five-membered rings (i.e. 4.39), vinyl cation intermediates 4.41 and 4.42 might be problematic (Scheme 4.7,
bottom). We originally anticipated the benzylic group on vinyl cation 4.40 would undergo a 1,2-shift to generate vinyl cation 4.41, though this pathway may be in competition with S_{E,Ar} to provide indene 4.42. Even if the second vinyl cation (4.41) is formed, it might also react with the pendant aromatic group to give a different indene (4.44). However, these products were not isolated, so their presence was not confirmed.

It is possible to imagine similar competing reactions for the vinyl cation generated from the phenyl precursor 4.33, which could explain why the C-H insertion products 4.34a and 4.34b were observed in such low yields. Despite the issues with these two substrates, we were still interested in determining if there was a migratory preference between an aromatic group and an alkyl group. To this end, we sought other substrates that might minimize side reactions.

4.3.5. Migratory aptitude of a selection of tetralone derivatives: comparison of 1° alkyl to electron-poor aryl rings

My coworker, Magenta, explored how tetralone derivatives behaved in the 1,2-shift of vinyl cations and sought to define the relative migratory aptitudes of the aryl and 1° alkyl substituents. We hoped that locking the aryl group into a ring might prevent competing reactions (such as S_{E,Ar}, summarized in Scheme 4.7) due to the now unproductive orbital overlap (4.45 and 4.47, Figure 4.5). The orbitals in the conjugated π-system (4.45) would be perpendicular to the empty p-orbital of the vinyl cation.

Figure 4.5 Unproductive orbital overlap of tetralone-derived vinyl cations for S_{E,Ar}
In most examples from existing literature, tetralone gives low yields of the corresponding lactone from the Baeyer-Villiger oxidation,\textsuperscript{212, 213} possibly because this reaction relies on nucleophilic attack of a conjugated ketone, which the electrophilicity is low relative to other ketones. Alternatively, the Beckmann rearrangement typically affords high yields of the resulting lactams from tetralone derivatives.\textsuperscript{85, 214, 215} In the instance of an unsubstituted tetralone tosyl oxime \textit{4.48} (X = H), the group that is \textit{anti} to the leaving group will migrate to form lactam \textit{4.49} (X = H, entry 1, Table 4.5).\textsuperscript{85}

Table 4.5 Beckmann Rearrangement of 8-substituted tetralone derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield 4.49 (%)</th>
<th>Yield 4.50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>72%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>29%</td>
<td>57%</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>4%</td>
<td>88%</td>
</tr>
</tbody>
</table>

One unique feature of 8-chloro and 8-bromo-tetralone tosyl oximes \textit{4.48}, X = Cl and Br) was their ability to reverse the mechanism of migration in the Beckmann rearrangement. In these two cases, rather than benzyl migration occurring in concert with the tosyl group leaving to give cation \textit{4.51}, the \textit{peri} halogen instead initiated a substitution with the tosyl to afford an imino-halonium cation (\textit{4.52}, Scheme 4.8). This made migration of the alkyl group more favorable to give stabilized cation \textit{4.53} which in turn afforded lactam \textit{4.50} in 88% yield.
Scheme 4.8 Neighboring halogen participation changes migration mechanism in Beckmann rearrangement

To test if vinyl cations generated from tetralone substrates followed a similar migratory trend, Magenta set out to prepare a scope of derivatives. An initial practical challenge was the formation of the β-hydroxy-α-diazo ketone of the unsubstituted tetralone (4.54), which was attributed to the decreased electrophilicity, or possibly the acidity, of the ketone. To combat this, Magenta synthesized tetralone analogs that contained electron-withdrawing substituents on the aryl moiety (4.56 and 4.58, Table 4.6), which were more amenable to nucleophilic attack by the lithiated diazo ketone. The β-hydroxy-α-diazo ketones were then treated with BCF and the products were analyzed.
Table 4.6 Migratory aptitude of tetralone-derived vinyl cations

\[
\text{Entry} \quad \text{Compound} \quad R^1 \quad R^2 \quad R^3 \quad \text{Compounds (a and b)} \quad \text{Yield a} \quad \text{Yield b} \\
1 \quad 4.54^b \quad H \quad H \quad H \quad 4.55 \quad -- \quad -- \\
2 \quad 4.56 \quad H \quad NO_2 \quad H \quad 4.57 \quad n.d. \quad 29\% \\
3 \quad 4.58 \quad H \quad H \quad NO_2 \quad 4.59 \quad n.d. \quad 31\% \\
\]

*Could not prepare \(^b\)Not detected

The 7-nitrotetralone analog (4.56, entry 2) and the 6-nitro analog (4.58, entry 3) demonstrated an alkyl migratory preference, which provided cyclopentenones 4.57b and 4.59b in 29% and 31% yield, respectively. The products of aryl migration (4.57a and 4.59a) were not observed in either case. Interestingly, Magenta observed the original tetralone materials as minor side products in these reactions. This competing reaction is likely the result of a retro-aldol-type mechanism that regenerated the nitrotetralones and the α-diazo ketones.

These migratory aptitude results contrast with the expectation that an aryl group (even with an electron-withdrawing substituent) will better stabilize the cation generated from diazo X compared with a 1° alkyl group. A search to find similar migratory aptitude results in other cationic rearrangements did not come up with any comparable examples. \(p\)-Nitroacetophenone provides a single regioisomer in the Baeyer-Villiger oxidation that results from the nitrophenyl group migrating.\(^{216}\) However, methyl groups tend to have the lowest relative migratory aptitude compared with other groups, so this is
not surprising. At this point, it seems as though Magenta’s elucidation of the migratory aptitudes of nitrotetralones is unprecedented.

Further investigation, such as variation of the electronics of the tetralone, could provide better insight into the relative migratory aptitudes, however the synthesis of the β-hydroxy-α-diazo ketones X could remain a challenge.

4.4. Future Work

We have defined the relative migratory aptitudes of various substituents in the 1,2-shift of vinyl cations generated from diazo ketones. The missing pieces of the puzzle are due to the difficulties in preparing the β-hydroxy-α-diazo ketone vinyl cation precursors, or due to difficulty separating the products of the reaction.

For example, I attempted to prepare the β-hydroxy-α-diazo ketone 4.61 derived from 1-cyclopropylpentan-1-one (4.60) in order to test the migratory aptitude of a 1° alkyl chain compared with a cyclopropyl group (Scheme 4.9). The preparation of 1-cyclopropylpentan-1-one (4.60) from cyclopropanecarbonyl chloride required multiple purifications, as did β-hydroxy-α-diazo ketone 4.61 which as not high yielding. I was unable to obtain an appreciable quantity of pure diazo ketone 4.61 in order to test the migratory aptitudes of 1° or cyclopropyl groups. However, adjusting the purification may help to overcome this limitation going forward.
I was interested in this substrate because cyclopropyl vinyl cations similar to 4.63 are known for their powerful cation stabilizing effect due to their favorable “bisected” conformation (4.67, Figure 4.6). The vacant p-orbital of the vinyl cation (shaded) receives a donating effect from the orbitals of the cyclopropane ring. Looking to our proposed structures, this stabilizing effect could make vinyl cation 4.63, the vinyl cation that results from alkyl migration, the thermodynamically favored product of 1,2-shift in our reaction (Scheme 4.9). This would align with previous reports that 1° alkyl groups migrate in preference to cyclopropyl in the Baeyer-Villiger oxidation.

Figure 4.6 Stabilization of cyclopropyl vinyl cations
The other relative migratory aptitude I was interested in investigating was olefin versus 1° alkyl. In the Beckmann rearrangement, olefinic groups tend to not migrate, therefore fail to form the expected lactam (i.e. 4.68, Scheme 4.10a). For example, when 3,5-dimethyl-2-cyclohexenone oxime (4.68) was treated with polyphosphoric acid (PPA), only the syn isomer rearranged to afford the expected lactam (4.69) in which the alkyl group migrated (Scheme 4.10a).\textsuperscript{218} However, when the stereoconformation of the oxime was biased toward olefin migration (4.68-anti), the ring did not rearrange to afford lactam 4.70, and instead underwent a Wolff aromatization to afford 3,5-dimethylaniline. Due to this trend in reactivity, I was interested to investigate if alkyl groups would migrate in preference to olefins with our vinyl cation rearrangement (generated from 4.71) to form 4.72 and/or 4.73 (Scheme 4.10b).

\begin{flushright}
\begin{align*}
4.68-\text{syn} & \xrightarrow{\text{PPA}} 4.69 \\
4.68-\text{anti} & \xrightarrow{\text{PPA}} 4.70
\end{align*}
\end{flushright}

\begin{flushright}
\begin{align*}
\text{a. Beckmann rearrangement with 3,5-dimethyl-2-cyclohexenone oxime (Horning et al.)}^x
\end{align*}
\end{flushright}

\begin{flushright}
\begin{align*}
\text{b. Migratory preference of olefin versus alkyl group in vinyl cation rearrangement/C-H insertion}
\end{align*}
\end{flushright}

I was unable to prepare the required β-hydroxy-α-diazo ketone 4.71 using typical LDA conditions (entry 1, Table 4.7).\textsuperscript{80} While I was initially concerned that the intended aldol-type addition might produce a mixture of regioisomers (1,2-addition and 1,4-addition products), only unreacted starting materials were recovered. Certain Lewis acids
can enhance 1,2-addition products in Grignard reactions, though optimization is often necessary as some Lewis acids can reverse the selectivity depending on the organometallic reagent.\textsuperscript{219} I also had to take into account the compatibility of diazo ketone 4.74 with Lewis acids, as strong Lewis acids are known to decompose similar substrates.\textsuperscript{24}

Table 4.7 Conditions to prepare 4.71

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Additive</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>None</td>
<td>Pace et al.\textsuperscript{220}</td>
</tr>
<tr>
<td>2</td>
<td>Li</td>
<td>LiBr</td>
<td>PACE et al.\textsuperscript{220}</td>
</tr>
<tr>
<td>3</td>
<td>Cl\textsubscript{3}CeLi</td>
<td>None</td>
<td>Imamoto et al.\textsuperscript{221}</td>
</tr>
</tbody>
</table>

Pace et al. reported the use of the mild LiBr as an additive to their organolithium addition reactions.\textsuperscript{220} They were able to induce 1,2-addition specificity using commercially available organolithium reagents. Unfortunately, the addition of LiBr did not improve reactivity of my substrate (entry 2, Table 4.7).

Finally, I attempted to use the oxophilic Lewis acid cerium(III) chloride, as it is known to enhance 1,2-addition of Grignard and organolithium reagents in $\alpha,\beta$-unsaturated ketones.\textsuperscript{219, 221} This strategy required preparing the organocerium reagent prior to addition into cyclohexenone: $n$-BuLi was added to diazo ketone 4.74, which was then added to anhydrous CeCl$_3$, to which cyclohexenone was added (entry 3, Table 4.7). This order of events did not result in the desired $\beta$-hydroxy-$\alpha$-diazo ketone 4.71, and
instead the product of \(n\text{-BuLi adding to diazo ketone 4.74}\) was detected. Further work is needed to optimize this reaction to prepare \(\beta\text{-hydroxy-\(\alpha\)}\text{-diazo ketone 4.71}\).

When we originally set out to take advantage of the reactivity of vinyl cations, we were curious about intermolecular trapping of nucleophiles (i.e. solvent). However, this never came to fruition as the examples we initially perused consistently reacted in unpredictable ways to give several inseparable compounds. Now, with the stabilization effect of the \(\alpha\)-chloro substrate (4.13), it might be possible to revisit this intermolecular trapping idea.

![Scheme 4.11 Capture of stabilized vinyl cation X](image)

If the conditions were optimized so that nucleophile and Lewis acid were compatible, it is likely that \(\gamma\text{-chloro-}\(\beta\)\text{-hydroxy-\(\alpha\)}\text{-diazo ketone 4.13}\) could generate stabilized vinyl cation 4.15 in high conversion, which could then be trapped by selected nucleophiles, presenting a new way to take advantage of vinyl cations.

### 4.5. Conclusion

We have established the relative migratory aptitudes of a number of substituents in the 1,2-shift of vinyl cations generated from \(\beta\text{-hydroxy-\(\alpha\)}\text{-diazo ketones}. The trend generally shows that the substituent that can best stabilize the vinyl cation will migrate
more readily. Comparing alkyl substituents, the aptitude trend is $Me < 1^\circ < 2^\circ$. Between alkyl and aromatic groups, the methyl did not migrate in preference to unsubstituted phenyl groups, however the nitrotetralone analogs showed that $1^\circ$ alkyl migration occurred in preference to aryl. Overall, our migratory aptitude trend aligns with other trends seen with unsymmetric cationic rearrangements.
CHAPTER 5: DISPARATE REACTIVITY OF DIAZO CARBONYL VINYL CATIONS

5.1. Introduction

Chapters 3 and 4 discussed a new method to prepare cyclopentenones (5.4) via a C-H insertion of vinyl cations (5.3), which were generated by treating β-hydroxy-α-diazo ketones (5.1) with Lewis acids (Scheme 5.1). Previous work

![Scheme 5.1 Cyclopentenones via ring expansion/C-H insertion of vinyl cations](image)

We looked to expand this methodology using β-hydroxy-α-diazo esters (i.e. 5.5) to prepare γ-lactones (5.6), and β-hydroxy-α-diazo amides (5.7) to prepare γ-lactams (5.8) via the corresponding vinyl cation intermediates (Scheme 5.2). γ-Lactones and γ-lactams are both motifs that are prevalent in bioactive and medicinally important compounds, and there is continual effort to discover new methods to prepare these motifs (see sections 1.8 and 1.9 for a summary of their importance and current ways to make them).
This work

\[
\begin{align*}
\text{Scheme 5.2 Proposed method for } \gamma\text{-lactone and } \gamma\text{-lactam via C-H insertion of vinyl cations} \\
5.2. & \text{ } \text{sp}^3 \text{ C-H insertion adjacent to heteroatoms} \\
\text{From the outset of this work, we wondered if diazo esters and diazo amides would react in a similar way to the diazo ketones when treated with a Lewis acid. If C-H insertion was productive with the ester and amide diazo precursors, then the C-H insertion would occur adjacent to a heteroatom. The following is a sample of precedence for insertion adjacent to } O \text{ and } N \text{ heteroatoms from the literature.} \\
5.2.1. & \text{C-H insertion adjacent to oxygen} \\
\text{Our proposed method for the synthesis of } \gamma\text{-lactones would proceed through C-H insertion at the methyl of an } O\text{-methyl ester (Scheme 5.2a). I was unable to find any examples from a literature search in which C-H insertion on an } O\text{-methyl ester had been achieved. However, C-H insertion adjacent to oxygen in other functional groups is well-known. For example, transition metal-generated carbenes are can selectively insert at a C-H site that is adjacent to an oxygen atom when there are multiple potential sites of insertion.}^{222} \text{ A representative example is shown in Scheme 5.3. Here, Adams and coworkers treated diazo ketone 5.9 with } \text{Rh}_2(O\text{Ac})_4, \text{ which catalyzed an intramolecular }
\end{align*}
\]
C-H insertion at the C6 position, adjacent to the oxygen, to provide furanone 5.10 in 84% yield.\textsuperscript{223,224} The cyclopentanone product (5.11) that would result from C-H insertion at the C4 position was not detected.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_5.3.png}
\end{center}

**Scheme 5.3 Regiospecific Rh-carbenoid C-H insertion reaction**

Similarly, Davies and coworkers reported the C-H insertion of metal carbenes derived from diazo esters (5.12) with alkyl ethers. For example, they observed alkylated product 5.13, the result of a C-H insertion on the O-CH\textsubscript{3} of dimethoxyethane (Scheme 5.4). This was a useful expansion of the intermolecular branch of carbene insertion chemistry, and provides precedence for C-H insertion at an O-methyl position.\textsuperscript{225}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_5.4.png}
\end{center}

**Scheme 5.4 Carbene C-H insertion of alkoxy ethers**

The MacMillan group has developed a metallaphotoredox C-H insertion reaction, involving an iridium photocatalyst and a nickel transition-metal catalyst. This merged catalytic system promoted selective \textit{sp}\textsuperscript{3} C-H alkylation adjacent to heteroatoms, including oxygen and nitrogen (mechanism illustrated in Scheme 5.6).\textsuperscript{226} While there was no example of C-H insertion adjacent to an ester, there were two examples of insertion adjacent to ethers that afforded \(\alpha\)-alkylated oxetane 5.14 and furan 5.15 in high yield (Scheme 5.5).
The iridium and nickel-catalyzed metallaphotoredox reaction developed by MacMillan et al. occurred selectively at sp³ C-H bonds adjacent to oxygen (discussed above, Scheme 5.5), or nitrogen. The mechanism depicted in Scheme 5.6 highlights a selective insertion adjacent to nitrogen. The iridium photocatalyst abstracts an electron from quinuclidine, which is the electrophilic source that initiates C-H alkylation on the substrate (i.e. Prozac®, 5.16). Quinuclidine promotes selective alkylation adjacent to the heteroatoms (in this example, nitrogen, “path a”) even in the presence of C-H sites that are traditionally thought to be more reactive toward homolytic cleavage (for example, the benzylic C-H in “path b”, Scheme 5.6). This selectivity is known as polarity-matched hydrogen-atom transfer (HAT), which allows radical generation to occur at the site that may not be thermodynamically favorable. In this case, because the hydrogen abstractor was electrophilic, the radical was generated at the more hydrolytic C-H bond, which explains why insertion adjacent to nitrogen or oxygen is selective.
The nickel complex catalyzes the cross-coupling of radical \( \text{5.17} \) (from path a) and alkyl halide “R” sources. This work by the MacMillan group is a rare example of C-H insertion at an \( N \)-methyl amide site. 1-Methylazepan-2-one and \( N,N \)-dimethylacetamide were cross-coupled with (bromomethyl)cyclohexane to afford \( \text{5.20} \) and \( \text{5.21} \), respectively (Figure 5.1). The majority of the examples from this work resulted in insertion at a Boc-\( N \)-methyl C-H bond (i.e. \( N \)-Boc Prozac\textsuperscript{®}, \( \text{5.18} \), Scheme 5.6), which would have similar electronics to an amide. Alkylation of tetramethylurea was also successful (\( \text{5.22} \), Figure 5.1).

**Figure 5.1 Selected examples of C-H alkylation of \( \text{N-methyl carbonyls} \) (bond formed is highlighted in bold)**

\( \text{5.18} \)
A different example of C-H insertion at an N-methyl carbonyl was reported by Wang et al. in which an acetoxylation of N-methyl was directed by a Boc protecting group.\textsuperscript{227} The C-H insertion occurred exclusively at N-methyl-substituted positions, and substrates that lacked an N-methyl position (for example an N-methylene, when R = Me) did not react (i.e. \textbf{5.24}, Scheme 5.7).

\begin{align*}
\begin{array}{c}
\text{t-BuO} \rightleftharpoons \text{N} \rightleftharpoons \text{O} \\
\text{n-alkyl} \\
\text{R}
\end{array} \\
\xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol\%}) \text{ IOAc (1.6 equiv)} \text{ CH}_2\text{Cl}_2, 60 \degree \text{C}, 40 \text{ h}} \\
\begin{array}{c}
\text{t-BuO} \rightleftharpoons \text{N} \rightleftharpoons \text{OAc} \\
\text{n-alkyl} \\
\text{R}
\end{array}
\end{align*}

\textbf{5.23} \quad \textbf{5.24}

R = H, 83\% yield
R = Me, 0\% yield

\textbf{Scheme 5.7} Pd(OAc)\textsubscript{2}-catalyzed acetoxylation of N-methyl derivatives

An example of C-H insertion into a Boc-N-alkyl group is the intermolecular insertion of metal carbenoids generated from diazo carbynols to form β-amino esters. Davies and coworkers reported the highly regio-, enantio-, and diastereoselective insertion of rhodium carbenes (generated from diazo esters, \textbf{5.25}) into C-H bonds adjacent to an N-Boc group (i.e. \textbf{5.26}), which provided highly useful β-amino ester derivatives (\textbf{5.27}, Scheme 5.8).\textsuperscript{228}

\begin{align*}
\begin{array}{c}
\text{Ar} \rightleftharpoons \text{N}_2 \\
\text{MeO}_2\text{C}
\end{array} + \\
\begin{array}{c}
\text{Boc} \\
\text{N}
\end{array} \\
\xrightarrow{1. \text{ Rh}_2(S\text{-DOSP})_4 (1 \text{ mol\%})} \\
\xrightarrow{2. \text{ TFA}}
\begin{array}{c}
\text{Ar} \rightleftharpoons \text{N} \rightleftharpoons \text{H} \\
\text{MeO}_2\text{C} \\
\text{N}
\end{array}
\end{align*}

\textbf{5.25} \quad \textbf{5.26} \quad \textbf{5.27}

67-72\% yield
94\% \textit{ee}, 94\% \textit{de}

\textbf{Scheme 5.8} Carbene insertion adjacent to N-Boc cyclic amines

A broadened literature search revealed that N-alkyl amines are potential substrates for C-H functionalization adjacent to nitrogen.\textsuperscript{229} However, many challenges exist with basic amine substrates that are not apparent when deactivated amines are used (such as N-
Boc, above). For example, the amine may poison the catalyst, side reactions can occur, or aza-ylides can form as the exclusive product (see 5.30, Scheme 5.9, which was avoided by screening rhodium complexes).229

\[
\text{Scheme 5.9 Site-selective C-H insertion of Brucine}
\]

He et al. found that judicial selection of the rhodium species could catalyze highly site-selective C-H insertion on complex, biologically and pharmacologically active alkaloids (Scheme 5.9 and Scheme 5.10).229 Each of the substrates examined exhibited the same site-selectivity for insertion at the primary N-methyl group over the secondary methylene groups (for example 5.32, Scheme 5.10).

\[
\text{Scheme 5.10 Site-selective C-H insertion into N-methyl}
\]
5.3. C-H Insertion into vinyl cations generated from β-hydroxy-α-diazo esters and amides

Satisfied that there was precedence in the literature for C-H insertion reactions adjacent to heteroatoms, and minding the importance of the synthesis of γ-lactones and γ-lactams, I proceeded to prepare model substrates 5.5 and 5.7, which are directly comparable to our diazo ketone substrate that provided the highest yield of cyclopentenone, based on ring size and substitution at the site of insertion (5.1, see Scheme 5.1 and Scheme 5.2 and discussions of ring size in 3.4.2 and substitution at site of insertion in 3.4.3). 80

5.3.1. Synthesis of model substrate methyl 2-diazo-2-(1-hydroxycyclohexyl)acetate

5.5 and treatment with Lewis acids

Pellicciari and Padwa have previously treated ethyl 2-diazo-2-(1-hydroxycyclohexyl)acetate (5.33) with BF₃•OEt₂ to generate carbenium intermediates 5.35, 5.37, and 5.38 (Scheme 5.11). 96, 104 Depending on reaction conditions, fluorine anion captured vinyl cation 5.35, or ring expansion occurred followed by ring contraction to give allylic cation 5.38. The major products of these reactions were a result of inter- or intramolecular trapping of allylic cation 5.38, but no C-H insertion was observed.
In our earlier work, we discovered that SnCl₄ and (C₆F₅)₃B provided higher yields of cyclopentenones from β-hydroxy-α-diazo ketones compared with BF₃•OEt₂ (see Chapter 3.4.1). It was also noted that insertion at a methyl position was higher yielding than at a methylene position. With this in mind, we reexamined the reactivity of vinyl cations generated from diazo esters under these conditions optimized for C-H insertion. Methyl 2-diazo-2-(1-hydroxycyclohexyl)acetate (5.5) was prepared in 99% yield by treating cyclohexanone with lithiated methyl-2-diazoacetate. This model substrate was selected specifically because insertion would occur at a methyl position (Scheme 5.12).

Reaction of diazo ester 5.5 with (C₆F₅)₃B only led to a complex mixture of inseparable products. Treatment with SnCl₄, however, provided distinct products. The
crude reaction mixture was analyzed by quantitative $^1$H NMR and the products were isolated (Scheme 5.13).

As shown in Scheme 5.13, these products are consistent with those described by Padwa and Pellicciari (Scheme 5.11). In our case, the initially generated vinyl cation (5.43) was trapped by chloride ion to afford vinyl chloride 5.44 in 7% yield. This exocyclic vinyl cation (5.43) also underwent rearrangement to give cyclic vinyl cation 5.45, which is the intermediate we would expect to undergo C-H insertion to provide 5,7-bicyclic lactone 5.6. However, we did not observe any of the insertion product and instead, consistent with Padwa’s observations, cyclic vinyl cation 5.45 underwent a ring-contraction event to give allylic cation 5.46 which was captured by chloride to give allylic chloride 5.47 in 66% yield. Cation 5.46 could also undergo intramolecular cyclization of the pendant ester and subsequent hydrolysis to provide 5,6-bicyclic lactone 5.39 in 14% yield.
The ring contraction that led to allyl chloride 5.47 and 5,6-lactone 5.39 was a rearrangement event that was not observed when we subjected β-hydroxy-α-diazo ketones to Lewis acids. This provides experimental evidence that insertion adjacent to an ester is slow in comparison to a ketone, thus allowing ring contraction to occur. We proposed that this could be due to a high energy barrier that prevents the enoate 5.45 from rotating to the S-cis conformation of the ester, which would be necessary for insertion. Additionally, I could not find precedence in the literature for C-H insertion that occurred at an O-methyl ester site, so there may be other challenges associated with insertion with these functional groups. With that, we were curious if diazo amides would lead to vinyl cations that reacted similarly to the diazo esters or diazo ketones, or if they might have a unique reactivity.

5.3.2. Synthesis of Model Substrate 2-Diazo-2-(1-hydroxycyclohexyl)-N,N-dimethylacetamide

To see if vinyl cations generated from β-hydroxy-α-diazo amides would undergo C-H insertion, I prepared 2-diazo-2-(1-hydroxycyclohexyl)-N,N-dimethylacetamide (5.7) from 2-diazo-N,N-dimethylacetamide (5.50) and cyclohexanone (summarized in Scheme 5.14). This tertiary amide would not suffer the geometrical constraints seen for the ester.
Scheme 5.14 Synthesis of β-hydroxy-α-diazo amide 5.7

\[ \text{aq. Me}_2\text{NH, toluene, 160 °C, } \mu\text{w, 10 min 73% yield} \]

\[ \text{i. p-ABSA, Et}_3\text{N, MeCN} \]

\[ \text{ii. 15% aq KOH 89% yield} \]

\[ \text{i. p-ABSA, Et}_3\text{N, MeCN} \]

\[ \text{cyclohexanone, LDA THF, -78 °C 91% yield} \]

\[ \text{Scheme 5.14 Synthesis of β-hydroxy-α-diazo amide 5.7} \]

\( N,N\text{-Dimethyl-3-oxobutanamide (5.49)} \) was prepared by treating ketene precursor 5.48 with aqueous Me₂NH under microwave conditions, which provided 5.49 in a yield that was comparable to that reported by Du et al.\(^{231}\) who used a THF solution of Me₂NH. The β-ketoamide (5.49) was converted to 2-diazo-\( N,N\text{-dimethylacetamide (5.50)} \) by reaction with \( \text{para-acetamidobenzenesulfonyl azide (p-ABSA)} \) and Et₃N, followed by stirring in aqueous KOH to afford 5.50 in 89% yield. The use of p-ABSA in place of tosyl azide may have contributed to an increase in yield of 5.50 to 89% from 50%, which was originally reported by Bartlett et al.\(^{232}\) Diazo acetamide 5.50 was then used in an LDA-mediated aldol-type reaction with cyclohexanone to afford 5.7 in 91% yield.

5.3.3. Reaction of 2-Diazo-2-(1-hydroxycyclohexyl)-\( N,N\text{-dimethylacetamide with Lewis acids} \)

With β-hydroxy-α-diazo amide 5.7 in hand, I set out to test whether ring expansion/C-H insertion would proceed to give the corresponding bicyclic γ-lactam (5.8). A diverse selection of Lewis acids were screened for their efficiency. The solvents and reaction temperatures tested were based on solubility of the Lewis acid (summarized in Table 5.1).
Upon treatment of diazo amide 5.7 with (C₆F₅)₃B, a complex mixture of products was returned (entry 1). Switching Lewis acids to SnCl₄ provided vinyl chloride 5.51 as the major isolable product (28% yield, entry 2). Analysis of the crude reaction mixture by NMR indicated the presence of small quantities of bicyclic lactam 5.8, but this product could not be isolated cleanly.

We considered that the amide could competitively coordinate with strong Lewis acids, so we next turned our focus to lanthanide salts which are known to be highly oxophilic Lewis acids. Eu(fod)₃ gave a mixture of unknown products, while LaCl₃ did not promote the reaction and starting material was recovered (entries 3-4). Dy(OTf)₃ required the use of MeCN at 30 °C in order to observe liberation of nitrogen. The bicyclic lactam 5.8 was obtained in 13% yield (entry 5). In(OTf)₃ in CH₂Cl₂ gave minimal yields of the desired γ-lactam, and the corresponding vinyl triflate was isolated in 28% yield (entry 6).
Table 5.1 Screening of Lewis acid to prepare bicyclic lactam 5.8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid (1 equiv)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Yield 5.8 (%)</th>
<th>X</th>
<th>Yield 5.51&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;B</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SnCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0 °C</td>
<td>Inseparable mixture</td>
<td>Cl</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>Eu(fod)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40 °C</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>LaCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Dy(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MeCN</td>
<td>30 °C</td>
<td>13%</td>
<td>OTf</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>In(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0 °C</td>
<td>17%</td>
<td>OTf</td>
<td>28%</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>24%</td>
<td>OTf</td>
<td>25% (47%)</td>
</tr>
<tr>
<td>8</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>26%</td>
<td>OTf</td>
<td>25%</td>
</tr>
<tr>
<td>9</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MeCN</td>
<td>40 °C</td>
<td>24%</td>
<td>OTf</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>Mg(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40 °C</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>TMSOTf&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0 °C</td>
<td>0%</td>
<td>OTf</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>TMSOTf</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0 °C</td>
<td>6%</td>
<td>OTf</td>
<td>62%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield in parentheses was determined by <sup>19</sup>F NMR using 4-fluorobenzophenone as internal standard.  
<sup>b</sup>Included 1 equiv iPr<sub>2</sub>NEt.

Sc(OTf)<sub>3</sub> was next selected for its strong Lewis acidity and oxophilicity (entries 7-9). Regardless of increasing the stoichiometric equivalents of Lewis acid (entry 8), or switching to MeCN from CH<sub>2</sub>Cl<sub>2</sub> (entry 9), Sc(OTf)<sub>3</sub> consistently gave the lactam in 24-26% yield. In entry 7, NMR of the crude reaction mixture indicated that vinyl triflate 5.51 was the major product, but this product proved to be fairly unstable to purification.
by chromatography. Quantitative $^{19}$F NMR revealed a 47% yield of vinyl triflate 5.51, but purification gave an isolated yield of only 25%.

In an effort to reduce the equivalents of triflate anion in solution, β-hydroxy-α-diazo amide 5.7 was treated with Mg(OTf)$_2$ and TMSOTf. The Mg(OTf)$_2$ failed to promote the reaction — even after heating in CH$_2$Cl$_2$ to reflux — and only starting material was recovered (entry 10). Typical conditions for silylation of an alcohol using TMSOTf were used (entry 11), which failed to convert the starting material to product. However, in the absence of base, the TMSOTf promoted the elimination of the β-hydroxy, but had the undesired effect of giving the vinyl triflate in an increased isolated yield of 62% (entry 12).

It is important to note that the outcome of these reactions is significantly different than the outcome of the ketone 5.1 or ester derivatives 5.5. The ketone derivative productively undergoes one rearrangement event, without further ring contraction, which allows C-H insertion to occur giving cyclopentenones in good yield. In the case of the ester, the major products were derived by capture of a cation that formed after several rearrangement events. In the case of the amide derivative, the cation 5.53 is captured before rearrangement occurs (proposed sequence summarized in Scheme 5.15). The desired lactam (5.8) would be achieved after vinyl cation 5.53 ring expanded to give 5.54. The subsequent 1,5-hydride shift should result in resonance-stabilized cation 5.55, which would cyclize and deprotonate for afford 5.8.
We could not immediately determine why there was a disparity in reactivity between vinyl cations generated from diazo ketones, esters, and amides. Assuming the first steps of these reactions occur through identical mechanistic steps, the differing results would seem to indicate that the rate of various steps in the reaction sequence change depending on whether a diazo ketone, diazo ester, or diazo amide is used as starting material. To gain a better understanding of the effects that dictate the course of the reaction, we collaborated with the Hong group, who modeled this process computationally for each diazo carbonyl precursor.
5.4. Computational mechanistic study of the reaction of Lewis acids with $\beta$-hydroxy-$\alpha$-diazo carbonyls

The Hong group first set out to model the carbenium intermediates generated from a diazo ketone precursor to elucidate why these cations were well-suited for the ring expansion/C-H insertion sequence. With that information in hand, we hoped to computationally compare that mechanistic data with the less successful diazo ester and diazo amide systems.

5.4.1. Computational modeling of the reaction of 1-diazo-1-(1-hydroxycyclohexyl)-3-methylbutan-2-one (5.1) with ($C_6F_5$)$_3$B

The Hong group utilized a B3LYP-D3/6-311+G(d,p)-PCM(dichloromethane)//B3LYP-D3/6-311+G(d,p)-PCM(dichloromethane) method for the computational study of the reaction of diazo ketone 5.1 with BCF (results summarized in Figure 5.2). The rate-limiting step was determined to be the release of nitrogen from the diazonium ($5.57 \rightarrow$ TS2) to provide vinyl cation 5.2. The ring expansion to go from exocyclic vinyl cation 5.2 to cyclic vinyl cation 5.3 only has a 1.9 kcal/mol transition state (TS3) energy barrier, and is thermodynamically favored by 6.1 kcal/mol. After the ring expansion, there is virtually no energy barrier for the 1,5-hydride transfer ($5.3 \rightarrow$ TS4 $\rightarrow$ 5.58), ring closure ($5.58 \rightarrow$ TS5 $\rightarrow$ 5.59), or deprotonation to obtain the $\alpha,\beta$-unsaturated bicyclic cyclopentenone (5.4).
Figure 5.2 Computational study of vinyl cations derived from diazo ketone (data provided by Xin Hong and coworkers)

The fact that vinyl cation 5.2 is less thermodynamically stable than the ring expanded vinyl cation 5.3 could explain why capture of this vinyl cation was only observed in 10% yield with SnCl₄, and no product that matched the capture of this cation was ever isolated when BCF was used. The energy barrier to reach the ring expansion transition state (TS3) is also relatively low. This may indicate that vinyl cation 5.2 is transient in nature and rapidly converts to the following cation (5.3). This preliminary computational study provides evidence that rearrangement/C-H insertion is thermodynamically and kinetically favorable, which aligns with the fact that we isolated bicyclic cyclopentenone in 82% yield.
5.4.2. Computational modeling of the reaction of 2-diazo-2-(1-hydroxycyclohexyl)acetate (5.5) with Lewis acids

Pellicciari and Padwa have previously optimized the geometries of the carbenium intermediates that result from the reaction of methyl diazo acetate 5.5 with BF₃•OEt₂ using 6-31G* ab initio optimizations. The computational data implicated an overall thermodynamic explanation, in which the most energetically stable cation (5.46) was also the source of the major products isolated. However, the kinetic aspect of the cationic rearrangements remained vague. Through our collaboration with the Hong group, we have gained information about the transition states of the rearrangements of cations 5.43, 5.45, and 5.46, which builds on the work of Padwa and Pellicciari to provide a more complete picture.

5.4.2.1. Review of Pellicciari’s computational considerations

Pellicciari and Padwa used the 6-31G* basis set to optimize the energies and geometries of carbocations 5.43, 5.45, and 5.46 (values reported in Figure 5.3 were calculated in the absence of solvent). With each rearrangement, the carbocation became more thermodynamically stable. The rearrangement from 5.43 to 5.45 was accompanied by a relative energy stabilization of −2.9 kcal/mol, while the formation of allyl cation 5.46 was accompanied by a significant energy difference of −26.0 kcal/mol from 5.45.

![Optimized energies of carbenium intermediates at the 6-31G* level](image)

Figure 5.3 Optimized energies of carbenium intermediates at the 6-31G* level (data from Padwa, Pellicciari et al.)
Experimentally, the system studied by Padwa and Pellicciari provided only minor products that results from the capture of exocyclic vinyl cation (5.43), which was also true for our system. The allylic cation (5.46) was the source of the major products in both systems. However, neither they nor we observed products that would be the result of trapping the cyclic vinyl cation 5.45, despite it being more thermodynamically stable than the exocyclic vinyl cation. It might be that the transition state going from 5.45 to 5.46 is low enough that 5.45 is a relatively transient species, therefore the rate of trapping is slower than proceeding to allylic cation 5.46. At this time, more computational data is needed to verify this hypothesis.

5.4.2.2. Computational considerations for the potential of vinyl cation X to undergo C-H insertion

We were interested to gain further insight as to why C-H insertion was not observed with the diazo ester precursor. To build off of the work of Pellicciari and Padwa, Hong and coworkers optimized the geometries of cations 5.43, 5.45, and 5.46 at the B3LYP-D3/6-311+G(d,p)-PCM(dichloromethane)/B3LYP-D3/6-311+G(d,p)-PCM(dichloromethane) level, and provided us with geometry optimizations and transition state energies for the cyclic cation rearrangements (summarized in Figure 5.4). The latter structures in the sequence provided by the Hong group (5.61 – 5.63) were calculated to gain insight into the C-H insertion process.
As with the diazo ketone substrate (5.1, Figure 5.2), the rate determining step was the release of nitrogen from the diazonium, where the transition state energy barrier was 14.7 kcal/mol (5.60 → TS6). The ring expansion to give the cyclic vinyl cation (5.43 → TS7 → 5.45) has an energy barrier of only 2.5 kcal/mol. The cyclic vinyl cation (5.45) was more thermodynamically stable than the exocyclic vinyl cation (5.43), with an energy difference of −7.3 kcal/mol, which is more significant than the −2.9 kcal/mol difference calculated by Pellicciari et al. using 6-31G* (see Figure 5.3). Empirically, Pellicciari et al. and we identified products which resulted from anion capture of vinyl cation 5.43 in 6-7% yields, respectively, while vinyl cation 5.45 was not trapped to provide any significant product. This could indicate that cyclic vinyl cation 5.45 is more short-lived than exocyclic cation 5.43, and likely proceeds to the next intermediate in the
sequence at a faster rate than it is trapped by an anion. Based on experimental evidence, the next step is likely rearrangement to afford allylic cation 5.46 (not shown in Figure 5.4).

Alternatively, the reaction pathway that would lead to C-H insertion requires a 1,5-hydride shift (depicted in Figure 5.4). The data that Hong and coworkers provided us revealed that the energy barrier to the hydride shift transition state was significant relative to the overall sequence at 7.7 kcal/mol (5.45 → TS8). The geometry of the product of 1,5-hydride shift was optimized to be formaldehyde-coordinated acylium 5.61. We did not anticipate this intermediate, and it does not coincide with any product that we observed. The release of formaldehyde to provide acylium 5.62 appears to be energetically barrierless, therefore would prohibit the cyclization pathway to occur via TS9. This essentially disqualifies a C-H insertion sequence. At this time, the Hong group is in the process of modeling the sequence of cations that could lead to allylic cation 5.46.

We anticipate, based on experimental evidence, that this route will be more energetically accessible compared with the C-H insertion pathway. I expect that the transition state that goes from cyclic vinyl cation 5.45 to the allylic cation (5.46) will be lower or equal in energy to the transition state that leads to 1,5-hydride transfer (≥7.7 kcal/mol, 5.45 → TS8). This would explain why the major products that we and Pellicciari observed were the result of inter- and intramolecular reactions of allyl cation 5.46.

5.4.3. Computational modeling of the reaction of 2-diazo-2-(1-hydroxycyclohexyl)-N,N-dimethylacetamide (5.7) with (C₆F₅)₃B

Using the same basis set as in 5.4.1, the Hong group next investigated the reaction mechanism of the ring expansion and C-H insertion of diazo amide-derived cations
(results summarized in Figure 5.5). As with the diazo ketone and diazo ester, the rate determining step in this case was the release of nitrogen from the vinyl diazonium to provide the exocyclic vinyl cation ($5.52 \rightarrow \text{TS11} \rightarrow 5.53$). In fact, the transition state energy barriers in this step for ketone and amide diazoniums were the same (13.7 kcal/mol). The ring expansion step going from vinyl cation $5.53$ to vinyl cation $5.54$ was not thermodynamically favorable: the exocyclic vinyl cation ($5.53$) was 1.4 kcal/mol lower in energy than $5.54$. Additionally, the energy cost to reach the ring expansion transition state is somewhat high at 8.1 kcal/mol ($5.53 \rightarrow \text{TS12}$). This is in contrast to the diazo ketone and diazo ester-derived vinyl cations, which provided rearranged vinyl cations that were 6.1 kcal/mol and 7.5 kcal/mol more stable, respectively, than their corresponding exocyclic cations.

We suspect that this difference in reactivity and stability of the exocyclic vinyl cations is due to the differing electron withdrawing powers these carbonyls display. Because the amide is less electron withdrawing, it would not destabilize the adjacent cation ($5.53$), which may be the key to drive the rearrangement step.
If and when ring expansion is achieved to generate vinyl cation 5.54, the 1,5-hydride shift would occur to provide the resonance-stabilized primary cation (5.54 $\rightarrow$ TS13 $\rightarrow$ 5.55), which is extremely low in energy. The cyclization step occurs via TS14, which has a high energy barrier of 18.7 kcal/mol, though it could be that the exothermicity of the hydride transfer (TS13 $\rightarrow$ 5.55) give sufficient energy to overcome this obstacle. Finally, the formation of $\alpha,\beta$-unsaturated lactam 5.8 is essentially barrierless after tertiary cation 5.56 is generated through the cyclization step.

Unlike the diazo ketone, overcoming the ring expansion transition state is more energetically expensive for the diazo amide at 8.1 kcal/mol (5.53 $\rightarrow$ TS12, compared with only 2.1 kcal/mol for the diazo ketone). This aligns with my experimental results in which capture of vinyl cation 5.53 with anion provided vinyl triflate 5.51 as the major
product (up to 47% yield). This might indicate that intermolecular trapping of vinyl cation 5.53 is more facile than ring expansion, which would explain the incongruence in products observed compared with the reactions of diazo ketone and diazo ester.

5.4.4. Comparison of reaction coordinates of diazo amide, diazo ketone, and diazo ester

This computational study in collaboration with the Hong group has revealed a disparity in reaction pathways of the diazo carbonyl-generated vinyl cations. This theoretical data helped us to explain why we obtained different products from the treatment of each diazo carbonyl with Lewis acids.

In comparing the reaction coordinate diagrams of the cations generated from diazo ketones, diazo esters, and diazo amides, the successful ring expansion and C-H insertion of the ketone-derived substrate exhibited a favorable pathway in terms of kinetics and thermodynamics. That is, ring expansion was favorable, followed by a favorable 1,5-hydride shift and ring closing step.

The diazo ester-derived cations exhibited a sequence in which ring expansion was favorable, however there appears to be a competing pathway after ring expansion that prevents the necessary 1,5-hydride shift, and instead a ring contraction event likely happens. We need more information in order to elucidate why allylic cation formation is more favorable than 1,5-hydride shift to form 5.61 from C-H insertion of the diazo ester vinyl cations. This branching in pathways might be under kinetic control if the transition state to generate allylic cation 5.46 is lower in energy than the transition state that leads to 1,5-hydride shift and thus C-H insertion.
The diazo amide exocyclic vinyl cation (5.53) is thermodynamically more stable compared to the corresponding endocyclic vinyl cation (5.54), and it costs more energy to reach the ring expansion transition state (8.1 kcal/mol) compared with the ketone and ester vinyl cations (1.9 kcal/mol and 2.5 kcal/mol, respectively). If intermolecular capture of the exocyclic vinyl cation occurs more readily than ring expansion, exocyclic vinyl cation-trapped products would likely be the major products. From our product distribution, we can rationalize that ring expansion occurs (though likely much slower than intermolecular cation capture), which is followed by the highly energetically favorable 1,5-hydride shift and ring closure. This pathway would provide the bicyclic lactam product that we isolated in 25% yield.

This preliminary computational data coincides with our experimental results. We have been able to rationalize why diazo ketones, diazo esters, and diazo amides behave differently when subjected to Lewis acid conditions.

5.5. Conclusions

We have compared the reactivities of vinyl cations generated from diazo ketones, diazo esters, and diazo amides at an empirical and theoretical level. Early on, the isolation of different types of products from the reaction of each class of diazo carbonyl vinyl cations indicated a clear disparity. Diazo ketones showed an ability to undergo a ring expansion and C-H insertion reaction to form cyclopentenones. The diazo ester-derived cations appeared to undergo a series of rearrangements, the major products of which were derived from an allylic cation. No γ-lactone that resulted from C-H insertion of diazo ester vinyl cations was observed. Finally, the diazo amide-derived vinyl cations primarily led to exocyclic vinyl triflate products. However, small quantities of the
expected $\gamma$-lactam that results from C-H insertion was isolated, indicating that ring expansion might occur, but slower than intermolecular cation capture.

Our collaboration with the Hong group has been insightful. They have provided us with computational data that allowed us to rationalize why each class of diazo carbonyl leads to the different types of products. While we have not achieved our original goal that targeted the synthesis of $\gamma$-lactones and $\gamma$-lactams through C-H insertion into vinyl cations, we have elucidated why these reactions would be difficult, if not impossible, from an energetic perspective.
CHAPTER 6 : EXPERIMENTAL PROCEDURES AND CHARACTERIZATION

DATA

6.1. General Experimental Information

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware or in a microwave reactor tube. A rotary evaporator equipped with a water condenser and attached to a dry vacuum pump was used to concentrate reaction mixtures in vacuo.

Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), acetonitrile (MeCN), and toluene were purchased from Thermo Fischer Scientific and dried via a solvent dispensing system. Diisopropylamine (iPr$_2$NH) and triethylamine (Et$_3$N) were freshly distilled from CaH$_2$ prior to each use. Pyridine was fractionally distilled from KOH, then stored over 4Å mol sieves. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was fractionally distilled under vacuum, passed over basic alumina, then stored over 4Å mol sieves. All other commercially available reagents were obtained from suppliers and used without further purification.

Reactions were monitored using thin-layer chromatography (TLC) carried out on silica gel on glass plates or neutral alumina on foil plates. Visualization of TLC plates was achieved using ultraviolet light and ceric ammonium molybdate. Flash column chromatography was performed on silica gel (230-400 mesh) as well as on a CombiFlash® R$_f$ 150 system using RediSep® R$_f$ Gold silica columns, or on neutral alumina.
$^1$H NMR (400 MHz), $^{13}$C NMR (125 MHz), and $^{19}$F NMR (471 MHz) spectra were recorded using a Bruker Asend 500 MHz spectrometer at room temperature. $^1$H NMR chemical shifts are reported in ppm ($\delta$ units) downfield from tetramethylsilane, and $^{13}$C NMR spectra are referenced to the CDCl$_3$ signal at 77.0 ppm. IR data were collected on a Shimadzu IR Affinity-1 FTIR and the values are reported in wavenumbers. Exact mass analysis was performed on a Waters Xevo G2-XS LCMS-QTOF operated in positive ESI mode.

All $\alpha$-diazo carbonyls used are known compounds and were synthesized according to known procedures: $\alpha$-diazo ketones were prepared using known procedures by reacting diazomethane with the corresponding acid chlorides: [t-butyl], [i-propyl], [n-propyl], [n-butyl], and [ethyl]. Methyl 2-diazoacetate was prepared from methyl glycine HCl following known procedure.

**General experimental procedure for the preparation of $\beta$-hydroxy-$\alpha$-diazo carbonyls**

A 0.28M solution of LDA (1.5 equiv) [freshly prepared by addition of $n$-butyllithium in hexanes (1.5 equiv) to a solution of iPr$_2$NH (1.7 equiv) in THF (3 mL per mmol of $n$-butyllithium)] was added dropwise over 15 min down the side of a chilled flask containing a cold (−78 °C) stirred solution of ketone (1 equiv) and $\alpha$-diazo carbonyl (1.6 equiv) in THF (2 mL per mmol of ketone). The mixture was maintained at −78 °C until complete conversion was achieved as monitored by TLC. AcOH (0.5 M in THF, 1.6 equiv) was added at −78 °C with rapid stirring under N$_2$, then the mixture was taken out of the cold bath, uncapped, and 10 mL water was added. Layers were separated and aqueous layer was extracted with 15 mL EtOAc. Combined organic layers were
washed with saturated aqueous NaHCO₃ (30 mL), water (30 mL), brine (30 mL), and
dried over anhydrous CaCl₂. The solvent was removed in vacuo to provide an oily residue
that was subjected to chromatography to afford the desired β-hydroxy-α-diazo carbonyl.

**Tin(IV) chloride-promoted cyclopentenone formation**

A 1M solution of SnCl₄ in CH₂Cl₂ (1 equiv) was added quickly as a stream to a
stirred −20 °C solution of diazo ketone (1 equiv) in CH₂Cl₂ (20 mL/mmol of diazo
ketone). The bright yellow reaction mixture was stirred at −20 °C for 10 min during
which gas evolved and the solution’s color diminished. Saturated aqueous NaHCO₃ (20
mL) was added and the mixture was transferred to a separatory funnel with the aid of 10
mL CH₂Cl₂. The layers were separated, and the aqueous layer was extracted three times
with Et₂O (10 mL). The organic layers were combined and washed with water and brine,
dried over MgSO₄, and concentrated under vacuum that did not exceed 125 mmHg. The
residue was purified by silica gel flash column chromatography.

**Tris(pentafluorophenyl)borane-promoted cyclopentenone formation**

A −15 °C solution of 0.1M diazo ketone (1 equiv) in CH₂Cl₂ was rapidly added to a
stirred −15 °C solution of 0.1M tris(pentafluorophenyl)borane (1 equiv) in CH₂Cl₂. The
reaction mixture was stirred at −15 °C for 10 min during which gas evolved and the
solution’s color diminished. Saturated aqueous NaHCO₃ (20 mL) was added and the
mixture was transferred to a separatory funnel with the aid of 10 mL CH₂Cl₂. The layers
were separated, and the aqueous layer was extracted three times with Et₂O (10 mL). The
organic layers were combined and washed with water and brine, dried over MgSO₄, and
concentrated under vacuum that did not exceed 125 mmHg. The residue was purified by
silica gel flash column chromatography.
6.2. Experimental procedures and compound characterization for Chapter 2

**Ethyl 1-hydroxy-2-oxocyclohexanecarboxylate (2.51):**\(^{171}\) Synthesized by the conditions laid forth by Monguchi et al. \(^1\)H and \(^{13}\)C NMR matched previously reported values.\(^{171}\)

**Ethyl 1,2-bis((tert-butyldimethylsilyl)oxy)cyclohex-2-enecarboxylate (2.52):**\(^{67}\)

Prepared by the conditions laid forth by Bayir et al. \(^1\)H and \(^{13}\)C NMR matched previously reported values.\(^{67}\)

**1-(1,2-Bis((tert-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)ethanone (2.55):** In accordance with Demuth,\(^{173}\) ester 2.52 (1.332 g, 3.05 mmol) was dissolved in dry pentane (15 mL), added to a flame dried flask, and brought to 0 °C under nitrogen. All at once, 0.7M (trimethylsilyl)methyl lithium dissolved in THF (11.75 mL, 8.23 mmol) was added and reaction stirred at 0 °C. After 2 hours, MeOH (12 mL) was added, and reaction mixture was warmed to room temperature and stirred for one hour. Resulting homogenous solution was diluted with hexanes (10 mL) and washed with water (25 mL), and the layers were separated. The mixture was extracted three times with hexanes (15 mL), and the combined organic layers were dried over MgSO\(_4\) and concentrated in vacuo to give a pure colorless oil (1.135 g, 2.95 mmol, 97%). \((R_t = 0.69 \text{ in hexanes/EtOAc 8:1}); \) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.96 \((t, J = 4.1 \text{ Hz, } 1\text{H})\), 2.19 \((s, 3\text{H})\), 2.10 \((m, J = 3.7 \text{ Hz, } 2\text{H})\), 1.81 \((td, J = 12.5, 3.7 \text{ Hz, } 1\text{H})\), 1.68 \((m, 3\text{H})\), 0.90 \((s, 9\text{H})\), 0.88 \((s, 9\text{H})\), 0.15 \((s, 6\text{H})\), 0.13 \((d, 6\text{H})\). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 211.94, 149.81, 107.55, 83.00, 36.00, 26.62, 26.40, 26.23, 24.44, 19.13, 18.55, 18.28, -2.54, -2.67. MS (ESI): Calculated for \([\text{C}_{20}\text{H}_{41}\text{O}_5\text{Si}_2]^+:\) 385.2594. Found: 385.2614.
1-(1,2-Bis((tert-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)ethanol (2.59):

Ketone 2.55 (1.1722 g, 3.047 mmol) was dissolved in MeOH (15 mL) and stirred at 0 °C. NaBH₄ (470.7 mg, 12.443 mmol) was added to reaction in four parts over one hour. Resulting mixture was stirred at 0 °C for 15 minutes. Saturated aqueous NH₄Cl (20 mL) was added, followed by extraction using hexanes (3 × 20 mL). Combined organic layers were dried over MgSO₄, then concentrated in vacuo. Crude colorless solid was purified using column chromatography (8:1 hexanes/EtOAc, Rᶠ = 0.55 in hexanes/EtOAc 8:1). Pure colorless solid was obtained (988.4 mg, 2.556 mmol, 84%). ¹H NMR (500 MHz, CDCl₃): δ 4.88 (dd, J = 5.1 Hz, 3.0 Hz, 1H), 4.15 (q, J = 7.0 Hz, 1H), 2.43 (s, 1H), 2.05 (m, 2H), 1.74 (m, 1H), 1.62 (m, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.94 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 150.49, 108.08, 78.44, 71.69, 30.16, 26.31, 26.27, 26.06, 24.74, 18.98, 18.68, 18.50, 16.96, -2.78, -3.21, -3.80, -4.67. MS (ESI): Calculated for [C₂₀H₄₂NaO₃Si₂]⁺: 409.2570. Found: 409.2568.

2-((tert-Butyldimethylsilyl)oxy)-2-(1-hydroxyethyl)cyclohexanone (2.56): In accordance with Katz and Overman,¹⁷² alcohol 2.59 (799 mg, 2.1 mmol) was stirred in a mixture of MeCN (14 mL) and MeOH (28 mL) at 0 °C, to which AcOH (0.59 mL, 10.3 mmol) and CsF (947 mg, 6.23 mmol) were added. Reaction mixture was warmed to room temperature and stirred overnight, after which saturated aqueous NaHCO₃ (40 mL) was added. Resulting white solid was filtered off, liquid filtrate layers were separated, and aqueous layer was extracted using Et₂O (3 × 30 mL). Combined organic layers were washed with saturated NaHCO₃ (40 mL), then brine, and were dried over MgSO₄. Crude colorless solid was purified using column
chromatography (8:1 hexanes/EtOAc, $R_f = 0.21$ in hexanes/EtOAc 8:1) to provide 570 mg (quantitative yield) of the title compound as a colorless solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.22 (dq, $J = 10.1$ Hz, 6.3 Hz, 1H), 2.57 (m, 2H), 2.14 (d, $J = 10.0$ Hz, 1H), 2.02 (m, 2H), 1.83 (m, 1H), 1.71 (m, 2H), 1.24 (d, $J = 6.3$ Hz, 3H), 0.93 (s, 9H), 0.28 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 211.42, 85.19, 70.37, 39.77, 38.50, 27.71, 26.43, 22.42, 19.21, 16.84, -2.15, -2.75. MS (ESI): Calculated for [C$_{14}$H$_{28}$NaO$_3$Si]$^+$: 295.1705. Found: 295.1708.

**1-(1-((tert-Butyldimethylsilyl)oxy)-2-oxocyclohexyl)ethyl 2-bromoacetate (2.60):**

Bromoacetyl bromide (0.71 mL, 8.27 mmol) was added dropwise to a 0 °C solution of alcohol 2.56 (636 mg, 2.34 mmol) and pyridine (0.57 mL, 7.08 mmol) in dry CH$_2$Cl$_2$ (23 mL). The resulting pale yellow suspension was warmed to room temperature and stirred for 3 h. The mixture was cooled to 0 °C, at which point saturated aqueous NaHCO$_3$ (25 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic layers were then washed with saturated aqueous NH$_4$Cl (20 mL), water, and brine then dried over MgSO$_4$. The solvent was removed in vacuo, and resulting oily residue was purified using silica gel chromatography (hexanes/EtOAc 8:1, $R_f = 0.38$ in hexanes/EtOAc 8:1) to provide 798 mg (87% yield) of the desired bromoacetate as a colorless oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.49 (q, $J = 6.3$ Hz, 1H), 3.74 (d, $J = 1.4$ Hz, 2H), 2.47 (m, 2H), 2.05 (m, 2H), 1.80 (m, 1H), 1.67 (m, 3H), 1.31 (d, $J = 6.3$ Hz, 3H), 0.90 (s, 9H), 0.23 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 209.10, 166.83, 83.28, 74.45, 39.44, 39.27, 27.52, 26.15, 25.76, 22.34, 19.01, 13.45, -2.51, -2.82. MS (ESI): Calculated for [C$_{16}$H$_{30}$BrO$_3$Si]$^+$: 393.1097. Found: 393.1090.

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1-(1-((tert-Butyldimethylsilyl)oxy)-2-oxocyclohexyl)ethyl 2-diazoacetate (2.61): In accordance with Toma, T et al.,\textsuperscript{16} N,N'-ditosylhydrazine (279 mg, 0.82 mmol) was added to a 0 °C solution of bromoacetate 2.60 (160 mg, 0.41 mmol) in THF (4 mL), at which point DBU (0.31 mL, 2.07 mmol) was added dropwise. The mixture was stirred for 45 min at 0 °C, then saturated aqueous NaHCO\textsubscript{3} (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 10 mL). Combined organic layers were washed with saturated aqueous NH\textsubscript{4}Cl (15 mL), then with water (10 mL) and brine. Organic layer was dried over CaCl\textsubscript{2} and concentrated in vacuo. Purification of the crude residue using silica gel flash column chromatography (hexanes/EtOAc 5:1, \( R_f = 0.44 \)) in hexanes/EtOAc 5:1 provided 33 mg (24% yield) of the title compound as a yellow oil; \( ^1\text{H} \) NMR (500 MHz, CDCl\textsubscript{3}): \( \delta 4.32 (q, J = 6.2 \text{ Hz}, 1\text{H}), 3.78 (s, 1\text{H}), 2.52 (td, J = 13.8, 5.9 \text{ Hz}, 1\text{H}), 2.39-2.46 (m, 1\text{H}), 2.01-2.14 (m, 2\text{H}), 1.56-1.83 (m, 4\text{H}), 1.20 (d, J = 6.2 \text{ Hz}, 3\text{H}), 0.82 (s, 9\text{H}), 0.07 (s, 3\text{H}), 0.03 (s, 3\text{H}); \textsuperscript{13}\text{C} \) NMR (125 MHz, CDCl\textsubscript{3}): \( \delta 212.0, 161.4, 81.4, 70.9, 38.8, 37.2, 27.8, 25.7, 22.3, 17.9, 17.0, -3.6, -5.0; IR (film) 2928.1, 2114.0, 1728.4, 1697.4, 1473.6, 1381.0, 1249.9. MS (ESI): Calculated for [C\textsubscript{16}H\textsubscript{29}N\textsubscript{2}O\textsubscript{4}Si]\textsuperscript{+}: 341.1897. Found: 341.1895.

2-(1-((tert-Butyldimethylsilyl)oxy)ethyl)-2-hydroxycyclohexanone (2.62): Isolated as a minor side product (18% yield) from the procedure described to form diazo ester 2.61: \( R_f = 0.53 \) in hexanes/EtOAc 5:1 \( ^1\text{H} \) NMR (500 MHz, CDCl\textsubscript{3}): \( \delta 4.32 (q, J = 6.2 \text{ Hz}, 1\text{H}), 3.78 (s, 1\text{H}), 2.48-2.57 (m, 2\text{H}), \)
2.04-2.15 (m, 2H), 1.63-1.81 (m, 3H), 1.54-1.61 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 0.82 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 212.0, 161.4, 81.4, 70.9, 38.8, 37.2, 27.8, 25.7, 22.3, 17.9, 17.0, -3.6, -5.0.

**1-(1-((tert-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 3-oxobutanoate (2.64):**

Alcohol 2.56 (238 mg, 0.874 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.36 mL, 2.7 mmol) were refluxed in toluene (3.5 mL) for 30 min in accord with Clemens et al. Solution was allowed to cool, then was concentrated under reduced pressure. Crude brown residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc; \(R_f = 0.21\) in hexanes/EtOAc 8:1). Any remaining dioxinone was azeotroped with CH\(_2\)Cl\(_2\) under reduced pressure to give the title compound as a colorless oil (239 mg, 77% yield); \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) trace enol; ketone: \(\delta\) 5.50 (q, \(J = 6.3\) Hz, 1H), 3.36 (s, 2H), 2.53 (td, \(J = 13.7, 6.0\) Hz, 1H), 2.44 (td, \(J = 11.8, 4.8, 3.3\) Hz, 1H), 2.21 (s, 3H), 1.98-2.10 (m, 2H), 1.76-1.83 (m, 1H), 1.58-1.73 (m, 3H), 1.30 (d, \(J = 6.3\) Hz, 3H), 0.88 (s, 9H), 0.19 (s, 3H), 0.03 (s, 3H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 209.3, 200.0, 166.6, 83.5, 73.5, 50.0, 39.4, 39.3, 30.2, 27.5, 26.1, 22.4, 19.0, 13.5, -2.5, -2.8. MS (ESI): Calculated for [C\(_{18}\)H\(_{33}\)O\(_5\)Si]\(^+\): 357.2097. Found: 357.2097.

**1-(1-((tert-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-diazo-3-oxobutanoate (2.63):** In accordance with Davies et al.,\(^{234}\) Et\(_3\)N (0.94 mL, 6.74 mmol) was added in a single stream to a cold stirred solution (0 °C) of ketoester 2.64 (804 mg, 2.25 mmol) and \(p\)-acetamidosulfonyl azide (541 mg, 2.25 mmol) in MeCN (17 mL) and the solution was stirred until \(^1\text{H}\) NMR showed the reaction was complete. Solvent was removed in vacuo.
to give a pink solid that was triturated using Et₂O. Slurry was vacuum filtered over a frit, solids were washed twice with Et₂O (10 mL) and the filtrate was concentrated in vacuo. The crude residue was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 35% EtOAc) to give title compound as a slightly yellow oil (157 mg, 0.41 mmol, 98%): \( R_f = 0.21 \) in hexanes/EtOAc 1:1; \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 5.61 (q, \( J = 6.2 \) Hz, 1H), 2.52 (td, \( J = 13.6, 6.0 \) Hz, 1H), 2.42-2.45 (m, 1H), 2.40 (s, 3H), 2.12 (dq, 13.7, 2.9 Hz, 1H), 2.06 (ddq, \( J = 12.5, 6.4, 3.2 \) Hz, 1H), 1.77-1.84 (m, 1H), 1.55-1.75 (m, 3H), 1.35 (d, \( J = 6.3 \) Hz, 3H), 0.86 (s, 9H), 0.19 (s, 3H), 0.00 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 209.0, 189.7, 161.0, 100.0, 73.6, 39.5, 38.9, 28.3, 27.3, 26.0, 22.6, 18.8, 13.9, -2.6, -2.9. MS (ESI): Calculated for \([C_{18}H_{30}N_{2}O_{5}SiNa]^+\): 405.1822. Found: 405.1819.

8a-((tert-butyldimethylsilyl)oxy)-4-diazo-4a-hydroxy-1-methylhexahydro-1\(H\)-isochromen-3(4\(H\))-one (2.4):

Procedure A: Prepared in 21% yield in 2:1 cis/trans ratio from bromoacetate 2.60 as a side product in the formation of diazo ester 2.61.

Procedure B: A solution of diazo ester 2.61 (0.19 mmol in 5.8 mL THF) was added dropwise via syringe pump over 1 hour to a cold (–78 °C) solution of LiHMDS (0.26 mL of 0.9M solution dissolved in another 37 mL dry THF) and stirred at –78 °C for 1 hour. Saturated aqueous NH₄Cl (25 mL) was added to the cold solution and reaction mixture was allowed to warm at which point the layers were separated. Aqueous layer was extracted from three times with EtOAc (10 mL) and combined organic layers were washed with H₂O and brine, then dried over MgSO₄ and concentrated in vacuo.
Purification by silica gel flash column chromatography afforded 59 mg (90% yield) of the title compound in a 3:1 cis/trans ratio.

Procedure C: A 5% w/w aqueous solution of KOH (22 mL) was added to a solution of β-keto-α-diazo ester 2.63 (844 mg, 2.21 mmol) in MeCN (6.6 mL) and acetone (9 mL), and resulting orange slurry was stirred at 650 rpm. Reaction progress was monitored by 1H NMR instead of TLC and was typically done after 1 hour. The slurry was diluted with Et₂O (25 mL) and saturated aqueous NH₄Cl (15 mL), and the layers were separated. NH₄Cl salt was added to the aqueous layer until acidic, which was then extracted three times with Et₂O (15 mL). The combined organic layers were washed with H₂O (25 mL) and brine (25 mL), dried over anhydrous CaCl₂ and filtered. The filtrated was concentrated in vacuo and the light yellow solid was subjected to silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc) to provide 591 mg (78% yield) of the title compound as a yellow solid in 5:2 cis/trans ratio.

rel-(4aS,8aS)-4a-((tert-butyldimethylsilyl)oxy)-4-diazo-8a-hydroxy-1-methylhexahydro-1H-isochromen-3(4H)-one (2.4-trans): R_f = 0.15 in hexanes/EtOAc 5:1; 1H NMR (500 MHz, CDCl₃): δ 4.26 (q, J = 7.0 Hz, 1H), s (2.76, 1H), 1.94 (ddd, J = 14.3, 11.3, 3.7 Hz, 1H), 1.74-1.84 (m, 3H), 1.61-1.72 (m, 2H), 1.50 (d, J = 7.0 Hz, 3H), 1.42-1.52 (m, 1H), 1.19-1.30 (m, 1H), 0.91 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); 13C NMR (125 MHz, CDCl₃): δ 163.8, 81.1, 76.3, 70.0, 35.1, 32.9, 26.0, 22.2, 20.5, 18.3, 16.8, -2.2, -2.7; IR (film) 2998.7, 2950.3, 2853.8, 2098.6, 1659.6, 1475.6, 1367.6, 1305.9, 1241.3. MS (ESI):


rel-(4aS,8aR)-8a-((tert-butyldimethylsilyl)oxy)-4-diazo-4a-hydroxy-1-methylhexahydro-1H-isochromen-3(4H)-one (2.4-cis): R_f = 0.13 in hexanes/EtOAc 5:1 1H NMR (500 MHz, CDCl₃):
MHz, CDCl$_3$): $\delta$ 4.57 (bs, 1H), 2.66 (s, 1H), 2.10-2.20 (m, 1H), 1.87-1.95 (m, 3H), 1.78-1.87 (m, 1H), 1.52-1.73 (m, 4H), 1.38 (d, $J = 7.1$), 0.91 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H);
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 164.9, 75.2, 74.6, 72.4, 53.4, 35.9, 30.9, 25.7, 22.3, 20.8, 18.7, 14.7; IR (film) 2951.2, 2926.1, 2854.8, 2100.6, 1658.9, 1463.1, 1368.6, 1245.1. MS (ESI): Calculated for [C$_{16}$H$_{29}$N$_2$O$_4$Si]$: 341.1897$. Found: 341.1895.

5-Methyl-4-oxa-cyclodecyne-3,6-dione (2.5): A solution of diazo lactone 2.4 (0.10 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added in a single stream to a refluxing solution of SnCl$_4$ (0.1 mmol) in CH$_2$Cl$_2$ (1.6 mL). 0.5 mL of CH$_2$Cl$_2$ was used to rinse vial and needle that contained diazo lactone. The yellow refluxing solution was allowed to stir for 10 min, during which gas was liberated and solution became colorless. Reaction mixture was cooled to 0 °C and 5% aqueous NaHCO$_3$ (5 mL) was added. Layers were separated, and the aqueous layer was extracted using three 5 mL portions of CH$_2$Cl$_2$. Combined organic layers were washed with water then brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 95% EtOAc over 30 minutes) provided title compound (yields varied depending on cis/trans substrate): $R_f = 0.19$ in hexanes/EtOAc 1:1; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.19 (q, $J = 7.0$ Hz, 1H), 2.70 (ddd, $J = 14.4$, 9.6, 2.2 Hz, 1H), 2.46 (ddd, $J = 14.6$, 9.3, 3.0 Hz, 1H), 2.33-2.42 (m, 2H), 2.00-2.10 (m, 1H), 1.89-1.99 (m, 2H), 1.72 (dtd, $J = 14.0$, 9.1, 5.1 Hz, 1H), 1.47 (d, $J = 7.0$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 207.7, 153.0, 99.5, 79.3, 75.9, 40.2, 26.2, 23.6, 19.1, 16.5. MS (ESI): Calculated for [C$_{10}$H$_{13}$O$_3$]: 181.0865. Found: 181.0866.
6-Methyl-7oxa-1,4-dithiaspiro[4.9]tetradec-9-yn-8-one (2.76): In accord with Perni, ketone 2.5 (46 mg, 0.26 mmol), 1,2-ethanediethiol (0.03 mL, 0.36 mmol), and Amberlyst-15 (88 mg) were stirred in CHCl₃ (4 mL) at refluxing temperature for 24 hours. The suspension was filtered over a plug of fluorisil, which was wash with CH₂Cl₂ (3 × 10 mL) and the filtrate was concentrated under reduced pressure. The crude residue was subjected to silica gel flash column chromatography (hexanes/EtOAc, 1.5 : 1, Rᵣ = 0.59) to provide 42 mg (64% yield) of the title compound as a colorless solid; ¹H NMR (500 MHz, CDCl₃): δ 4.68 (q, J = 6.7 Hz, 1H), 3.79 (m, 2H), 3.37 (m, 2H), 2.43 (m, 3H), 2.34 (dd, J = 16.7, 7.1, 4.4 Hz, 1H), 2.00 (m, 1H), 1.92 (dtt, J = 14.6, 7.2, 3.5 Hz, 1H), 1.80 (m, 2H), 1.39 (d, J = 6.7 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 170.7, 164.4, 130.7, 77.5, 65.0, 43.7, 41.8, 41.7, 25.2, 25.1, 24.7, 17.9. MS (ESI): Calculated for [C₁₂H₁₇O₂S₂]⁺: 257.0670. Found: 257.0662.

5-Methyl-4-oxacyclodecyne-3-one (2.6): A suspension of thioketal 2.76 (38 mg, 0.15 mmol) and Raney-nickel (493 mg in H₂O) in THF (2mL) was attached to a H₂ balloon via a three way stopcock. The air in the reaction flask was evacuated and refilled with N₂ three times, then degassed and refilled with H₂ three times and stirred overnight. The mixture was filtered through Celite, which was rinsed with Et₂O. The filtrate was dried over Na₂SO₄ and filtered, then concentrated under reduced pressure to afford 19 mg (77% yield) of pure alkyne as a colorless oil; ¹H NMR (500 MHz, CDCl₃): δ 4.78 (q, J = 6.7 Hz, 1H), 2.29-2.49 (m, 4H), 1.80-1.89 (m, 1H), 1.53-1.79 (m, 5H), 1.38 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 174.3, 166.6, 128.6, 78.8, 30.6, 28.2, 26.93, 26.86, 24.9, 18.0. MS (ESI): Calculated for [C₁₀H₁₉O₂]⁺: 167.1072. Found: 167.1077.
6.3. Compound characterization for Chapter 3

Characterization data for \(\beta\)-hydroxy-\(\alpha\)-diazo ketones

1-Diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylbutan-2-one (3.25): Prepared from cyclohexanone (75 \(\mu\)L, 0.73 mmol) and 1-diazo-3,3-dimethyl-2-butanone (147 mg, 1.17 mmol) in 86% yield: \(R_f = 0.65\) (hexanes/EtOAc 4:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 4.61\) (s, 1H), 1.92 (dt, \(J = 12.8, 4.5\) Hz, 2H), 1.76 (dtt, \(J = 14.2, 10.7, 3.7\) Hz, 2H), 1.62-1.50 (m, 3H), 1.46 (ddt, \(J = 13.9, 9.1, 4.8\) Hz, 2H), 1.37-1.24 (m, 1H), 1.22 (s, 9H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 203.0, 72.0, 68.3, 44.8, 36.0, 26.5, 25.4, 21.9\); IR (film) 3397 (br), 2934, 2860, 2068, 1620, 1248. MS (ESI): Calculated for [C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\)Na]\(^+\): 247.1422. Found: 247.1422.

1-Diazo-1-(1-hydroxycyclohexyl)-3-methylbutan-2-one (3.26): Prepared from cyclohexanone (130 \(\mu\)L, 1.3 mmol) and 1-diazo-3-methyl-2-butanone (248 mg, 2.21 mmol) in 88% yield: \(R_f = 0.50\) (3.7:1 hexane/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 4.36\) (s, 1H), 2.81 (hept, \(J = 6.8\) Hz, 1H), 1.96-1.88 (m, 2H), 1.81-1.71 (m, 2H), 1.63-1.56 (m, 3H), 1.49-1.40 (m, 2H), 1.35-1.24 (m, 1H), 1.13 (d, \(J = 6.8\) Hz, 6H); \(^13\)C NMR (125 Mhz, CDCl\(_3\)) \(\delta 201.0, 72.0, 68.3, 44.8, 36.0, 26.5, 25.4, 21.9\); IR (film) 3397 (br), 2934, 2860, 2070, 1620, 1248. MS (ESI): Calculated for [C\(_{11}\)H\(_{18}\)N\(_2\)O\(_2\)Na]\(^+\): 233.1266. Found: 233.1263.

1-Diazo-1-(1-hydroxycyclobutyl)-3-methylbutan-2-one (3.35a): Prepared from cyclobutanone (62 mg, 0.89 mmol) and 1-diazo-3-methyl-2-butanone (159 mg, 1.42 mmol) in 75% yield: \(R_f = 0.25\) (hexanes/EtOAc 5:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 4.07\) (bs, 1H), 2.83 (hept, \(J = 6.8\) Hz, 1H), 2.36 (m, 2H),
2.22-2.17 (m, 2H), 1.95 (dtt, J = 11.4, 9.4, 4.6 Hz, 1H), 1.63 (dp, J = 11.3, 8.5 Hz, 1H),
1.12 (d, J = 6.8 Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 200.5, 73.0, 36.5, 35.6, 18.5,
13.5; IR (film) 3435 (br), 2972, 2873, 2074, 1624, 1258. MS (ESI): Calculated for
\([C_9H_{14}N_2O_2Na]^+\): 205.0953. Found 205.0956.

1-Diazo-1-(1-hydroxycyclopentyl)-3-methylbutan-2-one (3.35b): Prepared from
cyclopentanone (90 \(\mu\)l, 0.77 mmol) and 1-diazo-3-methyl-2-butanone
(143 mg, 1.23 mmol) in 75% yield: \(R_f = 0.47\) (5:1 hexanes/EtOAc); \(^1\)H
NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.04 (bs, 1H), 2.83 (hept, \(J = 6.8\) Hz, 1H),
2.13-2.04 (m, 2H), 1.94-1.85 (m, 2H), 1.76-1.64 (m, 4H), 1.14 (d, \(J = 6.8\) Hz, 6H); \(^{13}\)C
NMR (125 MHz, CDCl\(_3\)): \(\delta\) 201.0, 79.4, 70.5, 39.2, 36.4, 23.0, 18.5; IR (film) 3437 (br),
2970, 2073, 1624, 1254. MS (ESI): Calculated for \([C_{10}H_{17}N_2O_2]^+\): 197.1290. Found:
197.1279.

1-Diazo-1-(1-hydroxycycloheptyl)-3-methylbutan-2-one (3.35c): Prepared from
cycloheptanone (0.16 mL, 1.4 mmol) and 1-diazo-3-methyl-2-butanone
(155 mg, 1.38 mmol). Unreacted cycloheptanone and 1-diazo-3-methyl-
2-butanone were removed under reduced pressure over 12 h. The
resulting oily residue was dissolved in 5 mL 4:1 hexanes/EtOAc and filtered through a
plug of silica, which was then rinsed with 4:1 hexanes/EtOAc (5 mL \(\times\) 3). The filtrate
was concentrated \textit{in vacuo} to give 175 mg (59% yield) of the title compound as a yellow
oil: \(R_f = 0.52\) (hexanes/EtOAc 5:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.64 (s, 1H), 2.82
(hept, \(J = 6.8\) Hz, 1H), 2.07 (ddd, \(J = 14.4, 9.9, 1.6\) Hz, 2H), 1.83 (ddd, 14.4, 9.9, 1.6 Hz,
2H), 1.75-1.61 (m, 4H), 1.57-1.49 (m, 2H), 1.44-1.36 (m, 2H), 1.13 (d, \(J = 6.8\) Hz, 6H);
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 201.3, 74.9, 72.0, 40.1, 36.5, 29.1, 21.8, 18.5; IR (film)
1-Diazo-1-(1-hydroxycyclooctyl)-3-methylbutan-2-one (3.35d): Prepared from cyclooctanone (107 mg, 0.85 mmol) and 1-diazo-3-methyl-2-butanone (147 mg, 1.31 mmol). Silica gel chromatography did not fully removed cyclooctanone. Converted cyclooctanone to its corresponding semicarbazide\textsuperscript{235} and filtered to provide title compound in 40% yield over two steps; \( R_f = 0.26 \) (5:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 4.61 (s, 1H), 2.82 (hept, \( J = 6.9 \) Hz, 1H), 2.02 (ddd, \( J = 14.5, 9.5, 2.2 \) Hz, 2H), 1.88 (dd, \( J = 14.5, 9.5 \) Hz, 2H), 1.68-1.78 (m, 2H), 1.39-1.68 (m, 8H), 1.13 (d, \( J = 6.9 \) Hz, 6H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 201.3, 75.2, 70.7, 36.5, 34.5, 28.1, 24.7, 21.8, 18.6. MS (ESI): Calculated for [C\(_{14}\)H\(_{21}\)N\(_2\)N\(_2\)O\(_2\)]\(^+\): 261.1579. Found: 261.1568.

1-Diazo-1-(1-hydroxy cyclohexyl) butan-2-one (3.47): Prepared from cyclohexanone (170 \( \mu \)L, 1.6 mmol) and 1-diazo-2-butanone (275 mg, 2.80 mmol) in 90% yield: \( R_f = 0.26 \) (6:1 hexane/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.28 (s, 1H), 2.50 (q, \( J = 7.4 \) Hz, 2H), 1.97 – 1.90 (m, 2H), 1.81 – 1.70 (m, 2H), 1.63 – 1.54 (m, 3H), 1.50 – 1.42 (m, 2H), 1.35-1.24 (m, 1H), 1.14 (t, \( J = 7.4 \) Hz, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 197.3, 72.2, 70.9, 36.2, 32.0, 25.3, 21.8, 8.3; IR (film) 3441, 2931, 2854, 2067, 1626 cm\(^{-1}\). MS (ESI): Calculated for [C\(_{10}\)H\(_{16}\)N\(_2\)O\(_2\)Na]\(^+\): 219.1109. Found: 219.1119.
1-Diazo-1-(1-hydroxycyclohexyl)pentan-2-one (3.49): Prepared from cyclohexanone (170 μL, 1.7 mmol) and 1-diazo-2-pentanone (307 mg, 2.74 mmol) in 88% yield: \( R_f = 0.29 \) (6:1 hexane/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 4.33 (s, 1H), 2.44 (t, \( J = 7.4 \) Hz, 2H), 1.96-1.89 (m, 2H), 1.80 – 1.71 (m, 2H), 1.67 (h, \( J = 7.4 \) Hz, 2H), 1.62-1.55 (m, 3H), 1.49 – 1.41 (m, 2H), 1.34 – 1.24 (m, 1H), 0.95 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 196.9, 72.6, 71.9, 40.6, 36.2, 25.3, 21.8, 18.1, 13.6; IR (film) 3425, 2931, 2862, 2067, 1620 cm\(^{-1}\). MS (ESI): Calculated for \([C_{11}H_{18}N_2O_2Na]^+\) : 233.1266. Found: 233.1262.

1-Diazo-1-(1-hydroxycyclohexyl)-4-methylpentan-2-one (3.51): Prepared from cyclohexanone (0.10 mL, 0.10 mmol) and 1-diazo-4-methyl-2-pentanone (189 mg, 1.50 mmol) in 65% yield: \( R_f = 0.33 \) (6:1 hexane/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 4.39 (s, 1H), 2.32 (d, \( J = 7.1 \) Hz, 2H), 2.19-2.09 (m, 1H), 1.97-1.89 (m, 2H), 1.81-1.70 (m, 2H), 1.63-1.53 (m, 3H), 1.50-1.41 (m, 2H), 1.35 – 1.23 (m, 1H), 0.96 (d, \( J = 6.6 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 196.8, 73.1, 71.0, 47.5, 36.2, 26.0, 25.3, 22.4, 21.8; IR (film) 3340, 2931, 2862, 2075, 1589 cm\(^{-1}\). MS (ESI): Calculated for \([C_{12}H_{20}N_2O_2Na]^+\) : 247.1422. Found: 247.1418.

1-(4-(tert-Butyl)-1-hydroxycyclohexyl)-1-diazo-3,3-dimethylbutan-2-one (3.62): Prepared from 4-tert-butylcylohexanone (119 mg, 0.77 mmol) and 1-diazo-3,3-dimethyl-2-butanone (156 mg, 1.24 mmol) to give 53% yield of the pure major diastereomer: \( R_f = 0.55 \) (hexanes/EtOAc 8:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 4.56 (s, 1H), 2.09 (dp, \( J = 12.8, 4.3 \) Hz, 2H), 1.54-1.60 (m, 2H), 1.52 (dq, \( J = 12.8, 3.3 \) Hz, 2H), 1.34 (td, \( J = 13.1, 4.3 \) Hz, 2 H),
1.19 (s, 9H), 0.97 (tt, J = 11.6, 3.5 Hz, 1H), 0.84 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 202.8, 70.9, 68.6, 47.7, 44.7, 36.3, 32.4, 27.6, 26.5, 22.2; IR (film) 3503, 2955, 2870, 2068, 1620, 1296. MS (ESI): Calculated for [C$_{16}$H$_{28}$N$_2$O$_2$Na]$^+$: 303.2048. Found: 303.2043.

**1-Diazo-1-(1-hydroxy-4,4-dimethylcyclohexyl)-3,3-dimethylbutan-2-one (3.64):**

Prepared from 4,4-dimethylcyclohexanone (125 mg, 0.99 mmol) and 1-diazo-3,3-dimethyl-2-butanone (204 mg, 1.62 mmol) in 86% yield: $R_f = 0.64$ (hexanes/EtOAc 3.7:1); $^1$H NMR (500 MHz, CDCl$_3$): δ 4.50 (s, 1H), 1.93-1.85 (m, 2H), 1.71-1.59 (m, 4H), 1.22 (s, 9H), 1.21-1.15 (m, 2H), 0.95 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 202.7, 71.4, 68.2, 44.6, 34.4, 31.9, 30.7, 29.2, 26.4, 25.2; IR (film) 3439, 2953, 2928, 2068, 1599, 1306, 1200. MS (ESI): Calculated for [C$_{14}$H$_{24}$N$_2$O$_2$Na]$^+$: 275.1735. Found: 275.1737.

**1-Diazo-1-(4-hydroxy-1-tosylpiperidin-4-yl)-3,3-dimethylbutan-2-one (3.66):**

Prepared from 1-tosylpiperidin-4-one (249 mg, 0.98 mmol) and 1-diazo-3,3-dimethyl-2-butanone (184 mg, 1.46 mmol) in 65% yield: $R_f = 0.15$ (5:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 4.68 (s, 1H), 3.64 (d, J = 11.6 Hz, 2H), 2.74 (td, J = 12.1, 2.5 Hz, 2H), 2.43 (s, 3H), 2.05 (d, J = 11.6 Hz, 2H), 1.76 (td, J = 12.8, 4.3 Hz, 2H), 1.21 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 203.0, 143.6, 133.2, 129.7, 127.6, 68.9, 67.9, 44.8, 41.8, 35.0, 26.4, 21.5. MS (ESI): Calculated for [C$_{18}$H$_{25}$N$_3$O$_4$SNa]$^+$: 402.1463. Found: 402.1464.
4-Diazo-5-hydroxy-2-methyl-5-propylocan-3-one (3.68): Prepared from 4-heptanone (0.20 mL, 1.44 mmol) and 1-diazo-3-methyl-2-butane (164 mg, 1.46 mmol) in 61% yield: \( R_f = 0.63 \) (5:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.80 (s, 1H), 2.82 (hept, \( J = 6.8 \) Hz, 1H), 1.59-1.70 (m, 4H), 1.25-1.46 (m, 4H), 1.12 (d, \( J = 6.8 \) Hz, 6H), 0.90 (t, \( J = 7.4 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 201.3, 74.5, 69.2, 41.5, 36.5, 18.6, 17.0, 14.3. MS (ESI): Calculated for [C\(_{12}\)H\(_{22}\)N\(_2\)O\(_2\)Na]+: 249.1579. Found: 249.1577.

4-Diazo-5-hydroxy-2,2-dimethyl-5-propylocan-3-one (3.70): Prepared from 4-heptanone (0.12 mL, 0.86 mmol) and 1-diazo-3,3-dimethyl-2-butane (175 mg, 1.39 mmol). Unreacted 4-heptanone was removed under reduced pressure over 12 h. The resulting oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 35% yield: \( R_f = 0.66 \) (5:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.98 (s, 1H), 1.64 (ddt, \( J = 18.0 \), 14.0, 5.0 Hz, 4H), 1.26-1.46 (m, 4H), 1.22 (s, 9H), 0.91 (t, \( J = 7.4 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 202.9, 75.2, 66.6, 44.8, 41.2, 26.5, 17.1, 14.3; IR (film) 3475 (br), 2963, 2870, 2068, 1605, 1466, 1312, 1204. MS (ESI): Calculated for [C\(_{13}\)H\(_{24}\)N\(_2\)O\(_2\)Na]+: 263.1735. Found: 263.1732.

Characterization data for cyclopentenones and vinyl chlorides

2,2-Dimethyl-2,3,5,6,7,8-hexahydroazulen-1(4\(H\))-one (3.27): Prepared by subjecting diazo ketone 3.25 (0.14 mmol) to tin(IV) chloride in 83% yield or tris(pentafluorophenyl)borane in 88% yield: \( R_f = 0.27 \) (100% CH\(_2\)Cl\(_2\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 2.42 (dd, \( J = 6.5 \), 5.8 Hz, 2H), 2.37 (s, 2H), 2.30, (t, \( J = 5.6 \), 2H), 1.76-1.81 (m, 2H), 1.67-1.62 (m, 2H), 1.51-1.55 (m, 2H), 1.08 (s, 6H); \(^{13}\)C NMR
(125 MHz, CDCl$_3$): $\delta$ 213.2, 173.4, 139.4, 48.9, 43.1, 33.5, 31.3, 26.8, 26.4, 25.1, 23.8.


2-Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (3.28) and 1-Chloro-1-cyclohexylidene-3-methylbutan-2-one (3.29):

Prepared by subjecting diazo ketone 3.26 to tin(IV) chloride in 70% yield or tris(pentafluorophenyl)borane in 82% yield: ($R_f$ = 0.15 in 10:1 hexane/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.74 (dd, $J$ = 18.4, 6.7 Hz, 1H), 2.46 (dd, $J$ = 7.6, 6.7 Hz, 2H), 2.39 (pd, $J$ = 7.5, 2.5 Hz, 1H), 2.32-2.26 (m, 2H), 2.09 (d, $J$ = 18.4 Hz, 1H), 1.82-1.75 (m, 2H), 1.65 (pent, $J$ = 5.4 Hz, 2H), 1.53 (pent, $J$ = 5.4 Hz, 2H), 1.15 (d, $J$ = 7.7, 1.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.5, 174.9, 140.9, 40.8, 39.9, 33.5, 31.2, 26.7, 26.3, 23.6, 16.6. MS (ESI): Calculated for [C$_{11}$H$_{16}$ONa]$^+$: 187.1099. Found: 187.1096.

In addition, treatment with tin(IV) chloride gave 1-chloro-1-cyclohexylidene-3-methylbutan-2-one (3.29) in 10% yield: $R_f$ = 0.83 (100% CH$_2$Cl$_2$); $^1$H and $^{13}$C NMR data matched previously reported values.$^{236}$ MS (ESI): Calculated for [C$_{11}$H$_{18}$ClO]$^+$: 201.1046. Found 201.1046.

2-Methyl-2,3,5,6-tetrahydro-1(4H)-pentalenone (3.36a)$^{337}$ and 1-Chloro-1-cyclobutylidene-3-methylbutan-2-one (3.37a): The title vinyl chloride 3.37a was prepared by subjecting diazo ketone 3.35a to tin (IV) chloride in 68% yield; (100% CH$_2$Cl$_2$, $R_f$ = 0.81) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.39 (hept, $J$ = 6.8 Hz, 1H), 2.78 (tt, $J$ = 7.9, 2.4 Hz, 2H), 2.69 (tt, $J$ = 7.8, 2.4 Hz, 2H), 1.92 (p, $J$ = 7.8 Hz, 2H), 1.10
(d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 202.8, 139.1, 136.0, 41.4, 38.0, 33.2, 20.2, 18.2. MS (ESI): Calculated for [C$_9$H$_{14}$ClO]+: 173.0733. Found: 173.0730.

In addition, cyclopentenone 3.36a was observed as a minor product (<5%) in the crude reaction mixture. $^1$H NMR matched previously reported values.

2-Methyl-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3.36b)$^{238}$ and 1-Chloro-1-cyclopentylidene-3-methylbutan-2-one (3.37b):

Prepared by subjecting diazo ketone 3.35b to Lewis acidic conditions to provide cyclopentenone 3.36b in 21% yield from tin(IV) chloride or 60% yield from tris(pentafluorophenyl)borane: $R_f = 0.41$ (4:1 pentane/Et$_2$O); $^1$H NMR and $^{13}$C NMR spectral data match previously reported data.$^{238}$

In addition, tin(IV) chloride provided 30% yield of vinyl chloride 3.37b as a yellow oil: $R_f = 0.77$ (4:1 pentane/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.41 (hept, $J = 6.8$ Hz, 1H), 2.76 (tt, $J = 5.6$, 1.2 Hz, 2H), 2.55 (tt, $J = 5.6$, 1.0 Hz, 2H), 1.79 (p, $J = 5.6$ Hz, 2H), 1.71 (p, $J = 5.6$ Hz, 2H), 1.10 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 201.2, 161.3, 121.8, 36.6, 36.4, 35.3, 27.9, 25.0, 18.4. MS (ESI): Calculated for [C$_{10}$H$_{16}$ClO]+: 187.0890. Found: 187.0887.

2-Methyl-2,3,4,5,6,7,8,9-octahydro-1H-cyclopenta[8]annulen-1-one (3.36c) and 1-Chloro-1-cycloheptylidene-3-methylbutan-2-one (3.37c):

Prepared in 42% yield by subjecting diazo ketone 3.35c to tin(IV) chloride or in 66% yield from tris(pentafluorophenyl)borane: $R_f = 0.78$ (9:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.73 (dd, $J = 18.3$, 6.6 Hz, 1H), 2.49 (dd, $J = 7.9$, 5.0 Hz, 2H), 2.37 (pd, $J =$
7.4, 3.9 Hz, 1H), 2.33 (t, J = 6.5 Hz, 2H), 2.07 (d, J = 14.8 Hz, 1H), 1.75 (p, J = 6.7, 6.2 Hz, 2H), 1.53 (m, 2H), 1.44 (m, 4H), 1.15 (d, J = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 211.6, 173.4, 139.2, 39.9, 39.2, 30.2, 28.5, 27.2, 26.2, 25.7, 21.3, 16.8. MS (ESI): Calculated for [C$_{12}$H$_{19}$O]+: 179.1436. Found: 179.1433.

In addition, tin(IV) chloride returned 24% yield of 1-chloro-1-cycloheptylidene-3-methylbutan-2-one (3.37c): $R_f = 0.80$ in (9:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$): δ 3.33 (hept, J = 6.9 Hz, 1H), 2.51 (ddd, J = 13.2, 7.1, 5.1 Hz, 4H), 1.67 (dp, J = 16.6, 5.7 Hz, 4H), 1.57-1.48 (m, 4H), 1.11 (d, J = 6.9 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 203.0, 150.6, 124.7, 37.3, 34.7, 32.9, 29.2, 28.6, 27.8, 25.7, 18.2. MS (ESI): Calculated for [C$_{12}$H$_{20}$ClO]+: 215.1203. Found: 215.1202.

2,3,5,6,7,8-Hexahydroazulen-1(4H)-one (3.48): Prepared in 70% yield by subjecting diazo ketone 3.47 to tris(pentafluorophenyl)borane: $R_f = 0.34$ (3.7:1 hexane/EtOAc); $^1$H NMR and $^{13}$C NMR values match previously reported data.$^{239}$

3-Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (3.50): Prepared in 55% yield by subjecting diazo ketone 3.49 to tris(pentafluorophenyl)borane: $R_f = 0.15$ (5:1 hexane/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 2.70 (p, J = 6.8 Hz, 1H), 2.61 (dd, J = 18.6, 6.5 Hz, 1H), 2.48 (dt, J = 15.9, 6.0 Hz, 1 H), 2.41 (dt, J = 15.9, 6.0 Hz, 1 H), 2.35-2.24 (m, 2H), 1.99 (dd, J = 18.5, 1.5 Hz, 1H), 1.85-1.73 (m, 2H), 1.66-1.60 (m, 2H), 1.54-1.48 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.0, 180.9, 141.8, 43.2, 37.1, 31.5, 31.2, 26.5, 26.4, 23.2, 19.1. MS (ESI): Calculated for [C$_{11}$H$_{16}$ONa]+ : 187.1099. Found: 187.1097.
1-(Cyclohept-1-en-1-yl)-3-methylbut-3-en-1-one (3.53): Prepared in 77% yield by subjecting diazo ketone 3.51 to tris(pentafluorophenyl)borane: $R_f = 0.74$ (3.7:1 hexane/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.11 (t, $J = 6.7$ Hz, 1H), 4.90 (s, 1H), 4.74 (s, 1H), 3.38 (s, 2H), 2.52-2.47 (m, 2H), 2.37-2.31 (m, 2H), 1.81-1.76 (m, 2H), 1.75 (s, 3H), 1.57-1.52 (m, 2H), 1.48-1.42 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 199.2, 146.0, 145.2, 140.8, 113.9, 46.4, 32.3, 29.1, 26.1, 25.6, 22.8. MS (ESI): Calculated for [C$_{12}$H$_{18}$ONa]$^+$ : 201.1255. Found: 201.1251.

6-(tert-Butyl)-2,2-dimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (3.63): Prepared in 66% yield by subjecting diazo ketone 3.62 to tris(pentafluorophenyl)borane and 1 equiv of MgSO$_4$: $R_f = 0.21$ (9:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.64 (ddd, $J = 16.0$, 6.2, 3.5 Hz, 1H), 2.50 (ddd, $J = 16.2$, 5.7, 3.0 Hz, 1H), 2.30-2.39 (m, 1H), 2.35 (s, 2H), 1.88-2.02 (m, 2H), 1.16-1.28 (m, 2H), 1.08 (s, 3H), 1.07 (s, 3H), 0.89 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 213.3, 172.7, 138.8, 52.1, 48.7, 43.1, 34.0, 33.1, 27.9, 27.7, 27.2, 25.19, 25.15, 22.9. MS (ESI): Calculated for [C$_{16}$H$_{26}$ONa]$^+$ : 257.1881. Found: 257.1884.

2,2,6,6-Tetramethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (3.65): Prepared in 78% yield by subjecting diazo ketone 3.64 to tris(pentafluorophenyl)borane: $R_f = 0.60$ (3.7:1 hexane/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.4-2.34 (m, 2H), 2.33 (s, 2H), 2.26-2.20 (m, 2H), 1.55-1.50 (m, 2H), 1.45-1.40 (m, 2H), 1.07 (s, 6H), 0.98 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.8, 173.0, 139.3, 49.2, 43.4, 39.8, 39.0, 34.1, 29.3, 28.9, 25.6, 19.3. MS (ESI): Calculated for [C$_{14}$H$_{25}$O]$^+$: 207.1749. Found: 207.1757.
7,7-Dimethyl-3-tosyl-2,3,4,5,7,8-hexahydrocyclopenta[d]azepin-6(1H)-one (3.67):

Prepared in 50% yield by subjecting diazo ketone 3.66 to scandium(III) triflate in CH$_2$Cl$_2$ at 0 °C, and quenched by the same procedure as tin(IV) and borane conditions: $R_f = 0.49$ (1:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 3.42 (dd, $J = 5.9$, 7.5 Hz, 2H), 3.32 (dd, $J = 5.9$, 7.5 Hz, 2H), 2.66 (t, $J = 5.3$ Hz, 2H), 2.54 (t, $J = 5.4$ Hz, 2H), 2.42 (s, 3H), 2.38 (s, 2H), 1.07 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.6, 167.0, 143.4, 137.2, 136.4, 129.8, 127.0, 48.7, 47.1, 43.2, 34.9, 25.2, 25.1, 21.5. MS (ESI): Calculated for [C$_{18}$H$_{23}$NO$_3$S]+: 334.1577. Found: 334.1479.

5-Methyl-2,3-dipropylcyclopent-2-enone (3.69): Prepared in 33% yield by subjecting diazo ketone 3.68 to tris(pentafluorophenyl)borane: $R_f = 0.24$ (9:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.73 (dd, $J = 17.8$, 6.6 Hz, 1H), 2.38 (t, $J = 7.8$ Hz, 2H), 2.34 (pd, $J = 7.2$, 2.3 Hz, 1H), 2.14 (t, $J = 7.8$ Hz, 2H), 2.06 (d, $J = 17.7$ Hz, 1H), 1.51-1.61 (m, 2H), 1.34-1.44 (m, 2H), 1.15 (d, $J = 7.8$ Hz, 3H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.4, 171.9, 139.1, 39.5, 38.1, 33.0, 25.1, 21.9, 20.8, 16.8, 14.2, 14.1. MS (ESI): Calculated for [C$_{12}$H$_{20}$ONa]$^+$: 203.1412. Found: 203.1405.

5,5-Dimethyl-2,3-dipropylcyclopent-2-enone (3.71): Prepared in 63% yield by subjecting diazo ketone 3.70 to tris(pentafluorophenyl)borane: $R_f = 0.38$ (9:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.38 (dd, $J = 8.5$, 7.5 Hz, 2H), 2.35 (s, 2H), 2.14 (dd, $J = 9.0$, 7.5 Hz, 2H), 1.55 (h, $J = 7.5$ Hz, 2H), 1.41 (h, $J = 7.5$ Hz, 2H), 1.07 (s, 2H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz,
3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.0, 170.2, 137.6, 46.1, 42.6, 32.8, 25.2, 25.1, 21.8, 20.8, 14.1, 14.0. MS (ESI): Calculated for [C$_{13}$H$_{22}$ONa]$: 217.1568. Found: 217.1569.

6.4. Compound characterization for Chapter 4

Characterization data for β-hydroxy-α-diazo ketones

1-Diazo-1-(1-hydroxy-2-methylcyclohexyl)-3,3-dimethylbutan-2-one (4.4): Prepared from the reaction of 2-methylcyclohexanone (0.10 mL, 0.82 mmol) with 1-diazo-3,3-dimethyl-2-butanone (165 mg, 1.31 mmol). Unreacted 2-methylcyclohexanone was removed under high vacuum to give the title compound in 33% yield: $R_f$ = 0.54 (5:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.00 (s, 1H), 2.01-2.06 (m, 1H), 1.64-1.73 (m, 2H), 1.47-1.59 (m, 5H), 1.23 (s, 9H), 1.18-1.28 (m, 1H), 0.93 (d, $J$ = 6.0 Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$): $\delta$ 203.1, 74.1, 67.8, 44.9, 37.8, 37.7, 30.0, 26.5, 25.5, 21.5, 16.1. MS (ESI): Calculated for [C$_{13}$H$_{22}$N$_2$O$_2$Na]$^+$: 261.1579. Found: 261.1576.

1-(2-Chloro-1-hydroxycyclohexyl)-1-diazo-3,3-dimethylbutan-2-one (4.13): Prepared from 2-chlorocyclohexanone (95 mg, 0.70 mmol) and 1-diazo-3,3-dimethylbutan-2-one (143 mg, 1.13 mmol) in 79% yield: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.72 (dd, $J$ = 11.9, 4.9 Hz, 1H), 3.36 (s, 1H), 1.94-2.10 (m, 4H), 1.72-1.79 (m, 1H), 1.68 (tt, $J$ = 13.1, 4.0 Hz, 1H), 1.50-1.54 (m, 1H), 1.39 (qt, $J$ = 13.1, 4.1 Hz, 1H), 1.22 (s, 9H); $^{13}$C (125 MHz, CDCl$_3$): $\delta$ 200.0, 72.9, 70.6, 64.9, 44.5, 35.1, 32.3, 26.5, 25.5, 20.6. MS (ESI): Calculated for [C$_{12}$H$_{19}$ClN$_2$O$_2$Na]$^+$: 281.1033. Found: 281.1029.
4-Diazo-5-hydroxy-2,2,5-trimethyldecan-3-one (4.22): Prepared by the reaction of 2-heptanone (0.11 mL, 0.79 mmol) and 1-diazo-3,3-dimethylbutan-2-one (163 mg, 1.29 mmol) in 69% yield: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.92 (s, 1H), 1.80 (ddd, $J = 13.8, 11.1, 4.7$ Hz, 1H), 1.69 (ddd, $J = 13.8, 11.0, 4.8$ Hz, 1H), 1.38 (s, 3H), 1.25-1.36 (m, 6H), 1.23 (s, 9H), 0.88 (t, $J = 6.7$ Hz); $^{13}$C (125 MHz, CDCl$_3$): $\delta$ 202.8, 73.1, 67.5, 44.7, 41.4, 31.9, 26.5, 25.1, 24.2, 22.5, 14.0. MS (ESI): Calculated for [C$_{13}$H$_{24}$N$_2$O$_2$Na]$^+$: 263.1735. Found: 263.1732.

4-Diazo-5-hydroxy-2,2,5,6-tetramethylheptan-3-one (4.24): Prepared by the reaction of 3-methyl-2-butanone (0.11 mL, 1.0 mmol) and 1-diazo-3,3-dimethylbutan-2-one (200 mg, 1.58 mmol) in 56% yield: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.99 (s, 1H), 2.18 (hept, $J = 6.9$ Hz, 1H), 1.21 (s, 3H), 1.20 (s, 9H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$): $\delta$ 202.8, 76.1, 67.5, 44.7, 37.3, 26.4, 19.2, 18.1, 16.6. MS (ESI): Calculated for [C$_{11}$H$_{20}$N$_2$O$_2$Na]$^+$: 235.1422. Found: 235.1413.

5-Cyclohexyl-4-diazo-5-hydroxy-2,2-dimethylhexan-3-one (4.26): Prepared by the reaction of 1-cyclohexylethanone (0.14 mL, 1.00 mmol) and 1-diazo-3,3-dimethylbutan-2-one (243 mg, 1.64 mmol) in 48% yield: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.99 (s, 1H), 1.88 (dp, $J = 13.4, 2.9$ Hz, 1H), 1.78 (tt, $J = 12.2, 3.3$ Hz, 1H), 1.69-1.77 (m, 2H), 1.61 (dd, $J = 24.7, 12.2$, Hz, 2H), 1.22 (s, 3H), 1.19 (s, 9H), 1.11-1.17 (m, 1H), 0.89-1.10 (m, 3H); $^{13}$C (125 MHz, CDCl$_3$): $\delta$ 202.7, 75.8, 67.4, 47.9, 44.7, 28.6, 27.0, 26.6, 26.5, 26.42, 26.36, 20.3. MS (ESI): Calculated for [C$_{14}$H$_{25}$N$_2$O$_2$]$^+$: 253.1916. Found: 252.1923.
**4-Diazo-5-hydroxy-2,2,5,6,6-pentamethylheptan-3-one (4.28):** Prepared by the reaction of pinacolone (0.11 mL, 0.89 mmol) and 1-diazo-3,3-dimethylbutan-2-one (158 mg, 1.42 mmol) in 32% yield: $^1$H NMR (500 MHz, CDCl$_3$): δ 6.43 (s, 1H), 1.40 (s, 3H), 1.25 (s, 9H), 0.95 (s, 9H); $^{13}$C (125 MHz, CDCl$_3$): δ 203.5, 78.0, 44.9, 43.6, 26.5, 25.6, 21.7.

**1-Diazo-1-(1-hydroxy-2,2-dimethylcyclohexyl)-3,3-dimethylbutan-2-one (4.30):**

Prepared by the reaction of 2,2-dimethylcyclohexanone$^{240}$ (73 mg, 0.58 mmol) and 1-diazo-3,3-dimethylbutan-2-one (122 mg, 0.97 mmol) in 19% yield: $^1$H NMR (500 MHz, CDCl$_3$): δ 6.53 (s, 1H), 1.62-1.86 (m, 4H), 1.53 (t, J = 17.6 Hz, 2H), 1.35-1.47 (m, 1H), 1.24 (s, 9H), 1.11 (d, J = 12.0 Hz, 1H), 0.95 (s, 3H), 0.85 (s, 3H); $^{13}$C (125 MHz, CDCl$_3$): δ 203.9, 44.9, 43.2, 36.1, 32.1, 26.5, 23.3, 21.4, 20.7.

**4-Diazo-5-hydroxy-2,2-dimethyl-5-phenylhexan-3-one (4.33):** Prepared from the reaction of acetophenone (0.08 mL, 0.69 mmol) and 1-diazo-3,3-dimethylbutan-2-one (136 mg, 1.08 mmol) in 31% yield with the modification that dry hexanes were used in place of THF to dissolve acetophenone and diazo X: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.44 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 5.24 (s, 1H), 1.61 (s, 3H), 1.22 (s, 9H); $^{13}$C (125 MHz, CDCl$_3$): δ 202.1, 147.1, 128.4, 127.4, 124.3, 75.1, 69.4, 44.6, 28.9, 26.3. MS (ESI): Calculated for [C$_{14}$H$_{18}$N$_2$O$_2$Na]$^+$: 269.1266. Found: 269.1263.
4-Diazo-5-hydroxy-2,2,5-trimethyl-6-phenylhexan-3-one (4.35): Prepared from the reaction of 1-phenylpropan-2-one\(^2\)\(^{41}\) (90 mg, 0.67 mmol) and 1-diazo-3,3-dimethylbutan-2-one (139 mg, 1.10 mmol) in 81% yield:

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.19-7.35 (m, 3H), 7.14 (dd, \(J = 8.0, 1.7\) Hz, 2H), 5.07 (s, 1H), 3.21 (d, \(J = 13.2\) Hz, 1H), 3.02 (d, \(J = 13.2\) Hz, 1H), 1.34 (s, 3H), 1.23 (s, 9H); \(^13\)C (125 MHz, CDCl\(_3\)): \(\delta\) 203.4, 136.8, 130.2, 128.2, 126.9, 73.4, 67.9, 47.7, 44.7, 26.5, 24.5. MS (ESI): Calculated for [C\(_{15}\)H\(_{20}\)N\(_2\)O\(_2\)Na\]^+: 283.1422. Found: 283.1411.

Characterization data for migratory aptitude products

2,2,8-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4\(H\))-one (4.5a) and 2,2,4-trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4\(H\))-one (4.5b):

Prepared in 39% yield and 6% yield, respectively, by subjecting diazo ketone 4.4 to 1 equivalent of SnCl\(_4\):

2,2,8-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4\(H\))-one (4.5a): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.93 (qt, \(J = 7.4, 3.8\) Hz, 1H), 2.46 (dddd, \(J = 15.2, 12.1, 3.4, 1.4\) Hz, 1H), 2.37 (td, \(J = 5.7, 5.0, 2.0\) Hz, 1H), 2.35 (s, 1H), 2.34 (s, 1H), 1.86-1.93 (m, 1H), 1.71-1.85 (m, 3H), 1.46-1.55 (m, 1H), 1.34-1.44 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 1.00 (d, \(J = 7.2\) Hz, 3H); \(^13\)C (125 MHz, CDCl\(_3\)): \(\delta\) 213.2, 171.1, 143.3, 49.3, 42.9, 33.1, 32.9, 28.0, 27.0, 25.2, 25.0, 24.8, 17.5. MS (ESI): Calculated for [C\(_{15}\)H\(_{20}\)ONa\]^+: 215.1412. Found: 215.1413.

2,2,4-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4\(H\))-one (4.5b): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.65 (td, \(J = 7.4, 2.8\) Hz, 1H), 2.43 (d, \(J = 18.4\) Hz, 1H), 2.32 (d, \(J = 17.6\) Hz, 1H), 2.24-2.36 (m, 2H), 1.86-1.93 (m, 1H), 1.66-1.78 (m, 2H), 1.44-1.61 (m, 4H), 1.15
(d, J = 7.2 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H); $^{13}$C (125 MHz, CDCl$_3$): δ 211.7, 177.0, 138.4, 46.6, 42.7, 37.3, 33.7, 27.6, 26.6, 25.3, 25.1, 23.3, 17.6.

2-Chloro-7-pivaloylcycloheptanone (4.17): Prepared by treating diazo ketone 4.13 with 30 mol% tris(pentafluorophenyl)borane. NMR of the crude mixture showed 4.17 was the major product (45% yield), and was isolated in 45% yield in a 92 : 8 dr by silica gel flash column chromatography: MS (ESI): Calculated for [C$_{12}$H$_{19}$ClNaO]+: 253.0971. Found: 253.0967.

*Major diastereomer (92%)*: $^1$H NMR (500 MHz, CDCl$_3$): δ 4.80 (dd, J = 11.1, 3.7 Hz, 1H), 4.32 (dd, J = 10.5, 6.0 Hz, 1H), 2.24-2.32 (m, 1H), 2.00-2.09 (m, 1H), 1.78-1.99 (m, 4H), 1.44-1.58 (m, 1H), 1.27-1.38 (m, 1H), 1.17 (s, 9H); $^{13}$C (125 MHz, CDCl$_3$): δ 211.1, 202.2, 62.6, 57.8, 45.7, 35.9, 29.1, 27.3, 26.8, 25.9.

*Minor diastereomer (8%)*: $^1$H NMR (500 MHz, CDCl$_3$): δ 4.75 (dd, J = 7.1, 4.5 Hz, 1H), 4.16 (dd, J = 9.1 Hz, 4.0 Hz, 1H), 2.54 (td, J = 13.7, 4.1 Hz, 1H), 1.78-2.07 (m, 4H) 1.70-1.77 (m, 2H), 1.59-1.67 (m, 1H), 1.26 (s, 9H).

3,5,5-Trimethyl-2-pentylcyclopent-2-enone (4.23a) and 2,5,5-trimethyl-3-pentylcyclopent-2-enone (4.23b): Prepared by subjecting diazo ketone 4.22 to 1 equivalent of tris(pentafluorophenyl)borane. $^1$H NMR of the crude mixture showed a 1.7:1 ratio of 4.23a and 4.23b. Purification by silica gel flash column chromatography provided 4.23a as a pure oil in 21% yield and 39% calculated yield based on recovered 4.23b. 4.23b was provided as a pure oil in 23% yield.
3,5,5-Trimethyl-2-pentylcyclopent-2-enone (4.23a): $^1$H NMR (500 MHz, CDCl$_3$): δ 2.35 (s, 2H), 2.15 (t, $J$ = 7.6 Hz, 2H), 2.01 (s, 3H), 1.37 (p, $J$ = 15.2 Hz, 2H), 1.20-1.33 (m, 6H), 1.07 (s, 6H), 0.87 (t, $J$ = 7.0 Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$): δ 213.7, 166.28, 100.0, 48.7, 42.7, 31.7, 28.0, 25.1, 23.1, 22.7, 22.5, 17.0, 14.0. MS (ESI): Calculated for [C$_{13}$H$_{22}$NaO]$^+$: 195.1749. Found: 195.1747.

2,5,5-Trimethyl-3-pentylcyclopent-2-enone (4.23b): $^1$H NMR (500 MHz, CDCl$_3$): δ 2.38 (t, $J$ = 8.1, 1H), 2.35 (s, 2H), 1.69 (s, 3H), 1.51 (p, $J$ = 7.6, 2H), 1.25-1.40 (m, 6H), 1.08 (s, 6H), 0.90 (t, $J$ = 7.0, 3H); $^{13}$C (125 MHz, CDCl$_3$): δ 214.3, 170.6, 133.2, 46.4, 42.7, 31.7, 30.9, 26.9, 25.2, 22.4, 14.0, 8.2. MS (ESI): Calculated for [C$_{13}$H$_{22}$NaO]$^+$: 195.1749. Found: 195.1747.

2-Isopropyl-3,5,5-trimethylcyclopent-2-enone (4.25a): Prepared as the only regioisomer by subjecting diazo ketone 4.24 to 1 equivalent of tris(pentafluorophenyl)borane. Calculated yield based on $^1$H NMR after concentration was 15% yield using 1,3,5-trimethoxybenzene as an internal standard. Due to lack of the isolation of other side products, this yield appears so low due to the volatility of the cyclopentenone: $^1$H NMR (500 MHz, CDCl$_3$): δ 2.77 (hept, $J$ = 7.1 Hz, 1H), 2.31 (s, 2H), 2.02 (s, 3H), 1.15 (d, $J$ = 7.1 Hz, 6H), 1.04 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 213.4, 165.1, 141.9, 48.9, 42.5, 25.1, 24.8, 20.3, 17.2. MS (ESI): Calculated for [C$_{11}$H$_{18}$O]$^+$: 167.1436. Found: 167.1441.

2-Cyclohexyl-3,5,5-trimethylcyclopent-2-enone (4.27a) and 3-cyclohexyl-2,5,5-trimethylcyclopent-2-enone (4.27b): Prepared by subjecting diazo ketone 4.26 to 1 equivalent of
tris(pentafluorophenyl)borane. $^1$H NMR of the crude mixture showed a 3.6:1 ratio of 4.27a and 4.27b. Purification by silica gel flash column chromatography provided 4.27a in a mixture with a side product (calculated yield 66% yield based on $^1$H NMR and GS-MS) and 4.27b as a pure oil in 19% yield.

2-Cyclohexyl-3,5,5-trimethylcyclopent-2-enone (4.27a): $^1$H NMR (500 MHz, CDCl$_3$): δ 2.40 (tt, $J = 12.1$, 3.7 Hz, 1H), 2.31 (s, 2H), 2.04 (s, 3H), 1.82-1.96 (m, 1H), 1.57-1.80 (m, 4H), 1.45 (dp, $J = 11.7$, 2.4 Hz, 2H), 1.20-1.30 (m, 3H), 1.04 (s, 6H); $^{13}$C (125 MHz, CDCl$_3$): δ 213.6, 166.5, 141.2, 49.0, 42.6, 35.3, 30.0, 26.8, 26.5, 26.0, 25.1, 17.5. MS (ESI): Calculated for [C$_{14}$H$_{22}$O]$^+$: 207.1749. Found: 207.1750.

3-Cyclohexyl-2,5,5-trimethylcyclopent-2-enone (4.27b): $^1$H NMR (500 MHz, CDCl$_3$): δ 2.66 (tp, $J = 11.3$, 3.5 Hz, 1H), 2.33 (q, $J = 2.0$ Hz, 2H), 1.70-1.96 (m, 3H), 1.69 (t, $J = 2.0$ Hz, 3H), 1.57-1.67 (m, 3H), 1.18-1.41 (m, 5H), 1.07 (s, 6H); $^{13}$C (125 MHz, CDCl$_3$): δ 214.6, 174.7, 131.8, 43.3, 39.7, 31.6, 30.3, 26.1, 25.3, 22.7, 14.1. MS (ESI): Calculated for [C$_{14}$H$_{22}$O]$^+$: 207.1749. Found: 207.1754.

3,5,5-Trimethyl-2-phenylcyclopent-2-enone (4.34a)$^{210}$ and 2,5,5-trimethyl-3-phenylcyclopent-2-enone (4.34b)$^{210}$: Prepared by subjecting diazo ketone 4.33 to 1 equivalent of SnCl$_4$ in 15% and 2% yield, respectively. Yields of the title compounds were determined using quantitative $^1$H NMR with 1,3,5-trimethoxybenzene as an internal standard. $^1$H NMR values matched those previously reported.$^{210}$
6.5. Experimental procedures and compound characterization for Chapter 5

Preparation of 2-Diazo-\(\text{N},\text{N}\)-dimethylacetamide (5.50)

\[
\text{\includegraphics[width=0.8\textwidth]{diazo-n-n-dimethylacetamide.png}}
\]

\(\text{N},\text{N}\)-Dimethyl-3-oxobutanamide (5.49):\textsuperscript{231} Prepared in accordance with Du \textit{et al.} with the modification that 40\% aqueous dimethylamine was used instead of 2.0 M dimethylamine in THF. Silica gel flash column chromatography provided the title compound as colorless oil (73\% yield). \(^1\)H NMR matched previously reported values.\textsuperscript{231}

2-Diazo-\(\text{N},\text{N}\)-dimethylacetamide (5.50):\textsuperscript{232} Prepared from \(\beta\)-ketoamide 5.49 using the procedure specified by Bartlett \textit{et al.} with the modification that \(p\)-acetamidobenzensulfonyl azide (\(p\)-ABSA) was used in place of tosyl azide. After basic aqueous work up, the crude material was dissolved in EtOAc and eluted over a plug of neutral alumina using EtOAc. Filtrate was concentrated in vacuo to give pure \(\alpha\)-diazo amide 5.50 as a yellow oil that solidified upon standing in freezer (89\% yield). \(^1\)H matched previously reported values.\textsuperscript{232}

Characterization data for \(\beta\)-hydroxy-\(\alpha\)-diazo carbonyls

Methyl 2-diazo-2-(1-hydroxycyclohexyl)acetate (5.5):\textsuperscript{242} Prepared from cyclohexanone (0.10 mL, 0.97 mmol) and methyl 2-diazoacetate (159 mg, 1.59 mmol) in 99\% yield. \(^1\)H and \(^{13}\)C NMR matched previously reported values.\textsuperscript{242}
2-Diazo-2-(1-hydroxycyclohexyl)-N,N-dimethylacetamide (5.7): Prepared from cyclohexanone (0.17 mL, 1.65 mmol) and 2-diazo-N,N-dimethylacetamide 5.50 (290 mg, 2.56 mmol) following the general procedure. The crude residue was dissolved in 1:1 hexanes/EtOAc and passed over a plug of neutral alumina. Alumina was washed with 1:1 hexanes/EtOAc (3 x 20 mL). Filtrate was concentrated in vacuo pressure and further dried under reduced pressure on high vacuum line to give 318 mg (91% yield) of the title compound as a yellow oil: $R_f = 0.43$ (hexanes/EtOAc 7:1 on neutral alumina); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.10 (s, 1H), 2.97 (s, 6H), 1.62-1.79 (m, 6H), 1.43 (dq, $J = 10.6, 4.9$ Hz, 2H), 1.32 (tq, $J = 11.6, 6.5$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.0, 72.2, 58.0, 37.2, 36.5, 25.3, 22.8. MS (ESI): Calculated for [C$_{10}$H$_{17}$N$_2$O$_2$Na]$: 234.1218$. Found: 234.1213.

**Reaction of Methyl 2-Diazo-2-(1-hydroxycyclohexyl)acetate (5.5) with Lewis acids**

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<td>Detected as</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>SnCl$_4$</td>
<td>Cl</td>
<td>66%$^a$</td>
<td>7%$^a$</td>
<td>14%$^a$</td>
</tr>
</tbody>
</table>

$^a$Yield determined by $^1$H NMR using 4-chlorobenzaldehyde as internal standard.
Methyl 2-(chloromethyl)cyclohex-1-enecarboxylate (5.47): Isolated from the reaction of 5.5 (43 mg, 0.22 mmol) with 1M SnCl₄ (0.22 mL, 0.22 mmol) in 12% yield; observed by quantitative ¹H NMR in 66% using 4-chlorobenzaldehyde as an internal standard: \( R_f = 0.88 \) (100% CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ 4.40 (s, 2H), 3.75 (s, 3H), 2.29-2.34 (m, 4H), 1.59-1.67 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.2, 143.3, 129.1, 51.7, 44.9, 29.0, 26.7, 21.9, 21.8. MS (ESI): Calculated for [C₉H₁₄ClO₂]⁺: 189.0682. Found: 189.0665.

Methyl 2-chloro-2-cyclohexylideneacetate (5.44):⁴⁴ Observed by quantitative ¹H NMR in 7% yield using 4-chlorobenzaldehyde as an internal standard. ¹H NMR matched previously reported values.⁴⁴

4,5,6,7-Tetrahydroisobenzofuran-1(3H)-one (5.39):⁹⁶ Observed by quantitative ¹H NMR in 14% yield using 4-chlorobenzaldehyde as an internal standard. ¹H NMR matched previously reported values.⁹⁶

**Reaction of 2-Diazo-2-(1-hydroxycyclohexyl)-N,N-dimethylacetamide (5.7) with Lewis acids**

Lewis acid (0.5 mmol) was dissolved in CH₂Cl₂ (6 mL) and solution was stirred at indicated temperature for 5 min. A solution of β-hydroxy-α-diazo amide 5.7 (0.5 mmol) in CH₂Cl₂ (2 mL) was added via syringe to Lewis acid solution, and syringe was rinsed with 2 mL CH₂Cl₂, which was also added to the Lewis acid and stirred for 10 min. Reaction was cooled to 0 °C, and was quenched with 5% aqueous NaHCO₃ (10 mL). Layers were separated, and aqueous layer was extracted three times using CH₂Cl₂ (10 mL). Combined organic layers were washed with H₂O and brine, dried over MgSO₄ and
filtered. At this point if quantitative NMR was used, 4-fluorobenzophenone (0.25 mmol) was dissolved in organic filtrate, which was concentrated under vacuum. The crude residue was analyzed by qNMR when applicable, then was purified by silica gel flash column chromatography.

Table 6.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid (1 equiv)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Yield lactam 5.8 (%)</th>
<th>X</th>
<th>Yield vinyl amide 5.51 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dy(OTf)(_3)</td>
<td>MeCN</td>
<td>30 °C</td>
<td>13%</td>
<td>OTf</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>0 °C</td>
<td>17%</td>
<td>OTf</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>24%</td>
<td>OTf</td>
<td>25% (47%)(^a)</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)(_3)</td>
<td>MeCN</td>
<td>40 °C</td>
<td>24%</td>
<td>OTf</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>26%</td>
<td>OTf</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>B(C(_6)F(_5))(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Eu(fod)(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>40 °C</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf</td>
<td>CH(_2)Cl(_2)</td>
<td>0 °C</td>
<td>6%</td>
<td>OTf</td>
<td>62%</td>
</tr>
<tr>
<td>9</td>
<td>SnCl(_4)</td>
<td>CH(_2)Cl(_2)</td>
<td>0 °C</td>
<td>Inseparable mixture</td>
<td>Cl</td>
<td>28%</td>
</tr>
</tbody>
</table>

\(^a\)Yield in parentheses was determined by \(^{19}\)F NMR using 4-fluorobenzophenone as internal standard
Characterization data for products

2-Methyl-2,3,5,6,7,8-hexahydrocyclohepta[c]pyrrol-1(4H)-one (5.8): Obtained by reacting 5.7 with a Lewis acid. Results summarized in Table 6.1; \( R_f = 0.23 \) (100% Et₂O); \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 3.71 (s, 2H), 3.00 (s, 3H), 2.40 (td, \( J = 5.0, 1.2 \) Hz, 2H), 2.36 (dd, \( J = 6.7, 5.8 \) Hz, 2H), 1.78 (tt, \( J = 6.0, 3.8 \) Hz, 2H), 1.64 (dddd, \( J = 11.5, 7.4, 4.8, 2.1 \) Hz, 2H), 1.59 (ddt, \( J = 11.5, 7.6, 4.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 172.7, 151.6, 134.8, 55.7, 31.1, 29.7, 29.1, 27.3, 27.2, 25.2. MS (ESI): Calculated for [C₁₀H₁₆NO]⁺: 166.1232. Found: 166.1232.

1-Cyclohexylidene-2-(dimethylamino)-2-oxoethyl trifluoromethanesulfonate (5.51, \( X = \text{OTf} \)): Obtained by reacting 5.7 with a Lewis acid. Results summarized in entries 2-5 and 8, Table 6.1; \( R_f = 0.10 \) (hexanes/EtOAc 1:1 on silica gel); \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 3.05 (s, 3H), 3.00 (s, 3H), 2.36 (br s, 2H), 2.21 (t, \( J = 5.9 \) Hz, 2H), 1.55-1.69 (m, 6H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 162.4, 138.3, 131.7, 118.4 (q, \( J = 321 \) Hz), 38.1, 34.8, 29.3, 28.0, 26.8, 26.5, 25.7; \(^{19}\)F (471 MHz, CDCl₃): \( \delta \) –73.06 (s, 3F). MS (ESI): Calculated for [C₁₁H₁₇F₃NO₄S]⁺: 316.0830. Found: 316.0829.

2-Chloro-2-cyclohexylidene-N,N-dimethylacetamide (5.51, \( X = \text{Cl} \)): Obtained from 5.7 in 33% yield (entry 9, Table 6.1); \( R_f = 0.40 \) (hexanes/EtOAc 1:1 on silica gel); \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 3.03 (s, 3H), 3.00 (s, 3H), 2.37 (t, \( J = 6.0 \) Hz, 2H), 2.16 (t, \( J = 5.2 \) Hz, 2H), 1.54-1.66 (m, 6H); \(^{13}\)C NMR (125 Mhz, CDCl₃) \( \delta \) 166.2, 139.3, 114.8, 37.9, 34.5, 31.7, 29.8, 27.2, 26.6, 26.0. MS (ESI): Calculated for [C₁₀H₁₇ClNO]⁺: 202.0999. Found: 202.1001.
CHRONOLOGICAL BIBLIOGRAPHY

133. Y. Wei, C. Wang, X. Jiang, D. Xue, J. Li and J. Xiao, *Chemical Communications*, 2013, **49**, 5408-5410.
174. A. Bayir, Doctor of Philosophy, University of Vermont, 2015.
233. H. Tsuruta, T. Imamoto and K. Yamaguchi, *Chemical Communications*, 1999, **1703-1704**.
COMPREHENSIVE BIBLIOGRAPHY (IN ALPHABETICAL ORDER)


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