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An Exploration Of β-Hydroxy-α-Diazo Carbonyls In Synthesis: Fragmentation, Vinyl Cation Formation And Conjugate Addition Reactions

Jian Fang
University of Vermont

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AN EXPLORATION OF β-HYDROXY-α-DIAZO CARBONYLS IN SYNTHESIS: FRAGMENTATION, VINYL CATION FORMATION AND CONJUGATE ADDITION REACTIONS

A Dissertation Presented

by

Jian Fang

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 Department

August, 2020

Defense Date: May 27, 2020
Dissertation Examination Committee:

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Christopher Francklyn, Ph.D., Chairperson
Rory Waterman, Ph.D.
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Cynthia J. Forehand, Ph.D., Dean of the Graduate College
β-hydroxy-α-diazo carbonyl compounds have been shown to display diverse reactivity profiles that can lead to a variety of useful products. This specific combination of functional groups can react in several mechanistically distinct ways depending on the presence or absences of other groups within the molecule. For example, γ-silyloxy-β-hydroxy-α-diazo carbonyls react with Lewis acids via fragmentation reactions to generate tethered aldehyde ynoate or ynone products. A portion of this thesis describes how this methodology was applied toward the synthesis of an important bioactive natural product: aspidospermidine. β-Hydroxy-α-diazo carbonyls are also convenient precursors to vinyl cations. The vinyl cation is generated by loss of N₂ gas from a vinyl diazonium intermediate, which is formed by the dehydroxylation of a β-hydroxy-α-diazo carbonyl compound. A portion of this thesis investigated the intramolecular reaction between vinyl cations and aromatic rings to form tricyclic indenones and naphthanols. Importantly, this research has also shown that the vinyl diazonium intermediates are themselves a strong electrophilic intermediate that can react with nucleophiles in conjugate addition reactions. These reactions occur faster than loss of N₂. More specifically, this thesis describes our finding that vinyl diazonium ions can be trapped by indole derivatives to provide all-carbon quaternary centers in high yield. This reaction provides a novel method to prepare structurally complex products that contain a diazo functional group that can be taken advantage of in subsequent synthetic transformations.
CITATIONS

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


ACKNOWLEDGEMENTS

There is a long list for me to thank for the great supports and inspiration. Firstly, I want to say that joining Professor Matthias Brewer’s research group was the best decision I had made during my Ph.D. career. Matthias is a great mentor. He created a friendly and supportive research group that every member helps and respects each other. As an inquisitive student, I always brought different ideas to him, and I never got criticisms about how stupid those ideas were, but guidance on finding the problem and advice on optimizing. This kind of training finally minted a chemist who is confident to face problems and be creative.

I would also like to express my gratitude to my committee members, Professor José Madalengoitia and Professor Rory Waterman. Your offices are always open to my questions. Your advice and questions about my research are important for my improvement. Also, many thanks to my chairperson: Christopher Francklyn, for helping me through the defending at this COVID-19 time.

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It is hard to accomplish this thesis without help, support, and encouragement from my group mates. I had learned a lot from them like the passion of research, lab techniques, the optimism towards difficulties, and hard working. Dr. Geoffrey Giampa, Dr. Ram Dhakal, Dr. Sarah Cleary, Dr. Ramya Srinivasan, Dr. Nicolas Dodge, Magenta Hesinger, Evan Howard, Rebecca Bogart, Islamiyat Lawal, and Avery Peck, I enjoyed every
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To my parents, as a naughty child, I decided to pursue a different life and career. I know this was out of your expectation. But still, you decided to send the single child to the other side of the earth for his dream. Your support is very important to me and always in my mind.

Most importantly I want to thank my beloved wife Jun. When I first met you as a freshman in college, I couldn’t imagine that we can come through all these. As a great partner, you and I traveled from China to American, overcome difficulties in life, and fought to stay together. When I was down and hopeless, you are the only one who stood firmly beside me, cared for my interest in chemistry, and foreseen my success. Without you, I don’t have any chance to accomplish this.
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<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
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<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>ACS</td>
<td>American Chemical Society</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
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<tr>
<td>BCF</td>
<td>Tris(pentafluorophenyl)borane</td>
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<td>BF3•OEt2</td>
<td>Boron trifluoride diethyl etherate</td>
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<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
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<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
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<td>DFT</td>
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<td>Dimethylformamide</td>
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<td>Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)</td>
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<td>DTBMP</td>
<td>2,6-di-tert- butyl-4-methylpyridine</td>
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<td>DTBP</td>
<td>Di-tert-buty1 peroxide</td>
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<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
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<td>EAS</td>
<td>Electrophilic aromatic substitution</td>
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<td>Ethyl diazoacetate</td>
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<td>ee</td>
<td>Enantiomeric excess</td>
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<td>Et,SiH</td>
<td>Triethylsilane</td>
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<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas chromatography–mass spectrometry</td>
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<td>HAT</td>
<td>Hydrogen-atom transfer</td>
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<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
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<td>HOtBu</td>
<td>tert-Butyl alcohol</td>
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<td>HWE</td>
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<td>iPr</td>
<td>iso-Propyl</td>
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<tr>
<td>L.A.</td>
<td>Lewis acid</td>
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<td>La(OTf)₃</td>
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<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
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</tr>
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<tr>
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<td>Methanol</td>
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<td>Nuclear Overhauser effect</td>
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<td>Microwave</td>
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<td>n-Butyllithium</td>
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<td>N-Bromosuccinimide</td>
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<td>Nu</td>
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<td>Rh₂(pfb)₄</td>
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<tr>
<td>Sc(OTf)₃</td>
<td>Scandium(III) trifluoromethanesulfonate</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>TIPSOTF</td>
<td>Triisopropylsilyl trifluoromethanesulfonate</td>
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</tr>
<tr>
<td>TMSI</td>
<td>Trimethylsilyl iodide</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
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<tr>
<td>TOF</td>
<td>The turnover frequency</td>
</tr>
<tr>
<td>Ts</td>
<td>Toluenesulfonyl or “tosyl”</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
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<tr>
<td>TsN$_3$</td>
<td>Toluenesulfonyl azide or “tosyl” azide</td>
</tr>
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<td>$N, N'$-di-tosylhydrazide</td>
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Chapter 1 Background on α-diazo carbonyls, fragmentation reaction, dipolar cycloadditions, vinyl cation and total synthesis

Organic chemistry is the study of the structure properties and reactions of organic compounds. These compounds are based on carbon and hydrogen but may also contain other elements (called heteroatoms) such as oxygen, nitrogen, sulfur, phosphorus and halogens. Organic molecules form the basis of all earthly life. Organic chemistry provides fundamental knowledge of those molecules, helps to explain observations in biology, and most importantly protects human health through development of medicines. One important sub-field of organic chemistry is synthetic organic chemistry. Here, chemists make new organic molecules, which often help biochemists to understand biological systems and is an integral component for drug development. However, complex molecules are difficult to prepare effectively. In order to overcome synthetic challenges, organic chemists develop new reactions and study the mechanism, and active intermediates in these reactions. With adequate knowledge, these new reactions allow chemists to assemble small molecules into larger and more complex molecules with efficiency and economic benefits.

Research work in the Brewer group focuses on developing new synthetic methods for organic chemistry. Work in our group has led to the development of new ways to form or break carbon-carbon bonds and we have applied those methodologies to the synthesis of bioactive, and structurally complex natural products. This research requires in-depth knowledge of reaction mechanisms, creative design of the synthetic route, and good experiment skills. The strategy of our group is to understand a certain type of reactive intermediate, and use that understandings to develop new reactions that allow us
to synthesize different molecules. Over the past six years my research has focused on a
group of reactive chemicals: β-hydroxy-α-diazo carbonyls. This combination of
functional groups can undergo different reactions depending on the presence or absence
of other groups. My first project focused on applying our recently developed γ-silyloxy-
β-hydroxy-α-diazo carbonyl fragmentation reaction into a diastereoselective total
synthesis of Aspidospermine, an important natural alkaloid. Then, I focused my research
interest on a group of highly reactive intermediates: vinyl cations. Vinyl cations can be
generated from β-hydroxy-α-diazo ketones via a vinyl diazonium intermediate.
Importantly this route to vinyl cations is much milder than previous reported methods
that generate these species. I started to utilize the strongly electrophilic nature of vinyl
cation to develop different electrophilic aromatic substitution reactions (EAS), and I
showed that vinyl cations can react intramolecularly with aryl rings to form tricyclic
indenones and naphthanols. While tuning the reaction conditions, I discovered that the
vinyl diazonium intermediates we were using to generate vinyl cations could react as
electrophiles in a 1,4-conjugate addition reaction, which provides a new method to make
functionalized diazo compounds.

1.1 α-Diazo carbonyls
The diazo functional group is one of the most synthetically versatile groups
known. However, its versatility is coupled to a high reactivity and instablility. For
example diazo compounds decompose under thermal conditions to generate nitrogen gas
and a carbon carbene. However, it was recognized that when an electron withdrawing
carbonyl group is adjacent to the diazo group it can stabilize the diazo through
This modification provides a well-behaved precursor for different reactive species such as carbocations, carbenes, and carbon radicals.  

![Resonance structure of α-diazo carbonyl for stabilization](image)

**1.1.1 α-Diazo carbonyl preparation**

Since diazo compounds have numerous applications in organic synthesis, organic chemists have developed several useful methods to install diazo groups into molecules. Several useful and general methods are described below.

A convenient way to prepare diazoketones 1.4 involves reacting acid chlorides 1.3 with a stoichiometric amount of fresh diazo methane, generated from Diazald 1.1. Excess (2-3eq) diazo methane 1.2 is required to trap acidic byproducts which result in decomposition. Adding extra base into the reaction system to neutralize the acidic proton seems like a simple fix, but often may cause ketene side products to form from the acid chloride. Unfortunately, diazo methane 1.2 is a toxic and explosive gas, and requires extreme precaution when using.  

![Scheme 1.1 Arndt-Eistert reaction in preparation of diazocarbonyl](image)

Diazo transfer reactions are an alternative method to install a diazo group next to a carbonyl. These reactions are often a more convenient and safer way to prepare diazo compounds.
These reactions require a carbonyl compound with an electron withdrawing group at the β-position (1.5, 1.7), which reacts with a sulfonyl azide 1.9 in the presence of a base to generate a diazocarbonyl compound (1.6, 1.8). (Scheme 1.2)

\[ \text{EWG} \overset{\text{OR}}{\text{O}} \text{1.5} \xrightarrow{\text{R-SO}_2\text{N}_3} \text{EWG} \overset{\text{N}_2}{\text{O}} \text{1.6} + \text{R-SO}_2\text{NH}_2 \]

\[ \text{EWG} \overset{\text{R}}{\text{O}} \text{1.7} \xrightarrow{\text{Base}} \text{EWG} \overset{\text{N}_2}{\text{O}} \text{1.8} \]

\( \text{EWG} = \text{COR, COOR, CONR}_2, \text{SO}_2\text{R, NO}_2, \text{PO(OR)}_2 \)

Scheme 1.2 Diazotization in preparation of diazocarbonyl compound

Diazocarbonyls can also be prepared from α-amino ketones or α-amino esters through diazotization reactions.14(Scheme 1.3) An alternative route was developed by Fukuyama and his coworkers, which generates diazo esters 1.16 from reaction between α-bromo esters 1.15 and N,N-ditosylhydrazine. This reaction is highly efficient to convert primary or secondary alcohols to diazo esters, and it was applied by our group.15

\[ \text{R-OH} \text{1.12} + \text{Cl} \overset{\text{Br}}{\text{O}} \text{1.13} \xrightarrow{\text{TsNHNHTs, DBU, THF, 0 °C}} \text{R-O} \overset{\text{N}_2}{\text{O}} \text{1.15} \]

Scheme 1.3 Diazotization in preparation of diazo ester compounds
1.1.2 Diazo carbonyl compound functionalization

Even though a lot of diazo preparation methods have been reported, most of these reported methods require highly basic conditions or dangerous reagents. Therefore it is still challenging to install a diazo group in complex molecules. An alternative solution to that problem is to functionalize an existing diazo carbonyl molecule. This strategy has also been studied by many groups and several elegant methodologies have been developed to generate very useful diazo motifs.

Scheme 1.4 Aldol condensation between carbonyl and diazo ester or diazo ketone

For example, both diazo esters 1.16 and diazo ketones 1.4 are able to undergo aldol condensation with aldehydes and ketones to form β-hydroxy-α-diazo carbonyl compounds (1.18, 1.19). When applied to aldehydes, this transformation can be done under mild conditions with a catalytic amount of DBU (an organic base) for diazo esters, but requires a strong base (LDA) for diazo ketones, or when adding to ketones. This reaction converts diazo carbonyls into products that can be further functionalized to other diazo compounds as presented in Scheme 1.5. For example, β-hydroxy-α-diazo esters can be converted to vinyl diazo esters 1.22 by treating with trifluoro acetic anhydride and triethyl amine. Oxidizing β-hydroxy-α-diazo esters with IBX generates diazoketoesters 1.21. These diazoketoesters can be transformed to silyl enol diazoacetates 1.23.
Davies and coworkers had discovered that vinyl diazo esters are ideal reagents for [3+4] cycloadditions and Doyle and coworkers reported nucleophilic additions between silyl enol diazoacetates and different electrophiles to forge diazoketoesters into complex structures.\(^{21,22,23}\)

![Scheme 1.5 Converting β-hydroxy-α-diazo carbonyl compounds into others usefully diazo motifs](image)

Although diazo groups are typically highly reactive towards transition metals, an interesting palladium-catalyzed cross-coupling reaction between diazoacetates and alkene iodides or aryl iodides was reported by the Wang group.\(^{24}\)

![Scheme 1.6 Palladium-Catalyzed Cross-Coupling reactions with EDA](image)
Through Wang’s proposed mechanism, the reaction starts with oxidative insertion of Palladium(0)L₈ 1.34 into the alkene iodide 1.35 to afford a palladium(II) intermediate (1.29), which then undergoes a ligand exchange between the diazo anion 1.31 and the iodide. Finally, reductive elimination of intermediate 1.32 forms the C-C bond and regenerates the palladium catalyst.

Scheme 1.7 Mechanism of Palladium-Catalyzed Cross-Coupling Reaction Proposed by Wang Group

1.1.3 Diazocarbonyl compounds’ application in modern chemistry

As described above, diazo compounds were discovered a long time ago.¹ Due to the instability of the diazo group, those compounds are prone to lose nitrogen gas and generate carbene intermediates through UV irradiation, thermolytic decomposition, Lewis acid activation, or transition metal activation.² ³ ²⁵⁻²⁸ (Scheme 1.8) The unstable carbene intermediates can then undergo a variety of reactions including cyclopropanation, Wolff rearrangements, Buchner reactions, C-H insertion reactions, N-H insertion
reactions, O-H insertion reactions, and ylide formation leading to 1,3-dipolar cycloadditions. Most of these reactions were discovered a long time ago but they are still highly useful methodologies to prepare structurally complex and medicinal important molecules. Therefore, modern organic chemists are still working on developing new diazo-based reactions, which has been the focus of my Ph.D. research projects. Several important and useful diazo reactions are introduced below, which are either related to my projects or inspired me in developing new research projects.

Scheme 1.8 Different carbene pathways

The Wolff rearrangement is a reaction which converts diazo ketones 1.36 to ketenes 1.37 though UV irradiation or silver catalysis. Ketenes can undergo [2+2] cycloaddition or act as electrophiles with oxygen or nitrogen nucleophiles to give amides or esters 1.38. (Scheme 1.9)

Scheme 1.9 Wolff rearrangement and applications
In 2016 Reisman and coworkers reported a nice total synthesis of (+)-Psiguadial B, in which she built up the key cyclobutane core though a tandem Wolff rearrangement/catalytic asymmetric ketene addition sequence.\(^\text{30}\) (Scheme 1.10)

**Scheme 1.10 Reisman's total synthesis of (+)-psiguadial B via a Wolff rearrangement**

Carbenes derived from diazo carbonyl compounds 1.4 readily react with alkenes 1.40 in cyclopropanation reactions. Early research tested this reaction by generating carbenes through UV irradiation. Modern chemists discovered that transition metals, such as Cu and Rh catalysts with chiral ligands could catalyze asymmetric cyclopropanation reactions.\(^\text{31-35}\)

**Scheme 1.11 Diazo cyclopropanation**
Recently, Davies reported a series of Rh catalysts with novel ligands, which would trigger an enantioselective cyclopropanation reaction with high ee (enantioselectivity) at super low catalyst loading (0.001mol%). $^{36}$ (Scheme 1.12)

\[
\begin{align*}
\text{Ar}_1 \equiv & \\
\text{N}_2 \equiv & \\
\text{CO}_2 \text{CH}_2 \text{CCl}_3 & \\
\text{Ar}_2 & \\
\text{Rh}_2(\text{S-}p\text{-Ph-TPCP})_4 & \\
0.001 \text{ mol}\% & \\
\rightarrow & \\
\text{Ar}_1 \equiv & \\
\text{CO}_2 \text{CH}_2 \text{CCl}_3 & \\
\text{Ar}_2 & \\
\end{align*}
\]

Scheme 1.12 Highly enantioselective cyclopropanation reaction catalyzed by a low Rh catalyst loading

Carbonyl ylides 1.45 can be formed by condensing diazo carbenes 1.4 with a carbonyl group 1.44. These reactive intermediates will undergo 1,3-dipolar cycloadditions with alkenes, alkynes and other kinds of dipolarophiles. $^{37-39}$ (Scheme 1.13)

![Diagram](image)

Scheme 1.13 Forming carbonyl ylide between diazo and ketone

This method is a powerful way to prepare substituted furan motifs, and has been applied extensively in natural products synthesis. The Padwa group published several total synthesis of complex natural products including Aspidospermine, Kopsifoline E and Lysergic acid, that harnessed the power of carbonyl ylide cycloadditions. $^{40-44}$ (Scheme 1.14) As you can tell from those elegant total syntheses, the carbonyl ylide intermediate undergoes efficient 1,3-dipolar addition to form complex structures in high yields (93-
98%), and the regio and enantioselectivity can be controlled by a pendant alkane chain between the ylide and the dipolarophile.

![Scheme 1.14 Synthesis of Aspidospermine, Kopsifoline, Lysergic acid via carbonyl ylide 1,3-dipolar cycloaddition](image)

Another important and special reaction that diazo compounds can perform is C-H insertion. For these reactions, a metal-stabilized carbene (1.49), generated from an α-diazo carbonyl (1.47), would insert into a carbon-hydrogen bond to form a new \( sp^3-sp^3 \) carbon-carbon bond between the two coupling reagents to give the product 1.51. (Scheme 1.15) The reaction occurs by concerted transition state 1.50, and requires an active carbenoid intermediate. Rhodium is the most efficient metal catalyst for this transformation.
Scheme 1.15 Mechanism of metal-carbenoid C-H insertion reaction

Organic chemists are very interested in these C-H insertion reactions because the metal carbenoid directly inserts into an unactivated C-H bond giving these reactions excellent atom economy. In contrast transition metal catalyzed C-H activation reactions are able to regioselectively active C-H bonds through directing groups, but requires an alkyl iodide or organozinc reagent as a reaction partner which is less atom economical and produces more waste.48 (Scheme 1.16)

Scheme 1.16 Metal carbenoid C-H insertion versus transition metal C-H activation
Although the C-H insertion of metal carbenoids doesn’t need a preactivated carbon source to form the new carbon bond, the reactivity of the C-H insertion reaction is challenging to control. An ideal solution is to initiate an intramolecular C-H insertion reaction, therefore the regioselectivity will be controlled by the linker chain. Recently scientists have made several important achievements on site and stereoselective intermolecular C-H insertion reactions. The Davies group reported an intermolecular C-H insertion reaction, which selectively inserted at an equatorial C-H bond on a cyclohexane scaffold.\(^{49}\) (Scheme 1.17)

Scheme 1.17 Intermolecular C-H insertion reaction reported by Davies group

Besides C-H insertion reactions, metal carbenoids can also insert into O-H bonds, which generates a new carbon oxygen bond. The reaction mechanism is presented in scheme 1.18.\(^{50,51}\) The diazo group is activated by the transition metal to form the metal carbenoid \(^{1,49}\), which reacts with the alcohol. Due to the nucleophilicity of the hydroxy group and the variant property of metal carbenoids, the reaction may undergo two possible pathways. The Metal carbenoid may undergo a concerted insertion into the O-H bond \(^{1,53}\).
Similar to the C-H insertion reaction, or alternatively, the hydroxy group 1.52 could attack the metal carbenoid 1.49 to form the C-O bond and cause transition metal dissociation, which would generate a ylide intermediate 1.55. The ylide intermediate would then undergo hydrogen atom transfer to complete the reaction and form 1.56. (Scheme 1.18)

Scheme 1.18 Different mechanism pathways for O-H insertion reaction

This method is a powerful way to form new C-O bonds and is a productive route to prepare hydro furans. Professor Fu and coworkers developed a Cu catalyst with chiral ligands to facilitate enantioselective O-H insertion.50

Scheme 1.19 Enantioselective O-H insertion reaction developed by Fu
1.1.4 Conclusion

In summary, diazo carbonyl compounds are versatile reagents, that can react by several different pathways. Diazo compounds have been researched for a long time, and scientists have taken advantage of diazo reactivity to developed many useful reactions, such as Wolff rearrangement, cyclopropanation, carbonyl ylide 1,3-dipolar cycloaddition, and C-H insertion reactions. These reactions are frequently used to prepare medicinal molecules and structurally complex natural products. New methodologies and applications that take advantage of the diazo functional group are being developed by researchers around the world.

1.2 Fragmentation reaction

1.2.1 Grob fragmentation

Fragmentation reactions are reactions that break carbon-carbon bonds. The ability to regioselectively break a neutral carbon-carbon bond is synthetically useful for effecting ring expansion or for generating reactive functional groups. The Grob fragmentation is an example of a reaction that breaks neutral carbon-carbon bonds.\textsuperscript{52,53} This reaction fragments a molecule 1.57 into 3 components: an electrofuge 1.58, an unsaturated neutral fragment 1.59 and a nucleofuge 1.60. (Scheme 1.20)

\begin{center}
\includegraphics[width=0.7\textwidth]{Scheme_1.20.png}
\end{center}

\textbf{Scheme 1.20 Grob fragmentation}

Importantly, fragmentation of cyclic compounds can provide linear alkenes with other functional groups attached. A very nice example to demonstrate the utility of this type reaction was presented by the Edwards group. Using Grob fragmentation reaction
two times, they were able to convert [5,6]-bicyclic tosylate 1.61 to a linear alkene 1.65 in order to synthesize cecropia juvenile hormone 1.66. \(^5^4\)

![Scheme 1.21 Dual fragmentation to prepare juvenile hormone](image)

Another important application of fragmentation reactions is converting bicyclic ring molecules to large monocyclic molecules. Cyclic molecules with 8-11 atoms are medium-size ring molecules, which are challenging to prepare by cyclization. The cyclization process is very slow, and intermolecular reaction often outcompetes the cyclization process. This is mostly due to entropy disfavoring conversion of a long-linear molecule to a cyclic molecule, as well as transannular strain in the ring product. \(^5^5\) (Scheme 1.22)

![Scheme 1.22 Medium ring cyclization challenge](image)

Therefore fragmenting bicyclic ring molecules is an alternative route to these products. For example, Muscenone 1.69, a 15-carbon cyclic molecule, was synthesized via a Grob fragmentation. \(^5^6\) (Scheme 1.23)
1.2.2 Eschenmoser-Tanabe fragmentation

Similar to the Grob fragmentation, Eschenmoser and Tanabe both reported a fragmentation reaction in 1967.\textsuperscript{57-62} The fragmentation occurs between a tosyl hydrazine 1.71 and an α,β-epoxy ketone 1.70. During the fragmentation a vinyl tosyl diazene act as a strong electrofuge to fragment the adjacent carbon-carbon bond 1.73 and generate the corresponding alkyne 1.74 and new ketone 1.75. This reaction has also been applied to the synthesis of macrocyclic molecules.\textsuperscript{57,59} (Scheme 1.24)

1.2.3 Dudley’s vinyl triflate fragmentation

More recently, Dudley and coworkers have developed a methodology to fragment vinylogous acyl triflates (1.76-Scheme 1.25), which can be prepared from 1,3-diketones. In this reaction, a strong nucleophile attacks he carbonyl to generate the nucleofuge and the strong leaving group triflate acts as an electrofuge to cleave the C-C bond between the carbonyl and the alkene. Dudley and his coworkers have shown this method is a general way to prepare different kinds of alkyne products that can be used in a variety of applications (1.80-1.83).\textsuperscript{63-65} (Scheme 1.25)
1.2.4 Brewer’s fragmentation

Our group discovered that \( \gamma \)-silyloxy- \( \beta \)-hydroxy-\( \alpha \)-diazo ketones 1.85 undergo fragmentation in the presence of a Lewis acid.66-68 The \( \gamma \)-silyloxy- \( \beta \)-hydroxy-\( \alpha \)-diazo ketones 1.85 can be prepared by aldol-type addition to a lithiated ethyl diazo acetate 1.24 to a \( \beta \)-silyloxy ketone 1.84. The mechanism begins with a Lewis acid mediated dehydroxylation that generates a vinyl diazonium intermediate 1.87. The vinyl diazonium intermediate is an electrophilic intermediate that drives the fragmentation by loss of \( \text{N}_2 \) gas to generate the alkyne group 1.89. The \( \gamma \)-Silyloxy acts as a nucleofuge to help the bond breaking and generates the aldehyde group 1.89. (Scheme 1.26)
Our group further explored this methodology into various applications. We have shown that this fragmentation can be applied to the synthesis macrocyclic rings, and also used this reaction as a key step in natural product synthesis.\textsuperscript{69,70} (Scheme 1.27)

More importantly, our group has shown that the fragmentation products 1.93, which contain an aldehyde and a ynoate, are ideal precursor for intramolecular azomethine ylide 1,3-dipolar cycloaddition reaction to generate polycyclic dihydropyrrrole scaffolds. To demonstrated this idea, our previous group member Dr. Cristian Draghici prepared several polycyclic dihydropyrrrole molecules 1.97 from fragmentation products 1.93 and proline or trimethyl ester proline 1.94.\textsuperscript{71} Our group
identified this methodology as a powerful tool for the synthesis of complex natural products since many of them contain polycyclic pyrrole structures. We have applied this methodology to the synthesis of demissidine\textsuperscript{72} and cycloclavine.\textsuperscript{73} (Scheme 1.28)

\begin{center}
\includegraphics[width=\textwidth]{scheme1.28.png}
\end{center}

**Scheme 1.28** Brewer group dihydropyrrole synthesis

### 1.3 1,3-Dipolar Cycloaddition and Azomethine Ylide

#### 1.3.1 1,3-dipolar cycloaddition reaction

A 1,3-dipolar cycloaddition is a reaction that occurs between 1,3-dipoles and dipolarophiles. It was first reported by Huisgen and is a powerful method to make pentacyclic heterocycles, which exist in a large amount of bioactive molecules.\textsuperscript{74-76} The high efficiency and convenience of this type of reaction makes it a powerful method to couple two fragments, which allowed it to become a key reaction for click chemistry.\textsuperscript{77} A general reaction mechanism is introduced in scheme 1.29. A lot of 1,3-dipoles have been discovered by scientists, and most commonly used dipolarophile are alkenes, alkynes, aldehydes and imines. These reactions have attracted many researcher’s interests and have led to the development of new methodology that has been applied broadly in new organic syntheses.\textsuperscript{78}
A particularly important and useful class of 1,3-dipoles are: azomethine ylides (1.98-1.100). These 1,3-diopes have an iminium cation next to a carbon anion, and they cyclize with alkenes 1.101 or alkynes 1.102 to form pyrrolidines (1.103,1.104) and dihydropyrroles (1.105,1.106) with multiple substituents. Those structures exist in many bioactive molecules, many of which contains multiple stereocenters and rigid scaffolds. Therefore, azomethine ylides are ideal intermediates to prepare those pyrrole-containing bioactive molecules. (Scheme 1.30)

Researchers have developed several methods to prepare azomethine ylides, which are typically formed in situ. First, azomethine ylides can be generated from the photolytic or thermal decomposition of aziridines 1.107. Although aziridines are hard to prepare,
the azomethine ylide generated from aziridines retain the stereochemistry during the 1,3-dipolar cycloaddition.\(^{58}\)

![Scheme 1.31 Azomethine ylide from aziridine](image)

A more convenient route to azomethine ylides, involves condensing a ketone or aldehyde with an \(\alpha\)-amino acid \(1.110\).\(^{83}\) The azomethine ylides are formed via deprotonation, decarboxylation, or desilylation at the \(\alpha\)-carbon position.\(^{84-86}\) This provides a general protocol to convert an aldehyde or ketone to an azomethine ylide for 1,3-dipolar cycloaddition. (Scheme 1.32)

![Scheme 1.32 Azomethine ylide from iminium](image)

Regio and enantioselectivity in intramolecular dipolar cycloadditions can be controlled by the pendant alkene and adjacent chiral centers.\(^{79}\) Researchers have developed several chiral organocatalysts or transition-metal catalysts for enantioselective cycloadditions. For instance, the Gong group has shown that chiral phosphoric acid derivative was able to facilitate an enantioselective cyclization between methylene indolinones and azomethine ylides.\(^{87}\) (Scheme 1.33)
Scheme 1.33 Enantioselective azomethine cycloaddition developed by Gong group

Besides chiral organocatalysts, chiral transition metal catalysts can also control enantioselectivity of azomethine ylide cycloadditions. The Reisman group reported an elegant total synthesis of acetylapoaranotin via an enantioselective azomethine ylide 1,3-dipolar cycloaddition reaction catalyzed by a chiral copper catalyst.\textsuperscript{88,89}(Scheme 1.34)

Scheme 1.34 Total synthesis of acetylapoaranotin through enantioselective 1,3-dipolar addition

1.4 Vinyl cation

1.4.1 Vinyl cation history

Vinyl cations were proposed in an alkyne formation reaction in 1944, and ever since then a lot of research has been done to understand this intermediate.\textsuperscript{90} Pioneering work on the physical properties and reactivities of this intermediate was conducted by Peter Stang, and Ronal Parry. However, even with a rich experiment data and long history of research, vinyl cations haven’t been used in organic synthesis as frequently as other types of carbon cations. It’s still a poorly-understood intermediate.\textsuperscript{91} The high reactivity, instability and difficulties in generating the intermediate have limited their use in organic synthesis.
1.4.2 Vinyl cation structure

Different from other trisubstituted carbo cations, vinyl cations have a positive charge on a double bond. Therefore vinyl cations have a $sp$ hybridized empty orbital. Unlike $sp^2$ hybridized trisubstituted carbocations, vinyl cations have a linear geometry, which has been confirmed by X-ray crystallography and NMR experiments.\textsuperscript{92,93} (Figure 1.2) Due to the electron deficiency of the double bond, vinyl cations are relatively unstable compared to other $sp^2$ hybridized carbo cations.

![Figure 1.2 Crystal structure of di-silyl stabilized vinyl cation](image)

1.4.3 Vinyl cation generation

There are two general strategies to generate vinyl cations. The first is spontaneous disassociation of a leaving group such as a halide, triflate, and diazonium from an alkene to form vinyl cation. (Figure 1.3)

\[
\begin{array}{c}
\text{R}_1 \equiv \text{R}_3 & \text{R}_1^+ \equiv \text{R}_3 \\
\text{R}_2 & \text{X} & \text{-X} & \text{R}_2 \\
\end{array}
\]

\[X = \text{halide, OTf, } N_2^+, \text{I}^+\text{Ar, } N_3^+\text{Ar}\]

![Figure 1.3 Vinyl cation generation](image)

The initial study of halide cleavage was done by Grob.\textsuperscript{94} However, it is too difficult to generate vinyl cation by halide cleavage. Scientists started to look for other more labile leaving groups. Professor Stang did nice work to show that triflate is a good leaving group for vinyl cation formation, but even under solvolysis conditions in the
presence of a polar protic solution, the reaction requires high temperature around 100ºC.\textsuperscript{95,96} Iodonium salts, presented by Hinkle as an activated halide, are another good leaving groups for vinyl cation formation,\textsuperscript{97} as are vinyl diazonium salts. This latter intermediate loses a nitrogen gas to form vinyl cations. The process presumably is more entropy favored than triflate cleavage, since the \textit{N}_2 gas will be removed from the reaction system. The initial study of vinyl diazonium intermediates as vinyl cation precursor were done by O’connor.\textsuperscript{98} The reaction pathway is presented on Scheme 1.35. Treating a vinyl amine 1.121 with nitrosyl chloride generates vinyl diazonium intermediate 1.123. The vinyl cation 1.124 was generated by loss of \textit{N}_2 and it reacted with chlorine anion to give products 1.126,1.127, or formed alkyne 1.128 via proton elimination. Products 1.127 and 1.128 indicated phenyl migration had occurred during reaction. (Scheme 1.35)

![Scheme 1.35 Vinyl cation generated by vinyl amine through vinyl diazonium intermediate](image)

Padwa and coworkers discovered that treating β-hydroxy-α-diazo ester 1.129 with Lewis acid cleaves the hydroxy group and generates vinyl diazonium intermediate 1.131.(Scheme 1.36) Nitrogen gas emission gives the α-carbonyl vinyl cation 1.132. The unstable vinyl cation undergoes ring expansion reaction to a cyclic vinyl cation 1.133, and then contracts to an allyl carbocation 1.134. Finally the allyl carbocation cyclizes with the attached ester to generate lactone 1.135.\textsuperscript{25} Our group believed this is a good
method to generate vinyl cation in a more controlled and milder way than previous methods. We have utilized this method in our group to develop several novel vinyl cation reactions.\textsuperscript{6,15,99-101} (Scheme 1.36)

![Scheme 1.36 Vinyl cation generated from β-hydroxy-α-diazo carbonyl](image)

Vinyl cations can also be generated from vinyl triazenes.\textsuperscript{102} According to the mechanism proposed, vinyl triazenes first decomposed to a vinyl diazonium, that then forms the vinyl cation.

The second general strategy to generate vinyl cations is to add an electrophile to an alkyne. The electrophile can be a proton from a strong Bronsted acid, such as triflic acid and triflimide, or a carbocation.(Figure 1.4) However, this method suffers from poor regioselectivity for vinyl cation generation. A common solution to this problem is to use an electron-rich functional group that biases the reaction to favor a more stabilized vinyl cation.\textsuperscript{103-105} (Scheme 1.37)
Vinyl cation through alkyne activation

\[ R_1-\equiv R_2 + X^+ \rightarrow R_1^+ + R_2^+ + R_1^+ \]

\( X = H^+, R^+, \text{Ph}^+ \)

Figure 1.4 Vinyl cation through alkyne activation

Scheme 1.37 Phenyl induced vinyl cation formation by Niggemann

1.4.4 Vinyl cation reactivity and rearrangement

Initial study of vinyl cations focused on kinetics of vinyl cation formation from vinyl triflates under solvolysis conditions. The rate of generating vinyl cations is much slower than the rate of generating other trivalent carbon cations. Studies show that vinyl cations are highly unstable intermediates with high reactivity compared to other carbon cations. For instance, even for a triphenyl substituted vinyl triflate, which should give fairly stable vinyl cation, to generated vinyl cation under solvolysis conditions only formed 54% of desired product at 150 °C after 24 hours reaction, which indicates a slow rate of vinyl cation generation. It is noteworthy that the slow rate of this reaction may be also due to the fact that solvolysis was in a nonpolar benzene solution. (Scheme 1.38)

Scheme 1.38 Vinyl cation reaction with benzene

Vinyl cations have a high tendency to undergo rearrangement as shown in scheme 1.39. The rearrangement occurs across the double bond and not only occurs for C-H
bonds but also happens for C-C bonds such as phenyl migration 1.142 or ring expansion 1.145. These rearrangements would generate a new vinyl cations or other more stable trivalent carbocations 1.149.95,108,109

![](image)

**Scheme 1.39 Examples of vinyl cation forced rearrangement**

Previous studies indicated that vinyl cation rearrangements outcompetes the rate of intermolecular bond formation. These rearrangements make it difficult to control the chemo and regio selectivity of vinyl cation reactions in organic synthesis.

One way to avoid vinyl cation arrangement is to use an electron-rich group to stabilize the vinyl cation such as phenyl groups, silyl groups and cyclopropyl groups. But early studies of vinyl cations under solvolysis conditions showed that vinyl cations react faster with heteroatoms with lone-pair electrons than other carbon nucleophiles. The products of vinyl cation reactions are mostly vinyl halides 1.151 from the counter anions
of the vinyl cation imitators or ketones 1.152 generated by vinyl cation reacting with polar protic solvent.\textsuperscript{95,102,106}

![Scheme 1.40 Major vinyl cation reaction products under solvolysis condition](image)

With all those difficulties mentioned above, the interest of applying the vinyl cation into new methodologies development faded away.

**1.4.5 Intrinsic energy barrier of vinyl cation**

As mentioned before, physical organic studies on vinyl cations had been carried out on solvolysis reactions. However, these studies cannot analyze vinyl cation formation and vinyl cation reaction with nucleophiles separately. In 2017 Mayr and coworkers studied the reaction of vinyl cations with laser flash photolysis technique. This technique allowed them to monitor the reaction process precisely, and independently observe the step of vinyl cation formation and vinyl cation reaction. To their surprise, they found that both the rate of formation of vinyl cation and the rate of reaction of vinyl cation with nucleophiles are slower than trivalent carbocations reactions. As shown in Scheme 1.41, benzhydryl bromide 1.156 solvolyzed $10^5$-$10^6$ times faster in 80% aqueous ethanol at 25 °C than the vinyl bromide 1.153. The benzhydrylium ion 1.157 also reacts 1-2 orders of magnitude faster with trifluoroethanol at 20 °C than diphenyl substituted vinyl cation 1.154.
Scheme 1.41 Rate comparison between vinyl cation and diphenyl cation

With this amazing observation and other detailed computation calculations, Mayer came to the conclusion that vinyl cations are not a much stronger electrophilic intermediate than other carbocations. The slow rate of generating and cleaving bonds on a vinyl group is due to an intrinsic energy barrier between \( sp \) bond hybridization and \( sp^2 \) hybridization. As presented on figure 1.5, the energy barrier between starting material and trivalent carbon cation and the energy barrier between vinyl halide and vinyl cation are similar. But to convert a \( sp^3 \) hybridized carbon to a \( sp^2 \) hybridized carbocation requires much less energy than convert a \( sp^2 \) hybridized carbon to a \( sp \) hybridized carbocation. Similar energy barriers are required to form new carbon-carbon bond. This theory nicely explained the question “why are vinyl cations sluggish electrophiles?”\textsuperscript{110}

Therefore, it is challenging to control the intermolecular reaction of vinyl cation.
1.4.6 Modern application of vinyl cations

Although for a long time there was an absence of interest in vinyl cations, they didn’t totally vanish from the organic community. In the modern synthetic community, the major method to form a carbon-carbon bond on alkene relies on transition metal catalyzed cross coupling reactions. Those reactions require rare transition metals for catalysis, which are being consumed rapidly. Also, due to the high sensitivity to water and oxygen, cross coupling reactions can be hard to operate on large scale for industry production. With this in mind, scientists stared to investigate methods to tame vinyl cations in order to undergo direct vinylation reactions. Those reactions are important because they provide an alternative way to functionalize akenes without transition metals.

Figure 1.5 Energy diagram of trivalent carbon cation and vinyl cation

It is noteworthy to mention that vinyl cation have a resonance structure that is a α-cationic carbene. (Figure 1.6) Although XRD and NMR structures don’t indicate a strong positive charge at the α position.\textsuperscript{92}
Comparing the orbital structure of a singlet carbene with that of a vinyl cation, we see that they both occupy an orbital perpendicular to another empty orbital. These ideas can help to explain the carbene-like C-H insertion reactivity of vinyl cations.

![Carbene orbital structure compared with vinyl cation orbital structure](image)

**Figure 1.7 Carbene orbital structure compared with vinyl cation orbital structure**

In 1970s, Hanack and others reported ring-contraction reactions when treating cyclonoenyl triflate 1.159 under solvolysis conditions. They proposed the reaction proceeded through a vinyl cation mediated that underwent an intramolecular 1,5-H shift to give carbocation 1.161 and then reacted with the alkene to eventually form the bicyclic products 1.163 and 1.164. The process looks very similar to a concerted vinyl cation insertion.111,112 (Scheme 1.42)

![Scheme 1.42 Observed vinyl cation rebound cyclization](image)

**Scheme 1.42 Observed vinyl cation rebound cyclization**

In 2006, Metzger and coworkers reported a concerted vinyl cation insertion into a non-activated \( sp^3 \) hybridized C-H bond.113 Vinyl cation 1.166 was generated by addition of an in situ generated isopropyl cation 1.165 to alkyne.
The vinyl cation (1.166) then inserted into methyl C-H bond to form the cyclopentane and a tertiary carbocation 1.168, which was trapped by Et₃SiH to final product 1.169. Their computational studies indicated that the vinyl cation insertion process is concerted. (Scheme 1.43)

Scheme 1.43 Metzger's intramolecular insertion of vinyl cations into C-H bonds

Similar reactivity also was presented by Ganut’s group,¹¹⁴ who developed a method to generate aryl cations 1.169 via a reaction between diaryliodonium salts and copper catalyst. The aryl cation 1.169 then added to alkyne 1.168 to form the vinyl cation 1.170, which subsequently inserted into the tertiary carbon to form the cyclopentene 1.181. It is nice to observe a total retention of the stereochemical integrity during the C-H insertion process. (Scheme 1.44)
Our group has a long history of research of γ-siloxy-β-hydroxy-α-diazo esters for fragmentation reactions. Without γ-siloxy group attached, in the presence of a Lewis acid, β-hydroxy-α-diaza esters generate vinyl diazonium intermediates (1.182), and subsequently lose nitrogen gas to generate vinyl cations (1.183). The unstabilized vinyl cation intermediate undergoes a ring expansion to generate a cyclic vinyl cation 1.184. Our group used a remote alkyl group to trap the vinyl cation through a C-H insertion process to form the cyclopentenone 1.185. (Scheme 1.45) This method provides a unique way to synthesize fused 5,7 or 5,8 bicyclic pentenone systems, which exist in many bioactive diterpenes including anadesin, mafarlandin E and the prostaglandin. (Figure 1.8)
Our group has also tested this cyclic vinyl cation in reactions with remote aromatic rings and alkenes. Reaction of vinyl cation with aromatic rings will be introduced in chapter 3. Our group members, Magenta Hensinger and Dr. Nicholas Dodge reported that vinyl cations could react with pendant alkenes to generate $\alpha$-alkylidene cyclopentenones through a series of rearrangement steps. It is noteworthy to mention that when the linear vinyl cation had a hydrogen across the alkene (1.187), the intermediate undergoes a 1,2-hydrogen shift to form the more stable vinyl cation 1.188 which then traps the alkene. The activated cationic cyclic 1.189 will rearrange to final product 1.190. We didn’t observe any alkyne formation as a result of hydrogen elimination.\(^6\)(Scheme 1.46)
Scheme 1.46 Brewer group vinyl cation reaction with alkene

The Nelson group has developed a system to generate vinyl cations from vinyl triflates 1.191 via catalytic amount of carborane acid [Ph₃C][HCB₁₁Cl₁₁] (1.192) and 1.5 equivalents of Et₃SiH. The strong acidity of carborane acid 1.192 activates triethyl silane into a strong Lewis acid, which helps to cleave the triflate group and generate cyclic vinyl cation (1.193). The cyclic vinyl cation 1.193 inserts into the C-H bond of an alkane or an aromatic ring via an ambimodal transition state to generate a β carbon cation 1.194. A 1,2-H shift was observed to form the tertiary carbocation 1.195 which Et₃SiH traps to form the desired product 1.196. (Scheme 1.47)
The Maulide group has taken advantage of the reactivity of vinyl cations in an interesting way. Instead of using the vinyl cation to form a C-C bond directly, they first trapped the vinyl cation 1.199 with the oxygen of an aryl sulfoxide. The aryl sulfoxonium then undergoes a cationic [3,3] rearrangement 1.200 to form a new carbon bond, giving an α-aryl ketone product 1.201, which is hard to prepare by other methods. They also showed that an β-silyl group could aid the vinyl cation formation on alkynes to achieve a border substrate scope.\(^{104,105}\)

![Scheme 1.48 Maulide's aryl ketone formation though vinyl cation trap and rearrangement](image)

### 1.4.7 Summary

For many years, vinyl cations were challenging to study because they were difficult to generate and underwent uncontrollable rearrangements. So, vinylation via vinyl cations did not receive as much attention from the organic chemistry community as alkylation with trivalent carbocations. But with advances in computational chemistry and physical organic chemistry, modern chemists have learned more about these species.
and have developed useful reactions from them. Importantly, recent discovery of vinyl cation C-H insertion reactions has attracted the attention of many organic chemists.

1.5 Total synthesis: history, importance and progress

The multi-steps synthesis towards a naturally occurring molecule is called natural product total synthesis. Many bioactive molecules are difficult to acquire from nature, due to their low natural abundance. Total synthesis becomes an alternative route to make these compounds, in order to support research and make use possible. Also, it is an important demonstration of the power of organic synthesis. Even though total synthesis has been an academic endeavor for a long time, the doubt about whether total synthesis is a worthwhile academic enterprise never perished. “We have travelled far since 1828 and the interest attached to 'total synthesis' has disappeared” is a quote from Sir Robert Robinson in 1936. With long synthetic routes and unpredictable failures, it took skilled organic scientist years of work to get small amounts of desired products. It seems the efforts that had been put into total synthesis were not worth with the results of the biomedical studies.

But with several generations of chemists efforts, total synthesis has changed the ability of biomedical chemists to understand biological systems. For instance, Aspidospermidine is a natural monoterpenoid indole alkaloids, which belongs to the Aspidosperma alkaloids group. This chemical has an interesting structure and valuable bioactivities, which has attracted many chemists to synthesize the molecule. The first total synthesis was completed in 1967 by Gilbert Stock using a Fischer indole cyclization reaction as a key step. Due to the limitation of synthesis-tools at that time, this synthesis is not enantioselective and had a low overall yield.
Since then, there have been more than 40 papers published related to the total synthesis of this compound. Chemists tried to synthesize this molecule using different methods, but didn’t have a high overall yield due to long synthetic route. Not surprisingly, some chemists have voiced concerns about whether it is worthwhile to put those efforts into total synthesis of such a molecule.

However, a ground breaking change eventually came with a sufficient amount of knowledge accumulated. In 2011, the MacMillan group reported a unified total synthesis of 6 well-known natural alkaloids via a organocascade catalysis. Through a one-flask asymmetric Diels-Alder/elimination/conjugate addition organocascade reaction, 2-vinyl indole 1.202 and propynal 1.203 are assembled into the key intermediate 1.204. This tetracycle processes the basic skeleton in those natural products. With several nice conversions, (-)-strychnine, (+)-aspidospermidine, (-)-kopsinine, (-)-akuammicine, (+)-vincadifformine and (-)-kopsanone were synthesized in short sequence and excellent overall yields. As you can imagine, this method would be able to provide a handful of complex natural products with modifications for biochemists to analyze and study bioactivities. This great work could not have been achieved without the development of
new methodologies, rich knowledge and past experiences in the preparation those natural alkaloids.

Scheme 1.50 MacMillan's organocascade catalysis and collective total synthesis
Chapter 2 Fragmentation of γ-siloxy-β-hydroxy-α-diazo ketone and total synthesis of Aspidospermidine

2.1 Brewer group’s polycyclic dihydropyrrole synthesis

Fragmentation reaction is an efficient way to break C-C bond, instead of forming bond. Reaction mechanism has been researched and reported by Grob. This reaction fragments molecule into 3 components: electrofuge, unsaturated neutral fragment and nucleofuge. Several similar-type reactions are developed such as Eschenmoser-Tanabe fragmentation and Dudley’s vinyl triflate fragmentation. As a powerful method to cleave C-C bond, this reaction was widely applied to synthesis the macrocyclic natural products. Another application is to convert small cyclic molecules into linear molecules with synthetic useful functional groups like aldehyde, alkyne, or ketone. Followed with other reactions, it will become a convenient way to prepare structure complex molecules from commercial cyclic molecules.

Recently our group developed a new type of fragmentation reaction, which utilizes diazonium cation as a nucleofuge. This reaction occurs by the mechanism shown in Scheme 2.1 and converts γ-silyloxy-β-hydroxy-α-diazo ketone (2.3) into a tethered aldehyde ynoate (2.7). The mechanism started from Lewis acid mediated hydroxy group cleavage, and subsequently generated vinyl diazonium intermediate 2.5. The vinyl diazonium intermediate, as an electrophilic intermediate will lose nitrogen gas, lead the lone pair donation from siloxy group and C-C bond breakage to generate alkyne, and subsequently loss of the tert-butylidimethylsilyl group would provide tethered aldehyde ynoate 2.7. This reaction is important because both functional groups are synthetically useful. (Scheme 2.1)
For example, our group developed a 1,3-dipolar cycloaddition methodology to convert the fragmentation products into polycyclic dihydropyrroles \(2.12\) (Scheme 2.2). This methodology is general and has been used to synthesis several key skeletons of natural products. Our group has already applied this methodology to the total synthesis of demissidine\(^7\) and cycloclavine.\(^{73}\) (Scheme 2.3)
My first project was to apply this unique dihydropyrrole synthesis to the total synthesis of Aspidospermidine.

### 2.2 Aspidospermidine

The Aspidosperma alkaloids are a group of monoterpenoid indole alkaloids with more than 250 members.\(^{116}\) These chemicals all contain a tricyclic tetrapyrrrole skeleton, which contains 5 chiral centers and an indole motif. Due to their structural complexity, and their interesting biological activity, Aspidosperma alkaloids have attracted interest from many synthetic chemists for over 50 years, and have remained a focus of research activity to the present day. Aspidospermidine comprises the basic skeleton of this family of natural product, and it is the primary target of synthesis of this alkaloid family. Many scientists have reported elegant total syntheses of this compound.\(^{118-167}\) (Figure 2.1)
Figure 2.1 Appidosperma Alkaloids

2.3 Retrosynthesis

Our group envisioned that the key aspidospermine core could be prepared diastereoselectively by our unique dihydropyrole synthesis methodology, as illustrated in retrosynthesis Scheme 2.4. The key aspidospermidine core structure 2.16 could be synthesized by a diastereoselective 1,3-dipolar cycloaddition of iminium salt 2.15, which could be prepared from aldehyde 2.14 via intramolecular iminium formation. The racemic aldehyde 2.14 could be generated by fragmentation reaction of γ-siloxy-β-hydroxy-α-diazo (2.13). We believed this retrosynthesis route would provide a faster way to make the aspidosperma alkaloid tricyclic cores, and in order to validate this hypothesis we decided to synthesis the natural product Aspidospermidine.
2.4 Initial Route towards the fragmentation precursor

With the retrosynthetic route in hand, we started to synthesize the fragmentation precursor 2.13. The initial route to 2.24 was developed by former group member Geoffrey Giampa, and I modified this route in order to achieve a higher yield and better reproducibility.

Scheme 2.4 Retrosynthesis analysis towards Aspidospermidine

Scheme 2.5 Previous method toward Boc protected enone amine 2.24

My initial route to fragmentation precursor 2.24 was largely based on Dr Giampa’s works and is shown in Scheme 2.5. First a Knoevenagel condensation was conducted...
between 3-anisaldehyde and cyanoacetic acid to generate cyano alkene \(2.19\), which was subjected to a \(\text{PtO}_2\) catalyzed hydrogenation reaction to generate amine \(2.20\).\(^{168}\) (scheme)

![Scheme 2.6 Side product of hydrogenation reaction](image)

The hydrogenation reaction, previously conducted by Giampa, was catalyzed by \(\text{Pd on carbon}\) and required 3 days to complete. However, when the reaction was scaled up, the \(\text{Pd on carbon}\) reduction reaction generated large quantities of partially reduced product \(2.25\), where only the alkene was reduced, as indicated in Scheme 2.6, and the reduction process couldn’t proceed further. In order to resolve this problem, I changed the catalyst to \(\text{PtO}_2\) with \(\text{MeOH}\) as solvent. This reaction ran smoothly to generate the desired product within only 12 hours. I also observed that if the hydrogenation reaction ran over 24 hours under \(\text{PtO}_2\) conditions, the aromatic ring was reduced giving side products that were observed by NMR. (Scheme 2.6.)

With the desired amine product \(2.20\) in hand, I started to install the TMS methylene unit with an \(\text{S}_2\text{N}_2\) reaction between TMSCH\(_2\)I and the amine to afford the desired product \(2.21\). The product \(2.21\) was subjected to Birch reduction to generate the 1,4-cyclohexadiene product \(2.22\). It is worth mentioning that the Birch reduction product \(2.22\) is highly sensitive to air oxidization, and starting material is regenerated through oxidation. Therefore reaction requires a quick workup to remove the liquid ammonia and the product \(2.22\) must be protected with nitrogen gas in order to achieve a high yield and clean characterization. Simply treating the birch reduction product \(2.22\) with hydrogen chloride
at room temperature gives the conjugated product 2.23 in 90% yield. Finally the amine on the product 2.23 was protected with a Boc group to afford product 2.24.

2.5 Optimized route towards the fragmentation precursor
At this point, although I was able to prepare the fragmentation precursor 2.24, the long synthetic route and the irreproducibility of the Birch reduction and hydrogenation reaction limited my ability to accumulate the desired product for further steps. Therefore a new synthetic route was proposed. As depicted in Scheme 2.7, the N-Boc protected product 2.24 could be prepared by a Suzuki coupling between a enone iodine 2.30 and a Boc allyl amine 2.28 with a in situ-generated boronic acid in 92% yield.169,170 The enone iodide 2.30 could be simply prepared more efficiently by 1,3-cyclohexanedione and Ph3P, I2 complex. The commercially available Boc protected allyl amine 2.26 was installed with a TMS methylene side chain by a simple SN2 reaction to product 2.28. This method changed our previous synthesis of 2.24 from 6 steps to 3 steps, which dramatically increased the efficiency of the total synthesis.

Scheme 2.7 Prepare compound 2.24 by Suzuki coupling reaction
At the very beginning, the yield of this coupling reaction was around 38% (table 2.1, entry 1), so I set about optimizing the conditions. An important observation was that
when I scaled up the reaction, I isolated 0.7 mmol allyl amine (32% of the starting allyl amine) 2.28 from the product mixture. (Table 2.1, Entry 2) This important observation indicated that the first step, hydroboration of allyl amine, was not going to completion, which is the key limiting step for this reaction. With this idea in mind, I increased the ratio of 9-BBN to allyl amine from 1:1 to 1.3:1 (Table 2.1, Entry 3), and the yield increased to 74%. Further increasing the ratio to 2:1, the yield was optimized at 82%. (Table 2.1, Entry 4) I suspected the quality of 9-BBN might be low, so I ran the reaction with a new bottle 9-BBN. It was exciting to observe a 92% yield for a gram scale reaction (Table 2.1, Entry 5), which successfully solved the problem of accumulating the fragmentation precursors.

![Chemical reaction](image)

**Table 2.1 Suzuki coupling optimization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl amine (mmol)</th>
<th>9-BBN (mmol)</th>
<th>Iodide enone 2.30</th>
<th>Product 2.24</th>
<th>yield (mmol)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>1</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>2.2</td>
<td>2</td>
<td>52%</td>
<td>Recover</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>2.9</td>
<td>2</td>
<td>74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>4.4</td>
<td>2</td>
<td>82%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48
With this much more efficient preparation route in hand, I continued the synthesis to prepare enoxy silane 2.31 via an copper catalyzed 1,4-addition of ethyl magnesium bromide and trapping the oxy anion with trimethyl silyl chloride. Rubottom oxidation using insitu-generated DMDO converted the enoxy silane 2.31 to epoxide 2.32. This method is convenient to conduct without the difficulty of distillation and titration of fresh DMDO. The epoxide 2.32 was opened and the resulting alcohol was protected by TMS group to give β-silyloxy ketone 2.33. Addition of lithiated ethyl diazoacetate to generate the fragmentation precursor 2.13 via an aldol-type addition. (Scheme 2.8)

Scheme 2.8 Synthesis towards the fragmentation precursor 2.13

2.6 Synthesis Aspidospermidine core through fragmentation/1,3-dioplar cycloaddition sequence

With enough fragmentation precursor 2.13 in hand, we started the key fragmentation and 1,3-dipolar cycloaddition reactions to build the Aspidospermidine core 2.16. Based on our previous research, Dr. Giampa treated the diazo precursor 2.13 with In(OTf)_3, he was pleased to observe the fragmentation product 2.14 generated. In addition, he also isolated trace amount of side product, which was identified as the
iminium salt 2.15, the desired 1,3-dipolar addition precursor. We believed that it is formed by a Boc deprotection and iminium condensation reaction sequence. (Scheme 2.9)

\[
\begin{align*}
\text{Diastereomixture} & \quad \xrightarrow{\text{In(OTf)}_3} \quad \text{CO}_2\text{Et} \\
2.13 & \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt, Molecular Sieves 90\%}} \quad 2.14
\end{align*}
\]

\[
\begin{align*}
2.15 & \quad \xrightarrow{\text{CsF, MeCN, reflux 60\%}} \quad \text{2.16}
\end{align*}
\]

**Scheme 2.9** Fragmentation/1,3-dipolar cycloaddition sequence to prepare Aspidospermidine core

Therefore we extended the reaction time to overnight and collected desired iminium salt 2.15 from the fragmentation reaction in 90\% yield. Treating the iminium salt 2.15 with CsF in acetonitrile reflux conditions, we were able to generate the azomethane ylide which underwent the 1,3-dipolar cycloaddition reaction.\(^{86}\) The desired tricyclic product 2.16 was collected in 70\% yield as a single diastereomer. (Scheme 2.9)

The diastereoselectivity of the cyclization between dipolar ylide and ynoate is controlled by the quaternary carbon center adjacent to the ylide. The alkyne would approach the ylide from the opposite face to generate the single diastereomer 2.16. NOE-NMR study of compound 2.16 observed a through-space correlation between the C-H and the methylene on ethyl group, which confirmed the structure as predicted. (Figure 2.2)
2.7 Installation of indole to the Aspidospermidine core 2.16

It was good to show that the fragmentation/1,3-cycloaddition reaction sequence is an efficient method to build the tricyclic core of Aspidospermidine. However, in order to finish the synthesis of Aspidospermidine we needed to install the indole motif on 2.16. (Figure 2.3)

Our proposed plan to finish the total synthesis started by converting the ester of tricyclic core 2.16 to a meta-methoxy phenyl amide 2.34. (Scheme 2.10) We hoped that an intramolecular Friedel-Crafts reaction would form a carbon bond between the phenyl ring and the enone to 2.35. It seemed likely that the phenyl ring would only approach from the convex face thus controlling the stereochemistry of the new all carbon quaternary center. The amide bond of 2.35 would be hydrolyzed and the amine would be protected by an acetyl group to give 2.36. Then a palladium-catalyzed amidation reaction, reported by Glorius and coworkers, would be applied to form a C-N bond and generate the indoline complex 2.37.¹⁷¹
The stereochemistry of the cyclization would be controlled by the adjacent chiral center. Last step would be a radical decarboxylation to cleave the ester and would generate the final product Aspidospermidine.

Scheme 2.10 Synthesis plan towards the final product

As planned, tricyclic core 2.16 was hydrolyzed by LiOH/dioxane to generate a highly polar zwitterion product, which was then treated with hydrochloric acid solution to form the ammonium salt 2.38 that was easier to handle in 78% yield. The product 2.38 was heated to reflux in thionyl chloride to form the acid chloride, which was allowed to react with meta-methoxy aniline 2.39 to generate amide 2.40 in 54% yield. (Scheme 2.11)
**Scheme 2.11 Prepare the amide 2.40**

With amide product 2.40 in hand, I started to test the ring closure though a AlCl$_3$ catalyzed Friedel-Crafts reaction. A similar transformation has been reported to proceed in nice yield to generate a quaternary carbon center.$^{172}$ (Scheme 2.12)

**Scheme 2.12 Previous reported lactam formation through Friedel-Crafts reaction**

Unfortunately, I tested this reported Friedel-Craft reaction with my amide 2.13, and I didn’t observe any product under a variety of reaction conditions.(Scheme 2.13) The reaction was first tested with AlCl$_3$ as catalyst, but there was no reaction with DCM or DCE as solvent under reflux and microwave conditions. (Table 2.2, entry 1-3), and I observed a demethylation reaction under toluene reflux. (Table 2.2, entry 4) After that, I started to test different Lewis acids, but there was still no reaction with In(OTf)$_3$ between 20 °C and 80 °C. SnCl$_4$ also failed to promote the reaction. (Table 2.2, entry 6-7)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Reaction condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>rt to reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>ClCH₂CH₂Cl</td>
<td>reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>ClCH₂CH₂Cl</td>
<td>Microwave</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110 °C</td>
</tr>
<tr>
<td>4</td>
<td>AlCl₃</td>
<td>toluene</td>
<td>reflux</td>
<td>lost MeO group</td>
</tr>
<tr>
<td>5</td>
<td>In(OTf)₃</td>
<td>ClCH₂CH₂Cl</td>
<td>rt to reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>SnCl₄</td>
<td>Chlorobenzene</td>
<td>100 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

During the reaction, I observed a strong coordination between the Lewis acid and the tertiary amine, which I hypothesized, would create a huge steric hindrance that would prevent the aryl ring from approaching.

![Steric effect](image)

**Figure 2.4 Steric effect due to Lewis acid coordinate**

After many failed attempts to build the indoline motif, the only way to finish this total synthesis was to redesign the strategy of indole synthesis. I had to prepare gram-scale 1,3-dipolar cycloaddition product 2.16 to test transition metal catalyzed cross coupling reaction as an alternative route, which requires a lot of work. Since we had already demonstrated our methodology in preparing Aspidospermidine core, further
research didn’t strongly represent our group’s research and we needed to apply a new funding for the future. I decided to stop this project and moved on to research vinyl cation.

2.8 Summary

Dr. Giampa and I accomplished a short and efficient synthesis of the tricyclo Aspidospermidine core. This route took advantage of fragmentation/1,3-dipolar cycloaddition approach to 2,5-dihydropyrolles developed by our group. This work led to a more efficient synthesis of the key fragmentation precursor by utilizing a palladium catalyzed cross coupling reaction. The \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo ketone with a tethered Boc-amine fragmentated and directly formed the iminium salt in one pot. The iminium salt was an ideal precursor to an azomethane ylide that underwent a 1,3-dipolar cycloaddition to form the tricyclic core of Aspidospermidine. The reaction was diastereoselective and generated the desired product with the correct relative configuration. Further attempts to install the indole motif were unsuccessful due to a failed intramolecular Friedel-craft reaction. Transition metal catalyzed cross coupling reactions would be necessary to install the indoline motif. It is unfortunate that I was not able to finish this total synthesis, but the training during the process is important especially for the experience on running different kinds of reactions, trouble-shooting problems and optimizing conditions.
Chapter 3 Vinylation the aryl rings by addition of vinyl cations

3.1 Interest of vinyl cation

Vinyl cation is an intermediate which was discovered a long time ago. But due to the high reactivity and low stability, the vinyl cation is hard to generate and difficult to control subsequent reaction pathways. The interest of vinyl cation faded away until recently its C-H insertion reactivity was discovered and got chemists’ attention once again. The detailed history and information of vinyl cation was introduced in chapter one.

As described in chapter one our group focused on a vinyl diazonium driven ring fragmentation reaction, which was facilitated by a siloxy group at the γ-position to facilitate bond breaking. Later we realized that without a γ-siloxy group attached, the insitu-generated vinyl diazonium intermediate will lose N₂ gas and generate a vinyl cation. This possibility was first recognized by Padwa and coworkers. They reported that a vinyl diazonium generated in this way would lose nitrogen gas to generate a vinyl cation 3.4. The linear vinyl cation then ring expanded to a cyclic vinyl cation 3.5. The cyclic vinyl cation, with ester group attached, then underwent a ring contraction reaction to an allylic cation to form a lactone (3.6).

Scheme 3.1 Padwa's lactone formation through vinyl cation
Vinyl diazonium salts were reported to be vinyl cation precursors a long time ago. Previously, the vinyl diazonium was generated from vinyl amines (3.7) reacting with NOCl. But the vinyl cation generated, was trapped by chloride anion to give products 3.9 and 3.10.\(^8\)

![Scheme 3.2 Vinyl diazonium reaction via vinyl amine](image)

Our group believed that the β-hydroxy-α-diazo carbonyls are useful vinyl cation precursors, since vinyl cation is generated under a much milder conditions compared to solvolysis conditions. The reactivity of vinyl cations generated from β-hydroxy-α-diazo carbonyls have never been studied. Therefore, our group decided to take advantage of the reactivity of vinyl cations generated from β-hydroxy-α-diazo carbonyls to develop new methodologies.

The first project was to test the C-H insertion reaction of cyclic vinyl cations. This work was done by Dr. Sarah Cleary and Magenta Hensinger. They found that changing β-hydroxy-α-diazo ester to β-hydroxy-α-diazo ketone, the cyclic vinyl cations 3.17, 3.19 will insert to a remote unactivated C-H bond to generate fused cyclopentenones 3.18, 3.20. Our group, in collaboration with Xin Hong’s group, investigated all the details of this reaction including substrate scope of the remote alkane, the ring expansion process, the C-H insertion process in the presence of heteroatoms (to generate lactone or lactam), and migratory aptitudes in rearrangements of destabilized vinyl cations.\(^15,99,101\)
3.2 Vinyl cation with aryl ring history

Vinyl cations are highly electron deficient intermediates, and should undergo electrophilic aromatic substitution (EAS) reactions. But direct vinylation of aryl rings didn’t get a lot of attention from the synthetic community compared to the broadly used Friedel-Craft reactions. Early studies on vinyl cations reacting with aromatic molecules intermolecularly were carried under solvolysis conditions.\[^{173}\]

Scheme 3.4 Vinyl cation EAS reaction under solvolysis condition

However, solvolysis reactions typically occur in polar protic solution conditions. In benzene, it is hard to generate vinyl cations, and the reaction is very slow.
Intramolecular reaction of vinyl cations with aromatic rings should be easier than intermolecular reactions due to a faster cyclization rate. In 2013 Gaunt’s group developed an intramolecular vinyl cation cyclization reaction in which vinyl cation 3.31 reacts with aromatic rings to form polyaromatic molecules with good yield. This result indicates that as long as vinyl cations are formed with good regioselectivity, EAS reactions should occur easily.

Scheme 3.5 Gaunt group’s vinyl cation cyclization

Vinyl cations can also be generated by reaction of an oxonium ion with an alkyne and cyclize with a pendant phenyl group. Several research groups studied this process. As shown in scheme 3.6, the vinyl cation is generated by an acyl chloride reacting with an alkyne in the presence of a Lewis acid. The vinyl cations react with a pendant phenyl ring to form indenone, naphthanol, and spiro decane structures. But, this process is not efficient, researchers observed a large amount of chloride ion trapped. Also the poor
regioselectivity of vinyl cation generation by this method limited the substrate scopes mostly to symmetric alkynes.\(^{175-177}\) (Scheme 3.6)

![Scheme 3.6 Vinyl cation cyclization through oxonium ion](image)

3.3 Brewer group’s research on vinyl cation reaction with pendant benzyl group

3.3.1 Proposed vinyl cation reaction with pendant benzyl group

After proving vinyl cations generated from β-hydroxy-α-diazo ketones are strong intermediates to undergo C-H insertion reactions, our group started to investigate the reactivity of vinyl cations with aromatic rings. My first target was to test cyclic vinyl cation reacting with pendant benzyl group to generate 2-naphthol with an attached 7-member ring.(Scheme 3.7) This type of naphthol hasn’t been prepared before. Since naphthols are important precursors for chiral ligands, it is worth to start with this substrate.
3.3.2 Precursor preparation

The substrates for thesis studies were prepared following the route in Scheme 3.8. First diazo methane (3.55) was generated from Diazald® and allowed to react with phenylacetyl chloride to form diazo ketone 3.54. This diazo ketone 3.54 was deprotonated by freshly generated lithium diisopropyl amide (LDA) and the resulting anion was added to cyclohexanone to generate β-hydroxy-α-diazo 3.56. A small modification of the procedure is changing the quench reagent of the LDA reaction from ammonium chloride solution to acetic acid in order to protonate the product at lower temperature.

3.3.3 Reaction condition screen and results

With the precursor for the vinyl cation cyclization in hand, I started to test the cyclization reaction using conditions developed for the fragmentation reaction. With the Lewis acid used for the fragmentation reaction: (SnCl₄), I only isolated 11% of the
desired product 3.61, and the major side product was vinyl chloro 3.60. A similar result was observed with AlCl₃ as Lewis acid. (Table 3.1, entry 1, 2) In order to avoid the chloro trap by product I changed Lewis acid to tripentafluorophenyl borane (BCF), which was used in the C-H insertion reactions, and has a strong Lewis acidity and strong carbon-borane bond. The yield of the desired product 3.61 optimized only to 25% and I was able to identify a side product 3.59, which is presumably formed from the linear vinyl cation 3.57 cyclizing with the aryl ring. Since the reaction would generate water as a side product during the EAS process, I assumed the water would attenuate the BCF acidity and I increase the amount of BCF to 1.5eq. The yield of the desired product slightly increased to 37% with 15% of undesired cyclization. (Table 3.1, entry 4) During the purification and isolation process, I was able to isolate trace amounts of a vinyl pentafluorophenyl side product. Increasing the reaction temperature to room temperature, I collected 42% desired product 3.61 and 35% 3.59. (Table 3.1, entry 5) This indicates higher temperature may favor vinyl cation generation and bond migration. Instead of using a excess amount of BCF, I added 1 eq MgSO₄ to remove water in the reaction and got 48% naphthol 3.61 and 21% 3.59, which is the highest yield. (Table 3.1, entry 6) Increasing the ratio of BCF in the presence of MgSO₄ didn’t change the reaction outcome. (Table 3.1, entry 7)
Table 3.1 Reaction condition screen for naphthal formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Eq</th>
<th>Temperature</th>
<th>Yield</th>
<th>Byproduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl(_4)</td>
<td>1</td>
<td>-20 °C</td>
<td>11%</td>
<td>Chloro trap</td>
</tr>
<tr>
<td>2</td>
<td>AlCl(_3)</td>
<td>1</td>
<td>-20 °C</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>B(C(_6)F(_5))(_3)</td>
<td>1</td>
<td>-20 °C</td>
<td>25%</td>
<td>11% 3.59</td>
</tr>
<tr>
<td>4</td>
<td>B(C(_6)F(_5))(_3)</td>
<td>1.5</td>
<td>-20 °C</td>
<td>37%</td>
<td>15% 3.59</td>
</tr>
<tr>
<td>5</td>
<td>B(C(_6)F(_5))(_3)</td>
<td>1.5</td>
<td>rt</td>
<td>42%</td>
<td>35% 3.59</td>
</tr>
<tr>
<td>6</td>
<td>B(C(_6)F(_5))(_3) + MgSO(_4)</td>
<td>1</td>
<td>rt</td>
<td>48%</td>
<td>21% 3.59</td>
</tr>
<tr>
<td>7</td>
<td>B(C(_6)F(_5))(_3) + MgSO(_4)</td>
<td>1.5</td>
<td>rt</td>
<td>43%</td>
<td>20% 3.59</td>
</tr>
</tbody>
</table>

At this stage, the reaction has been optimized, and I couldn’t control the regioselectivity due to the competitive rate of ring expansion and five-member ring cyclization. To slow down the reaction of the linear vinyl cation 3.57 with the aryl ring, I prepared p-chloro substituted precursor 3.62. Upon subjecting this compound to the standard reaction conditions I only isolated 45% of the desired product 3.63 and I didn’t observe any linear vinyl cation side product 3.64. I didn’t observe any other side product in the reaction and couldn’t explain why the yield is only 45%, but I was able to confirm the yield via internal labeled NoD-NMR integration. (Scheme 3.9)

Scheme 3.9 vinyl cation with p-chloro benzyl groups
I also prepared para-methoxy substituted benzyl diazo ketone 3.65 in hopes of forming a spiro decane. Several different reaction conditions were tested. I was able to collect 33% yield of desired spiro decane product (3.66) and 39% yield of the five-member ring product 3.67. (Table 3.2, entry 1) It is not surprised that the five-member ring product has a higher yield than the spiro product due to the high nucleophilicity of the para-methoxy phenyl ring. With another Lewis acid used in the fragmentation reaction: In(OTf)_3, I only observed trace amounts of product generated. (Table 3.2, entry 2) Increasing the temperature slightly higher to 0 °C, gave the highest yield of vinyl cation products with 38% 3.66 and 41% 3.67. (Table 3.2, entry 2) I also tried the reaction at a much lower temperature. The diazo ketone 3.65 did not react at -78 °C so I let it slowly warmed up to room temperature and collected 20% 3.66 and 27% 3.67, respectively. (Table 3.2, entry 4) A reaction run at room temperature only gave 20% 3.66. (Table 3.2, entry 5) Another nonpolar solvent, pentane, was tried, but this reaction only gave 15% yield. (Table 3.2, entry 6) As has been mentioned before, vinyl cations prefer to be generated in polar solutions. I didn’t observe any product when the reaction was run at reflux in dichloromethane. (Table 3.2, entry 7)

![Chemical structure](image)

<p>| Table 3.2 Reaction condition screen for spiro decane formation |
|---------------------------------|-------|-----|------|------------------|---------|</p>
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>L.A.</th>
<th>Eq</th>
<th>Temperature</th>
<th>Yield 3.66</th>
<th>Side product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.66</td>
<td>3.67</td>
</tr>
</tbody>
</table>

64
<table>
<thead>
<tr>
<th></th>
<th>CH₂Cl₂</th>
<th>BCF</th>
<th>1</th>
<th>-20 °C</th>
<th>33%</th>
<th>39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>In(OTf)₃</td>
<td>1</td>
<td>-20 °C</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>BCF</td>
<td>1</td>
<td>0 °C</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>BCF</td>
<td>1</td>
<td>-78°C-rt</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>BCF</td>
<td>1</td>
<td>rt</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>pentane</td>
<td>BCF</td>
<td>1</td>
<td>0 °C</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>BCF</td>
<td>1</td>
<td>40 °C</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

3.3.4 Computational analysis of reaction process

Our group has an on-going collaboration with Professor Xin Hong’s group to rationalize the mechanism of vinyl cations and predict reaction pathways. They did a detailed computational study on intramolecular reaction of vinyl cation reactions with aromatic rings to elucidate the divergent reaction pathways. Figure 3.2 presents the DFT-computed free energy profile of the competing reaction pathways with diazonium. The vinyl diazonium intermediate has two different conformers, one in which phenyl ring is oriented towards the diazonium (3.68) or in the other it is sitting distal from the diazonium (3.70). The intermediates interconvert with a 3.9 kcal/mol energy barrier through the rotation transition state 3.69. For the intermediate 3.68 the nitrogen cation dissociation will generate the 2-indene-2-one product 3.59 immediately. The linear cation with benzyl group pointing at 3.80 is no longer a local minimum structure in the free energy surface, and the carbon-carbon bond formation would occur spontaneously if the benzyl moiety is proximal to the forming linear vinyl cation. This result is confirmed by intrinsic coordinate calculation as shown on Figure 3.1. For the intermediate 3.68 when the N₂ gas starts to dissociate, the free energy increases to a
transition state (3.79) and then slowly goes down. But the energy drops dramatically after nitrogen gas fully dissociates, which is due to the electron donation from benzene to vinyl cation and bond formation.\textsuperscript{178}

![Graph of energy change along IRC](image)

**Figure 3.1 Intrinsic reaction calculation for TS3.79**

Vinyl diazonium conformer (3.70), it will generate the linear vinyl cation 3.72 through diazonium dissociation intermediate 3.71, which is a local minimum. Then, 3.72 undergoes ring expansion to cyclic vinyl cation 3.73. The Benzyl group on intermediate 3.74 will rotate and cyclize with the cyclic vinyl cation to give a spiro intermediate 3.76. Then, a methylene migration via TS3.77 generates the tricyclic intermediate 3.78, which will deprotonate to 2-naphthol (3.61). This reaction pathway unifies the formation mechanisms of 2-naphthol (3.61) and spiro decane (3.66). Based on the computational analysis the chemoselectivity is determined by the two N\textsubscript{2} dissociation transition states 3.71 and 3.79. The transition state TS3.71, which benzyl group is distal to diazonium cation, is 0.3 kcal/mol more favorable than transition state TS3.79. Therefore, naphthol is the major product, which is also correlated to experiment data.
Figure 3.2 DFT-computed free energy profile of intramolecular C-H vinylation by the vinyl cation with the benzyl moiety
3.4 Brewer group's research on vinyl cation reaction with pendant benzoyl group

3.4.1 Design for chemoselectivity control

As been described above, based on the experiment and computational data, it is impossible to control the chemoselectivity for the intramolecular EAS reaction between a benzyl ketone with linear vinyl cation and cyclic vinyl cation. In order to control the reactivity, I decided to prepare precursor 3.84 which doesn’t contain the methylene between the phenyl and carbonyl. The precursor was prepared from benzoyl chloride (3.82) following the previous procedure without any modification. (Scheme 3.10)

![Scheme 3.10 Synthesis route to precursor 3.84](image)

This material reacted productively to give indenone 3.89 by the proposed mechanism depicted in Scheme 3.11. The vinyl diazonium intermediate (3.85) is generated by Lewis acid mediated hydroxyl cleavage. Linear vinyl cation 3.86 is formed via nitrogen gas dissociation, but this does not cyclize with aryl ring to a 4-member ring intermediate. Instead, the intermediate 3.86 only undergoes ring expansion to cyclic vinyl cation 3.87, which cyclizes to form a five-member intermediate (3.88) then rearomatizes to give indenone 3.89.
3.4.2 Reaction condition optimize

After this initial success, I focused on optimizing the reaction. All reactions were carried out at room temperature and I first tested different Lewis acids. Starting with the SnCl₄, a 45% yield of desired indenone product 3.89 was obtained. Using AlCl₃ as Lewis acid only gave 24% yield. In this case I observed a major side product: vinyl chloride. Switching to Sc(OTf)₃ as Lewis acid gave 60% yield of product 3.89. In this case, the major side product is vinyl triflate. Aluminium triflate, another Lewis acid for vinyl cation generation, didn’t provide a good yield for reaction either. Finally, BCF as a strong and stable Lewis acid provided 80% yield of the desired indenone product. But, I was still able to isolate the pentafluorophenyl trapped side product, which indicates the BCF is decomposing. The unavoidable counter anion trapping may occur because the Lewis acid coordinates on the carbonyl group and delivers the ligand to the linear vinyl cation intermolecularly. (Figure 3.3)
Table 3.3 Reaction condition test for indenone formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield</th>
<th>Major side product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl(_4)</td>
<td>45%</td>
<td>Vinyl chloride</td>
</tr>
<tr>
<td>2</td>
<td>AlCl(_3)</td>
<td>24%</td>
<td>Vinyl chloride</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)(_3)</td>
<td>60%</td>
<td>Vinyl triflate</td>
</tr>
<tr>
<td>4</td>
<td>Al(OTf)(_3)</td>
<td>26%</td>
<td>Vinyl triflate</td>
</tr>
<tr>
<td>5</td>
<td>B(C(_6)F(_5))(_3)</td>
<td>80%</td>
<td>C(_6)F(_5) anion trap</td>
</tr>
</tbody>
</table>

Figure 3.3 Counter ion trap process

Treating diazo precursor 3.84 with trifluoro acetic acid, a strong protic acid, TFA didn’t give desired product but instead generated 2-benzoylcycloheptan-1-one (3.87) in 74% yield. This is due to the fact that the protic acid doesn’t cleave the hydroxyl group, but instead activates the diazo and generates a carbocation (3.86). A Pinacol type rearrangement leads to the seven-member 1,3-diketone product 3.87.
3.4.3 Computational analysis on mechanism

Professor Hong’s group also did computational analysis on this reaction process. The DFT-computed reaction free energy profile is shown in Figure 3.4. Starting from the vinyl diazonium intermediate 3.87, which is generated through Lewis acid mediated cleavage of the β-hydroxy group, a N₂ dissociation generates the linear vinyl cation intermediate 3.89 through TS3.88. It is noteworthy to mention this step has the highest energy barrier and is the rate limiting step for whole reaction process. Ring expansion proceeds through transition state TS3.90 to give the cyclic vinyl cation 3.91. The cyclic vinyl cation can undergoes electrophilic aromatic substitution with the phenyl ring to give intermediate 3.93 which rearomatizes to final product 3.89. Padwa’s research on vinyl cation insertion which generates lactones indicates that seven-member vinyl cation intermediates may have an alternative reaction pathway, which involves a ring contraction process through TS3.94 to give allylic cation intermediate 3.95. Professor Hong also did calculations on this reaction pathway and found that the transition state from ring contraction is 2.7 kcal/mol higher than C-C bond formation, therefore the ring
contraction process is less favored. This computational result is corroborated with the experimental observation that I didn’t observe any ring contraction product generated.

Figure 3.4 DFT-calculated reaction energy profile of intramolecular arene C-H vinylation by the vinyl cation

3.4.4 Substrate scope on aryl ring substitution

With optimized conditions in hand, I started to investigate how aryl ring substitution affected the reaction process. It is interesting to observe that the para-methyl substituted aryl ring precursor gave 72% yield of indenone 3.96, and para-methoxy substituted gave 68% yield of 3.97. Both yields are lower than the non-substituted precursor 3.89. In contrast, a less nucleophilic para-chloro substituted diazo precursor (3.98), gave the indenone in 77% yield. This change in yield with respect to the nucleophilicity of the aryl ring was unexpected. I repeated each reaction several times and this result was consistently observed. Since I was able to collect higher amounts of counter ion trapped side products (3.101) for the electron-rich aryl ring precursors, I came to a conclusion that although the electron-rich aryl ring would facilitate a faster EAS
reaction, it also stabilized the linear vinyl cation intermediate 3.89 and slowed down the ring expansion process, thus leading to a higher yield of counter ion trapped side products. (Figure 3.5)

![Scheme 3.13 Substrate scopes of aryl substitution](image)

**Figure 3.5 Explanation of slow ring expansion**

Although Hong’s group didn’t calculate the energy barrier of ring expansion for the para-methoxy substituted aryl ring linear cation intermediate, a nitro-substituted aryl ring expansion process was investigated computationally. By comparing the ring expansion process of the nitro intermediate 3.102 to the phenyl system (3.89), we see that the nitro-substituted cation 3.102 has a 1.2 kcal/mol lower energy barrier to ring expansion than intermediate 3.89. This indicates the nitro intermediate 3.102 undergoes
a faster ring expansion. In return, it is probable that the electron-rich aryl ring linear vinyl cations will have a higher energy barrier to ring expansion and a slower ring expansion process.

Figure 3.6 DFT-calculated reaction energy profile of ring expansion process with different substitutes

A meta-chloro substituted aryl ring precursor only gave 32% yield of the desired product (3.99). This is probably because there are fewer positions for the EAS to occur. For substituted aryl rings with a strong electron withdrawing group, (i.e. nitro group), the reaction was inhibited substantially. I was only able to isolate 8% of the desired product 3.100. Hong and coworkers use computational methods to understand these results. They found that the non-substituted aryl ring cyclic vinyl cation intermediate 3.91 only requires a 2.3 kcal/mol barrier via TS3.92. However, for the para-nitro substituted intermediate 3.104, the energy barrier increases to 4.5 kcal/mol, which indicates a slow cyclization process and long life time for intermediate 3.104.
Hong’s group also suggested the *para*-nitro substituted intermediate 3.104 will be more likely to undergo other side reactions. For instance, the ring contraction process of transition state 3.107 is only 0.3 kcal/mol higher than carbon-carbon bond formation 3.105. And the barrier for the reverse reaction from 3.106 to 3.105 is only 14.6 kcal/mol suggesting the possibility the intermediate 3.106 may undergo C-C bond dissociation to regenerate vinyl cation 3.104. (Figure 3.7)

![Figure 3.7 Computational results of vinylation reactivity with para-nitro substitution](image)

I also prepared the *meta*-methyl substituted precursor 3.109, which gave a mixture of two regioisomeric indenones 3.110 and 3.111. The total yield is 82% and the less sterically hindered product (3.111) is the major product. The ratio of 3.111 to 3.110 is 1.5 to 1 based on NMR integration. (Scheme 3.14)
Scheme 3.14 Reaction outcome of meta-substituted aryl ring

3.4.5 Substitution on cyclohexane ring

After finishing the investigation of the aromatic substitution substrate scope, I started to research how substitution on the cyclohexane ring effects the reaction process. I prepared di-methyl cyclohexane substrate 3.112, which reacts with BCF to generate the desired product 3.113 in 75% yield. With more atoms on hexane ring, the ring expansion process requires more energy and become less entropically favorable. Therefore the yield decreases. (Scheme 3.15)

Scheme 3.15 dem-methyl indenone formation

4-t-Butyl substituted cyclohexanone reacted with diazo ketone to generate two diastereoisomers of aldol addition product. I was able to separate those two isomers through a neutral alumina column. The two isomers have the hydroxyl group sitting in either the axial (3.114) or on the equatorial position (3.116). Subjecting those diazo precursors (3.114, 3.116) to the standard reaction conditions for indenone formation, gave the same product 3.115 in similar yields 67% and 72%. This results shows that the conformation of the hydroxyl group did not affect the reaction outcome. (Scheme 3.16)
I was also interested to test different ring sizes to see if that had an effect on the vinylation of phenyl ring. Cyclopentane diazo precursor 3.116 was prepared and subjected in standard reaction conditions. To my surprise, this reaction generated a mixture contain vinyl chloro trapped product. In this case, the chlorine must be transferred from the dichloromethane solution. Switching to dichloroethane gave the desired indenone product 3.117 in only 14% yield. This dramatic drop in yield may be due to the fact that the vinyl cation is a $sp$ hybridized linear intermediate, and so the six-member cyclic vinyl cation has significant strain, which inhibits the ring expansion process. (Scheme 3.17)
This postulate was confirmed by Hong’s computational results. As shown on Scheme 3.18, the energy barrier for expansion of cyclic vinyl cation 3.119 through TS3.118 is 4.9 kcal/mol. While previous linear vinyl cation 3.89 expands to seven-member cyclic vinyl cation 3.91 with a 3.4 kcal/mol energy barrier. The higher energy barrier for expansion of intermediate 3.117 results in a longer lifetime for the linear vinyl cation and thus greater quantities of chloro trapped product. It is important to mention that the cyclic vinyl cation 3.119 only has a 2.3 kcal/mol energy barrier to cyclize with the phenyl ring. So only the ring expansion step is the challenge. (Scheme 3.18)

Scheme 3.18 Computational results of vinylation reactivity with the cyclopentane moiety

I even tried the precursor with a cyclobutane moiety 3.120 and I was unable to observe any desired product. The reaction only generated pentafluorophenyl trapped side product 3.121. (Scheme 3.19)

Scheme 3.19 Reaction of diazo ketone with cyclobutane moiety
In attempting to prepare cycloheptane derived substrate (3.122), I faced a big difficulty. It seems the steric effect of the heptanone ring prohibited the lithiated diazo ketone addition, and I didn’t observe any desired aldol-addition product. (Scheme 3.20)

![Scheme 3.20 Failed reaction in prepare the precursor](image)

3.4.7 Other Substrates that did not work

In order to explore the substrate scope of this reaction, I decided to test the reaction in tolerance of heteroatoms. β-Hydroxy-α-diazo ketone with methyl piperidine 3.124 was prepared, but was inert to BCF catalysis. The reaction returned only starting material. Protecting the strongly basic nitrogen with a tosyl group gave precursor 3.125 but it also didn’t afford any rearrangement product. The starting material decomposed upon BCF treatment but I didn’t collect any desired product. This is probably due to the coordination of BCF on nitrogen which prevented the ring expansion. (Scheme 3.21)

![Scheme 3.21 Substrates with nitrogen atom](image)

It is unfortunate to see that a linear ketone system also didn’t work in this reaction. It seems the alkane migration step is challenging. (Scheme 3.22)
Since indole is another good aromatic nucleophile, I prepared precursor 3.132 by the sequence shown in Scheme 3.23. 3-Carboxylic indole (3.128) was protected by a tosyl group to 3.129 in order to avoid the chemoselectivity issue on LDA reaction. The carboxylic group was converted to an acyl chloride which was converted to the diazo 3.131. Aldol-like addition with cyclohexanone gave 3.132. Unfortunately, while this material 3.132 was able to generate vinyl cation intermediate in the presence of Lewis acid, the vinyl cation did not cyclize with indole due to the low nucleophilicity of N-tosyl indole. Similar reactivity was reported by Bour group.\textsuperscript{179}

\begin{align*}
\text{O} & \quad \text{OH} \\
\text{N} \quad \text{HO} \\
\text{BCF, DCM,rt} & \quad \text{3.126} \\
\text{THF, nBuLi, TosCl} & \quad \text{3.127} \\
\text{Thionyl chloride} & \quad \text{3.128} \\
\text{CH}_2\text{N}_2 & \quad \text{3.130} \\
\text{N} & \quad \text{Tos} \\
\text{LDA, THF} & \quad \text{-78°C} \\
\text{3.131} & \quad \text{3.132} \\
& \quad \text{3.133}
\end{align*}
3.4.8 Summary

Vinyl cations can be generated from β-hydroxy-α-diazo ketones through a Lewis acid mediated OH cleavage/vinyl diazonium decomposition sequence. The initially generated linear vinyl cation will rearrange to give a cyclic vinyl cation, which is a strong electrophile and will undergo intramolecular EAS reactions with aromatic rings to form tricyclic indenones in moderate to high yield. Both DFT-calculations and experiment results indicated that the ring expansion process has a low functional group tolerance. Strong electron-releasing groups, heteroatoms and ring strain will suppress the ring expansion and thus a limited substrate scope for the reaction.

Extending the length between the carbonyl and the phenyl group by one methylene results in a mixture of 2-napthol and 2-indenone products. The chemoselectivity is due to the high reactivity of vinyl cations and the rotational isomers of the benzyl group. Based on DFT-computational analysis, the mechanism for the generation of each products is well established. Unfortunately, it is impossible to control the chemoselectivity issue under current reaction conditions.
Chapter 4 Discovery and mechanistic investigation into the conjugate addition of vinyl diazonium salts

4.1 Initially proposed intermolecular Vinyl cation EAS reaction

While investigating the vinyl cation reactions, described in chapter 2 and 3, I observed that the ring expansion process is highly dependent on structure of the initially formed vinyl cation. As indicated on previous chapters, highly electron donating groups on the aryl ring or small ring size would slow down the ring expansion process. The major side products isolated were formed by trapping the linear vinyl cation with the counter ion of the Lewis acid. (Figure 4.1)

![Figure 4.1 Side reaction of vinyl cation]

These side products are generated by an intermolecular reaction between the vinyl cation and the Lewis acid. As we know, vinyl cations do not easily undergo intermolecular reactions. The observance of these types of intermolecular reactions inspired me to consider the possibility of designing a reaction between a vinyl cation and a heteroarenes. I hypothesized that, heteroarenes with oxygen or nitrogen atoms would coordinate the Lewis acid and would be delivered to the vinyl cation via an intramolecular reaction.(Figure 4.2)
4.2 Searching for Potential heteroarene nucleophile searching

Based on this coordination-delivery assumption, I screened several different heteroarenes for their ability to react with diazo ketones under Lewis acid catalysis. But, I found the reaction pathway changed dramatically based on the Lewis basicity of the heteroarene. (Scheme 4.1)

I started this work by treating diazo ketones or diazo esters with different kinds of Lewis acids at different temperatures, and I tried to trap the vinyl cation intermediate with heteroarenes as nucleophiles. Due to the high price of BCF, most of the reactions were tested with cheaper Lewis acids such as tin tetrachloride, and scandium triflate. First I tested phenol as a nucleophile reacting with ethyl diazo esters (4.5, and 4.4 Table 4.1) at -20 °C and -78 °C. I didn’t observe any intermolecular reaction, and the diazo esters were decomposed by the Lewis acid (Table 4.1, entry 1,2). It is interesting to note that diazo ketone 4.7 didn’t react at -78 °C with SnCl₄, I was able to recover all starting material (Table 4.1, entry 3). Treating diazo ketone and phenol, with Sc(OTf)₃ at room temperature, gave only the intramolecular vinyl cation reaction product (the tricyclic indenone 3.89) Table 4.1, entry 4. These results indicate phenol is not a good candidate for this reaction. I then tested furan and anisole as nucleophiles and still observed only diazo decomposition (Table 4.1, entry 5, 6). I decided to increase the nucleophilicity of the heteroarene and started to
investigate nitrogen containing aromatic systems. Adding diazo ester 4.4 into a mixture of aniline and SnCl₄ generated vinyl diazo product 4.8. Similar reactivity was reported by the Padwa group. The same result was observed when aniline was replaced by pyridine. (Table 4.1, entry 7, 8) However, in the presence of Sc(OTf)₃ and pyridine diazo ketone 4.7 didn’t give any reaction (Table 4.1, entry 9). I tried to lower the Lewis basicity by converting aniline to acetanilide, but the acetanilide acted as a bystander and diazo ketone 4.7 underwent the expected intramolecular reaction to give the indenone 3.89 (Table 4.1, entry 10). Realizing that I attenuated the nucleophilicity too much, I reviewed Mayr’s reactivity database and decided to investigate the pyrrole as a nucleophile. Pyrrole is a good candidate as it is a mild base and good nucleophile. It was glad to observe some pyrrole addition product generated by adding diazo ester 4.4 to a mixture pyrrole and SnCl₄ at -78 °C. However, I couldn’t resolve the structure and it seems that there were two pyrrole rings on the structure. Switching the Lewis acid to Sc(OTf)₃ gave similar results, but less side products. (Table 4.1, entry 11, 12) I then tested diazo ketone 4.7 in reacting with N-methyl pyrrole, and this time I was able to isolate the structure of the product which according to NMR resulted from a vinyl cation reaction with pyrrole (Table 4.1, entry 13).

![Scheme 4.1 Initial nucleophile searching result](image_url)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Lewis acid</th>
<th>Nucleophile</th>
<th>temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 1$</td>
<td>SnCl$_4$</td>
<td>Phenol</td>
<td>-78 °C</td>
<td>Diazo decomposed</td>
</tr>
<tr>
<td>2</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>BCF</td>
<td>Phenol</td>
<td>-20 °C</td>
<td>Diazo decomposed</td>
</tr>
<tr>
<td>3</td>
<td>$R = \text{Ph}$&lt;br&gt;$n = 1$</td>
<td>SnCl$_4$</td>
<td>Phenol</td>
<td>-78 °C</td>
<td>Recover SM</td>
</tr>
<tr>
<td>4</td>
<td>$R = \text{Ph}$&lt;br&gt;$n = 1$</td>
<td>Sc(OTf)$_3$</td>
<td>Phenol</td>
<td>rt</td>
<td>Tricyclic indenone X</td>
</tr>
<tr>
<td>5</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>SnCl$_4$</td>
<td>Furan</td>
<td>rt</td>
<td>Diazo decomposed</td>
</tr>
<tr>
<td>6</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 1$</td>
<td>SnCl$_4$</td>
<td>Anisole</td>
<td>rt</td>
<td>Diazo decomposed</td>
</tr>
<tr>
<td>7</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>SnCl$_4$</td>
<td>Aniline</td>
<td>0 °C</td>
<td>Vinyl diazo X</td>
</tr>
<tr>
<td>8</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>SnCl$_4$</td>
<td>Pyridine</td>
<td>0 °C - rt</td>
<td>Vinyl diazo X</td>
</tr>
<tr>
<td>9</td>
<td>$R = \text{Ph}$&lt;br&gt;$n = 1$</td>
<td>Sc(OTf)$_3$</td>
<td>Pyridine</td>
<td>0 °C - rt</td>
<td>Recover SM</td>
</tr>
<tr>
<td>10</td>
<td>$R = \text{Ph}$&lt;br&gt;$n = 1$</td>
<td>Sc(OTf)$_3$</td>
<td>Acetanilide</td>
<td>rt</td>
<td>Tricyclic indenone X</td>
</tr>
<tr>
<td>11</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>SnCl$_4$</td>
<td>Pyrrole</td>
<td>-78 °C</td>
<td>Observe pyrrole added but can’t resolve structure. Same as 12</td>
</tr>
<tr>
<td>12</td>
<td>$R = \text{OEt}$&lt;br&gt;$n = 0$</td>
<td>Sc(OTf)$_3$</td>
<td>N-Methyl pyrrole</td>
<td>-78 °C</td>
<td>Same as 12</td>
</tr>
<tr>
<td>13</td>
<td>$R = \text{Ph}$&lt;br&gt;$n = 1$</td>
<td>Sc(OTf)$_3$</td>
<td>N-Methyl pyrrole</td>
<td>rt</td>
<td>Observe potential intermolecular reaction</td>
</tr>
</tbody>
</table>
4.3 Discovery of first intermolecular reaction between indole and diazo ketone 4.7

Even though all previous results didn’t show any evidence of a regulated intermolecular reaction, I decided to test another mild nucleophile: indole. It was very exciting to observe indole addition product 4.10 formed in 63% yield by adding diazo ketone 4.7 into a mixture of indole and Sc(OTf)₃ at room temperature. I also isolated indenone 3.89 at 24% yield, which indicates that indole trapping is not efficient enough to suppress the ring expansion (Scheme 4.2, table 4.2 entry 1).

![Scheme 4.2 β-hydroxy diazo ketone 4.7 reaction with indole](image)

Table 4.2 Reaction condition screening for β-hydroxy diazo ketone with indole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Lewis acid</th>
<th>Eq of indole</th>
<th>4.10</th>
<th>3.89</th>
<th>4.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>Sc(OTf)₃ 1eq</td>
<td>1</td>
<td>63%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>SnCl₄ 1eq</td>
<td>1</td>
<td>28%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>BCF 1eq</td>
<td>1</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>rt</td>
<td>AlCl₃ 1eq</td>
<td>1</td>
<td>16%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>rt</td>
<td>Sc(OTf)₃ 1eq</td>
<td>3</td>
<td>80%</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>rt</td>
<td>Sc(OTf)₃ 1eq</td>
<td>4</td>
<td>90%</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>rt</td>
<td>Sc(OTf)₃ 0.5 eq</td>
<td>2</td>
<td>79%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>40 °C</td>
<td>Sc(OTf)₃ 1eq</td>
<td>4</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-20 °C</td>
<td>Sc(OTf)₃ 1eq</td>
<td>4</td>
<td>33%</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

I then screened Lewis acids at the room temperature, and found that Sc(OTf)₃ had the best results compared to other Lewis acids. SnCl₄ only gave 28% yield of the desired...
product 4.10 and 36% yield of tricyclic indenone 3.89. BCF, typically the Lewis acid for vinyl cation reactions, didn’t generate any desired product 4.10, and AlCl₃ generated only 16% yield of the desired product 4.10 and 27% yield of indenone 3.89 (table 4.2, entry 2-4). Having identified Sc(OTf)₃ as the best Lewis acid, I decided to increase the equivalents of indole in reaction. Changing the equivalents of indole from 1 to 3 gave the desired product (4.10) in 80% yield. With 4 eq of indole in the reaction system, I was able to collect product 4.10 in 90% yield and only trace amounts of tricyclic indenone 3.89 were isolated (table 4.2, entry 5-6). In order to test whether this reaction could operate with catalytical amount of Lewis acid, I decreased the Sc(OTf)₃ to 0.5 eq and the yield dropped to 79% (table 4.2, entry 7). Increasing the temperature to 40 °C didn’t optimize the reaction, instead the yield decreased to 67%. Importantly, running this reaction at -20 °C, gave only 33% yield of the product while another important byproduct 4.11 was formed in 53% yield. According to NMR and XRD structure analysis, byproduct 4.11 still contains the diazo group, and the indole is connected to the β-position of the diazo ketone. Diazo product 4.11 must be generated before vinyl cation formation, with indole most likely adding to vinyl diazonium intermediate 4.12. Since vinyl cation formation occurs by C-N bond breaking with loss of N₂ gas, this step should be highly temperature sensitive. Therefore, diazo product 4.11 would be favored at lower temperature.

![Figure 4.3 Diazo product 4.11 formation](image-url)
4.4 Mechanistic investigation of the indole addition reactions

4.4.1 Proposed mechanism

Originally I thought, the reaction to form enone products like 4.10 would occur by the mechanism shown in scheme 4.3.

Scheme 4.3 Original proposed mechanism

However, after more thought, that path seems unlikely because this intermolecular reaction should be slower than intramolecular vinyl cation rearrangement. Indeed, professor Hong’s research revealed that there is a very small energy barrier for ring expansion, which raised a question: Why didn’t I observe indole trapped product 4.15 that forms after ring expansion? (Figure 4.4)

Figure 4.4 Unobserved indole product 4.15

4.4.2 Alternative mechanism

By reviewing all my research data, I realized that another alternative reaction pathway that proceeds through initial formation of diazo product 4.11 followed by indole migration could explain the formation of vinyl indole product 4.10. (Scheme 4.4)

For the second pathway, Lewis acid activation of diazo ketone would create an electron deficient active site α to the ketone, and the most electron rich indole ring would migrate.29

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Scheme 4.4 Proposed mechanism and alternative mechanism

**4.4.3 Mechanism validation**

Luckily, the reaction system is not complicated and a simple reaction can be done to experimentally support the proposed mechanism without the help of computational chemistry. If the reaction occurs by the suggested rearrangement pathway, then treating the conjugate addition product (4.11) with the same Lewis acid conditions should lead to the final product 4.10. I tested that reaction and within 30 mins diazo product 4.11 totally converted to the final product 4.10 in a quantitative yield. (Scheme 4.5)
Unfortunately, this reaction successfully revoked the previously proposed vinyl cation mechanism for this reaction. Originally, we believed that we discovered a new way to tame vinyl cation and undergo intermolecular reaction. But as a matured researcher I had to accept and respect this objective result and I followed up to further understand this reaction.

**4.4.4 Mechanism in detail**

Overall, the formation of 4.10 occurs by a multi-step process.

A plausible mechanism for the conjugated addition of indole to the vinyl diazonium intermediate is shown in Scheme 4.6. The sequence starts with Sc(OTf)$_3$ mediated dehydroxylation of β-hydroxy-α-diazo ketone 4.7 to generate vinyl diazonium intermediate 4.12. Indole would attack at the β position of the diazonium to form the quaternary carbon center giving 4.16. Re-aromatizing the indole would give diazo ketone product 4.11. (Scheme 4.6)

![Scheme 4.6 Mechanism proposed for 1,4-vinyl diazonium addition](image)

It is unclear whether the indole migration occurs through a carbene intermediate or by a cationic mechanism. Based on previously reported Lewis acid catalyzed diazo ketone reactions, I propose that the reaction is initiated by Sc(OTf)$_3$ activation of the
diazo ketone to give enal diazonium 4.17. Subsequent loss of nitrogen would afford vinyl cation intermediate 4.18. Under thermal conditions, vinyl cation intermediate 4.18 would generate and then cyclize with indole to give cyclopropane intermediate 4.19. The observed product 4.10 would be generated by ring opening of the cyclopropane. (Scheme 4.7)

Scheme 4.7 Sc(OTf)$_3$ mediated indole migration

4.5 Substrate scope for the indole migration reaction

4.5.1 Reaction at room temperature

With optimized reaction conditions in hand, I started to investigate the substrate scope of the reaction based on different β-hydroxy diazo ketones. At room temperature with 4 equivalents of indole. Reactions of β-hydroxy-β-cyclohexyl systems with various groups at the α’ position (e.g 4.7) generally went well giving 4.10, 4.22 and 4.25 in 90%, 88%, and 85% yield respectively (Scheme 4.8). However, the corresponding α’ t-butyl didn’t undergo indole migration and only gave 66% yield of the 1,4-vinyl diazonium product 4.28. In this case, extending the reaction time to 24 hours only lead to a mixture of decomposition products, which did not contain the desired product. This may be the result of the steric hinderance of the t-butyl group prohibiting the Lewis acid coordination.
and indole migration. Incorporating two methyls at the 4-position of the cyclohexyl ring gave 4.39 in 84% yield. It was also glad to see that the N-tosyl piperidine substituted diazo reacted smoothly to give 88% yield of product 4.30. This indicates that a protected heteroatom is compatible to the reaction conditions. Extending the ring size from six to seven resulted in 70% yield of 4.27. On the other hand, shrinking the ring size to five caused a dramatic yield drop. The cyclopentyl based systems gave 4.21 and 4.24 in just 10% and 33% yield. This may due to the rigidity of the smaller ring which may prevent indole addition. I also tested β-dipropyl substituted diazo ketones in this reaction. The results were not as good as the β-cyclohexane based systems. Ketones 4.20, 4.23 and 4.26 were formed in only 27%, 54% and 52% yield respectively. It seems that the more rigid cyclic ring promotes indole migration better. (Scheme 4.8)

4.5.2 Reaction at -20°C then warm up

From the proposed mechanism, I thought that low temperature conditions would favor the first step (vinyl diazonium addition) and suppress the second step (indole migration). So I tested new conditions, where the diazo was added into the indole and Sc(OTf)₃ mixture at -20 ºC and the solution was slowly warmed to room temperature. These optimized conditions immensely increased the yields of β-dipropyl substituted diazo ketones’ reactions, and both n-butyl and cyclohexane diazo ketones 4.23, and 4.26 gave 81% yield. Phenyl diazo ketone’s yield improved from 27% to 51% (4.20). Even the β-cycloheptane system gave increased yields of 4.27 yield from 70% to 88%. The β-cyclopentane system, which previously gave 33% yield, increased slightly to 44% percent. It is worth mentioning that the low yield obtained for cyclopentyl based systems is consistent with the conjugated addition/rearrangement mechanism. Based on Hong’s
computational result, vinyl cations with a 5-member ring attached should have less tendency to ring expand, and therefore a longer life time. If the reaction occurred by addition of indole to the vinyl cation, then product yield of 4.21 should be higher than 6-member ring substituted product 4.10. The low yield actually can be explained by the difficulty of generating a quaternary carbon center on cyclopentane. (Scheme 4.8)
Scheme 4.8 Substrate scopes of indole migration
4.6 Indole migration of diazo ester

This one-pot 1,4-vinyl diazonium addition/indole migration reaction only works with diazo ketones. Diazo esters gave a totally different result. During the reaction process, I was able to observe the conjugated addition product generated, but extended reaction times did not lead to an indole migration product but only random decomposition. (Scheme 4.9)

Scheme 4.9 Failed diazo ester indole migration with Lewis acid

After isolating the 1,4-addition product, I treated the diazo compound with Rh$_2$(OAc)$_4$. I was glad to observe the desired indole migration product 4.33 formed in at 88% yield.(Scheme 4.10)

Scheme 4.10 Diazo ester indole migration by Rh$_2$(OAc)$_4$

4.7 Research on 1,4-vinyl diazonium addition reaction

After finishing research about indole migration reactions, we know that this type of migration would only happen for highly electron-rich romatics. So it would not be general for a lot of different nucleophiles. However, we found the first step the conjugated addition to a vinyl diazonium very interesting. This type of electrophilic
addition to vinyl diazonium was basically unknown, and we thought it might be very useful.

### 4.7.1 Background of vinyl diazonium

Vinyl diazoniums were reported a long time ago as a potentially useful synthetic intermediates, but very few studies had been done to explore their application. Alkane substituted vinyl diazonium salts are highly unstable intermediates compared to widely known aryl diazonium salts. Unstabilized vinyl diazoniums are commonly known as precursors to vinyl cations, and our group took advantage of this property. But the electrophilicity of the β-carbon of this species is barely reported and researched. Previous researchers found that β,β-dialkoxyethenediazonium salts and β,β-dichloro diazonium salts are stable and isolable with SbCl₆ as counter anion. The stability is due to the lone pair electrons from oxygen or chlorine that form a carbenium resonance (4.35 and 4.38). (Figure 4.5)

![Figure 4.5 Stabilized vinyl diazonium salt](image)

There is one example to show that those stabilized vinyl diazoniums salt could perform electrophilic aromatic substitution reactions with anisole reported by Kaspar Bott. (Scheme 4.11)
Recently, Crich and his coworkers reported that in situ-generated vinyl diazonium reacts with naphthol to generate dihydrofuran. But these are the only examples of this type of reactivity I was able to locate.

Our research showed that unstabilized vinyl diazonium could be trapped by mild nucleophiles to give new diazo products. This reaction would take advantage of the strong electron withdrawing nature of diazonium cations to install a quaternary or tertiary carbon center beta to the diazo ketone or diazo ester in high yield. It is rare to form all
carbon quaternary centers by conjugate addition due to steric effects.\textsuperscript{182} Also, those type of diazo compounds are usually hard to prepare by diazo transfer reactions due to the high steric hindrance. With those ideas we altered our research interest to focus on this unprecedented conjugate addition reaction.

\textbf{4.8.1 Vinyl diazonium addition reaction condition screen}

As always we needed to find ideal reaction conditions before testing the substrate scope of this reaction. Since diazo esters are not easily decomposed by Lewis acid. I started my studies with ethyl 2-diazo-3-hydroxy-3-propylhexanoate (4.31). I began by screening different Lewis acids for this reaction. Strong Lewis acids like BCF or SnCl\textsubscript{4} caused decomposition, and gave 0\% and 5\% yield respectively. Al(OTf)\textsubscript{3} didn’t decompose the desired product and gave 83\% yield, whereas Sc(OTf)\textsubscript{3}, a more mild Lewis acid, gave the best yield 90\%. I also tested the reaction at room temperature, and was impressed to observe a 79\% yield. Since vinyl diazonium intermediates decompose quickly at higher temperature, this yield indicates that the addition step is faster and C-N bond cleavage. (Table 4.3)

![Reaction Scheme 4.3](image-url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis. Acid</th>
<th>temperature</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>-20 °C</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>rt</td>
<td>79%</td>
</tr>
</tbody>
</table>
### 4.8.2 Substrate scopes research of vinyl diazonium addition

With optimized conditions in hand, I started to investigated different substituted indoles as nucleophiles. With electron-releasing methoxy group at the 5 position of indole, the reaction gave 91% yield if 4.48. Instead of electron-rich indoles, 5-bromo indole and 5-methyl carboxylate indole give 86% 4.51 and 88% yield 4.49, respectfully. Thus mild electron withdrawing groups are tolerated. However, with a strongly electron deficient 4-nitrile indole 4.50, the reaction only gave 33% yield. This would be due to the low nucleophilicity and steric effect between the nitrile group and the propyl group. N-methyl indole, is a strong nucleophile, and gave 93% yield 4.54. While N-acyl protected indole and N-tosyl indole didn’t give any desired products (4.55, and 4.56). Apparently the acyl group and tosyl group attenuated the nucleophilicity of the indole. Instead of indole, pyrrole as a nucleophile gave 85% yield of 4.53. NOE studies indicated that the reaction generates bond at the 2-position of pyrrole. A similar observation was found with benzotriazole as a nucleophile, which gave 49% yield of 4.52. (Scheme 4.13)

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<tr>
<td>3</td>
<td>Al(OTf)$_3$</td>
<td>-20 °C</td>
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<tr>
<td>4</td>
<td>SnCl$_4$</td>
<td>-20 °C</td>
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<tr>
<td>5</td>
<td>BCF</td>
<td>-20 °C</td>
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Scheme 4.13 Substrate scopes of aromatic nucleophiles

4.31

$\text{EtO}_2\text{C} = \text{OH}$

Aromatic nucleophile

Lewis acid, $\text{CH}_2\text{Cl}_2$

$\text{EtO}_2\text{C} = \text{Nu}$

4.32

EtO

$\text{N}_2$

90%

4.48

EtO

$\text{N}_2$

91%

4.49

EtO

$\text{N}_2$

88%

4.50

OEt

33%

4.51

EtO

86%

4.52

EtO

49%

4.53

85%

4.54 R= Me 93%

4.55 R= Ac 0%

4.56 R= Tos 0%
I also investigated different on vinyl diazonium intermediates in this reaction Scheme 4.14. The β-hydroxy-α-diazo esters substrates are easily prepared by addition of lithiated diazo esters to ketones or aldehydes. I prepared β-hydroxy-α-diazo esters from cyclopentanone, and the Michael addition reaction gave 90% yield of 4.57. With a six member ring attached at the β position of the diazo ester, the reaction only gave 75% yield 4.58. Based on our previous research, vinyl diazoniums with a 6-member ring attached generate vinyl cations easily. Therefore the yield of the conjugate addition shrinks. We also tested precursors which are prepared from benzaldehyde and pentanal, and observed 73% yield of 4.59 and 64% yield of 4.60. These yields are really out of our expectation. It has been previously reported vinyl diazonium intermediates with hydrogen atom attached at β-position would rapidly undergo elimination reactions to generate alkynes.

In addition, I also studied the reactivity of vinyl diazoniums formed from diazo ketones. The α’-t-butyl α-diazo substituted ketone reacted with indole to give 4.61 in 87% yield. The cyclohexyl derivatives, example of a secondary carbon at the α’ position provided 87% yield of 4.62. A benzyl in this position gave a slightly lower yield of 4.64 (78%) and the n-propyl ketone gave only 75% yield of 4.63. This yield decreasing trend followes with the electron donation ability of the alkyl groups, more electron rich alkanes should stabilize the vinyl diazonium intermediate, and result of a higher yield of addition. We also prepared vinyl diazonium t-butyl ketone with six member ring attached at the β-position, which under standard reaction conditions gave 91% yield of 4.28. Consistent with earlier observations, having a five-member ring attached at the β-position gave lower product yields (65%) of 4.66. Due to the thermal instability of the product, I
observed product decomposing during the work up. A secondary alcohol on the β position was acceptable and 4.65 was formed in 65% yield. Last, this reaction also tolerates to tosyl protected amine, giving 4.67 in 95% yield.

Scheme 4.14 Substrate scopes on different diazo ketone
**4.8.3 Intramolecular addition to a vinyl diazonium addition**

Up to this point we had only studied intermolecular additions to vinyl diazonium salts. However, a large number of natural products are polycyclic indoles.\(^{194-196}\) Therefore, an intramolecular indole vinyl diazonium addition, that would afford polycyclic indole scaffolds is worth investigating. To validate this reaction, I prepared the \(\beta\)-hydroxy-\(\alpha\)-diazo ester with a pendant indole 6 atoms away 4.71 Scheme 4.15. The indole carboxylic acid 4.68 was converted to ethyl ester 4.69 and then reduced to aldehyde 4.70 by DIBAL-H.\(^{197}\) The diazo ester was installed under DBU conditions to afford the desired product 4.71 in 37% yield. Subjecting the starting material to Sc(OTf)\(_3\) gave 78\% yield of the desired cyclization product 4.72. (Scheme 4.15)

![Scheme 4.15 intramolecular cyclization between vinyl diazonium and indole](image)

I also prepared \(\beta\)-hydroxy-\(\alpha\)-diazo ester 4.74 with a pendant phenyl ring attached 5 atoms away. Unfortunately, activating the starting material with Sc(OTf)\(_3\) didn’t result in desired product. This result is consistent with previous intermolecular reactions and confirms that benzene can’t trap the vinyl diazonium intermediate. It can be concluded that the nucleophilicity of phenyl ring is not strong enough to react with vinyl diazoniums. (Scheme 4.16)
4.8.4 Searching for other nucleophiles

I had researched all kinds of diazo carbonyl structures reacting with indole. To further extended this reaction’s utility, I started to search for other non-aromatic nucleophilic partners. Different nucleophiles were tested including allyl amine, enamine, 1,3-diketone, and 1,3-diester. None of those nucleophiles trapped the vinyl diazonium intermediate. Another group member Evan M. Howard, discovered that silyl enol ethers were a good nucleophiles that reacted with the vinyl diazonium to give addition products in 53-70% yield. Silyl enol ethers are a much larger group of substrates than indole, so this reaction would be a more broadly useful intermediate to build complex diazo structures. (Scheme 4.7)

4.8.5 Catalytic reaction condition with thiourea catalyst

I had proven the vinyl diazonium ions are good electrophiles that generate complex diazo containing scaffold. However, this reaction requires stoichiometric amount of Lewis acid to achieve a high product yield reaction.
I think catalytic amounts of Sc(OTf)₃ do not work well could due to deactivation of the Lewis acid by water that is formed in the reaction. If we could find a Lewis acid, that is inert to water, then the problem could be solved.

In 2019, I attended the ACS national meeting in Orlando. During the meeting, Professor Jacobsen presented his beautiful work on enantioselective chiral thiourea reactions, and the thiourea catalyst caught my attention. Those catalysts use hydrogen bonding interactions to activate electron rich functional groups.¹⁹⁸⁻²⁰³ This property is different with classical Lewis acids, which provide empty orbitals for long pair interaction. Thiourea organo catalysts possess several important green chemistry properties including low catalyst loading, high TOF, catalysis under mild conditions and most importantly they are water compatible.²⁰⁴,²⁰⁵ Previously, thiourea catalysts have been used to activate carbonyl or nitro groups for reaction.²⁰³ Recently professor Jacobsen presented an example in which a thiourea catalyst was able to catalyze an aza-Sakurai cyclization reaction. In this reaction, the hydroxy group on 4.76 was cleaved by the thiourea catalyst, which indicated that the thiourea catalyst was able to generate a vinyl diazonium intermediate.²⁰⁶ (Scheme 4.18) So I believed it would be worth testing the vinyl diazonium reaction under thiourea catalyst conditions.

![Scheme 4.18 aza-Sakurai cyclization reaction catalyzed by thiourea catalyst](image)

I started with the simplest thiourea catalyst: Schreiner’s catalyst (4.78).²⁰³ Mixing β-hydroxy-α-diazo 4.31 with indole and 10 mol% catalyst loading gave trace amount of 105
the desired product. But there was still a lot of diazo starting material left unreacted. I realized that the water byproduct may suppress the thiourea catalyst’s reactivity, so I added molecular sieves to remove water. I was glad to see that the vinyl diazonium addition reaction then generated the desired product in 80% yield (Scheme 4.19). This provides a more economical way to run these reactions.

Scheme 4.19 thiourea catalyzed vinyl diazonium addition

4.8.6 Catalytic reaction using La(OTf)₃

The discovery that La(OTf)₃ could be used in catalytic quantities to facilitate this reaction was a chance discovery. During lab cleaning, I found a bottle of La(OTf)₃ sitting in the corner of a desiccator. Lanthanum, as an element on the same column with Scandium I didn’t know how it can be applied in organic synthesis. Out of curiosity, I did some research on this Lewis acid and realized that La(OTf)₃ is considered a green catalyst. It has similar Lewis acid property as AlCl₃, but it is stable in water and can even catalyze Michael additions in water.²⁰⁷-²⁰⁹ As consequence, I test La(OTf)₃ in the vinyl diazonium addition reaction with indole. Using a catalytic amount (20 mol%) of La(OTf)₃ the reaction ran smoothly and finished in 15 minutes with 87% yield of the desired product. (Scheme 4.20)
Scheme 4.20 \( \text{La(OTf)}_3 \) catalyzed vinyl diazonium addition with indole

Importantly, \( \text{La(OTf)}_3 \) also catalyzes the silyl enol ether addition, developed by Evan. When Evan first used TBS enol ether 4.79 in these reactions, he didn’t observe a good yield of the desired product only 23% of 4.80 formed. A large amount of the enol ether was desilated to give ketone 4.81.

Scheme 4.21 Desilylation process explained by Evan
Evan thought that during the reaction, the byproduct silanol (4.85) would be reactivated by Sc(OTf)$_3$ and would decompose the silyl enol ether 4.79 to give ketone 4.81. (Scheme 4.21) This hypothesis could be validated by adding a proton sponge, such as 2,6-di-tert-butyl-4-methylpyridine (DTBMP), to the reaction which improved the yield. But Evan also observed the formation of vinyl diazo side product 4.9 in 45% yield, due to a competing elimination. Switching TBS enoxy silane to TIPS enoxy silane increased the yield to 70%, indicating the side reaction is sensitive to acid.(Scheme 4.22)

![Scheme 4.22 Vinyl diazonium addition with silyl enol optimized by Evan](image)

During my research time, I had to prepare the silyl enol added product 4.89 by Evan’s reported method. However due to the poor nucleophilicity of the TIPS enoxy silane of acetophenone (4.88), this reaction only gave 55% yield. Realizing that the main issue for this reaction is the strong acidic proton from Sc(OTf)$_3$ activating silanol, I decided to test La(OTf)$_3$ as the Lewis acid for this reaction. The water resistant property of La(OTf)$_3$ indicates it may also be inert to silanol. The reaction ran very smoothly with 10 mol% La(OTf)$_3$ loading and giving 87% yield of the desired product 4.89.
Therefore the vinyl diazonium addition reaction with an enoxy silane was optimized to a catalytic reaction with synthetically useful yield. This reaction has great potential to prepare structurally complex diazo compounds with tertiary and quaternary carbon centers at the β-position.

**4.9 Application of vinyl diazonium addition products**

**4.9.1 1,3-dipolar cycloaddition**

We had successfully shown that vinyl diazoniums, generated by activating the β-hydroxy-α-diazo, are good electrophiles for indoles and siloxy enols. These reactions formed tertiary and quaternary centers at the β-position of diazo carbonyls. These complex diazo compounds are difficult to make by other diazo-preparation or diazo-functionalization methods. The diazo functional group is very useful for many kinds of reactions, as has been described in chapter one. It is important to explore the application of these diazo products. I had shown that β-indole-α-diazo esters can be converted to highly substituted vinyl indoles. As indole motifs are observed in numerous natural alkaloids and bioactive molecules, this reaction could provide new synthetic routes towards natural products and important drug leads.¹⁹⁴-¹⁹⁶,²¹⁰,²¹¹
For the product of vinyl diazonium addition with enoxy silanes, those products contain a carbonyl group close to the diazo, which are ideal structures to generate 1,3-dipolar carbonyl ylides. Padwa had shown that treating similar structures with Rh$_2$(OAc)$_4$ in the present of dimethyl acetylene dicarboxylate(DMAD) would effect a 1,3-dipolar cycloaddition reaction.$^{37,39}$ To demonstrate this application, I prepared diazo product 4.89 as described above, and subjected it to Rh$_2$(OAc)$_4$ and DMAD (4.90). After about 5 hours, I observed that the diazo product had been consumed and I collected desired spirocyclic furan 4.91 in 94% yield.

![Scheme 4.24 Test for 1,3-dipolar cycloaddition](image)

4.9.2 C-O insertion reaction

I was also interested to take advantage of these functional groups in other ways. So, I reduced carbonyl group to a hydroxy and tested a metal carbenoid O-H insertion reaction. Diazo carbonyl product 4.89 was reduced to corresponding diazo hydroxy product 4.92 with NaBH$_4$ in 90% yield. (Scheme 4.25)

![Scheme 4.25 Ketone reduction](image)
Treating the diazo hydroxy product 4.92 with Rh$_2$(OAc)$_4$ at room temperature gave the desired spiro hydro furans as a diastereomeric mixture. Due to the steric effect, trans furan 4.93 was the major product for 54% and cis furans 4.94$^+'$+4.94$''$ were found in 17% yield. A detailed NOE study confirmed the structure of trans furans 4.93$^+$+4.93$''$. (Scheme 4.26) Through space coupling was observed between the hydrogen $\alpha$ to the ester and the phenyl ring for trans furans 4.93$^+$+4.93$''$. (Figure 4.6) This reaction presents an alternative route to prepare highly substituted furan ring systems, which are difficult to prepare from other methods, and those highly substituted furans exists in many bioactive molecules. This method might be applicable to the synthesis substituted prolines, too. If reductive amination can incorporate nitrogen atom in place of OH.

![Scheme 4.26 Rh catalyzed O-H insertion](image)

**Figure 4.6** NOE study of structure 4.93$^+$+4.93$''$

### 4.10 Enantioselective catalysis
Since vinyl diazonium addition with indole could be catalyzed by thiourea catalyst, may be possible to use chiral thiourea catalyst to control the stereochemistry of the addition step.
The reaction would, in theory, started from a racemic β-hydroxy-α-diazo ester, which would be activated by a chiral thiourea catalyst to generate a prochiral vinyl diazonium intermediate. If the hydroxy anion, coordinated by chiral thiourea catalyst, would pair up with the vinyl diazonium intermediate to form a chiral salt then the addition might be stereoselective. (Scheme 4.27)

![Scheme 4.27 Proposed enantioselective vinyl diazonium addition by chiral thiourea catalyst](image)

I prepared two different chiral thiourea catalysts 4.96, 4.97, which previously been reported for chiral Michael addition with indole. Both catalysts were able to generate the desired product, but unfortunately these reaction didn’t show any enantioselectivity.

![Figure 4.7 Chiral thiourea catalysts 4.96, 4.97](image)

Even though there have not been any positive results, I believe more effort should be put into this research to screen different kinds of thiourea catalyst and different reaction conditions. An enantioselective vinyl diazonium addition could potentially lead
to enantioselective natural alkaloid synthesis and stereocontrolled 1,3-dipolar cycloadditions.

4.11 Summary

With carefully and extensive research, I discovered that vinyl diazonium intermediates, generated by dehydroxylation of β-hydroxy-α-diazo carbonyls, are not only vinyl cation precursors but are also good electrophiles to react with indoles and silyl enol ethers. These reactions are able to generate tertiary and quaternary centers at the β-position of diazo carbonyls in good to excellent yields, which provides a unique method to prepare structure complex diazo compounds. The vinyl diazonium intermediates can be generated either from β-hydroxy diazo ketones or from β-hydroxy diazo esters, and the reaction has a good tolerance to heteroatoms. The products, formed from vinyl diazonium ketones reacting with indole, can be further activated by Lewis acid at room temperature to generate tetrasubstituted alkenes. Diazoo ester analogs are inert to Lewis acid activation, but can be converted to the corresponding vinyl indoles by Rh$_2$(OAc)$_4$ activation. Vinyl diazonium addition reactions perform well with stoichiometric amounts of Sc(OTf)$_3$ and I have demonstrated that catalytic amounts of thiourea catalysts or La(OTf)$_3$ give competitive results for catalyzing these reactions.

The vinyl diazonium products have many synthetic utilities since the diazo group is a progenitor for many reactive intermediates. Diazoo indoles are important motifs for natural alkaloids. The enoxy silanes products are good precursors to carbonyl ylides, which undergo 1,3-dipolar additions to generate polycyclic furans. The products can also be converted into highly substituted tetrahydro furans by modifying the ketone on the
diazot products to a hydroxy group and then reacting with Rh$_2$(OAc)$_4$ to catalyze a C-O insertion reaction.

We are still looking for new nucleophiles to explore the application of this vinyl diazonium intermediate. Also, research on enantioselective catalysis draws our attentions.
Chapter 5  Experiment procedure and characterization

5.1 General experiment details

All reactions were performed under an atmosphere of nitrogen in flame-dried glassware. Solvents were removed in vacuo using a rotary evaporator attached to a dry vacuum pump, and further dried under reduced pressure on a high vacuum line.

Tetrahydrofuran (THF) and dichloromethane (CH$_2$Cl$_2$) were dried via a solvent dispensing system. Diisopropylamine (iPr$_2$NH) was freshly distilled from CaH$_2$ prior to use. Tin(IV) chloride (SnCl$_4$) was distilled twice from P$_2$O$_5$ under inert atmosphere conditions and was stored as a 1M solution in CH$_2$Cl$_2$ in a sealed tube under an atmosphere of nitrogen. All other commercially available reagents were used without further purification. Reactions were cooled to $-40^\circ$C or $-78^\circ$C via dry ice–acetone baths, to $-15^\circ$C via ice–salt baths and to 0 $^\circ$C via ice–water baths.

Flash column chromatography was performed using manually packed silica gel (230-400 mesh) columns, or on commercially available prepacked silica gel columns for automated flash chromatography. TLC analysis was carried out using silica on glass backed plates. TLC results were visualized by ultraviolet light, or stain (ceric ammonium molybdate, or potassium permanganate).

$^1$H and $^{13}$C NMR data were collected at room temperature on a 500 MHz spectrometer in CDCl$_3$. $^1$H NMR chemical shifts are reported in ppm (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 QTof LCMS operated in positive ESI mode.
All α-diazo ketones used are known compounds that were prepared by reacting diazomethane with the corresponding acid chlorides in accordance with standard literature procedures: 2-diazo-1-phenylethanone,212 1-diazo-3,3-dimethyl-2-butanone,213 2-cyclohexyl-1-diazo-2-ethanone,214 n-butyldiazomethylketone,215 [1-(4-chlorophenyl)-2-diazoethanone],216 [2-diazo-1-(p-tolyl)ethanone],217 [1-(2-chlorophenyl)-2-diazoethanone],218 [2-diazo-1-(m-tolyl)ethanone],219 [2-diazo-1-(4-methoxyphenyl)ethanone],220 [2-diazo-1-(4-nitrophenyl)ethanone],220 [1-diazo-3-phenylpropan-2-one],221 [1-diazo-3-(4-methoxyphenyl)propan-2-one],220 and [1-(4-chlorophenyl)-3-diazopropan-2-one].222

The following diazo esters are known compounds and prepared using known procedures: methyl diazoacetate223, benzyl diazoacetate224, prop-2-yn-1-yl diazoacetate224.

The following β-hydroxy-α-diazo carbonyl compounds are known and were prepared via literature procedures: 1-diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylbutan-2-one,99 4-diazo-5-hydroxy-2,2-dimethyl-5-propylocan-3-one,99 ethyl diazo(1-hydroxycyclohexyl)acetate,25 ethyl diazo(1-hydroxycyclopentyl)acetate,25 ethyl 2-diazo-3-hydroxy-3-phenylpropanoate,225 ethyl 2-diazo-3-hydroxyheptanoate,225

5.2 Chapter 2 Experimental procedures and compound characterization data

General Procedure 2.A: Preparation of β-hydroxy-α-diazo ketones

A –78 °C solution of LDA (1.5 equiv) [prepared by addition of n-butyllithium in hexanes (1.5 equiv) to a solution of iPr₂NH (1.6 equiv) in THF (3 mL per mmol of n-butyllithium)] was added dropwise over 30 min via cannula down the inside wall of a chilled flask containing a –78 °C stirred solution of ketone (1 equiv) and α-diazo ketone
(1.6 equiv) in THF (3 mL per mmol of ketone). The mixture was maintained at −78 °C until complete conversion was achieved as monitored by TLC. A 1M solution of acetic acid in THF (2.0 equiv) was added quickly to the reaction mixture at −78 °C, at which point the reaction flask was removed from the cold bath and warmed to room temperature. The mixture was poured in to a saturated aqueous NH₄Cl solution and extracted three times with ethyl ether (15 mL), the organic layers were combined, washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), and dried over anhydrous MgSO₄. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

**3-(3-methoxyphenyl)-N-((trimethylsilyl)methyl)propan-1-amine (2.21):**

(Iodomethyl)trimethylsilane (90 μL, 0.607 mmol) was added over 2 h via syringe pump to a refluxing MeCN (10 mL) solution of m-(3-aminopropyl)anisole 2.20 (0.094g, 0.57 mmol) and the reaction mixture was heated at reflux for an additional 22 hours. After cooling to room temperature, the solvent was removed in vacuo and the residue was dissolved in CHCl₃ (10 mL) and washed with a 10% NaOH solution. The organic layer was separated, dried over MgSO₄, and filtered. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.1153 g (80% yield) of the title compound. Rf = 0.48 (EtOAc: Hexanes = 1: 4); ¹H NMR (500 MHz, Chloroform-d) δ 7.21 (t, J = 7.8 Hz, 1H), 6.80 (ddd, J = 7.5, 1.7, 0.9 Hz, 1H), 6.78 – 6.71 (m, 2H), 3.81 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 2.08 (s, 2H), 1.89 – 1.77 (quint, J = 7.6 Hz, 2H), 0.06 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 159.6, 143.9, 129.2, 120.8, 114.1, 111.0, 55.1, 53.8, 117.
3-(3-((trimethylsilyl)methylamino)propyl)cyclohex-2-enone hydrochloride

(2.23): Sodium metal (0.988 g, 43 mmol) was added in small portions to a -78 °C solution of 23 (0.803 g, 3.19 mmol), EtOH (1.3 mL), THF (16 mL), and ammonia (16 mL) at a slow rate to avoid forming a bronze colored pool. The reaction mixture was stirred for 5 hours and excess sodium was quenched by the addition of EtOH (5 mL) and the ammonia was allowed to evaporate under a stream of nitrogen while warming to room temperature. A brine solution (20 mL) was added to the reaction mixture, which was extracted three times with CHCl₃ (10 mL). The organic extracts were washed with H₂O (20 mL), dried over MgSO₄, and filtered. The solvents were removed in vacuo to provide 0.698 g of the crude Birch reduction product as an oil. The crude material was dissolved in THF (30 mL) and stirred with 10% HCl (2.6 mL) at room temperature for 12 h. The solvent was removed in vacuo and the residue was dissolved in CH₂Cl₂, dried over MgSO₄, and filtered. The solvents were removed in vacuo to provide 0.735 g (84% yield) of the title compound as a white solid, that was taken on without further purification; ¹H NMR (500 MHz, Chloroform-d) δ 9.38 (s, 2H), 5.91 (s, 1H), 3.06 – 2.88 (m, 2H), 2.46 – 2.29 (m, 6H), 2.25 – 2.10 (m, 2H), 2.08 – 1.95 (m, 2H), 1.82 (brs, 2H), 0.30 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 199.6, 163.9, 126.1, 50.5, 37.5, 37.3, 34.8, 29.5, 22.6, 22.4, 1.6; MS (ESI): Calculated for [C₁₃H₂₅NOSiH]⁺: 240.1784. Found: 240.1792.

A sample of this material was free based by washing with NaOH; Spectral data for the free base: ¹H NMR (500 MHz, Chloroform-d) δ 5.91 (s, J = 1.4 Hz, 1H), 2.65 (t,
$J = 8.1, 7.6$ Hz, 2H), 2.38 (t, $J = 7.4$, 2H), 2.35 – 2.30 (t, 2H), 2.27 (t, $J = 7.8$ Hz, 2H), 2.07 (s, 2H), 2.05 – 1.97 (m, 2H), 1.77 – 1.66 (p, 2H), 0.07 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.5, 166.2, 125.5, 53.7, 40.0, 37.2, 35.6, 29.6, 26.8, 22.6, -2.6.

t-butyl 3-(3-oxocyclohex-1-enyl)propyl((trimethylsilyl)methyl)carbamate

(2.24): Di-t-butyl dicarbonate was added in one portion to a 0 °C solution of 2.23 (1.924 g, 6.97), 4-dimethylaminopyridine (40 mg, 0.33 mmol), and trimethylamine (0.98 mL, 7.03 mmol) in MeCN (25 mL). The reaction was removed from the ice bath and stirred for 3 hours at room temperature. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 1.702 g (72% yield) of the title compound as a yellow-green oil. R$_f$ = 0.21 (EtOAc: Hexanes = 1: 4); $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 5.88 (s, 1H), 3.18 (bs, 2H), 2.71 (s, 2H), 2.36 (t, $J = 6.7$ Hz, 2H), 2.30 (t, $J = 5.9$ Hz, 2H), 2.19 (t, $J = 7.8$ Hz, 2H), 2.00 (quint, $J = 5.9$ Hz, 2H), 1.75 (brs, 2H), 1.45 (s, 9H), 0.06 (s, 9H); $^{13}$C NMR (126 MHz, Chloroform-d, rotational isomers observable) $\delta$199.7, 165.7, 165.3, 155.5, 155.3, 125.7, 79.3, 79.0, 48.8, 48.3, 38.3, 38.1, 37.3, 35.2, 29.7, 28.5, 25.2, 24.7, 22.7, -1.5; MS (ESI): Calculated for [C$_{18}$H$_{33}$NO$_3$SiNa]$^+$ : 362.2127. Found: 362.2125.

More direct preparation of intermediate 2.24 through palladium cross coupling: A solution of 9-BBN in THF (0.5 M, 52.80 ml 1.1 equiv) was added dropwise to a -10 °C solution of 2.28 (3.21 g, 13.2 mmol 1.1 equiv) in THF (36 mL). The mixture was warmed to room temperature and stirred overnight. A 3 M aqueous NaOH solution (24 mL) was added to the mixture. After 15 min. the reaction mixture was cannulated into a room temperature mixture of 2.30 (2.66 g, 12 mmol, 1 equiv) and Pd(dpdpf)Cl$_2$
(0.79 g, 1.08 mmol) in THF (36 mL). After stirring for 45 min, hexane (120 mL), 30% \( \text{H}_2\text{O}_2 \) (15 mL) and Ph 7 phosphate buffer (30 mL) were added sequentially. Any exotherm was controlled by cooling in an ice bath. After 10 min a precipitate was removed by passing though Celite. The organic layer was separated, washed with brine and dried over MgSO\(_4\). The solvent was removed \textit{in vacuo} and the residue was purified by silica gel flash column chromatography (Ethyl Acetate/Hexane; 1:4) to provide 3.78 g (92% yield) of the title compound as a colorless oil.

**tert-Butyl (3-(1-ethyl-3-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)propyl) ((trimethylsilyl)methyl)carbamate (2.31):** A solution of 2.24 (0.615 g, 1.81 mmol) in THF (1 mL), \((\text{CH}_3)_3\text{SiCl} \) (0.25 mL, 1.97 mmol) and trimethylamine (0.30 mL, 2.15 mmol) were added in sequence to a 0 °C homogeneous solution of LiCl (19 mg, 0.45 mmol) and CuI (52 mg, 0.27 mmol) in THF (8 mL). After stirring for 10 minutes, a 3M ethylmagnesium bromide solution in diethyl ether (0.72 mL, 2.16 mmol) was added dropwise via syringe. After stirring for 0.5 h, the solution was poured into a saturated aqueous ammonium chloride solution (10 mL) and extracted three times with diethyl ether (5 mL). The organic layers were combined, dried over MgSO\(_4\), and filtered. The solvent was removed \textit{in vacuo} to provide 0.711 g (89% yield) of the title compound as a clear colorless oil. \( R_f = 0.89 \) (EtOAc: Hexanes = 1: 4); \(^1\text{H}\) NMR (500 MHz, Chloroform-\( d \)) \( \delta 4.63 \) (s, 1H), 3.17 – 3.05 (m, 2H), 2.71 (s, 2H), 1.98 (t, \( J = 6.2 \text{ Hz}, 2\text{H})\), 1.65 (quint, \( J = 6.2 \text{ Hz}, 2\text{H})\), 1.48-1.40 (m, 12H), 1.37-1.14 (m, 5H), 0.79 (t, \( J = 7.2 \text{ Hz}, 3\text{H})\), 0.18 (s, 9H), 0.06 (d, \( J = 1.2 \text{ Hz}, 9\text{H})\); \(^{13}\text{C}\) NMR (126 MHz, Chloroform-\( d \), rotational isomers observable) \( \delta 155.4, 149.8, 112.9, 78.9, 78.6, 50.0, 49.2, 38.1, 37.8, 37.0, 36.7, 36.2, 32.5, \ldots \)
31.9, 31.7, 29.9, 28.5, 22.6, 21.9, 19.4, 8.3, 2.6, 0.4, -1.5; MS (ESI): Calculated for [C<sub>23</sub>H<sub>47</sub>NO<sub>3</sub>Si<sub>2</sub>Na]<sup>+</sup>: 464.2992. Found: 464.2990.

**tert-Butyl (3-(1-ethyl-3-oxo-2-((trimethylsilyl)oxy)cyclohexyl)propyl)((trimethylsilyl)methyl)carbamate (2.33):** A solution of Oxone (3.59 g, 11.7 mmol, 4 equiv) in water (15 mL) was added over a 15 min period to a vigorously stirred biphasic mixture of 2.31 (1.29 g 2.92 mmol), CH<sub>2</sub>Cl<sub>2</sub> (15 mL), acetone (1.5 mL), and saturated aqueous NaHCO<sub>3</sub> (30 mL) cooled in an ice bath. The mixture was stirred vigorously (to ensure efficient mixing of the layers) at 0 °C for 6 hours. The organic phase was separated and the aqueous phase was extract with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic phases were combined and dried over MgSO<sub>4</sub>. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (Ethyl Acetate / Hexane; 1:4) to provide 0.89 g (79% yield) of the alcohol. This material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and TMSCl (0.84 mL, 6.60 mmol), DMAP (0.08 g, 0.66 mmol), and imidazole (0.45 g, 6.60 mmol) were added. After 12 h the mixture was washed with saturated aqueous NH<sub>4</sub>Cl. The layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times. The organics were combined, dried over MgSO<sub>4</sub>, the solvent was removed in vacuo and the residue was purified by silica gel flash column chromatography (Ethyl Acetate/Hexane; 1:5) to give 0.87 g (82% yield) of the desired product. R<sub>f</sub> = 0.79 (EtOAc: Hexanes = 1: 4); <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 3.91 – 3.75 (m, 1H), 3.21-2.97 (m, 2H), 277-261 (m, 2H), 2.60-2.46 (m, 1H), 2.24-2.10 (m, 1H), 1.83-1.60 (m, 3H), 1.55-0.99 (m, 16H), 0.83 (t, J = 7.1 Hz, 1H), 0.74 (t, J = 7.6 Hz, 1.7H), 0.8 (s, 9H), 0.5 (s, 4H), 0.4 (s, 5H); <sup>13</sup>C
NMR (126 MHz, Chloroform-\textit{d}, rotational isomers observable) \(\delta\) 211.6, 155.4, 81.2, 78.7, 50.0, 49.9, 49.5, 49.3, 45.2, 45.2, 45.0, 38.7, 38.2, 29.5, 29.4, 28.6, 28.5, 26.0, 25.7, 24.4, 24.3, 21.5, 21.2, 21.1, 20.6, 7.5, 7.0, 0.2, 0.1, -1.5; MS (ESI): Calculated for \([\text{C}_{23}\text{H}_{47}\text{NO}_{4}\text{Si}_{2}\text{H}]^+\): 458.3122. Found: 458.3123.

**Ethyl 2-(3-(tert-butoxycarbonyl)((trimethylsilyl)methyl)amino)propyl)-3-ethyl-1-hydroxy-2-((trimethylsilyl)oxy)cyclohexyl)-2-diazoacetate (2.13):** Diazo ester 2.13 was prepared in 73% yield as a yellow oil from ketone 2.33 (1.527 g, 3.34 mmol) following the General procedure 2.A. Flash silica gel chromatography (EtOAc: Hexanes = 1: 4). \(R_f = 0.55\) (EtOAc: Hexanes = 1: 9); \(^1\)H NMR (500 MHz, Chloroform-\textit{d}) \(\delta\) 4.29 – 4.12 (m, 2H), 4.07 (m, \(J = 4.5\) Hz, 1H), 3.36 – 2.95 (m, 3H), 2.82-2.61 (m, 2H), 2.11 – 2.00 (m, 1H), 1.95 – 1.86 (m, 1H), 1.81 – 1.59 (m, 3H), 1.57-1.32 (m, 14H), 1.28 (t, \(J = 7.1\) Hz, 3H), 1.26-1.04 (m, 2H), 0.87-0.76 (m, 3H), 0.13 (s, 4.9H), 0.12 (s, 4.1H), 0.07 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 165.8, 155.4, 78.9, 78.8, 78.5, 76.5, 75.8, 75.6, 72.7, 72.6, 65.3, 60.2, 50.7, 50.0, 49.1, 41.1, 38.4, 38.1, 37.9, 34.7, 34.0, 33.6, 31.1, 30.8, 30.6, 29.3, 28.9, 28.5, 24.2, 22.6, 21.8, 21.1, 16.9, 14.6, 8.5, 7.8, 0.6, 0.5, -1.5; MS (ESI): Calculated for \([\text{C}_{27}\text{H}_{53}\text{N}_{3}\text{O}_{6}\text{Si}_{2}\text{Na}]^+\): 594.3371. Found: 594.3372.

**Ethyl 10-((tert-butoxycarbonyl)((trimethylsilyl)methyl)amino)-7-ethyl-7-formyldec-2-ynoate (2.14):** In(OTf)\textsubscript{3} (0.750 g, 1.33 mmol) was added to a -5 °C solution of 2.13 (0.690 g, 1.21 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL). After stirring for 4 hour at -5 °C the reaction was quenched with a saturated solution of NaHCO\textsubscript{3} (15 mL). The aqueous layer
was extracted three times with CH₂Cl₂ (10 mL), the organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo. The residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.361 g (66% yield) of the title compound. Rᵣ = 0.64 (EtOAc: Hexanes = 1: 4); ¹H NMR (500 MHz, Chloroform-d) δ 9.43 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.15 (bs, 2H), 2.71 (s, 2H), 2.35 (t, J = 6.9 Hz, 2H), 1.64 – 1.52 (m, 8H), 1.52 – 1.35 (m, 5H), 1.46 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.5 Hz, 2H), 0.10 – 0.04 (s, 9H); ¹³C NMR (126 MHz, Dimethylformamide-d at 320 K) δ 206.6, 155.2, 153.3, 89.0, 78.3, 73.5, 61.6, 54.7, 51.6, 38.4, 38.3, 30.3, 28.3, 28.0, 24.5, 22.0, 18.5, 13.6, 7.4, -1.8.

5-(6-Ethoxy-6-oxohex-4-yn-1-yl)-5-ethyl-1-((trimethylsilyl)methyl)-2,3,4,5-tetrahydropyridin-1-ium trifluoromethanesulfonate salt (2.15):

In(OTf)₃ (0.416 g, 0.74 mmol) was added to a mixture of 2.13 (0.419 g, 0.73 mmol) in CH₂Cl₂ (12 mL) and mol sieves, and the reaction was allowed to stir overnight at room temperature. H₂O (2 mL) was added to the reaction mixture and the aqueous layer was extracted with CH₂Cl₂ (2 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with hexanes to provide 0.319 g (90% yield) of the title compound as a brownish orange oil, which was taken on without further purification. ¹H NMR (500 MHz, Chloroform-d) δ 8.45 (s, 1H), 4.16 (q, J = 7.5 Hz, 2H), 3.86 – 3.60 (m, 4H), 2.36 (t, J = 6.5 Hz, 2H), 1.97 (quint, J = 6.1 Hz, 2H), 1.78–1.55 (m, 8H), 1.26 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 018 (s, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 179.7, 153.6, 120.5 (q, J = 319.7), 87.8, 73.9, 61.8, 55.4, 53.8, 42.9, 35.0, 29.3, 25.0, 21.8, 18.7,
18.4, 14.0, 7.8, -2.6; MS (ESI): Calculated for \([C_{19}H_{34}NO_2Si]^+\): 336.2353. Found: 336.2361.

**rel-(31R,6aS)-ethyl 6a-ethyl-31,4,5,6,6a,7,8,9-octahydro-2H-pyrrolo[3,2,1-ij]quinoline-1-carboxylate (2.16):** A solution of 7 (0.055 g, 0.11 mmol) and cesium fluoride (40 mg, 0.26 mmol) were heated to reflux in MeCN (5 mL) for 2 hours. The reaction was allowed to cool to rt and the mixture was poured into water (5 mL). The aqueous layer was extracted three times with diethyl ether (2.5 mL), the organic layers were combined, dried over MgSO\(_4\), and filtered. The solvents were removed *in vacuo*, and the residue was subjected to silica gel flash column chromatography (CH\(_2\)Cl\(_2\): MeOH: Et\(_3\)N = 95: 5: 0.1) to provide 0.017 g (60% yield) of the title compound. \(R_f = 0.34\) (CH\(_2\)Cl\(_2\): MeOH: Et\(_3\)N = 95: 5: 0.1); \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta 4.21\) (q, \(J = 7.1\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 1H), 3.68 (dt, \(J = 14.5, 4.3\) Hz, 1H), 3.54-3.47 (m, 1H), 3.44 (d, \(J = 14.5\) Hz, 1H), 3.38 (bs, 1H), 2.72 (bd, \(J = 10.4\) Hz, 1H), 2.35 – 2.27 (m, 2H), 2.06-1.90 (m, 2H), 1.80 – 1.50 (m, 4H), 1.49-1.38 (m, 2H), 1.38-1.20 (m, 3H), 1.30 (t, \(J = 7.1\) Hz, 3H) 0.84 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta 165.3, 155.5, 124.0, 73.4, 60.1, 59.9, 50.2, 35.6, 33.9, 32.3, 26.5, 26.3, 20.0, 18.8, 14.4, 7.4; MS (ESI): Calculated for \([C_{16}H_{25}NO_2H]^+\): 264.1964. Found: 264.1970.

![HOOC](image)

(6aS,9bR)-1-carboxy-6a-ethylpyrrolo[3,2,1-ij]quinolinium chloride 2.38 3 ml Li(OH) 1M solution was degassed with N\(_2\) gas for 15 minutes then added into a flamed-dried flask with 133mg 2.15 and 30ml dioxane. The
mixture was stirred for 48 hours and poured into water and extract with ether. The aqueous lay was separated and added 3ml 1M HCl. Then water was removed in vacuo and the residue was extracted with DCM to collect 0.0989g desired product 72%. $^1$H NMR (500 MHz, CDCl$_3$): δ 11.66(s, 1H), 4.50-4.19(m, 2H), 4.12-4.36(m, 5H), 2.81(s, 1H), 2.30-1.91(m, 3H), 1.83-1.23(m, 7H), 0.88(t, $J = 6.4$Hz, 3H).

(6aS, 9bR)-6a-ethyl-N-(2-methoxyphenyl)-2,5,6,6a,7,8,9,9b-octahygro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxamide 2.40 To a flamed-dried flask (0.0898g, 0.36mmol) 2.38 was added with 10ml thionyl chloride. The mixture was heated to reflux for 4 hours and then thionyl chloride was removed by vacuum distillation. Catalytic amount DMAP and 0.067ml(0.828mmol) pyridine and 0.061ml(0.54mmol) 2.39 were added into flask with 5 ml THF. The mixture was stirred at room temperature for 24 hours and poured into sodium bicarbonate solution and extracted with ether 3 times. The organic layer was separated, dried with MgSO$_4$ and removed the solvent by vacuum. The residue was purified with column chromatography (Hexane: ethylacetate = 4:1 ) and 0.0659g desired product was collected as white solid in 54% yield. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.45(dd, $J = 7.9$, 1.5Hz, 1H), 7.82(s,1H), 7.06(td, $J = 7.6$, 1.6Hz, 1H), 6.99(td, $J = 7.6$, 1.4Hz, 1H), 6.91(dd, $J = 8.1$, 1.4Hz, 1H), 3.92(s, 3H), 3.83-3.76(m, 1H), 3.53-3.44(m, 2H), 3.37(s, 1H), 2.73(d, 10.6Hz, 1H), 2.40-2.31(m, 1H), 2.10-2.07(m, 1H), 2.03-1.93(m, 1H), 1.80-1.58(m, 4H), 1.53-1.36(m, 3H), 1.35-1.24(m, 2H), 0.88(t, $J = 7.5$Hz, 3H).
5.3 Chapter 3 Experimental procedures and compound characterization data

5.3.1 General Procedure 3.A: Preparation of β-hydroxy-α-diazo ketones

A cold (–78 °C) solution of LDA (1.5 equiv) [prepared by addition of n-butyllithium in hexanes (1.5 equiv) to a solution of iPr₂NH (1.6 equiv) in THF (3 mL per mmol of n-butyllithium)] was added dropwise over 30 min via cannula down the inside wall of a chilled flask containing a cold (–78 °C) stirred solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in THF (3 mL per mmol of ketone). The mixture was maintained at –78 °C until complete conversion was achieved as monitored by TLC. Acetic acid (2.0 equiv) in THF (1mL per mmol of acetic acid) was added quickly to the reaction mixture at -78 °C, the reaction flask was removed from the cold bath and slowly warmed to room temperature. The mixture was poured in to a saturated aqueous NH₄Cl solution and extracted three times with EtOAc (15 mL), the organic layers were combined, washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), and dried over anhydrous MgSO₄. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

![Chemical structure](image)

2-diazo-2-(1-hydroxycyclohexyl)-1-phenylethanone (3.84):

Prepared from cyclohexanone (93 μL, 0.90 mmol) and 2-diazo-1-phenylethanone 3.83 (195 mg, 1.30 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 195 mg (89% yield) of the title compound as a yellow oil:  : \( R_f = 0.55 \) (hexanes/EtOAc 4:1), \(^{1}H\) NMR (500 MHz, CDCl₃): \( \delta \) 7.63-7.61(m, 2H), 7.53(tt, \( J = 1.4, 7.3 \) Hz, 1H), 7.48-7.44(m, 2H), 4.56(s, 1H), 2.05-2.00(m, 2H), 1.89-1.73(m, 4H),
1.65-1.59 (m, 1H), 1.57-1.50 (m, 2H), 1.44-1.36 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 191.9, 137.5, 132.2, 128.8, 127.5, 72.5, 71.9, 36.4, 25.5, 22.2; IR (film) 3333, 2931, 2862, 2090, 1689, 1558, 1450, 1342, 1226, 1172. MS (ESI): Calculated for [C₁₄H₁₆N₂O₂Na⁺]: 267.1109. Found: 267.1111.

2-diazo-2-(1-hydroxycyclohexyl)-1-(p-tolyl)ethanone

(SI 3.1): Prepared from cyclohexanone (100 μL, 1.0 mmol) and 2-diazo-1-(p-tolyl)ethanone (233 mg, 1.45 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 187 mg (72% yield) of the title compound as a yellow solid: Rf = 0.50 (hexanes/EtOAc 4:1), ¹H NMR (500 MHz, CDCl₃): δ 7.53 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 4.63 (s, 1H), 2.42 (s, 3H), 2.05-1.98 (m, 2H), 1.90-1.71 (m, 4H), 1.66-1.58 (m, 1H), 1.57-1.49 (m, 2H), 1.47-1.36 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 191.7, 142.7, 134.7, 129.3, 127.5, 71.8, 36.3, 25.4, 22.1, 21.6; IR (film) 2931, 2862, 2075, 1604, 1512, 1319, 1265, 1172. MS (ESI): Calculated for [C₁₅H₁₈N₂O₂Na⁺]: 281.266. Found: 281.256.

2-diazo-2-(1-hydroxycyclohexyl)-1-(4-methoxyphenyl)ethanone (SI 3.2): Prepared from cyclohexanone (100 μL, 1.0 mmol) and 2-diazo-1-(4-methoxyphenyl)ethanone (256 mg, 1.47 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column
chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 228 mg (83\% yield) of the title compound as a yellow oil: $R_f = 0.35$ (hexanes/EtOAc 4:1). $^1\text{H}$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.63(d, $J = 8.8$ Hz, 2H), 6.95(d, $J = 8.5$, 2H), 4.68(s, 1H), 3.88(s, 3H), 2.04-1.97(m, 2H), 1.88-1.73(m, 4H), 1.65-1.58(m, 1H), 1.56-1.49(m, 2H), 1.47-1.37(m, 1H); $^{13}\text{C}$ NMR (125 MHz, CDCl$_3$): $\delta$ 190.8, 162.7, 130.1, 129.6, 113.9, 71.9, 55.5, 36.3, 25.4, 22.2; IR (film) 3379, 2931, 2854, 2083, 1581, 1558, 1512, 1303, 1249. MS (ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_3$Na]$^+$: 297.125. Found: 297.1207.

![1-(4-chlorophenyl)-2-diazo-2-(1-hydroxycyclohexyl)ethanone](image)

**1-(4-chlorophenyl)-2-diazo-2-(1-hydroxycyclohexyl)ethanone (SI 3.3):** Prepared from cyclohexanone (94 μL, 0.91 mmol) and 1-(4-chlorophenyl)-2-diazoethanone (247 mg, 1.36 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 175 mg (69\% yield) of the title compound as a yellow solid: $R_f = 0.58$ (hexanes/EtOAc 4:1), $^1\text{H}$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.57(d, $J = 8.6$Hz, 2H), 7.45(d, $J = 8.6$Hz, 2H), 4.44(s, 1H), 2.06-2.00(m, 2H), 1.89-1.79(m, 2H), 1.78-1.72(m,2H), 1.68-1.60(m,1H), 1.57-1.50(m, 2H), 1.46-1.36(m, 1H); $^{13}\text{C}$ NMR (125 MHz, CDCl$_3$): $\delta$ 190.3, 138.2, 135.7, 129.0, 128.8, 71.8, 36.2, 25.3, 22.1; IR (film)3433, 2939, 2854, 2083, 1581, 1558, 1512, 1303, 1249. MS (ESI): Calculated for [C$_{14}$H$_{15}$ClN$_2$O$_2$Na]$^+$: 301.0720. Found: 301.0714.

![1-(2-chlorophenyl)-2-diazo-2-(1-hydroxycyclohexyl)ethanone](image)

**1-(2-chlorophenyl)-2-diazo-2-(1-hydroxycyclohexyl)ethanone (SI 3.4):** Prepared from cyclohexanone (114 μL, 1.1 mmol) and 1-(2-chlorophenyl)-2-diazoethanone (281 mg, 1.71 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 202 mg (69\% yield) of the title compound as a yellow oil: $R_f = 0.35$ (hexanes/EtOAc 4:1), $^1\text{H}$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.63(d, $J = 8.8$ Hz, 2H), 6.95(d, $J = 8.5$, 2H), 4.68(s, 1H), 3.88(s, 3H), 2.04-1.97(m, 2H), 1.88-1.73(m, 4H), 1.65-1.58(m, 1H), 1.56-1.49(m, 2H), 1.47-1.37(m, 1H); $^{13}\text{C}$ NMR (125 MHz, CDCl$_3$): $\delta$ 190.8, 162.7, 130.1, 129.6, 113.9, 71.9, 55.5, 36.3, 25.4, 22.2; IR (film) 3379, 2931, 2854, 2083, 1581, 1558, 1512, 1303, 1249. MS (ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_3$Na]$^+$: 297.125. Found: 297.1207. 

![1-(2-chlorophenyl)-2-diazo-2-(1-hydroxycyclohexyl)ethanone](image)
mmol) and 1-(2-chlorophenyl)-2-diazoethane (275 mg, 1.52 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 296 mg (97% yield) of the title compound as a yellow solid: $R_f = 0.44$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46-7.39(m, 3H), 7.38-7.34(m, 1H), 4.22(s, 1H), 2.09-2.01(m, 2H), 1.88-1.76(m, 4H), 1.67-1.59(m, 1H), 1.58-1.51(m, 2H), 1.46-1.36(m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.9, 137.1, 131.6, 130.5, 128.6, 127.3, 71.6, 36.2, 25.3, 21.9; IR (film) 3325, 2939, 2862, 2098, 1589, 1435, 1350, 1242. MS (ESI): Calculated for [C$_{14}$H$_{15}$ClN$_2$O$_2$Na]$^+$: 301.0720. Found: 301.0714.

2-diazo-2-(1-hydroxycyclohexyl)-1-(4-nitrophenyl)ethane (SI 3.5): Prepared from cyclohexane (84 μL, 0.8 mmol) and 2-diazo-1-(4-nitrophenyl)ethane (234 mg, 1.20 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 119 mg (51% yield) of the title compound as a yellow solid: $R_f = 0.28$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.31(d, $J = 8.9$, 2H), 7.76(d, $J = 8.8$, 2H), 4.20(s, 1H), 2.09-2.01(m, 2H), 1.91-1.73(m, 4H), 1.70-1.62(m, 1H), 1.60-1.52(m, 2H), 1.46-1.36(m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.1, 149.6, 142.6, 128.5, 124.1, 74.1, 71.9, 36.2, 25.34, 22.0; IR (film) 3464, 2083, 1735, 1589, 1519, 1342, 1234. MS (ESI): Calculated for [C$_{14}$H$_{15}$N$_3$O$_4$Na]$^+$: 312.0960. Found: 312.0951.
2-diazo-2-(1-hydroxycyclopentyl)-1-phenylethanone

(3.116): Prepared from cyclopentanone (87 μL, 1.0 mmol) and 2-diazo-1-phenylethanone (217 mg, 1.50 mmol) following General Procedure 3.A. The oily yellow residue was purified by neutral aluminum gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc) to give 181 mg (79% yield) of the title compound as a yellow oil: $R_f = 0.33$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.66-7.61(m, 2H), 7.54(tt, $J = 1.3, 6.6$Hz, 1H), 7.49-7.45(m, 2H), 4.24(s, 1H), 2.24-2.19(m, 2H), 2.02-1.95(m, 2H), 1.91-1.84(m, 2H), 1.81-1.73(m, 2H); $^1$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.5, 137.3, 132.0, 128.7, 127.3, 80.1, 39.2, 23.0; IR (film) 3417, 2924, 2075, 1604, 1573, 1450, 1327, 1257. MS (ESI): Calculated for [C$_{13}$H$_{14}$N$_2$O$_2$Na]$^+$: 253.0953. Found: 253.0950.

2-diazo-2-(1-hydroxycyclohexyl)-1-(m-tolyl)ethanone

(3.109): Prepared from cyclohexanone (100 μL, 1.0 mmol) and 2-diazo-1-(m-tolyl)ethanone (240 mg, 1.50 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 222 mg (86% yield) of the title compound as a yellow solid: $R_f = 0.58$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.42 (s, 1H), 7.41-7.38(m, 1H), 7.35-7.32(m, 2H), 4.59 (s, 1H), 2.41(s, 3H), 2.06-2.00(m, 2H), 1.89-1.79(m, 2H), 1.78-1.73(m, 2H), 1.66-1.59(m, 1H), 1.58-1.50(m, 2H), 1.47-1.35(m, 1H); $^1$C NMR (125 MHz, CDCl$_3$): $\delta$ 192.1, 138.7, 137.4, 132.8, 128.5, 127.9, 124.4, 130
2-diazo-2-(1-hydroxy-4,4-dimethylcyclohexyl)-1-phenylethanone (3.112): Prepared from 4,4-dimethylcyclohexanone (141 mg, 1.1 mmol) and 2-diazo-1-phenylethanone (246 mg, 1.70 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 138 mg (45% yield) of the title compound as a yellow solid: $R_f = 0.38$ (hexanes/EtOAc 4:1); $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64-7.60 (m, 2H), 7.53 (tt, $J = 1.4$ 6.6 Hz, 1H), 7.48-7.44 (m, 2H), 4.46 (s, 1H), 2.04-1.97 (m, 2H), 1.84 (ddd, $J = 3.8$, 11.0, 14.6 Hz, 2H), 1.72 (ddd, $J = 3.8$, 14.2, 17.2 Hz, 2H), 1.31-1.24 (m, 2H), 1.02 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.8, 137.4, 132.0, 128.7, 127.3, 72.4, 71.6, 34.6, 32.2, 29.4; IR (film) 3086, 2106, 1604, 1450, 1357, 1226. MS (ESI): Calculated for [C$_{16}$H$_{20}$N$_2$O$_2$Na]$^+$: 295.1422. Found: 295.1422.

2-(4-(tert-butyl)-1-hydroxycyclohexyl)-2-diazo-1-phenylethanone (3.114) and (3.116): Prepared from 4-tert-butylocyclohexanone (170 mg, 1.1 mmol) and 2-diazo-1-phenylethanone (238 mg, 1.62 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 235 mg (71% yield) of the title compound as a yellow solid: $R_f = 0.38$ (hexanes/EtOAc 4:1); $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64-7.60 (m, 2H), 7.53 (tt, $J = 1.4$ 6.6 Hz, 1H), 7.48-7.44 (m, 2H), 4.46 (s, 1H), 2.04-1.97 (m, 2H), 1.84 (ddd, $J = 3.8$, 11.0, 14.6 Hz, 2H), 1.72 (ddd, $J = 3.8$, 14.2, 17.2 Hz, 2H), 1.31-1.24 (m, 2H), 1.02 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.8, 137.4, 132.0, 128.7, 127.3, 72.4, 71.6, 34.6, 32.2, 29.4; IR (film) 3086, 2106, 1604, 1450, 1357, 1226. MS (ESI): Calculated for [C$_{16}$H$_{20}$N$_2$O$_2$Na]$^+$: 295.1422. Found: 295.1422.
yield) of the title compound as a yellow solid two diastereomers are isolated by neutral aluminum column chromatography (hexanes/EtOAc = 10:1). Diastereomer 3.114 200mg (60% yield) and diastereomer 3.116 35mg(10% yield.): For diastereomer 3.114 $R_f = 0.60$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.65-7.61(m, 2H), 7.59-7.54(m, 1H), 7.46(t, $J = 7.7$Hz, 2H), 4.54(s, 1H), 2.31-2.24(m, 2H), 1.72-1.65(m, 2H), 1.64-1.51(m, 4H), 1.08(tt, $J = 3.1$, 11.6Hz, 1H), 0.92(s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.8, 137.5, 131.9, 128.7, 127.3, 72.9, 70.8, 47.6, 36.6, 32.5, 27.6, 22.3; IR (film) 3433, 2954, 2870, 2075, 1712,1597, 1573, 1512, 1450, 1311, 1242. MS (ESI): Calculated [C$_{18}$H$_{25}$N$_2$O$_2$]$^+$: 301.1916. Found: 301.1906.

For diastereomer 3.116: $R_f = 0.57$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.65-7.61(m, 2H), 7.59-7.54(m, 1H), 7.51-7.46(m, 2H), 4.47(s, 1H), 2.40-2.32(m, 2H), 1.88-1.80(m, 2H), 1.73-1.63(m, 2H), 1.18(tt, $J = 3.2$, 12Hz, 1H), 1.12-1.02(m, 2H), 0.93(s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.9, 137.2, 132.3, 128.8, 127.6, 73.4, 46.9, 36.8, 32.3, 27.5, 24.7; IR (film)3425, 2974, 2862, 2090, 1735, 1597, 1365, 1327, 1226. MS (ESI): Calculated [C$_{18}$H$_{24}$N$_2$O$_2$Na]$^+$: 323.1735. Found: 323.1736.

![1-diazo-1-(1-hydroxycyclohexyl)-3-phenylpropan-2-one (3.56):](attachment:image)

1-diazo-1-(1-hydroxycyclohexyl)-3-phenylpropan-2-one (3.56): Prepared from cyclohexanone (124 μL, 1.2 mmol) and 1-diazo-3-phenylpropan-2-one (310 mg, 1.93 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 258 mg (83% yield) of the title compound as a yellow solid: $R_f = 0.47$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39-
7.34(m, 2H), 7.32-7.29(m, 1H), 7.24-7.22(m, 2H), 4.21(s, 1H), 3.81(s, 2H), 1.97-1.91(m, 2H), 1.80-1.71(m, 2H), 1.63-1.55(m, 3H), 1.48-1.41(m, 2H), 1.34-1.24(m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.8, 133.6, 129.0, 128.9, 127.2, 71.1, 46.1, 36.1, 25.23, 21.7; IR (film) 3441, 2931, 2854, 2067, 1620, 1311, 1242, 1157. MS (ESI): Calculated for $[C_{15}H_{18}N_{2}O_{2}Na]^+$: 281.1266. Found: 281.1262.

![1-diazo-1-(1-hydroxycyclohexyl)-3-phenylpropan-2-one](image)

**1-diazo-1-(1-hydroxycyclohexyl)-3-phenylpropan-2-one (3.62)**: Prepared from cyclohexanone (100 μL, 0.95 mmol) and 1-(4-chlorophenyl)-3-diazopropan-2-one (277 mg, 1.42 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 220 mg (79% yield) of the title compound as a yellow solid: $R_f = 0.44$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.33(d, $J = 8.4$ Hz, 2H), 7.16(d, $J = 8.3$, 2H), 4.11, (s, 1H), 3.77(s, 2H), 1.98-1.90(m, 2H), 1.81-1.70(m, 2H), 1.64-1.56(m,2H), 1.50-1.42(m, 2H), 1.35-1.25(m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.1, 133.3, 132.0, 130.4, 129.0, 71.1, 45.2, 36.1, 25.3, 21.7; IR (film) 3456, 2939, 2862, 1705, 1620, 1489, 1350, 1249, 1157. MS (ESI): Calculated for $[C_{17}H_{17}ClN_{2}O_{2}Na]^+$: 315.0876. Found: 315.0871.

![1-diazo-1-(1-hydroxycyclohexyl)-3-(4-methoxyphenyl)propan-2-one](image)

**1-diazo-1-(1-hydroxycyclohexyl)-3-(4-methoxyphenyl)propan-2-one (3.65)**: Prepared from cyclohexanone (41 μL, 0.4 mmol)
and 1-diazo-3-(4-methoxyphenyl)propan-2-one (115 mg, 0.6 mmol) following General Procedure 3.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 92 mg (80% yield) of the title compound as a yellow solid: \( R_f = 0.38 \) (hexanes/EtOAc 4:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.14 (d, J = 8.2\text{Hz}, 2H), 6.88 (d, J = 8.7\text{Hz}, 2H), 4.23 (s, 1H), 3.82 (s, 3H), 3.75 (s, 2H), 1.96-1.88 (m, 2H), 1.80-1.69 (m, 2H), 1.63-1.54 (m, 3H), 1.48-1.40 (m, 2H), 1.33-1.22 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 194.3, 158.7, 130.1, 125.6, 114.3, 72.9, 71.1, 55.3, 45.3, 36.1, 25.3, 21.8; \) IR (film) 3441, 2931, 2075, 1705, 1612, 1512, 1458, 1242, 1180. MS (ESI): Calculated for [C\(_{16}\)H\(_{20}\)N\(_2\)O\(_3\)Na]\(^+\): 311.1372. Found: 311.1368.

### 5.3.2 General Procedure 3.B: Tris(pentafluorophenyl)borane-promoted indenone formation

A solution of 0.1M \( \beta \)-hydroxy-\( \alpha \)-diazo ketone (1 equiv) in CH\(_2\)Cl\(_2\) was added dropwise to a stirred solution of 0.025M tris(pentafluorophenyl)borane (1 equiv) in CH\(_2\)Cl\(_2\). The reaction mixture was stirred at room temperature for 10 min during which gas evolved. The solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography.

![6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one](image)

\textbf{6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one} (3.89):

Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 3.84 (50.5 mg, 0.2 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH\(_2\)Cl\(_2\)) which gave the title compound (32.7 mg, 80% yield) as
an orange solid: $R_f = 0.73$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.38(d, $J = 7.0$Hz, 1H), 7.32(t, $J = 7.4$, 1H), 7.16(t, $J = 7.4$Hz, 1H), 7.03(d, $J = 7.32$Hz, 1H), 2.65-2.57(m, 2H), 2.46-2.38(m, 2H), 1.88-1.81(m, 2H), 1.81-1.72(m, 2H), 1.68-1.58(m, 2H); $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 197.7, 159.9, 146.3, 136.6, 133.2, 132.0, 128.0, 122.0, 118.5, 31.0, 27.2, 27.1, 26.6, 23.4; MS (ESI): Calculated for [C₁₄H₁₅O]⁺: 199.1123. Found: 199.1126.

![Chemical structure](image)

**3-methyl-6,7,8,9-tetrahydrobenzo[α]azulen-10(5H)-one (3.96):** Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 3.1 (68.7 mg, 0.27 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound 40.6 mg (72% yield) as an orange solid: $R_f = 0.75$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.27(d, $J = 7.2$, 1H), 6.94(d, $J = 7.1$Hz, 1H), 6.85(s, 1H), 2.62-2.57(m, 2H), 2.44-2.38(m, 2H), 2.36(s, 3H), 1.87-1.80(m, 2H), 1.79-1.72(m, 2H), 1.66-1.60(m, 2H); $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 197.5, 159.3, 146.7, 144.0, 137.0, 128.6, 127.8, 122.1, 119.9, 31.0, 27.1, 27.1, 26.6, 23.4, 22.2; MS (ESI): Calculated for [C₁₅H₁₇O]⁺: 213.1279. Found: 213.1278.

![Chemical structure](image)

**3-methoxy-6,7,8,9-tetrahydrobenzo[α]azulen-10(5H)-one (3.97):** Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 3.2 (57.6 mg, 0.21 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound 32.7 mg (68% yield).
As an orange solid: $R_f = 0.6$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$):

$\delta$ 7.33(d, $J = 7.9$Hz, 1H), 6.60(d, $J = 2.1$Hz, 1H), 6.52(dd, $J = 2.2$, 7.9Hz, 1H), 3.85(s, 3H), 2.59-2.54(m, 2H), 2.43-2.38(m, 2H), 1.86-1.79(m, 2H), 1.78-1.72(m, 2H), 1.65-1.58(m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): 196.5, 164.5, 157.3, 149.0, 138.3, 123.8, 123.7, 108.9, 108.0, 55.8, 31.0, 27.1, 27.0, 26.7, 23.6; MS (ESI): Calculated for [C$_{15}$H$_{17}$O$_2$]$^+$: 229.1229. Found: 229.1227.

3-chloro-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.98): Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 3.3 (51.0 mg, 18 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound 32.6 mg (77% yield) as an orange solid: $R_f = 0.65$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30(d, $J = 7.6$Hz, 1H), 7.14(dd, $J = 1.6$, 7.5Hz, 1H), 7.01(d, 1.4Hz, 1H), 2.61-2.56(m, 2H), 2.45-2.40(m, 2H), 1.88-1.81(m, 2H), 1.81-1.74(m, 2H), 1.68-1.61(m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 196.2, 158.5, 148.3, 139.5, 138.1, 129.1, 127.5, 122.9, 119.5, 30.9, 27.3, 26.9, 26.5, 23.5; MS (ESI): Calculated for [C$_{14}$H$_{14}$ClO]$^+$: 233.0733. Found: 233.0727.

1-chloro-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.99): Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 3.4 (74.6 mg, 0.27 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound 20.0 mg (32% yield) as
an orange solid: $R_f = 0.65$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25(dd, $J = 7.0$ 8.2Hz, 1H), 7.08(d, $J = 8.2$ Hz, 1H), 6.96(d, $J = 7.1$ Hz, 1H), 2.64-2.59(m, 2H), 2.47-2.42(m, 2H), 1.89-1.81(m, 2H), 1.80-1.71(m, 2H), 1.67-1.61(m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 194.5, 157.9, 148.5, 137.5, 134.0, 130.4, 130.1, 126.1, 117.1, 30.9, 27.2, 26.9, 26.6, 23.4; MS (ESI): Calculated for [C$_{14}$H$_{14}$ClO]$^+$: 233.0733. Found: 233.0737.

3-nitro-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.100): Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 3.5 (46.5 mg, 0.16 mmol) to General Procedure 3.B. The green oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound 3.0 mg (8% yield) as an orange solid: $R_f = 0.63$ (hexanes/EtOAc 4:1), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.12(dd, $J = 1.9$, 7.7Hz, 1H), 7.86(d, $J = 1.8$, 1H), 7.53(d, $J = 7.7$, 1H), 2.74-2.68(m, 2H), 2.51-2.46(m, 2H), 1.92-1.86(m, 2H), 1.86-1.79(m, 2H), 1.71-1.64(m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.1, 159.1, 148.0, 139.5, 135.6, 124.6, 122.1, 113.3, 30.7, 27.5, 26.8, 26.4, 23.6; MS (ESI): Calculated for [C$_{14}$H$_{14}$NO$_3$]$^+$: 244.0974. Found: 244.0966.

2-methyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.111) and 4-methyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.110): A solution of 2-diazo-2-(1-hydroxycyclohexyl)-1-(m-tolyl)ethanone (3.109) (288 mg, 1.11 mmol) in CH$_2$Cl$_2$ (10
mL) was added dropwise to a stirred solution of tris(pentafluorophenyl)borane (571 mg, 1.11 mmol) in CH₂Cl₂ (40 mL). The reaction mixture was stirred at room temperature for 10 min during which time gas evolved. The solution was concentrated under vacuum, and the brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) to give 194 mg (82% yield) of title compounds 3.111 and 3.110 as a 1.5 to 1 mixture as an orange oil.

2-methyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.111): \( R_f = 0.74 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.21 (s, 1H), 7.11 (d, \( J = 7.4 \text{Hz} \), 1H), 6.90 (d, \( J = 7.4 \text{Hz} \), 1H), 2.64-2.57 (m, 2H), 2.42-2.38 (m, 2H), 2.33 (s, 3H), 1.87-1.81 (m, 2H), 1.79-1.73 (m, 2H), 1.66-1.59 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 197.9, 160.1, 143.3, 138.0, 135.9, 132.8, 131.2, 123.2, 118.2, 30.9, 27.2, 27.0, 26.5, 23.3, 21.3; MS (ESI): Calculated for [C₁₅H₁₇O]⁺: 213.1279. Found: 213.1279.

4-methyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.110): \( R_f = 0.74 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.27-7.24 (dd, \( J = 2.0 \text{ 6.0Hz} \), 1H), 7.06-7.03 (m, 2H), 2.93-2.87 (m, 2H), 2.48 (s, 3H), 2.45-2.39 (m, 2H), 1.88-1.80 (m, 4H), 1.71-1.64 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 197.8, 162.9, 142.9, 137.5, 137.2, 131.9, 131.0, 128.0, 120.2, 30.5, 30.0, 26.3, 25.8, 22.0, 20.7; MS (ESI): Calculated for [C₁₅H₁₇O]⁺: 213.1278. Found: 213.1278.

7,7-dimethyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5H)-one (3.113): Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 3.112 (40.3 mg, 15 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound 25.0 mg (75%
yield) as an orange solid: \( R_f = 0.75 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.37 (d, J = 7.0\text{Hz}, 1\text{H}), 7.32 (td, J = 1.2, 7.5\text{Hz}, 1\text{H}), 7.15 (t, J = 7.4\text{Hz}, 1\text{H}), 7.01 (d, J = 7.2\text{Hz}, 1\text{H}), 2.59-2.54 (m, 2\text{H}), 2.39-2.34 (m, 2\text{H}), 1.68-1.63 (m, 2\text{H}), 1.55-1.50 (m, 2\text{H}), 1.04 (s, 6\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 197.9, 159.3, 146.3, 136.3, 133.3, 130.9, 128.0, 121.9, 118.4, 39.6, 38.9, 33.8, 29.0, 22.5, 18.7; MS (ESI): Calculated for [C\(_{16}\)H\(_{19}\)O\(^+\)]: 227.1436. Found: 227.1433.

7,7-dimethyl-6,7,8,9-tetrahydrobenzo[a]azulen-10(5\(H\))-one (3.115): Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 3.114 (53.1 mg, 0.18 mmol) (diastereomer A) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH\(_2\)Cl\(_2\)) which gave the title compound 30.1 mg (67% yield) as an orange solid. The product can also be prepared from \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 3.116 (19.5 mg, 0.065 mmol) (diastereomer B) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH\(_2\)Cl\(_2\)) which gave the title compound 12 mg (73% yield) as an orange solid. \( R_f = 0.62 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.38 (d, J = 7.0\text{Hz}, 1\text{H}), 7.32 (td, J = 1.1, 7.6\text{Hz}, 1\text{H}), 7.15 (t, J = 7.1\text{Hz}, 1\text{H}), 7.02 (d, J = 7.3\text{Hz}, 1\text{H}), 2.91-2.83 (m, 1\text{H}), 2.79-2.71 (m, 1\text{H}), 2.41-2.32 (m, 1\text{H}), 2.16-2.02 (m, 3\text{H}), 1.40-1.30 (m, 1\text{H}), 1.28-1.21 (m, 1\text{H}), 1.21-1.14 (m, 1\text{H}), 0.94 (s, 9\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): 197.8, 159.3, 146.3, 136.0, 133.2, 131.1, 128.0, 122.0, 118.4, 51.8, 34.2, 28.2, 27.8, 27.4, 27.1, 22.4; MS (ESI): Calculated for [C\(_{18}\)H\(_{23}\)O\(^+\)]: 255.1749. Found: 255.1745.
3,4-dihydro-1H-fluoren-9(2H)-one (3.117): Prepared by subjecting β-hydroxy-α-diazo ketone 3.116 (48.6 mg, 0.21 mmol) to General Procedure 3.B, and using dichloroethane as solvent instead of DCM. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound 5.4 mg (14% yield) as an orange solid: \( R_f = 0.63 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta 7.38(d, J = 7.0Hz, 1H), 7.33-7.30(m, 1H), 7.17(t, J = 7.4Hz, 1H), 6.96(d, J = 7.0Hz, 1H), 2.48-2.45(m, 2H), 2.28-2.24(m, 2H), 1.86-1.82(m, 2H), 1.78-1.73(m, 2H); \(^1\)C NMR (125 MHz, CDCl₃): \( \delta 197.7, 158.3, 145.1, 133.9, 133.2, 131.8, 128.3, 121.8, 118.3, 23.0, 22.1, 22.1, 19.8; \) MS (ESI): Calculated for \([\text{C}_{13}\text{H}_{12}\text{O}]^+\): 185.0966. Found: 185.0969.

8,9,10,11-tetrahydro-7H-cyclohepta[\(a\)]naphthalen-6-ol (3.61) and 1-cyclohexylidene-1H-inden-2(3H)-one (3.59) Prepared by dissolving β-hydroxy-α-diazo ketone 3.56 (45.0 mg, 0.17 mmol) into 1.7 mL DCM. The solution was slowly added into a stirred solution of tris(pentafluorophenyl)borane (89.3 mg, 0.17mmol) and MgSO₄ (2 mg, 0.17 mmol) in 5 mL DCM. The reaction mixture was stirred at room temperature for 10 min during which gas evolved and the solution’s color diminished. Solution was concentrated under vacuum. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the 8,9,10,11-tetrahydro-7H-cyclohepta[\(a\)]naphthalen-6-ol
17.3 mg (47% yield) as an red solid and 1-cyclohexylidene-1H-inden-2(3H)-one 7.7 mg (21% yield) for 8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalen-6-ol (3.61): \( R_f = 0.44 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 8.02(d, J = 8.1\text{Hz}, 1\text{H}), 7.63(d, J = 7.1\text{Hz}, 1\text{H}), 7.39-7.29(m, 2\text{H}), 6.99(s, 1\text{H}), 4.95(s, 1\text{H}), 3.30-3.23(m, 2\text{H}), 3.13-3.04(m, 2\text{H}), 1.97-1.87(m, 2\text{H}), 1.75-1.61(m, 4\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 204.1, 140.6, 133.7, 129.8, 128.6, 128.5, 127.0, 100.0, 49.2, 39.6, 31.0, 30.8, 25.8, 25.0; \) MS (ESI) Calculated for \([\text{C}_{15}\text{H}_{17}\text{O}]^+\): 213.1279. Found: 213.1284.

For 1-cyclohexylidene-1H-inden-2(3H)-one (3.59): \( R_f = 0.70 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.66(d, J = 7.7\text{Hz}, 1\text{H}), 7.35-7.31(m, 1\text{H}), 7.30-7.23(m, 2\text{H}), 3.51(s, 2\text{H}), 3.22-3.16(m, 2\text{H}), 2.85-2.77(m, 2\text{H}), 1.87-1.79(m, 2\text{H}), 1.77-1.67(m, 4\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 205.4, 158.0, 140.5, 136.6, 127.2, 126.9, 235.1, 124.3, 43.5, 32.3, 29.7, 28.1, 27.8, 25.8; \) MS (ESI): Calculated for \([\text{C}_{15}\text{H}_{17}\text{O}]^+\): 213.1279. Found: 213.1268.

2-chloro-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalen-6-ol (3.63): Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 3.62 (58.7 mg, 0.2 mmol) to General Procedure 3.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH2Cl2) which gave the title compound 22 mg (45% yield) as a red solid: Rf =0.40 (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 8.01(s, 1\text{H}), 7.58(d, J = 8.8\text{Hz}, 1\text{H}), 7.32(dd, J = 1.8, 8.7\text{Hz}, 1\text{H}), 6.99(s, 1\text{H}), 5.02(s, 1\text{H}), 3.25-3.19(m, 2\text{H}), 3.13-3.07(m, 2\text{H}), 1.98-1.89(m, 2\text{H}), 1.77-1.63(m, 4\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 151.5, 141.2, 132.8, 131.7, 129.3, 128.3,

5,6,7,8-tetrahydro-2\textit{H}-spiro[azulene-1,1'-cyclohexa[2,5]diene]-3,4'(4\textit{H})-dione (3.66) and 1-cyclohexylidene-6-methoxy-1\textit{H}-inden-2(3\textit{H})-one (3.67): Prepared by subjecting β-hydroxy-α-diazo ketone 3.65 (50.7 mg, 0.18 mmol) to General Procedure 3.B at 0°C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH_2Cl_2) which gave the title compound 5,6,7,8-tetrahydro-2\textit{H}-spiro[azulene-1,1'-cyclohexa[2,5]diene]-3,4'(4\textit{H})-dione (3.66) 15.4 mg (38% yield) as a white solid and 1-cyclohexylidene-6-methoxy-1\textit{H}-inden-2(3\textit{H})-one (3.67) 16.5 mg (39% yield) as a white solid. For 5,6,7,8-tetrahydro-2\textit{H}-spiro[azulene-1,1'-cyclohexa[2,5]diene]-3,4'(4\textit{H})-dione (3.66): R_f = 0.15 (hexanes/EtOAc 4:1), \textit{1}H NMR (500 MHz, CDCl_3): \delta 6.62(d, J = 10.1 Hz, 2H), 6.45(d, J = 10.0 Hz, 2H), 2.66(s, 2H), 2.45-2.39(m, 2H), 2.18-2.12(m, 2H), 1.84-1.78(m, 2H)1.61-1.48(m, 4H); \textit{13}C NMR (125 MHz, CDCl_3): \delta 204.1, 185.2, 174.4, 150.4, 145.3, 131.0, 51.3, 44.2, 31.4, 29.1, 26.7, 26.4, 24.0; MS (ESI): Calculated for [C_{15}H_{17}O_2]^+: 229.1229. Found: 229.1228.

For 1-cyclohexylidene-6-methoxy-1\textit{H}-inden-2(3\textit{H})-one (3.67): R_f = 0.67 (hexanes/EtOAc 4:1), \textit{1}H NMR (500 MHz, CDCl_3): \delta 7.25-7.22(m, 2H), 6.83(dd, J = 2.1, 8.4Hz, 1H), 3.86(s, 3H), 3.45(s, 2H), 3.21-3.15(m, 2H), 2.82-2.77(m, 2H), 1.87-1.79(m, 2H), 1.77-1.67(m, 4H); \textit{13}C NMR (125 MHz, CDCl_3): \delta 205.7, 158.5, 158.2, 141.5, 128.9,
128.9, 125.6, 112.3, 110.9, 55.5, 42.8, 32.2, 29.8, 28.1, 27.8, 25.7; MS (ESI): Calculated for [C_{16}H_{19}O_2]^+: 243.1385. Found: 243.1376.

2-benzoylcycloheptanone (3.87) Prepared by dissolving β-hydroxy-α-diazo ketone 3.84 (18 mg, 0.074 mmol) into 2 mL DCM. The solution was slowly added into a stirred solution of trifluoroacetic acid (0.0056 mL, 0.08 mmol) in 5 mL DCM. The reaction mixture was stirred at room temperature for 10 min during which gas evolved and the solution’s color diminished. Solution was concentrated under vacuum. The brown oily residue was subjected to silica gel flash column chromatography (100% CH_2Cl_2) which gave the title compound 11.8 mg (74% yield) as an oil: R_f = 0.44 (hexanes/EtOAc 4:1), ^1H and ^13C NMR data matched previously reported values.\(^ {226}\) MS (ESI): Calculated for [C_{14}H_{17}O_2]^+: 239.1048. Found: 239.1040.

5.4 Chapter 4 Experimental procedures and compound characterization data

5.4.1 General Procedure 4.A: Preparation of β-hydroxy-α-diazo ketones

A -78 °C solution of LDA (1.5 equiv) [prepared by addition of n-butyllithium in hexanes (1.5 equiv) to a solution of iPr_2NH (1.6 equiv) in THF (3 mL per mmol of n-butyllithium)] was added dropwise over 30 min via cannula down the inside wall of a chilled flask containing a -78 °C stirred solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in THF (3 mL per mmol of ketone). The mixture was maintained at -78 °C until complete conversion was achieved as monitored by TLC. A 1M solution of acetic acid in THF (2.0 equiv) was added quickly to the reaction mixture at -78 °C, at which point the reaction flask was removed from the cold bath and warmed to room temperature.
The mixture was poured into a saturated aqueous NH₄Cl solution and extracted three times with ethyl ether (15 mL), the organic layers were combined, washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), and dried over anhydrous MgSO₄. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

2-diazo-3-hydroxy-1-phenyl-3-propylhexan-1-one

(SI4.1): Prepared from 4-heptanone (0.2 mL, 1.43 mmol) and 2-diazo-1-phenylethanone (314 mg, 2.15 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 266 mg (72% yield) of the title compound as a yellow oil: \( R_f = 0.57 \) (hexanes/EtOAc 4:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta 7.60-7.57 \) (m, 2H), 7.52 (tt, \( J = 6.7, 1.4 \) Hz, 1H), 7.47-7.42 (m, 2H), 4.84 (s, 1H), 1.84-1.73 (m, 4H), 1.58-1.38 (m, 4H), 0.97 (t, 7.2 Hz, 6H); \(^13\)C NMR (125 MHz, CDCl₃): \( \delta 192.0, 137.6, 131.9, 128.7, 127.2, 75.1, 71.0, 41.4, 17.2, 14.3 \); IR (film): 2916, 2075, 1616, 1600, 1145. HRMS (RSI-TOF) m/z: \([M + Na]^+ \) Calcd for C₁₅H₂₀N₂O₂Na 283.1422; Found 283.1424.

1-diazo-1-(1-hydroxycyclohexyl)hexan-2-one

(SI4.2): Prepared from cyclohexanone (0.10 mL, 1.09 mmol) and 1-diazo-2-hexanone (206 mg, 1.63 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 222 mg (91% yield) of the title compound as a yellow solid: \( R_f = 0.62 \)
(hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.33 (s, 1H), 2.46 (t, \(J = 7.1\) Hz, 2H), 1.97-1.87 (m, 2H), 1.81-1.71 (m, 2H), 1.66-1.53 (m, 5H), 1.50-1.40 (m, 2H), 1.39-1.24 (m, 3H), 0.92 (t, \(J = 7.3\) Hz, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 197.3, 71.1, 38.7, 36.4, 26.8, 25.5, 22.4, 21.9, 13.9; IR (film): 2931, 2067, 1612, 1265. HRMS (RSI-TOF) m/z: [M + Na]^+ Calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\)Na 247.1422.; Found 247.1423.

\[ \text{6-diazo-7-hydroxy-7-propyldecan-5-one (SI4.3)} \]

Prepared from 4-heptanone (0.15 mL, 1.05 mmol) and 1-diazo-2-hexanone (200 mg, 1.58 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 209 mg (83% yield) of the title compound as a yellow solid: \(R_f = 0.6\) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.81 (s, 1H), 2.48 (t, \(J = 7.3\) Hz, 2H), 1.73-1.56 (m, 6H), 1.47-1.28 (m, 6H), 0.92 (t, \(J = 7.2\) Hz, 9H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 197.5, 70.7, 41.6, 38.7, 26.9, 22.4, 17.2, 14.4, 13.9; IR (film): 3425, 2931, 2075, 1604, 1458, 1335, 12801, 1103. HRMS (RSI-TOF) m/z: [M + Na]^+ Calcd for [C\(_{13}\)H\(_{24}\)N\(_2\)O\(_2\)Na]^+: 263.1735. Found: 263.1737.

\[ \text{1-cyclohexyl-2-diazo-2-\{1-hydroxycyclopentyl\}ethanone (SI4.4)} \]

Prepared from cyclopentanone (0.06 ml, 0.67 mmol) and 2-cyclohexyl-1-diazo-2-ethanone (270 mg, 1.01 mmol) following General Procedure 4.A. The oily yellow residue was purified by neutral aluminium gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 113mg (71% yield) of the
title compound as a yellow solid: \( R_f = 0.25 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 4.08 (s, 1H), 2.49 (tt, \( J = 11.8, 3.0 \) Hz, 1H), 2.09-1.98 (m, 2H), 1.92-1.81 (m, 2H), 1.81-1.57 (m, 9H), 1.50-1.37 (m, 2H), 1.29-1.13 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 200.3, 79.4, 46.6, 39.2, 28.7, 25.7, 25.6, 23.0; IR (film): 3387, 2931, 2854, 2075, 1597, 1342, 1273. HRMS (RSI-TOF) m/z: \([\text{M+Na}]^+\) Calcd for C₁₃H₂₀N₂O₂Na 259.1422; Found 259.1427.

1-cyclohexyl-2-diazo-2-(1-hydroxycyclohexyl)ethanone(SI4.5) Prepared from cyclohexanone (0.06 ml, 0.06 mmol) and 2-cyclohexyl-1-diazo-2-ethanone (151 mg, 1.00 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 130 mg (84% yield) of the title compound as a yellow solid: \( R_f = 0.63 \) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 4.40 (s, 1H), 2.50 (tt, \( J = 11.9, 3.6 \) Hz, 1H), 1.96-1.87 (m, 2H), 1.86-1.65 (m, 9H), 1.63-1.55 (m, 2H), 1.52-1.40 (m, 4H), 1.35-1.16 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 200.7, 71.2, 46.8, 36.4, 28.9, 25.8, 25.7, 25.5, 22.0; IR (film): 3356, 2931, 2854, 2075, 1604, 1265. HRMS (RSI-TOF) m/z: \([\text{M+Na}]^+\) Calcd for C₁₄H₂₂N₂O₂Na 273.1579; Found 273.1582.

1-cyclohexyl-2-diazo-3-hydroxy-3-propylhexan-1-one(SI4.6) Prepared from 4-heptanone (0.14 mL, 0.98 mmol) and 2-cyclohexyl-1-diazo-2-ethanone (225 mg, 1.48 mmol) following General Procedure 4.A. The oily yellow
residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 241 mg (92% yield) of the title compound as a yellow solid: \( R_f = 0.66 \) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 4.89 (s, 1H), 2.53 (tt, \( J = 11.8, 3.4 \) Hz, 1H), 1.85-1.73 (m, 4H), 1.72-1.59 (m, 5H), 1.52-1.16 (m, 9H), 0.92 (t, \( J = 7.4 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 200.9, 74.7, 46.9, 41.6, 28.9, 25.8, 25.7, 17.2, 14.5; IR (film): 3398, 2954, 2916, 2850, 2079, 1601, 1273. HRMS (RSI-TOF) m/z: \([\text{M+Na}]^+\) Calcd for C\(_{15}\)H\(_{26}\)N\(_2\)O\(_2\)Na 289.1892; Found 289.1892.

ethyl diazo(4-hydroxy-1-((4-methylphenyl)sulfonyl)piperidin-4-yl)acetate(SI4.7) Prepared from N-tosyl-4-piperidone(760 mg, 3.00 mmol) and ethyl diazoacetate (0.5 ml, 4.80 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 720 mg (65% yield) of the title compound as a yellow solid: \( R_f = 0.25 \) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.65 (d, \( J = 8.4 \) Hz, 2H), 7.32 (d, \( J = 8.4 \) Hz, 2H), 4.23 (q, \( J = 7.3 \) Hz, 2H), 3.68-3.57 (m, 3H), 2.75 (td, \( J = 12.3, 2.6 \) Hz, 2H), 2.44 (s, 3H), 2.08-2.03 (m, 2H), 1.86 (td, \( J = 12.5, 4.1 \) Hz, 2H), 1.28 (t, \( J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 167.3, 143.8, 133.3, 129.9, 127.8, 67.3, 61.3, 41.9, 35.5, 21.7, 14.5; IR (film): 2102, 1666, 1367, 1389, 1302. HRMS (RSI-TOF) m/z: \([\text{M+Na}]^+\) Calcd for C\(_{16}\)H\(_{21}\)N\(_3\)O\(_5\)SNa 390.1100; Found 397.1094. 147
1-diazo-1-(4-hydroxy-1-((4-methylphenyl)sulfonyl)piperidin-4-yl)hexan-2-one (SI4.8) Prepared from \(N\)-tosyl-4-piperidone (282 mg, 1.11 mmol) and 1-diazo-2-hexanone (211 mg, 1.67 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 219 mg (82% yield) of the title compound as a yellow solid: \(R_f = 0.29\) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.65 (d, \(J = 8.4\) Hz, 2H), 7.32 (d, \(J = 8.4\) Hz, 2H), 4.52 (s, 1H), 3.66-3.62 (m, 2H), 2.73 (td, \(J = 12.3, 2.6\) Hz, 2H), 2.48-2.44 (m, 5H), 2.09-2.03 (m, 2H), 1.81 (td, \(J = 12.5, 4.1\) Hz, 2H), 1.64-1.56 (m, 2H), 1.39-1.30 (m, 2H), 0.91 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 197.6, 143.8, 133.3, 130.0, 127.8, 68.2, 41.9, 38.6, 35.4, 26.6, 22.4, 21.7, 13.9; IR (film): 3348, 2083, 1589, 1342. HRMS (RSI-TOF) m/z: [M + NH\(_4\)]\(^+\) Calcd for C\(_{18}\)H\(_{29}\)N\(_4\)O\(_4\)S 397.1910; Found 397.1916.

ethyl 2-diazo-3-hydroxy-3-propylhexanoate (4.31)

Prepared from 4-heptanone (1.13 mL, 8.15 mmol) and ethyl diazoacetate (0.88 ml, 8.15 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 1.06g (57% yield) of the title compound as a yellow oil: \(R_f = 0.57\) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.24 (q, \(J = 7.2\) Hz, 2H), 3.84 (s, 1H), 1.75-1.63 (m, 4H), 1.49-1.32 (m, 4H), 1.29 (t, \(J = 7.1\) Hz, 3H), 0.93 (t, \(J = 7.2\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 167.8, 73.4, 60.9, 41.6, 17.2, 14.5, 14.4; IR (film): 3479, 2962, 2854, 1724, 1463, 1372, 1242, 1157, 1058, 999, 879, 767.
2087, 1670, 1369, 1300. MS (ESI): Calculated for [C_{11}H_{20}N_{2}O_{3}Na]^+: 251.1372. Found: 251.1381.

2-diazo-1-hydroxy-1-phenylheptan-3-one (SI 4.9) Prepared from benzaldehyde (0.11 ml, 1.10 mmol) and 1-diazo-2-hexanone (208 mg, 1.65 mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 178.3 mg (70% yield) of the title compound as a yellow solid: \( R_f = 0.15 \) (CH\(_2\)Cl\(_2\)), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.43-7.36 (m, 4H), 7.35-7.30 (m, 1H), 6.02 (s, 1H), 3.33 (s, 1H), 2.50 (t, \( J = 7.6 \) Hz, 2H), 1.7-1.61 (m, 2H), 1.42-1.32 (m, 2H), 0.92 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 194.7, 138.8, 128.9, 125.9, 73.1, 68.5, 38.4, 26.9, 22.5, 13.9; IR (film): 2610, 2931, 1734, 1604, 1450, 1381, 1188, 1026. MS (ESI): Calculated for [C\(_{13}\)H\(_{16}\)N\(_2\)O\(_2\)Na\(^+\)(NH\(_4\))\(^+\) adduct: 255.1109. Found: 255.1109.

1-cyclohexyl-2-diazo-2-(1-hydroxycycloheptyl)ethanone (SI 4.10) Prepared from cycloheptanone(0.081ml, 0.69mmol) and 2-cyclohexyl-1-diazo-2-ethanone (275.1mg, 1.03mmol) following General Procedure 4.A. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 157.0 mg (86% yield) of the title compound as a yellow solid: \( R_f = 0.71 \) (hexanes/EtOAc 5:1), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 4.65 (s, 1H), 2.47 (tt, \( J = 11.6, 3.6 \) Hz, 1H), 2.06-1.97 (m, 2H), 1.84-1.55 (m, 11H), 1.54-1.31 (m, 6H), 1.28-1.12 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 200.7, 75.0, 72.1, 46.7, 40.1, 29.1, 28.7, 25.7, 25.7,

5.4.2 General Procedure 4.B: Vinyl diazonium addition with indole
A 1M solution of β-hydroxy-α-diazo ketone (1 equiv) in CH$_2$Cl$_2$ was added dropwise to a stirred suspension of Sc(OTf)$_3$ (1 equiv) and indole (1.2 equiv) in CH$_2$Cl$_2$ (10 ml per mmol of Sc(OTf)$_3$) at -20 °C. The reaction mixture was stirred at -20 °C for 20 min and then poured into a saturated NaHCO$_3$ solution which was extracted with CH$_2$Cl$_2$ three times. The organic layers were combined, dried with MgSO$_4$, and concentrated under vacuum. The residue was purified by silica gel flash column chromatography to give the conjugate addition products.

![Structural formula of ethyl 2-diazo-3-(1H-indol-3-yl)-3-propylhexanoate (4.32)](image)

Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (57 mg, 0.25 mmol) and indole (35 mg, 0.30 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (74 mg, 90% yield) as a yellow solid: $R_f$ = 0.51 (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.26 (s, 1H), 7.62 (d, $J$ = 7.9 Hz, 1H), 7.31-7.26 (m, 1H), 7.18-7.13 (m,1H), 7.12-7.07 (m, 1H), 6.87 (d, $J$ = 2.5 Hz, 1H), 4.10 (q, $J$ = 7.1 Hz, 2H), 2.13-1.99 (m, 4H), 1.39-1.27 (m, 2H), 1.21-1.10 (m, 5H), 0.91 (t, $J$ = 7.3 Hz, 6H) $^{13}$C NMR (125 MHz, CDCl$_3$): δ 166.7, 137.0, 125.8, 122.8, 121.6, 119.9, 119.8, 111.6, 61.0, 60.2, 40.3, 36.9, 17.4, 14.6,
14.4; IR (film): 3341, 2962, 2075, 1681, 1288, 1103, 1087. HRMS (ESI-TOF): [M + H]^+ Calcd for C_{19}H_{26}N_{3}O_{2} 328.2025; Found 328.2031.

![Ethyl 3-(5-bromo-1H-indol-3-yl)-2-diazo-3-propylhexanoate (4.51)](image)

Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (51 mg, 0.22 mmol) and 5-bromoindole (53 mg, 0.27 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (78 mg, 86% yield) as a yellow solid: $R_f = 0.49$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.22 (s, 1H), 7.67 (d, $J = 1.7$ Hz, 1H), 7.21 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 2.5$ Hz, 1H), 4.09 (q, $J = 7.0$ Hz, 2H), 2.07-1.90 (m, 4H), 1.34-1.22 (m, 2H), 1.18 (t, $J = 7.0$ Hz, 3H), 1.15-1.04 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.5, 135.6, 127.5, 124.7, 124.0, 122.3, 120.0, 113.0, 112.7, 62.5, 60.4, 40.2, 37.0, 17.4, 14.6; IR (film): 3352, 2075, 1670, 1458, 1091. HRMS (RSI-TOF) m/z: [M + H]^+ Calcd for C$_{19}$H$_{25}$BrN$_3$O$_2$ 406.1130; Found 406.1136.

![Ethyl 2-diazo-3-(5-methoxy-1H-indol-3-yl)-3-propylhexanoate (4.48)](image)

Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (53 mg, 0.27 mmol) and 5-methoxyindole (53 mg, 0.27 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (62 mg, 85% yield) as a yellow solid: $R_f = 0.48$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.22 (s, 1H), 7.70 (d, $J = 1.7$ Hz, 1H), 7.21 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 2.5$ Hz, 1H), 4.09 (q, $J = 7.0$ Hz, 2H), 2.07-1.90 (m, 4H), 1.34-1.22 (m, 2H), 1.18 (t, $J = 7.0$ Hz, 3H), 1.15-1.04 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.8, 135.6, 127.7, 124.7, 124.0, 122.3, 120.0, 113.0, 112.7, 62.8, 60.6, 40.2, 37.0, 17.4, 14.6; IR (film): 3352, 2075, 1670, 1458, 1091. HRMS (RSI-TOF) m/z: [M + H]^+ Calcd for C$_{19}$H$_{25}$BrN$_3$O$_2$ 406.1130; Found 406.1136.
0.23 mmol) and 5-methoxyindole (41 mg, 0.28 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (77 mg, 91% yield) as a yellow solid: \( R_f = 0.33 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.89 (s, 1H), 7.23 (d, \( J = 8.9 \) Hz, 1H), 7.05 (d, 2.4 Hz, 1H), 6.98 (d, \( J = 2.5 \) Hz, 1H), 6.83 (dd, \( J = 8.9, 2.5 \) Hz, 1H), 4.07 (q, \( J = 7.1 \) Hz, 2H), 3.85 (s, 3H), 2.14-1.95 (m, 4H), 1.41-1.24 (m, 2H), 1.23-1.07 (m, 5H), 0.89 (t, \( J = 7.2 \) Hz, 6H). \(^1^3\)C NMR (125 MHz, CDCl₃): \( \delta \) 166.7, 153.5, 132.2, 126.2, 123.6, 119.5, 111.3, 102.4, 62.7, 50.2, 56.0, 40.3, 36.7, 17.4, 14.6, 14.4; IR (film): 3395, 2075, 1681, 1288, 1103. HRMS (RSI-TOF) m/z: [M + H]⁺ Calcd for C₂₀H₂₈N₃O₃ 358.2131; Found 358.2142.

Methyl 3-(4-(1-diazo-2-ethoxy-2-oxoethyl)heptan-4-yl)-1H-indole-5-carboxylate (4.49) Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 4.31 (60 mg, 0.26 mmol) and methylindole-5-carboxylate (55 mg, 0.31 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (82 mg, 88% yield) as a yellow solid: \( R_f = 0.22 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 8.81 (s, 1H), 8.35 (s, 1H), 7.81 (dd, \( J = 8.5, 1.6 \) Hz, 1H), 7.18 (d, \( J = 8.5 \) Hz, 1H), 6.83 (d, \( J = 2.6 \) Hz, 1H), 4.09 (q, \( J = 7.1 \) Hz, 2H), 3.95 (s, 3H), 2.10-1.94 (m, 4H), 1.35-1.23 (m, 2H), 1.21-1.05 (m, 5H), 0.89 (t, \( J = 7.3 \) Hz, 6H). \(^1^3\)C NMR (125 MHz, CDCl₃): \( \delta \) 168.5, 166.8, 139.7, 125.2, 124.3, 123.0, 122.6, 121.2, 121.1, 111.3, 62.8, 60.5, 60.4, 52.0, 40.1, 37.0, 17.3,
ethyl 3-(4-cyano-1H-indol-3-yl)-2-diazo-3-propylhexanoate (4.50) Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (55 mg, 0.24 mmol) and 4-cyanooindole (41 mg, 0.28 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (28 mg, 33% yield) as a yellow solid: $R_f = 0.11$ (CH₂Cl₂), $^1$H NMR (500 MHz, CDCl₃): δ 9.01 (s, 1H), 7.49 (dd, $J = 7.4, 0.8$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.05 (t, $J = 7.7$ Hz, 1H), 7.00 (d, $J = 2.9$ Hz, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 2.11 (td, $J = 13.0, 4.3$ Hz, 2H), 2.06-1.87 (m, 2H), 1.37-1.23 (m, 2H), 1.22-1.01 (m, 4H), 1.01-0.77 (m, 7H). $^{13}$C NMR (125 MHz, CDCl₃): δ 166.9, 137.7, 128.3, 126.6, 124.2, 121.0, 120.5, 119.6, 116.6, 102.2, 64.0, 60.3, 39.2, 37.4, 17.1, 14.53, 14.51; IR (film): 3310, 2962, 2098, 1658, 1288, 1149, 1087. HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C₂₀H₂₅N₄O₂ 353.1978; Found 353.1982.

ethyl 2-diazo-3-(1-methyl-1H-indole-3-yl)-3-propylhexanoate (4.54) Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (56 mg, 0.25 mmol) and N-methylindole (80 mg, 0.30 mmol) to General Procedure 4.B.
The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (78 mg, 93% yield) as a yellow solid: \( R_f = 0.61 \) (hexanes:EtOAc = 4:1), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.61 (d, \( J = 8.1 \) Hz, 1H), 7.29 (d, \( J = 8.1 \) Hz, 1H), 7.21 (t, \( J = 7.5 \) Hz, 1H), 7.08 (t, \( J = 7.5 \) Hz, 1H), 6.88 (s, 1H), 4.08 (q, \( J = 7.3 \) Hz, 2H), 3.75 (s, 3H), 2.12-1.99 (m, 4H), 1.39-1.25 (m, 2H), 1.21-1.11 (m, 5H), 0.90 (t, \( J = 7.4 \) Hz, 6H). \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 166.5, 137.5, 127.3, 126.3, 121.2, 120.1, 119.8, 118.5, 62.8, 60.0, 40.4, 37.1, 32.8, 17.4, 14.5, 14.3; IR (film): 2955, 2068, 1693, 1465, 1280, 1080. HRMS (RSI-TOF) m/z: [M + Na]⁺ Calcd for C₂₀H₂₇N₃O₂Na 364.2001; Found 364.2000.

![3-diazo-1-ethoxy-4-propyl-4-(1H-pyrrol-2-yl)heptan-2-one](image)

(4.53) Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ketone 4.31 (55 mg, 0.24 mmol) and pyrrole (0.02 ml, 0.29 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (57 mg, 85% yield) as a yellow solid: \( R_f = 0.63 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 9.10 (s, 1H), 6.71-6.68 (m, 1H), 6.10-6.07 (m, 1H), 5.96-5.93 (m, 1H), 4.17 (q, 7.2 Hz, 2H), 2.07-1.98 (m, 2H), 1.86-1.78 (m, 2H), 1.33-1.19 (m, 7H), 0.92 (t, 7.2 Hz, 6H). \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 168.3, 136.5, 117.3, 107.3, 104.8, 63.4, 60.8, 39.8, 36.5, 17.5, 14.5; IR (film): 3387, 2958, 2079, 1670, 1285. HRMS (RSI-TOF) m/z: [M + H]⁺ Calcd for C₁₅H₂₄N₃O₂ 278.1869; Found 278.1870.
**ethyl 3-(2H-benzotriazol-2-yl)-2-diazo-3-propylhexanoate (4.52)**

Prepared by subjecting β-hydroxy-α-diazo ketone 4.31 (64 mg, 0.28 mmol) and benzotriazole (40 mg, 0.33 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (45 mg, 49% yield) as a yellow solid: $R_f = 0.58$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.87 (dd, $J = 6.5$, 3.0 Hz, 2H), 7.35 (dd, $J = 6.5$, 3.0 Hz, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 2.57-2.44 (m, 4H), 1.43-1.33 (m, 2H), 1.13 (t, $J = 7.1$ Hz, 3H), 1.09-1.00 (m, 2H), 0.96 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 146.9, 143.8, 126.3, 118.5, 70.9, 60.9, 37.4, 17.1, 14.3, 14.1; IR (film): 2935, 2090, 1701, 1292, 1242, 1172. HRMS (RSI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{17}$H$_{23}$N$_4$O$_2$Na 352.1749; Found 352.1748.

**ethyl diazo(1-(1H-indol-3-yl)cyclopentyl)acetate (4.57)**

Prepared by subjecting ethyl diazo(1-hydroxycyclopentyl)acetate 4.4 (64 mg, 0.32 mmol) and indole (46 mg, 0.39 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (87 mg, 90% yield) as a yellow solid: $R_f = 0.38$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.24 (s, 1H), 7.64 (d, 8.1 Hz, 1H), 7.36-7.32 (m, 1H), 7.22-7.17 (m, 1H), 7.16-7.12 (m, 1H), 6.99 (d, $J = 2.5$ Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.45-2.36 (m, 2H), 2.33-2.25 (m, 2H), 1.87-1.75 (m, 4H), 1.13 (t, $J = 7.1$ Hz, 3H), 1.09-1.00 (m, 2H), 0.96 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 146.9, 143.8, 126.3, 118.5, 70.9, 60.9, 37.4, 17.1, 14.3, 14.1; IR (film): 2935, 2090, 1701, 1292, 1242, 1172. HRMS (RSI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{17}$H$_{23}$N$_4$O$_2$Na 352.1749; Found 352.1748.
1.21 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 166.8, 137.1, 126.1, 122.1, 121.8, 120.3, 120.2, 119.4, 111.6, 60.3, 44.1, 36.8, 23.2, 14.4; IR (film): 3367, 2955, 2075, 1670, 1292. HRMS (RSI-TOF) m/z: [M + NH$_4$]$^+$ Calcd for C$_{17}$H$_{23}$N$_4$O$_2$ 315.1821; Found 315.1835.

ethyl diazo(1-(1H-indol-3-yl)cyclohexyl)acetate (4.58)

Prepared by subjecting β-hydroxy-α-diazo ketone 4.5 (67 mg, 0.31 mmol) and indole (44 mg, 0.38 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (73 mg, 75% yield) as a yellow solid: $R_f$ = 0.36 (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.11 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.37-7.33 (m, 1H), 7.19-7.15 (m, 1H), 7.13-7.18 (m, 1H), 7.02 (d, J = 2.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.55-2.45 (m, 2H), 2.12-2.01 (m, 2H), 1.72-1.63 (m, 3H), 1.59-1.48 (m, 2H), 1.46-1.35 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H) $^{13}$C NMR (125 MHz, CDCl$_3$): δ 166.7, 137.1, 125.7, 122.1, 122.0, 121.8, 120.5, 119.4, 111.6, 62.5, 60.3, 37.9, 34.7, 26.0, 23.1, 14.5; IR (film): 3352, 2931, 2858, 2083, 1670, 1458, 1269, 1246, 1087. HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{22}$N$_3$O$_2$ 312.1712; Found 312.1724.
ethyl 2-diazo-3-(1H-indol-3-yl)-3-phenylpropanoate (4.59)

Prepared by subjecting ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (48 mg, 0.22 mmol) and indole (31 mg, 0.26 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (51 mg, 73% yield) as a yellow solid: $R_f = 0.28$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.12 (s, 1H), 7.46 (d, $J = 7.9$ Hz, 1H), 7.39-7.33 (m, 5H), 7.32-7.27 (m, 1H), 7.24-7.20 (m, 1H), 7.13-7.07 (m, 1H), 6.76 (dd, $J = 2.4$, 1.0 Hz, 1H), 5.45 (s, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.1$, 3H) $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 141.0, 136.8, 128.8, 127.9, 127.3, 126.4, 123.6, 123.6, 122.6, 120.0, 119.3, 115.7, 111.4, 61.1, 37.7, 14.6; IR (film): 3360, 2083, 1662, 1296, 1219. HRMS (RSI-TOF) m/z: [M + NH$_4$]$^+$ Calcd for C$_{19}$H$_{21}$N$_4$O$_2$ 337.1665; Found 337.1662.

ethyl 2-diazo-3-(1H-indol-3-yl)hexanoate (4.60)

Prepared by subjecting $\beta$-ethyl 2-diazo-3-hydroxyheptanoate (99 mg, 0.49 mmol) and indole (69 mg, 0.59 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (95 mg, 64% yield) as a yellow solid: $R_f = 0.53$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.06 (s, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 1H), 7.24-7.19 (m, 1H), 7.16-7.11 (m, 1H), 7.05 (d, $J = 2.1$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.10-4.05 (m, 1H), 2.05-1.96 (m,
1H), 1.95-1.86 (m, 1H), 1.50-1.35 (m, 4H), 1.28 (t, \( J = 7.1 \) Hz, 3H), 0.92 (t, \( J = 7.1 \) Hz, 3H) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 167.5, 136.6, 126.6, 122.5, 121.2, 119.8, 119.4, 116.6, 111.3, 60.8, 32.2, 31.4, 29.9, 22.6, 14.6, 14.1; IR (film): 3348, 2954, 2083, 1666, 1280, 1118, 1087. HRMS (RSI-TOF) m/z: [M + Na]\(^+\) Calcd for C\(_{17}\)H\(_{21}\)N\(_3\)O\(_2\)Na 322.1531; Found 322.1535.

![Ethyl diazo(4-(1H-indol-3-yl)-1-((4-methylphenyl)sulfonyl)piperidin-4-yl)acetate](image)

ethyl diazo(4-(1H-indol-3-yl)-1-((4-methylphenyl)sulfonyl)piperidin-4-yl)acetate (4.67) Prepared by subjecting \( \beta \)-hydroxy-\( \alpha \)-diazo ester SI4.7 (43 mg, 0.12 mmol) and indole (17 mg, 0.14 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH\(_2\)Cl\(_2\)) which gave the title compound (52 mg, 95% yield) as a yellow solid: \( R_f = 0.26 \) (CH\(_2\)Cl\(_2\)), \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.27 (s, 1H), 7.68 (d, \( J = 8.0 \) Hz, 2H), 7.56 (d, \( J = 8.0 \) Hz, 1H), 7.37 (d, \( J = 8.0 \) Hz, 1H), 7.34 (d, \( J = 8.0 \) Hz, 2H), 7.20 (t, \( J = 7.1 \) Hz, 1H), 7.12 (t, \( J = 7.1 \) Hz, 1H), 6.97 (d, \( J = 2.6 \) Hz, 1H), 4.08 (q, \( J = 7.1 \) Hz, 2H), 3.47-3.39 (m, 2H), 2.97-2.89 (m, 2H), 2.64-2.57 (m, 2H), 2.46 (s, 3H), 2.44-2.36 (m, 2H), 1.16 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 166.0, 143.7, 137.1, 133.7, 129.9, 127.7, 125.2, 122.2, 122.1, 120.1, 119.8, 119.2, 111.8, 60.6, 43.1, 36.0, 33.4, 21.7, 14.4; IR (film): 3379, 2982, 2075, 1678, 1161. HRMS (RSI-TOF) m/z: [M + Na]\(^+\) Calcd for C\(_{24}\)H\(_{26}\)N\(_4\)O\(_4\)SnNa 489.1572; Found 489.1573.
4-diazo-5-(1H-indol-3-yl)-2,2-dimethyl-5-propyloctan-3-one (4.61) Prepared by subjecting 4-diazo-5-hydroxy-2,2-dimethyl-5-propyloctan-3-one (41 mg, 0.17 mmol) and indole (24 mg, 0.20 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂).

That gave the title compound (50 mg, 87% yield) as a yellow solid: \( R_f = 0.63 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 8.35 (s, 1H), 7.52 (d, \( J = 8.0 \) Hz, 1H), 7.22-7.18 (m, 1H), 7.12-7.07 (m, 1H), 7.06-7.02 (m, 1H), 6.38 (d, \( J = 2.5 \) Hz, 1H), 2.17-2.05 (m, 2H), 1.99-1.91 (m, 2H), 1.33-1.22 (m, 2H), 1.19 (s, 9H), 1.16-1.05 (m, 2H), 0.89 (t, \( J = 7.3 \) Hz, 6H) \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 199.3, 137.0, 125.7, 123.0, 121.4, 120.0, 119.6, 118.8, 111.7, 68.6, 44.8, 41.6, 36.1, 26.7, 17.4, 14.6; IR (film): 3348, 2954, 2056, 1627, 1300. HRMS (RSI-TOF) m/z: [M + H]⁺ Calcd for \( \text{C}_{21}\text{H}_{30}\text{N}_3\text{O} \) 340.2389; Found 340.2388.

6-diazo-7-(1H-indol-3-yl)-7-propyldecan-5-one (4.63)

Prepared by subjecting β-hydroxy-α-diazo ketone S14.3 (54 mg, 0.23 mmol) and indole (32 mg, 0.27 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (58 mg, 75% yield) as a yellow solid: \( R_f = 0.43 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃):
δ 8.44 (s, 1H), 7.53 (d, J = 8 Hz, 1H), 7.29-7.26 (m, 1H), 7.16-7.11 (m, 1H), 7.09-7.04 (m, 1H), 6.87 (d, J = 2.5 Hz, 1H), 2.50-2.35 (m, 2H), 2.18-1.96 (m, 4H), 1.56-1.44 (m, 2H), 1.35-1.05 (m, 6H), 0.89 (t, J = 7.3 Hz, 6H), 0.83 (t, J = 7.2 Hz, 3H) 13C NMR (125 MHz, CDCl3): δ 194.7, 137.0, 125.7, 123.0, 121.6, 119.6, 119.5, 119.1, 111.7, 73.0, 41.1, 38.9, 36.6, 26.9, 22.3, 17.4, 14.5, 13.8; IR (film): 3317, 2870, 2476, 2339, 2052 HRMS (RSI-TOF) m/z: [M + H]+ Calcd for C21H30N3O 340.2389; Found 340.2397.

2-diazo-3-(1H-indol-3-yl)-1-phenyl-3-propylhexan-1-one (4.64) Prepared by subjecting β-hydroxy-α-diazo ketone SI4.1 (32 mg, 0.12 mmol) and indole (17 mg, 0.15 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH2Cl2) which gave the title compound (35 mg, 78% yield) as a yellow solid: Rf = 0.23 (CH2Cl2), 1H NMR (500 MHz, CDCl3): δ 8.41 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.58-7.52 (m, 2H), 7.47-7.42 (m, 1H), 7.41-7.36 (m, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.19-7.10 (m, 2H), 6.95 (d, J = 2.5 Hz, 1H), 2.27 (td, J = 12.5, 4.6 Hz, 2H), 2.14 (td, J = 12.5, 4.6 Hz, 2H), 1.44-1.32 (m, 2H), 1.27-1.13 (m, 2H), 0.93 (t, J = 7.3 Hz, 6H) 13C NMR (125 MHz, CDCl3): δ 190.0, 138.9, 137.1, 131.2, 128.6, 127.3, 125.8, 123.3, 121.7, 119.7, 119.34, 119.27, 111.8, 73.4, 42.1, 36.7, 17.6, 14.6; IR (film): 3325, 2958, 2063, 1597, 1454, 1323. HRMS (RSI-TOF) m/z: [M + H]+ Calcd for C23H36N3O 360.2076; Found 360.2084.
1-cyclohexyl-2-diazo-3-(1H-indol-3-yl)-3-propylhexan-1-one (4.62) Prepared by subjecting β-hydroxy-α-diazo ketone SI 4.6 (52 mg, 0.19 mmol) and indole (27 mg, 0.23 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (61 mg, 87% yield) as a yellow solid: \( R_f = 0.25 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta 8.35 \) (s, 1H), 7.52 (d, \( J = 8.0 \) Hz, 1H), 7.21 (d, \( J = 8.0 \) Hz, 1H), 7.12-7.08 (m, 1H), 7.07-7.02 (m, 1H), 6.90 (d, \( J = 2.5 \) Hz, 1H), 2.55 (tt, \( J = 11.3, 3.5 \) Hz, 1H), 2.18-1.95 (m, 4H), 1.81-1.56 (m, 5H), 1.41-1.04 (m, 9H), 0.88 (t, \( J = 7.4 \) Hz, 6H). \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta 197.9, 137.0, 125.7, 122.9, 122.2, 121.6, 119.7, 119.0, 111.7, 71.8, 46.8, 41.1, 36.6, 28.9, 25.8, 25.7, 17.4, 14.6. \) IR (film): 2962, 2056, 1616, 1450, 1330, 1249. HRMS (RSI-TOF) m/z: \([M + H]^+\) Calcd for C₂₃H₃₂N₃O 366.2545; Found 366.2557.

2-diazo-1-(1H-indol-3-yl)-1-phenylheptan-3-one (4.65)

Prepared by subjecting β-hydroxy-α-diazo ketone SI4.9 (43 mg, 0.19 mmol) and indole (26 mg, 0.22 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (40 mg, 65% yield) as a white solid: \( R_f = 0.28 \) (CH₂Cl₂), \(^1\)H NMR (500 MHz, CDCl₃): \( \delta 8.24 \) (s, 1H), 7.43-7.35 (m, 7H), 7.21 (t, \( J = 7.6 \) Hz, 1H), 7.08 (t, \( J = 7.6 \) Hz, 1H), 6.75
(d, J = 1.5 Hz, 1H), 5.63 (s, 1H), 2.62-2.48 (m, 2H), 1.73-1.59 (m, 2H), 1.42-1.27 (m, 2H), 1.0-0.82 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 193.1, 140.8, 136.8, 128.8, 128.0, 127.3, 126.5, 123.6, 122.8, 120.1, 119.3, 115.7, 111.4, 71.9, 38.3, 36.8, 27.2, 22.5, 13.9; IR (film): 3255, 2067, 1604, 1342, 1171. HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{22}$N$_3$O 332.1763; Found 332.1770

1-cyclohexyl-2-diazo-2-(1-(1H-indol-3-yl)cyclopentyl)ethanone (4.66) Prepared by subjecting β-hydroxy-α-diazo ketone SI4.4 (42 mg, 0.17 mmol) and indole (25 mg, 0.21 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (38 mg, 65% yield) as a yellow solid: $R_f$ = 0.4 (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.19 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.18-7.13 (m, 1H), 7.11-7.07 (m, 1H), 7.03 (d, J = 2.5 Hz, 1H), 2.50 (tt, J = 11.6, 3.3 Hz, 1H), 2.40-2.22 (m, 4H), 1.81-1.67 (m, 6H), 1.65-1.53 (m, 3H), 1.40-1.24 (m, 2H), 1.23-1.07 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 197.8, 137.1, 126.1, 122.2, 121.8, 120.3, 120.0, 119.4, 111.6, 46.9, 44.9, 36.7, 28.8, 25.83, 25.79, 23.4; IR (film): 3325, 2931, 2060, 1620, 1319. HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{26}$N$_3$O 336.2076; Found 336.2083.
Prepared by subjecting 1-diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylbutan-2-one (42 mg, 0.18 mmol) to General Procedure 4.B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (54 mg, 90% yield) as a yellow solid: Rf = 0.63 (CH$_2$Cl$_2$), 1H NMR (500 MHz, CDCl$_3$): δ 8.33 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.30-7.25 (m, 1H), 7.15-7.10 (m, 1H), 7.09-7.05 (m, 1H), 6.96 (d, J = 2.5 Hz, 1H), 2.57-2.46 (m, 2H), 2.04-1.94 (m, 2H), 1.74-1.63 (m, 3H), 1.53-1.36 (m, 3H), 1.17 (s, 9H). 13C NMR (125 MHz, CDCl$_3$): δ 199.8, 137.0, 125.7, 122.3, 122.0, 121.4, 119.9, 119.1, 111.7, 68.2, 45.0, 39.4, 34.5, 26.8, 26.1, 23.3; IR (film): 3321, 2928, 2056, 1621, 1458, 1296. HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{20}$H$_{26}$N$_3$O$_2$ 324.2076; Found 324.2080.

5.4.3 Preparation of Vinyl indole

**General Procedure 4.C:** A 1M solution of β-hydroxy-α-diazo ketone (1 equiv) in CH$_2$Cl$_2$ was added dropwise to a stirred suspension of Sc(OTf)$_3$ (1 equiv) and indole (4 equiv) in CH$_2$Cl$_2$ (10ml per mmol of Sc(OTf)$_3$) at room temperature. The reaction mixture was stirred at room temperature for 20 min during which gas evolved. The solution was poured into saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ three times. The organic layers were combined, dried with MgSO$_4$ and concentrated under vacuum. The residue was purified by silica gel flash column chromatography.
**General Procedure 4.D:** A solution of 1M β-hydroxy-α-diazo ketone (1 equiv) in CH$_2$Cl$_2$ was added dropwise to a stirred solution mixture of Sc(OTf)$_3$ (1 equiv) and indole (1.2 equiv) in CH$_2$Cl$_2$ (10ml/mmol of Sc(OTf)) at -20°C. The reaction mixture was stirred at -20°C for 20 min during which desired product was observed on TLC. Solution was poured into saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$ three times. The organic layers were combined and dried with MgSO$_4$. Solution was concentrated under vacuum. The residue was purified by silica gel flash column chromatography.

![2-cyclohexylidene-2-(1H-indol-3-yl)-1-phenylethanone](image)

(4.10) Prepared by subjecting 2-diazo-2-(1-hydroxycyclohexyl)-1-phenylethanone (40 mg, 0.16 mmol) and indole (76 mg, 0.65 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (45.5 mg, 90% yield) as a white solid: $R_f = 0.23$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.24 (s, 1H), 8.06-8.01 (m, 2H), 7.70-7.64 (m, 1H), 7.45 (tt, $J = 6.8$, 1.2 Hz, 1H), 7.39-7.34 (m, 2H), 7.34-7.30 (m, 1H), 7.22-7.15 (m, 2H), 7.09 (d, $J = 2.6$ Hz, 1H), 2.39-2.33 (m, 2H), 2.28-2.22 (m, 2H), 1.70-1.57 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 199.3, 143.6, 137.3, 136.2, 133.0, 129.6, 128.6, 126.7, 126.0, 124.2, 122.2, 120.2, 120.1, 112.2, 111.5, 33.0, 32.0, 28.3, 28.2, 26.6; HRMS (RGI-TOF) m/z: [M + H]$^+$ Calcd for C$_{22}$H$_{22}$NO 316.1701; Found 316.1706
1-cyclohexylidene-1-(1H-indol-3-yl)hexan-2-one (4.22)

Prepared by subjecting β-hydroxy-α-diazo ketone SI4.2 (53 mg, 0.24 mmol) and indole (11 mg, 0.95 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (61.6 mg, 88% yield) as a white solid: $R_f = 0.36$ (Hexane: ethylacetate = 5:1), $^1$H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.25-7.21 (m, 1H), 7.18-7.13 (m, 1H), 7.03 (d, $J = 2.5$ Hz, 1H), 2.51-2.46 (m, 2H), 2.35 (t, $J = 7.4$ Hz, 2H), 2.16-2.09 (m, 2H), 1.74-1.68 (m, 2H), 1.64-1.58 (m, 2H), 1.58-1.53 (m, 2H), 1.53-1.46 (m, 2H), 1.22-1.13 (m, 2H), 0.78 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl₃): δ 208.4, 147.7, 136.2, 128.6, 127.5, 123.7, 122.3, 120.1, 119.8, 112.6, 111.4, 42.0, 32.6, 32.2, 28.8, 28.6, 26.6, 26.5, 22.4, 14.0; HRMS (RSM-TOF) m/z: [M + H]$^+$ Calcd for C₂₀H₂₆NO₃ 296.2014; Found 296.2018.

1-cyclohexyl-2-cyclohexylidene-2-(1H-indol-3-yl)ethanone (4.25) Prepared by subjecting β-hydroxy-α-diazo ketone SI4.5 (57 mg, 0.23 mmol) and indole (107 mg, 0.91 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (62.0 mg, 85% yield) as a white solid: $R_f = 0.25$ (CH₂Cl₂), $^1$H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 165
1H), 7.22 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 2.42-2.32 (m, 3H), 2.20-2.12 (m, 2H), 1.81-1.72 (m, 2H), 1.72-1.49 (m, 9H), 1.36-1.24 (m, 2H), 1.15-0.97 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 211.5, 146.4, 136.2, 128.4, 127.5, 123.8, 122.3, 120.1, 119.9, 112.4, 111.4, 48.6, 32.7, 32.4, 28.8, 28.7, 28.6, 26.7, 26.0, 25.7; HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{22}$H$_{28}$NO 322.2171; Found 322.2172.

$\text{6-}(1\text{H-indol-3-yl})\text{-7-propyldec-6-en-5-one \hspace{1cm} (4.23)}$

Prepared by subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI4.3 (62 mg, 0.26 mmol) and indole (121 mg, 1.03 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (43.5 mg, 54% yield) as a white solid. Compound can also be prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI3 (45.6mg, 0.19mmol) and indole (26.7mg, 0.23mmol) to General Procedure 4.D. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (47.8mg, 81% yield) as a white solid: $R_f = 0.63$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.36 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.25-7.20 (m, 1H), 7.17-7.12 (m, 1H), 7.03 (d, J = 2.4 Hz, 1H), 2.41-2.35 (m, 2H), 2.35-2.29 (m, 2H), 2.04-1.98 (m, 2H), 1.64-1.55 (m, 2H), 1.50-1.34 (m, 4H), 1.19-1.09 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H), 0.79-0.70 (m, 6H) $^{13}$C NMR (125 MHz, CDCl$_3$): δ 207.4, 149.7, 136.1, 131.6, 127.6, 123.5, 122.4, 120.1, 119.8, 113.4, 111.3, 41.9, 35.2, 34.4, 26.4, 22.5, 22.4, 21.8, 14.5, 14.3, 14.0; HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{30}$O 312.2327; Found 312.2331.
1-cyclohexyl-2-(1H-indol-3-yl)-3-propylhex-2-en-1-one

(4.26) Prepared by subjecting β-hydroxy-α-diazo ketone SI4.6 (54 mg, 0.2mmol) and indole (94 mg, 0.81mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (36.1 mg, 52% yield) as a white solid. Compound can also be prepared from subjecting β-hydroxy-α-diazo ketone SI4.6 (43.2mg, 0.16mmol) and indole (22.8mg, 0.19mmol) to General Procedure 4.D. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (44.6mg, 81% yield) as a white solid: $R_f = 0.66$ (hexane:EtOAc = 5:1), $^1$H NMR (500 MHz, CDCl$_3$): δ 8.34 (s, 1H), 7.45 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 8.1$ Hz, 1H), 7.22 (t, $J = 7.0$ Hz, 1H), 7.13 (t, $J = 7.0$ Hz, 1H), 7.04 (d, $J = 2.4$ Hz, 1H), 2.35 (tt, $J = 11.7$, 3.3 Hz, 1H), 2.31-2.25 (m, 2H), 2.07-2.00 (m, 2H), 1.74-1.66 (m, 2H), 1.66-1.55 (m, 4H), 1.55-1.48 (m, 1H), 1.44-1.35 (m, 2H), 1.33-1.22 (m, 2H), 1.14-0.97 (m, 6H), 0.78-0.71 (t, $J = 7.2$ Hz, 3H) $^{13}$C NMR (125 MHz, CDCl$_3$): δ 210.7, 148.6, 136.1, 131.3, 127.6, 123.4, 122.3, 120.1, 119.9, 113.2, 111.3, 48.6, 34.7, 34.6, 28.9, 26.0, 25.8, 22.5, 21.8, 14.5, 14.3; HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{23}$H$_{32}$NO 338.2484; Found 338.2483.
1-(1H-indol-3-yl)-1-(1-((4-methylphenyl)sulfonyl)piperidin-4-ylidene)hexan-2-one (4.30) Prepared by subjecting β-hydroxy-α-diazo ketone S14.8 (50 mg, 0.13 mmol) and indole (61 mg, 0.52 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂).

That gave the title compound (51.2 mg, 88% yield) as a white solid: \( R_f = 0.25 \) (hexane:EtOAc = 5:1), \(^1\text{H} \text{NMR} \) (500 MHz, CDCl₃): δ 8.45 (s, 1H), 7.61 (d, \( J = 8.4 \text{ Hz} \), 2H), 7.40 (d, \( J = 8.2 \text{ Hz} \), 1H), 7.34-7.30 (m, 3H), 7.25-7.20 (m, 1H), 7.14-7.10 (m, 1H), 6.99 (d, \( J = 2.5 \text{ Hz} \), 1H), 3.18 (t, \( J = 5.5 \text{ Hz} \), 2H), 2.98 (t, \( J = 5.5 \text{ Hz} \), 2H), 2.67 (t, \( J = 5.8 \text{ Hz} \), 2H), 2.43 (s, 3H), 2.34 (t, \( J = 5.8 \text{ Hz} \), 2H), 2.27 (t, \( J = 7.2 \text{ Hz} \), 2H), 1.46-1.37 (m, 2H), 1.16-1.07 (m, 2H), 0.74 (t, \( J = 7.3 \text{ Hz} \), 3H) \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCl₃): δ 207.2, 143.8, 140.3, 136.1, 133.3, 131.9, 129.8, 127.7, 127.0, 123.8, 122.7, 120.5, 119.4, 111.6, 111.5, 47.7, 47.4, 41.8, 31.3, 30.5, 26.3, 22.3, 21.7, 13.9; HRMS (RSI-TOF) m/z: [M + H]⁺ Calcd for C₂₆H₃₁N₂O₃S 451.2055; Found 451.2062.

2-(4,4-dimethylcyclohexylidene)-2-(1H-indol-3-yl)-1-phenylethanone (4.29) Prepared from subjecting β-hydroxy-α-diazo ketone 3.112 (44.7 mg, 0.16 mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound
(47.3mg, 84% yield) as a white solid: $R_f = 0.35$ (DCM), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.22 (s, 1H), 8.05-8.00 (m, 2H), 7.69-7.74 (m, 1H), 7.78-7.73 (m, 1H), 7.39-7.31 (m, 3H), 7.22-7.16 (m, 2H), 7.09 (d, $J = 2.6$ Hz, 1H), 2.41-2.35 (m, 2H), 2.29-2.24 (m, 2H), 1.43 (q, $J = 7.1$ Hz, 4H), 0.99 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.3, 143.4, 137.3, 136.2, 133.0, 129.6, 128.6, 126.7, 126.1, 124.2, 122.3, 120.2, 120.1, 112.3, 111.5, 40.6, 40.5, 30.4, 28.8, 28.2, 27.8; MS (ESI): Calculated for [C$_{24}$H$_{26}$N$_2$O]$: 344.2014$. Found: 344.2021.

1-cyclohexyl-2-cyclopentylidene-2-(1H-indol-3-yl)ethanone (4.24) Prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI4.4 (43.6mg, 0.18mmol) and indole (86.4mg, 0.74mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (18.3mg, 32% yield) as a white solid. Compound can also be prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI4.4 (26.6mg, 0.11mmol) and indole (15.8mg, 0.14mmol) to General Procedure 4.D. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (15.4mg, 45% yield) as a white solid: $R_f = 0.3$ (DCM), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.29 (s, 1H), 7.44-7.38 (m, 2H), 7.22 (t, $J = 7.0$, 1H), 7.12 (t, $J = 6.9$ Hz, 1H), 7.08 (d, $J = 2.4$ Hz, 1H), 2.84-2.76 (m, 2H), 2.47 (tt, $J = 11.6$, 3.5 Hz, 1H), 2.25-2.18 (m, 2H), 1.81-1.73 (m, 2H), 1.71-1.64 (m, 2H), 1.65-1.54 (m, 4H), 1.53-1.47 (m, 1H), 1.32 (qd, $J = 12.5$, 3.4 Hz, 2H), 1.11 (qt, $J = 12.8$, 3.6 Hz, 1H), 0.95 (qt, $J = 12.8$, 3.5 Hz, 2H) $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 208.3, 160.9, 136.1, 127.1, 125.9, 123.0, 122.3, 120.0, 119.7, 115.0, 111.4, 47.8, 34.9, 34.0, 29.0, 27.2, 26.0, 25.8, 25.7; MS (ESI): Calculated for [C$_{21}$H$_{26}$NO]$: 308.2014$. Found: 308.2018.
2-cycloheptylidene-1-cyclohexyl-2-(1H-indol-3-yl)ethanone (4.27)

Prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI 4.10 (35.5mg, 0.13mmol) to General Procedure 4.C. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (32.6mg, 70% yield) as a white solid. Compound can also be prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone SI4.10 (40.1mg, 0.15mmol) and indole (21.2mg, 0.18mmol) to General Procedure 4.D. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (44.5mg, 88% yield) as a white solid: $R_f = 0.38$ (DCM), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.23 (s, 1H), 7.47 (d, $J = 7.8$Hz, 1H), 7.40 (d, $J = 8.1$Hz, 1H), 7.22 (t, $J = 7.0$Hz, 1H), 7.13 (t, $J = 7.0$Hz, 1H), 7.06 (d, $J = 2.4$Hz, 1H), 2.55-2.49 (m, 2H), 2.35 (tt, $J = 11.5$, 3.4Hz, 1H), 2.30-2.24 (m, 2H), 1.80-1.67 (m, 4H), 1.66-1.55 (m, 4H), 1.55-1.46 (m, 5H), 1.28 (qd, $J = 12.5$, 3.6Hz, 2H), 1.15-0.94 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 210.7, 150.2, 136.1, 130.8, 127.5, 123.5, 122.4, 120.1, 120.0, 113.3, 111.3, 48.5, 34.0, 33.5, 29.6, 29.3, 28.8, 28.5, 27.6, 26.0, 25.8; MS (ESI): Calculated for [C$_{23}$H$_{30}$NO]$: 336.2327$. Found: 336.2330.

2-cyclopentylidene-2-(1H-indol-3-yl)-1-phenylethanone (4.21)

Prepared from subjecting $\beta$-hydroxy-$\alpha$-diazo ketone 3.116 (69.0mg, 0.3mmol) and indole (140.5mg, 1.20mmol) to General Procedure 4C. The brown oily residue was subjected to
silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (6.7mg, 10% yield) as a white solid: $R_f = 0.20$ (DCM). $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.80 (s, 1H), 7.65-7.61 (m, 3H), 7.20-7.11 (m, 2H), 7.10-7.01 (m, 4H), 6.83 (d, $J = 2.6$ Hz, 1H), 2.72-2.67 (m, 2H), 2.55-2.49 (m, 2H), 1.97-1.85 (m, 4H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 202.0, 137.2, 136.1, 135.0, 134.9, 131.9, 128.7, 127.8, 126.2, 124.2, 122.2, 120.4, 119.8, 118.4, 111.1, 31.0, 27.9, 23.0, 22.5; MS (ESI): Calculated for [C₂₁H₂₅N₀]⁺: 302.1545. Found: 302.1549.

![Chemical Structure](image)

2-(1H-indol-3-yl)-1-phenyl-3-propylhex-2-en-1-one  (4.20)

Prepared from subjecting β-hydroxy-α-diazo ketone SI4.1 (52.3mg, 0.20mmol) and indole (94.1mg, 0.80mmol) to General Procedure B. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (17.7mg, 27% yield) as a white solid. Compound can also be prepared from subjecting β-hydroxy-α-diazo ketone SI4.1 (42.3mg, 0.16mmol) and indole (22.8mg, 0.19mmol) to General Procedure 4.D. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the title compound (27.3mg, 51% yield) as a white solid: $R_f = 0.30$ (DCM). $^1$H NMR (500 MHz, CDCl₃): $\delta$ 8.18 (s, 1H), 8.03-7.99 (m, 2H), 7.68-7.63 (m, 1H), 7.44 (t, $J = 7.5$, 1.2 Hz, 1H), 7.38-7.33 (m, 2H), 7.33-7.29 (m, 1H), 7.21-7.14 (m, 2H), 7.05 (d, $J = 2.5$ Hz, 1H), 2.30-2.21 (m, 2H), 2.20-2.14 (m, 2H), 1.59-1.46 (m, 4H), 0.91-0.80 (m, 6H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 198.9, 144.5, 137.2, 136.2, 132.9, 129.7, 129.6, 128.5, 126.8, 124.0, 122.3, 120.4, 120.2, 112.7, 111.4, 34.7, 33.7, 21.8, 21.5, 14.4, 14.3; MS (ESI): Calculated for [C₂₃H₂₆NO]⁺: 332.2014. Found: 332.2019.
5.4.4 Rh$_2$(OAc)$_4$ catalyzed rearrangement of indole diazo ester 4.32

![Chemical Structure](image)

**ethyl 2-(1H-indol-3-yl)-3-propylhex-2-enoate (4.33)** A solution of α-diazo ketone 4.32 (23.2 mg, 0.07 mmol) in CH$_2$Cl$_2$ (2 mL) was slowly added to a solution of Rh$_2$(OAc)$_4$ (3 mg, 0.007 mmol) in CH$_2$Cl$_2$ (3 mL), and the mixture was refluxed overnight under a nitrogen atmosphere. The solution was poured into a saturated solution of NaHCO$_3$ and the mixture was extracted with CH$_2$Cl$_2$ three times. The organic layers were combined and dried with MgSO$_4$, and the solution was concentrated under vacuum. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (18.8 mg, 88% yield) as a white solid: $R_f = 0.31$ (CH$_2$Cl$_2$), $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.17 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.21-7.17 (m, 1H), 7.14-7.09 (m, 1H), 7.08 (d, $J = 2.4$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 2.47-2.39 (m, 2H), 2.10-2.01 (m, 2H), 1.70-1.58 (m, 2H), 1.44-1.33 (m, 2H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.3$ Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.0, 141.2, 135.8, 127.6, 123.4, 123.2, 122.1, 120.1, 110.8, 113.2, 111.1, 60.4, 35.2, 35.1, 22.3, 21.8, 14.46, 14.37, 14.3; HRMS (RSI-TOF) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{26}$NO$_2$ 451.2055; Found 451.2062.
5.4.5 Vinyl diazonium reaction with enoxy silane

\[
\text{(1-phenylethenyl)oxy(tripropan-2-yl)silane (50):} \quad \text{Pyridine (0.65 mL, 8.0 mmol, 1.6 eq.) and trisopropylsilyl trifluoromethanesulfonate (2.0 mL, 7.5 mmol, 1.5 eq.) were added sequentially to a 0 °C solution of acetophenone (0.40 mL, 5.0 mmol, 1.0 eq.) in CH}_2\text{Cl}_2 (20 mL). The mixture was allowed to stand overnight during which time it warmed room temperature in the cooling bath. The mixture was poured into saturated aqueous NaHCO}_3 and the mixture was extracted with CH}_2\text{Cl}_2 three times. The organic layers were combined, dried with MgSO}_4, and concentrated under vacuum. The residue was purified by silica gel flash column chromatography (100% hexanes) to give the desired product (731 mg, 53% yield) as a clear, colorless oil. Spectral data matched those reported in the literature.}^{227}
\]

**Ethyl diazo(1-(2-oxo-2-phenylethyl)cyclohexyl)acetate (4.89)**

Prepared by subjecting diazo ester 4.5 (66.5 mg, 0.31 mmol) and enoxy silane 4.88 (173.0 mg, 0.62 mmol) to General Procedure 4.B. The yellow oily residue was subjected to silica gel flash column chromatography (100% CH}_2\text{Cl}_2) which gave the title compound (55.0 mg, 55% yield) as a yellow solid: \( R_f = 0.45 \) (CH}_2\text{Cl}_2), \(^1\text{H NMR (500 MHz, CDCl}_3): \delta 7.94-7.91 \) (m, 2H), 7.56-7.52 (m, 1H), 7.44 (dd, \( J = 7.9, 7.4 \) Hz, 2H), 4.10 (q, \( J = 7.1 \) Hz, 2H), 3.30 (s, 2H), 7.25-7.15 (m, 2H), 1.66-1.54 (m, 3H), 1.50-1.24 (m, 5H), 1.20 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\text{C NMR (125 MHz, CDCl}_3): \delta 100.5, 167.0, 138.0, 133.1, 128.6, 128.1, 60.2, 46.7, 36.2, 173
34.8, 25.9, 22.5, 14.5; IR (film): 2932, 2858, 2087, 1678, 1446, 1273, 1084. MS (ESI):
Calculated for [C$_{18}$H$_{22}$N$_2$O$_3$Na]$^+$: 337.1528. Found: 337.1523.

5.4.6 1,3-dipolar cycloaddition

1-ethyl 5,6-dimethyl 4-phenyl-7-oxaspiro[bicyclo[2.2.1]heptane-2,1’-cyclohexan]-5ene-1,5,6-tricarboxylate (4.91) A solution of α-diazo ester 4.89 (16.1 mg, 0.051 mmol) in CH$_2$Cl$_2$ (5 mL) was slowly added to a solution of Rh$_2$(OAc)$_4$ (1.1 mg, 0.002 mmol) and dimethyl acetylenedicarboxylate (15.0 mg, 0.102 mmol) in CH$_2$Cl$_2$ (5 mL) under an atmosphere of N$_2$. The mixture was stirring at room temperature for 4 hours at which point the solution was poured into saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$ three times. The organic layers were combined and dried with MgSO$_4$, then concentrated under vacuum. The brown oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound (20.6 mg, 94% yield) as a white oil: $R_f$ = 0.28 (CH$_2$Cl$_2$), ³H NMR (500 MHz, CDCl$_3$): $\delta$ 7.56-7.50 (m, 2H), 7.39-7.31 (m, 3H), 4.43-4.40 (m, 2H), 3.82 (s, 3H), 3.56 (s, 3H), 2.22 (d, $J$ = 11.2 Hz, 1H), 2.03 (d, $J$ = 11.2 Hz, 1H), 1.83-1.64 (m, 5H), 1.56-1.49 (m, 1H), 1.39-1.33 (m, 4H), 1.31-1.21(m, 2H)1.18-1.10 (m, 1H). ³C NMR (125 MHz, CDCl$_3$): $\delta$ 166.7, 163.5, 162.8, 145.0, 143.6, 136.5, 128.8, 128.2, 127.4, 93.7, 90.3, 61.8, 52.7, 52.2, 52.1, 40.6, 34.1, 33.0, 25.3, 24.5, 23.9, 14.4; HRMS (RSI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{24}$H$_{28}$O$_7$Na 451.1733; Found 451.1735.
5.4.7 C-O insertion

![Ethyl diazo(1-(2-hydroxy-2-phenylethyl)cyclohexyl)acetate](image)

To a flame-dried flask NaBH4 (8.7mg, 0.23mmol) was added with 5 ml MeOH and cooled to 0 °C. (48.6mg, 0.15mmol) diazo carbonyl 4.89 was dissolved in 5 ml MeOH and slowly added into solution. The mixture was stirring at 0 °C for 30 mins until reaction was completed, confirmed by TLC. The mixture was poured into water and extracted with DCM 3 times. Organic layer was collected, dried with MgSO4, and concentrated under vacuum. The yellow oil residue was subjected to silicon column chromatography (Hexane: ethyl acetate = 5:1), which gave desired product 55mg in 90% yield as a yellow oil. \( R_f = 0.39 \) (Hexane: ethyl acetate = 5:1). \(^1\)H NMR (500 MHz, CDCl3): \( \delta \) 7.34-7.29 (m, 4H), 7.27-7.22 (m, 1H), 4.79 (dt, \( J = 8.0, 4.3 \) Hz, 1H), 4.14 (q, \( J = 7.1 \) Hz, 2H), 2.16 (d, \( J = 3.4 \) Hz, 1H), 2.14-1.93 (m, 3H), 1.65-1.51 (m, 3H), 1.50-1.41 (m, 1H), 1.40-1.22 (m, 8H).

\(^{13}\)C NMR (125 MHz, CDCl3): \( \delta \) 167.4, 145.4, 128.6, 127.6, 125.8, 72.1, 60.4, 49.3, 36.6, 35.6, 35.3, 25.9, 22.7, 22.6, 14.6.

![Ethyl (1R, 3R)-3-phenyl-2-oxaspiro[4,5]decane-1-carboxylate](image)
Ethyl (1S, 3S)-3-phenyl-2-oxaspiro[4,5]decane-1-carboxylate 4.93’’,

Ethyl (1S, 3R)-3-phenyl-2-oxaspiro[4,5]decane-1-carboxylate 4.94’,

Ethyl (1R, 3S)-3-phenyl-2-oxaspiro[4,5]decane-1-carboxylate 4.94’’

A solution of α-diazo ketone 4.92 (20.3 mg, 0.064 mmol) in CH₂Cl₂ (4 mL) was slowly added to a solution of Rh₂(OAc)₄ (0.3 mg, 0.0007 mmol) in CH₂Cl₂ (6 mL), and the mixture was stirred at room temperature under a nitrogen atmosphere. The solution was poured into water and the mixture was extracted with CH₂Cl₂ three times. The organic layers were combined and dried with MgSO₄, and the solution was concentrated under vacuum. The brown oily residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the diastereomer mixtures (4.93’, 4.93’’) (10.0 mg, 54% yield) as a white oil and the diastereomer mixtures (4.94’, 4.94’’)(3.2mg, 17% yield). For 4.93’ and 4.93’’ ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.30(m, 4H), 7.27-7.22(m, 1H), 5.35(dd, J = 9.0, 6.9Hz, 1H), 4.36(s, 1H), 4.32-4.21(m, 2H), 2.55(dd, 12.6, 6.8Hz, 1H), 1.78-1.60(m, 5H), 1.57-1.51(m, 1H), 1.48-1.38(m, 1H), 1.33(t, J = 7.1Hz, 3H), 1.30-
1.16 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.8, 143.2, 128.5, 127.4, 125.6, 87.4, 80.7, 60.8, 48.2, 44.8, 36.9, 31.0, 26.0, 23.9, 23.3, 14.6. For 4.94' and 4.94" $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58 (d, $J = 7.2$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.28-7.24 (m, 1H), 5.08 (dd, $J = 10.6$, 5.9 Hz, 1H), 4.28-4.20 (m, 3H), 2.28 (dd, $J = 12.4$, 5.7 Hz, 1H), 1.86 (dd, $J = 12.5$, 10.8 Hz, 1H), 1.81-1.73 (m, 1H), 1.71-1.50 (m, 3H), 1.45-1.40 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 128.4, 127.6, 126.6, 81.3, 60.7, 48.35, 35.8, 33.3, 26.0, 23.6, 23.3, 14.4.

![ethyl 4-(1H-indole-3-yl)butanoate](image)

**ethyl 4-(1H-indole-3-yl)butanoate 4.69** 1.69 g, 8.21 mmol indole-3-butyric acid was dissolved in 55 ml ethanol. 0.04 ml sulfuric acid was added into solution. The solution was refluxed overnight. The mixture was cooled to room temperature. The mixture was poured into sodium bicarbonate solution and extracted with ethyl acetate. The organic layers were combined and dried with MgSO$_4$, and the solution was concentrated under vacuum. The solid residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the desired product 1.824 g in 100% yield. NMR matches the literature reported.$^{197}$

![4-(1H-indol-3-yl)butanal](image)

**4-(1H-indol-3-yl)butanal 4.70** 0.4493 g, 1.943 mmol 4.69 was dissolved in 20 ml toluene and cooled to -78ºC. Then 1.9 ml (1 M) DIBAL-H solution was added into solution dropwise. The mixture was stirred at 78ºC until reaction completion. The mixture was poured into NH$_4$Cl and extracted with diethyl ether. The organic layers
were combined and dried with MgSO₄, and the solution was concentrated under vacuum.

The solid residue was subjected to silica gel flash column chromatography (Hexane: ethyl acetate = 5:1) which gave the desired product 0.205g in 56% yield. NMR matches the literature reported.¹⁹⁷

![Structural diagram](image)

**ethyl 2-diazo-3-hydroxy-6-(1H-indol-3-yl)hexanoate 4.71** To a flamed-dried flask (0.205g, 1.09mmol) 4.70, (0.23ml, 1.64mmol) ethyl diazo acetate, (0.015ml, 0.1mmol) DBU were dissolved in 15 ml acetone nitrile. The mixture was stirred in rt overnight. Then the solution was concentrated under vacuum. The solid residue was subjected to silica gel flash column chromatography (100% CH₂Cl₂) which gave the desired product 0.106g in 37% yield. Rf = 0.22(DCM). ¹H NMR (500 MHz, CDCl₃): δ 8.08(s,1H), 7.62(d, J = 7.8Hz, 1H), 7.33(d, J = 8.1Hz, 1H), 7.24-7.19(m, 1H), 7.17-7.12(m, 1H), 6.92(d, J = 2.2Hz, 1H), 4.75-4.70(m, 1H), 4.25(q, J = 7.2 Hz, 2H), 3.12(s, 1H), 2.86-2.80(m, 2H), 1.96-1.76(m, 3H), 1.74-1.67(m, 1H), 1.30(t, J = 7.2Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 136.4, 127.4, 121.9, 121.5, 119.1, 118.9, 115.9, 111.2, 66.5, 61.1, 33.9, 26.1, 24.7, 14.5.
solution of (0.0475g, 0.16mmol) **4.71** (1 equiv) in 5ml CH$_2$Cl$_2$ was added dropwise to a stirred solution of 0.025M Sc(OTf)$_3$ (1 equiv) in CH$_2$Cl$_2$. The reaction mixture was stirred at -20°C for 10 min. The solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography to give 0.0348g desired product in 78% yield. **$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 8.38(s, 1H), 7.48(d, $J = 7.8$Hz, 1H), 7.30(d, $J = 8.1$Hz, 1H), 7.18-7.13(m, 1H), 7.11-7.07(m, 1H), 4.37-4.28(m, 2H), 4.07(t, $J = 6.1$Hz, 1H), 2.80-2.69(m, 2H), 2.27-2.19(m, 1H), 1.97-1.90(m, 2H), 1.90-1.82(m, 1H), 1.33(t, $J = 7.2$Hz, 3H). **$^{13}$C NMR (125 MHz, CDCl$_3$):** $\delta$ 168.5, 136.0, 132.9, 127.2, 122.1, 119.4, 118.4, 111.8, 111.0, 61.3, 28.4, 28.0, 21.8, 20.9, 14.7.
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NMR Appendix
\[
\text{H}_3\text{C} \quad \text{O} \quad \text{O} \\
\text{N} \quad \text{N} \quad \text{N}
\]

4.59

\[\text{f (ppm)}\]

0.92
0.95
0.99
1.00
2.02
3.21
Nuclear Overhauser Enhancements data of 3-diazo-1-ethoxy-4-propyl-4-(1H-pyrrol-2-yl)heptan-2-one
Nuclear Overhauser Enhancements data of 3-diazo-1-ethoxy-4-propyl-4-(1H-pyrrol-2-yl)heptan-2-one
Nuclear Overhauser Enhancements data of 3-diazo-1-ethoxy-4-propyl-4-(1H-pyrrol-2-yl)heptan-2-one

3.78
Nuclear Overhauser Enhancements data of 3-diazo-1-ethoxy-4-propyl-4-(1H-pyrrol-2-yl)heptan-2-one