AN ABSTRACT OF THE THESIS OF

Yi Lu for the degree of Doctor of Philosophy in Chemistry presented on August 6, 2018.

Title: Strategies for the Synthesis of Nitrogeous Compounds: Aminal Radical Reactions and Pyridinium Oxide Cycloadditions

Abstract approved:

______________________________________________________

Christopher M. Beaudry

Pharmaceuticals, molecular catalysts, and secondary metabolites often contain nitrogen. The problems faced synthesizing compounds which contain nitrogen was because of the Lewis base reactivity of nitrogen lone pairs, and the acidic protons of some nitrogenous functional groups. We developed two methods for the synthesis of nitrogeous compounds. Additionally, we successfully constructed the heterotetracyclic core of himgaline.

The aminal radicals were generated by reduction of the corresponding amidine or amidinium ion. The intermediate radicals participate in C−C bond-forming reactions to produce fully substituted aminal stereocenters. No toxic additives or reagents are required.

The regioselectivity and diastereoselectivity was investigated in pyridinium oxide cycloadditions using complex substrates. The reaction is reversible under the reaction conditions. High levels of diastereoselectivity and regioselectivity are observed, which can be attributed to minimization of syn-pentane interactions in the products.

The stereo- and region-selective intramolecular pyridinium oxide cycloaddition successfully forms two bonds and builds four stereocenters in a single step. These key cycloaddition reactions are particularly suitable to the challenge of preparing multiple rings with control of stereochemistry. It has been shown that the new methodology replacing acid-base strategy would enhance the efficiency of alkaloid synthesis.
Strategies for the Synthesis of Nitrogeous Compounds: Aminal Radical Reaction and Pyridinium Oxide Cycloadditions

by
Yi Lu

A THESIS

submitted to

Oregon State University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Presented August 6, 2018
Commencement June 2019
Doctor of Philosophy thesis of Yi Lu presented on August 6, 2018

APPROVED:

Major Professor, representing Chemistry

Head of the Department of Chemistry

Dean of the Graduate School

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

Yi Lu, Author
ACKNOWLEDGEMENTS

I would like to express my thanks to my wife, Wanyu, for all of her support to complete my degree. I would also like to thank my family for the encouragement during my time in Oregon. I would like to thank my mentor, Cem Celik, for all of the help from first to the end. I would like to thank David Schiedler for teaching me in lab and helping with the chapter 1 and 2. I would also like to thank the members of the Beaudry research group, both past and present for their support. I am appreciated for all my friends here. In the end, I would like to thank my advisor, Professor Chris Beaudry, for his guidance over the last six years. Professor Beaudry led me to the field of chemistry, taught me to think critically about chemistry.
CONTRIBUTION OF AUTHORS

David A. Schiedler assisted with the data collection for chapter 2 and the writing of chapters 2.
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Strategies for the Synthesis of Nitrogeous Compounds: Aminal Radical Reactions and Pyridinium Oxide Cycloadditions.

by

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August 6, 2018

LPSC 2pm
1. Introduction

Nitrogenous molecules are abundant in nature. Pharmaceuticals, molecular catalysts, and secondary metabolites often contain nitrogen. Some examples of nitrogen containing natural products are morphine, saxitoxin, vallesine, noscapine, daphmanidin E, and strychnine (Figure 1.1).

It is difficult to synthesize nitrogen rich compounds. The problems faced synthesizing compounds which contain nitrogen are the Lewis base reactivity of nitrogen lone pairs and the acidic protons of some nitrogenous functional groups. Solubility and reactivity can sometimes become the major difficulty in synthesizing nitrogen-containing compounds. Overcoming these challenges with the development and application of new methods for synthesis of nitrogen rich compounds is necessary and relevant to the improvement of human health. There are different ways to work with nitrogen in organic molecules. The most common way protection. Examples in which nitrogen protection have been used are dinitrobenzene sulfonyl (DNs) of nitrogen in morphine synthesis of Fukuyama (Scheme 1.1, entry 1), Woodward’s nitrogen protection with toluenesulfonyl (Ts) in the strychnine synthesis (Scheme 1.1, entry 2), or tert-butyloxycarbonyl (Boc) protection of nitrogen in the vallesine synthesis by Movasagghi (Scheme 1.1, entry 3).
Scheme 1.1 Alkaloid synthesis utilizing the protecting group strategies.

Another similar idea to protection is to incorporate unreactive nitrogenous groups and convert them to the final desired functional group later. These methods work well but take additional steps and cause lower yields. One example is daphmanidin E synthesis by Weiss and Carreira (Scheme 1.2), where a nitro group was used to install the nitrogen.\(^7\)

Scheme 1.2 Alkaloid synthesis utilizing the strategy of unreactive nitrogenous groups.
Another common approach is to introduce the nitrogen in at a late stage of synthesis. This strategy usually limits flexibility of the synthetic route and might also increase step count. An example is sieboldine A synthesis by Mukai and co-workers. In this synthesis, it took 19 steps to reach the intermediate which had the nitrogen atom, and only took 5 steps to finish this synthesis (Scheme 1.3).\(^8\)

![Scheme 1.3 Alkaloid synthesis utilizing the strategy of late stage nitrogen installation.](image)

Alkaloids are difficult to synthesize due to the mentioned properties of nitrogen atom(s) found in the molecule. Therefore chemists have pursued different strategies to overcome this challenge. The earliest and most followed strategy is based on Lewis acid-base reactions. Recently developed and frequently used strategies are radical- and pericyclic reactions, which have proven to reduce the number of Lewis acid-base manipulations and step count because it forms C-C bonds directly. This outcome requests the need for the development of new methodologies to decrease the step count and improve the yield further. The relevant support is provided by the study of strychnine done by famous synthetic chemists.

The application and importance of radical and pericyclic reactions in the alkaloid syntheses is elaborated in the strychnine synthesis. The first racemic synthesis of strychnine was published by Woodward et al in 1954.\(^9\) The retrosynthetic analysis is shown in Scheme 1.4. Strychnine has hexacyclic ring system with two nitrogen atoms and six stereocenters. At that time it was thought that it is extremely difficult to synthesize an alkaloid such as strychnine’s structural complexity. By the standards of the time, the first synthesis is impressive, with a longest linear step count of 28 and an overall yield of 0.0002 %. To overcome the difficulty of alkaloid synthesis, Woodward has used Lewis acid-base type reactions in the strychnine synthesis. The
rings needed to be fused consecutively in Woodward’s synthesis, because there were no reactions involved that form multiple C-C bonds in the single step. It is noticeable that Woodward did not use any reactions belonging to the radical or pericyclic reaction type which could have probably decreased the step count and led also to a higher yield. According to their analysis, (±)-strychnine could be obtained from compound 1 via alkylation and allylic rearrangement. The hexacyclic ring system in compound 1 could be yielded from compound 2 by oxidative cyclization which closes ring E and the Dieckmann condensation which forms ring D. The spiro tetracyclic compound 2 should be formed from indole 3, by which ring F would form by a oxidative veratryl cleavage and the spiro cycle C should be obtained via a Pictet-Spengler cyclization.

Scheme 1.4 Woodward’s retrosynthetic analysis of strychnine.

The Overman group reported their enantioselective synthesis of strychnine in 1993. The retrosynthetic analysis of Overman’s strychnine synthesis is outlined in Scheme 1.5. The strategy that Overman used to overcome the difficulty of alkaloid synthesis was to set the radical and pericyclic reactions as their key step and to avoid Lewis acid-base reactions. For this purpose, Overman made use of aza-cope rearrangement / Mannich cyclization reactions as their key step. The use the radical and pericyclic reactions in their synthesis resulted in decrease of the step count and increased yield. Based on Overman’s retrosynthetic analysis, the hexacyclic Wieland-Gumlich aldehyde should be obtained from the tricyclic compound 4, installing rings B and G by indole synthesis and carbonylation respectively. Tricyclic compound 4 would be yielded from bicyclic compound 5 through a sequential aza-cope rearrangement and
Mannich cyclization accordingly forming ring C and D. Compound 5 would be obtained from cyclopentene 6 via an epoxide opening reaction which could form ring E.

Scheme 1.5 Overman’s retrosynthetic analysis of strychnine.

In 1994, Rawal et al published their racemic synthesis of strychnine. Their retrosynthetic analysis of strychnine is depicted in Scheme 1.6. Rawal’s strategy to overcome the challenge linked with alkaloid synthesis was also to employ the radical and pericyclic reactions as a key step in order to avoid Lewis acid-base reactions. The further improvement in yield and decrease in the overall step count in Rawal and coworkers synthesis was due to their Diels-Alder key step, belonging to the category of pericyclic reactions. More and more well-known chemists are using radical and pericyclic reaction in their strategies for the syntheses of alkaloids, to avoid the Lewis acid-base reaction disadvantages. Considering Rawal’s retrosynthetic analysis, (±)-isostrychnine would be yielded from pentacyclic compound 7 by a Heck reaction which installs ring E. The pentacyclic compound 7 should be obtained from diene 8 via Diels-Alder reaction that installs ring B and D. Pyrrolidine 8 could be obtained from construction of ring C via ring expansion of cyclopropane 9.
Kuehne’s group reported their strychnine synthesis in 1998. They also avoided Lewis acid base reactions and have used in their key step Mannich / Cope / Mannich cyclization to improve yield and step count. According to Kuehne’s analysis, Wieland-Gumlich aldehyde would be generated from tetracyclic compound 10 through a nucleophilic cyclization to close ring E and a Wittig reaction to form ring G. Compound 10 could be yielded from compound 11. This tetracyclic compound 11 should be obtained from iminium ion 12 by Mannich / Cope / Mannich cyclization reactions thereby forming ring C and D.

In 2000, Vollhardt and coworkers published their strychnine synthesis (Scheme 1.8). The group used the radical and pericyclic reaction strategy as a key step. Their key step involved a Co-mediated cycloaddition reaction, which is a pericyclic reaction. Vollhardt’s retrosynthesis indicates (±)-isostrychnine could be obtained from compound 13 via a Heck reaction with the formation of ring E. The pentacyclic
compound 13 should be obtained through an N-alkylation conjugate addition from tetracyclic compound 14, which in turn would be yielded from indole 15 by a Co-mediated cycloaddition reaction whereby rings D and F are installed.

Scheme 1.8 Vollhardt’s retrosynthetic analysis of strychnine.

Martin and coworkers synthesized strychnine in 2001. Their retrosynthesis is shown in Scheme 1.9. The same trend in favoring radical and pericyclic reactions over Lewis acid-base reactions is also recognizable in their work. Martin group’s choice of pericyclic reaction was the hetero Diels-Alder reaction. Considering Martin’s retrosynthetic analysis, the Wieland-Gumlich aldehyde could be obtained from pentacyclic compound 16 via functional group manipulations, which could be yielded from biomimetic rearrangement that results in the C and D ring formation from tetracyclic compound 17. Compound 17 should result diene 18 via a hetero Diels-Alder reaction which installs ring E.

Scheme 1.9 Martin’s retrosynthetic analysis of strychnine.

Fukuyama et al. published their strychnine synthesis in 2004. The retrosynthetic analysis is outlined in Scheme 1.10. Their analysis indicates that the Wieland-
Gumlich aldehyde could be obtained from iminium ion 19 via a Mannich reaction that forms ring C and D. Compound 19 should yield from aldehyde 20 through an iminium ion formation which closes ring E. Amine 20 would result from alcohol 21 by a Mitsunobu reaction that installs the amine. The interesting feature about Fukuyama’s synthesis is that no radical or pericyclic reaction was used.

Scheme 1.10 Fukuyama’s retrosynthetic analysis of strychnine.

In 2010 Reissig et al. reported their strychnine synthesis. Scheme 1.11 depicts their retrosynthetic analysis. Similarly, a radical reaction, SmI2 induced cyclization cascade reaction, was involved as a key step instead of a Lewis acid-base reaction. Reissig’s retrosynthetic analysis indicates that (±)-isostrychnine could be obtained from pentacyclic compound 22, which should be yielded from tetracyclic compound 23 by installation of ring C through a reductive amination reaction. The tetracyclic compound 23 would be obtained from indole 24 via SmI2 induced cyclization cascade which results in the formation of ring D and F.

Scheme 1.11 Reissig’s retrosynthetic analysis of strychnine.
Vanderwal’s strychnine synthesis was published in 2011, and Scheme 1.12 shows the retrosynthetic analysis. The group used an intramolecular Diels-Alder reaction to avoid the Lewis acid-base reaction to obtain a better yield and shorter route. In Vanderwal’s analysis, the Wieland-Gumlich aldehyde could be obtained from tetracyclic compound 25 via an intramolecular Diels-Alder reaction which installs rings C and D. Compound 25 should be yielded from Diels-Alder precursor 26, which should be formed from indole 27 and pyridinium 28 through a Zincke pyridine ring opening reaction.

Scheme 1.12 Vanderwal’s retrosynthetic analysis of strychnine.

MacMillan and coworkers published their strychnine synthesis in 2011. The retrosynthetic analysis is outlined in Scheme 1.13. The latest trend of favoring radical and pericyclic reactions over Lewis acid-base reactions is also the case in MacMillan’s synthesis. To shorten the route and increase the yield their choice was to employ the enantioselective organo-catalytic alkyne Diels-Alder reaction as their key step, which belongs to the pericyclic reactions. According to MacMillan’s retrosynthetic analysis, the Wieland-Gumlich aldehyde should be yielded from tetracyclic compound 29, which would be obtained from compound 30. Tetracyclic compound 30 could result diene 31 and alkyne 32 via an enantioselective organocatalytic alkyne Diels-Alder reaction, thereby forming ring C and D.
As elaborated on the strychnine example, the total synthesis has gradually been improved over the past 65 years. The first synthesis of strychnine was reported in 1954 with overall 28 steps and 0.0002 % yield. Whereas, the last outlined synthesis was made in 2011 with overall 12 steps and 6 % yield. The strategy to overcome the challenge linked with alkaloid synthesis was also in to use more radical and pericyclic reactions which decreased the step count and increased the yield. Essentially, for the further improvement in yield and decrease in the overall steps, more and more chemists are using radical and pericyclic reaction in their strategies for the syntheses of alkaloids with the aim to avoid the disadvantages of Lewis acid-base reaction. The first strychnine syntheses used more strategies based on Lewis acid-base reactions, whereas the recent strychnine syntheses have avoided this strategy by using more radical or pericyclic reactions.

Figure 1.2 shows the racemic strychnine synthesis made by different research groups. The diagram shows the synthesis step count over the course of time, the red numbers show the amount of newly formed C-C sigma bonds resulted from a single radical or pericyclic reaction step. The figure shows clearly how the step count decreases as the amount of C-C bonds formed by radical or pericyclic reaction increases.
Figure 1.2 Racemic strychnine syntheses over the course of time.

Figure 1.3 shows the enantioselective strychnine synthesis published by different research groups. The racemic and enantioselective syntheses were analyzed separately to obtain a better comparison. The diagram shows the synthesis step count over the course of time, the red numbers show the amount of newly formed C-C sigma bonds resulted from a single radical or pericyclic reaction step. The figure gives the same conclusion as the racemic strychnine synthesis and confirms that the step count decreases as the amount of C-C bonds formed by radical or pericyclic reaction increases.
In conclusion, alkaloids have been known for many years as difficult targets. The difficulty in synthesizing them is mainly due to the properties of the nitrogen atom(s) in the compound. Therefore, the common strategies that chemists have pursued to overcome this challenge was to use Lewis acid-base strategy. This approach to the alkaloid syntheses either involved the protection of nitrogen atoms, or the employment of unreactive nitrogen groups, or the installation of the nitrogen atom in the late stage of the total synthesis. This approach resulted in high step counts and low yields. Better solutions were provided by the use of radical or pericyclic reactions instead of Lewis acid-base reactions, which led to shorter synthesis and higher yields.

In addition, the reduction in step count and improvement in yield is due to the development of new methodologies and reagents by organic chemists such as the radical and pericyclic reactions. These new C-C bond formation reactions, based on radical and pericyclic reactions, made the cascade possible and enabled the installation of two rings in one step. Besides the traditional ways to overcome alkaloid syntheses the new methodologies have enriched the toolbox with more alternatives. Therefore, it is worthwhile to discover new methodologies or expand on existing strategies that can overcome the limitations and difficulties in the synthesis of alkaloids.
2. Reductive Synthesis of Aminal Radicals for Carbon–Carbon Bond Formation

2.1. Radicals in the Synthesis of Nitrogen Containing Molecules

In order to mask the Lewis acid-base reactivity of nitrogen while progressing towards the target compound, synthetic chemists often resort to the use of protecting groups. One efficient way to avoid this is single-electron processes, such as radical reactions, which can be used to prevent the interference of the acid–base reactivity of nitrogen. Radical reactions are generally tolerant of N–H bonds, O–H bonds, and heteroatom lone pairs; they are ideally suited to the synthesis of heteroatom-rich substrates. The method of incorporating carbon-centered radicals containing heteroatoms to C–C multiple bonds was introduced more than 50 years ago. Hart and coworkers reported that N,S acetal was converted to the α-amido radical intermediate, which subsequently formed the bicycle through a 5-exodig radical reaction yielding the formal synthesis of (−)-dehydrohastanecine (Scheme 2.1). The effect of the lone pair on the adjacent nitrogen is to increase the stability of α-aminoalkyl and α-amido radicals and forming C–C bonds with the unsaturated carbon atoms. The advantage of this approach is the key disconnection of bonds that would be challenging to be formed with classic cationic or anionic reaction conditions and it has already been demonstrated in the synthesis of heterocycles and alkaloid natural products.

Scheme 2.1 C–C bond formation of α-aminoalkyl radical.

It is known that carbon-centered radicals having two adjacent heteroatoms form C–C bond after reacting with C–C multiple bonds. The acetal radical was obtained from
acetal 33 by a homolytic C-H bond cleavage with photosensitized benzophenone. Compound 35 forms after the propagation step in which the radical 34 adds across the unsaturated enone system (Scheme 2.2, entry 1). The reaction between 2-bromobenzoyl enamides 36 and AIBN and Bu3SnH is thought to form via N,S- and N,O- acetal radical intermediates 37 while the C–C bond forms to yield the ring fused compound 38 (Scheme 2.2, entry 2).12

![Scheme 2.2 C-C bond formation of acetal radical.](image)

Since the reactivity of acetal and α-aminoalkyl radicals are well known, the observation of a new reaction was thought to be formed in which the aminal radical adds to alkenes yielding a C-C bond. Based on findings of computational chemistry the aminal radicals are 1–2 kcal/mol lower in energy compared to the analogous α-aminoalkyl radicals.13 This result suggested a promising selectivity in favor of aminal radical formation over carbon atoms containing a single nitrogen atom.

Carbon-centered radical reactions of nitrogen-rich functional groups, such as the aminal, would enjoy useful application in synthesis. Aminals can be conveniently prepared from condensation reactions, and also can functionalize several nitrogen atoms in the same step of carbon-centered radical reactions. Thus, the aminal functional group was identified as a particularly attractive substrate for radical-based bond-forming reactions. It illustrates some biologically active pharmaceuticals
bearing aminal (Figure 2.1), that are in the focus of many synthetic organic chemists. Additionally, quinethazone and metolazone are some commercial pharmaceuticals that contain the aminal functionality.

Previously, our lab reported the formation of C–C bonds using aminal radical intermediates. The hydrogen atom abstraction of iodobenzyl-substituted aminals undergo radical translocation to generate aminal radical intermediates. The aminal radicals add to a radical acceptor, such as an electron poor alkene to give products with carbon–carbon bond formation (Scheme 2.3). It demonstrates a new methodology to construct an aminal group by forming a carbon–carbon bond allowing new strategies for synthesizing nitrogen-rich compounds.

Despite the effectiveness of the radical translocation method to obtain aminal radical intermediates, it requires foul smelling or toxic reagents, leading us to develop alternative methods. Ideally, the starting materials should be easy to be obtained and should not need a 2-iodobenzyl substituent. Due to the success of starting material in the radical translocation reaction product should be formed if aminal radical is obtained through an alternative radical acceptor (Scheme 2.4). It was expected that
the reaction of known\textsuperscript{16} amidine 43 by protonation and single electron reduction should yield intermediate 41.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme2.4.png}
\end{center}

Scheme 2.4 Alternative method to generate aminal radicals.

For many years, \(\alpha\)-amino radicals have been formed from iminium ions by single electron reduction with the aid of a proton source.\textsuperscript{17} Imminium ion 44 was converted by Martin to the fused bicyclic compound 46 via \(\alpha\)-amino radical 45 (Scheme 2.5).

This strategy had the potential to be widened for the formation of aminal radicals because it was an alternative way to obtain an aminal radical in a regioselective fashion without a poor atom economy in contrast to the C–X bond homolysis method.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme2.5.png}
\end{center}

Scheme 2.5 Generation of \(\alpha\)-amino radicals by single electron reduction of iminium ions

2.2. Result

Searching different conditions for this conversion, amidine 43 was produced with reductive condition in the presence of acrylonitrile (Table 2.1). The use of Zn metal yielded no reaction and LiDBB induced the decomposition (entries 1–4). We found that aminal radical 41 could be generated by protonation and single electron reduction
of 43 with samarium(II) iodide and camphor sulfonic acid (entry 5). Although the reaction worked in the absence of a proton source, yields were significantly lower and some starting material remained unreacted (entry 6). Ammonium chloride was the best choice as proton source because it is mild, cheap, and provided high yields (entry 7). In comparison, the amidine reduction strategy had several advantages over the translocation strategy; it formed quickly at room temperature, no toxic or foul smelling additives were necessary, easy to handle, and higher yields were obtained.

![Chemical structure](image)

Table 2.1 Development of the amidine reduction reaction.

<table>
<thead>
<tr>
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<th>conditions</th>
<th>result</th>
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<tr>
<td>1</td>
<td>Zn (2.2 equiv), HOAc (0.1 M), rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>Zn (2.2 equiv), HOAc (0.1 M), 118 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>LiDBB (2.5 equiv), CSA (1.1 equiv), THF (0.3 M), rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>LiDBB (2.5 equiv), THF (0.3M), rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>SmI₂ (2.5 equiv), CSA (1.1 equiv), THF (0.3 M), rt</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>SmI₂ (2.5 equiv), THF (0.3 M), rt</td>
<td>57%</td>
</tr>
<tr>
<td>7</td>
<td>SmI₂ (2.5 equiv), NiI₂Cl (1.1 equiv), THF (0.3 M), rt</td>
<td>99%</td>
</tr>
</tbody>
</table>

After determining the optimal reaction conditions, different substrate combinations were investigated. Quinazolinones which have the N-acyl amidine incorporated in the structure, show interesting biological activities, and can be obtained from the corresponding aminobenzamide derivatives. The reaction between amidine, methyl and tertbutyl acrylates yielded 47b and 47c (Table 2.2). The quinazolinone containing a tethered alkene would still react with acrylonitrile 49a, tert-butyl acrylate 49b, and methyl acrylate 49c in a bimolecular radical fashion disfavoring the unimolecular 5-exo-trig radical cyclization that contained the tethered alkene.
Table 2.2 Scope of the amidine and amidinium reduction reaction.

The execution of the amidine reduction strategy does not require a benzyl substituent and substrates that contain N-alkyl \(54a,b\), N-aryl \(54a-c\), and unprotected nitrogen \(54a-c\) all participated in the reaction. However, for the translocation alternative, completely substituted aminals needed to be formed in high yield through a reductive alkylation of the relevant amidines \((51a-c, 52a-c)\). Interestingly, the amidine containing an even more sterically demanding tert-butyl moiety reacted also to form the desired aminal \((53)\). The reaction of dihydroquinazolinone-derived amidinium ion gave an excellent yield with methyl acrylate \(55a\), tert-butyl acrylate \(55b\), and acrylonitrile \(55c\), and this condition also reacted perfectly with amidinium ion to produce fully substituted aminal \(56\).
In summary, aminal radicals are obtained through the reduction of the relevant amidine and amidinium ions with the employment of a proton source. The C–C bonds are formed by the reaction of radical intermediates and radical acceptors in good yields, without using heavy metal hydrides or thiols. The reaction is versatile and can be used inter- and intramolecularly with high yields. Moreover, this methodology enables fully substituted aminal stereocenters formation in good yields.
3. Cycloadditions of Pyridinium Oxide

3.1. Intramolecular Pyridinium Oxide Cycloadditions: Regioselectivity, and Diastereoselectivity.

Polycyclic nitrogenous architectures are widespread in biologically active natural products. For example, the tropane alkaloids, exemplified by cocaine, are characterized by a 8-aza-bicyclo[3.2.1]octane structure.\textsuperscript{57} Amaryllidaceae alkaloids such as siculine display a topologically distinct 1-azabicyclo[3.2.1]octane (58) core.\textsuperscript{20} Homopumiliotoxin 223G is a quinolizidine (59) alkaloid isolated from poison dart frogs.\textsuperscript{21} Finally, the intriguing structure of the galulimbima alkaloid,\textsuperscript{22} himgaline, displays all of these component aza-bicyclic fragments in a 2-azatricyclo[4.4.1.0\textsuperscript{2,7}]undecane architecture (60) (Figure 3.1.1).

![Figure 3.1.1 Polycyclic architecture featuring bridgehead nitrogen atoms.](image)

Such bridged polycyclic alkaloids represent enduring challenges for synthetic chemists. A notable difficulty associated with the synthesis of the natural products shown are the stereogenic carbons bearing nitrogen; the himgaline structure displays stereogenic carbon atoms at all three adjacent positions. Many synthetic strategies have appeared to access nitrogenous bicycles, and particularly successful approaches create multiple rings in a single transformation with control of stereochemical configuration of the substituents.
Cycloaddition reactions are particularly well-suited to the challenge of preparing multiple rings with control of stereochemistry, and we wondered if such polycyclic nitrogenous frameworks could be prepared using a suitable cycloaddition. We decided to focus on the tricyclic motif found in himgaline, complete with the equatorial methyl substituent (60). Any method capable of preparing this tricyclic architecture could, at least in principle, be used to construct any of the component bicyclic structures (57–59).

We envisioned tricyclic molecules such as 61 arising from a molecule such as enone 62, which contains functional handles suitable for the construction of additional C–C bonds. Consideration of the topology of 62 suggested that an intramolecular dipolar cycloaddition of a pyridinium oxide with a tethered alkene dipolarophile (63) would give the required molecular connectivity. Moreover, it appeared that the diastereoselectivity of the cycloaddition may be controlled by a favored orientation of the molecular tether, which positions the methyl substituent in an equatorial position. The starting material for this cycloaddition would be the relatively simple pyridinium oxide 64 (Scheme 3.1.1). One question was the regiochemistry of the cycloaddition; specifically, regioisomeric tricycle 65 would arise from cycloaddition of conformer 66, and it was unclear to us which pathway would be favored.

![Scheme 3.1.1 Retrosynthetic analysis of azatricyclo[4.4.1.0^2,7]undecanes.](image-url)
Pyridinium oxide cycloadditions are well known in the literature. Since the first report by Katrizky in 1988, there have been dozens of intermolecular examples. Intermolecular pyridinium oxide cycloadditions require electron-poor alkene dipolarophiles (e.g. acrylonitrile, maleamide) for successful reactivity. Conversely, intramolecular pyridinium oxide cycloadditions are much fewer in number (Scheme 3.2). Simple $N$-pentenyl pyridinium oxide 67 and tolyl-substituted substrate 68 react to form 69 and 70, respectively (Scheme 3.2, entry 1). Substrate 71 featured a substituted tether between the dipole and dipolarophile (Scheme 3.2, entry 2). Pyridinium oxide 72 featured a tethered dipolarophile linked to the pyridinium ring, rather than the nitrogen atom (Scheme 3.1.2, entry 3). It is notable that these intramolecular examples do not require a polarized dipolarophile, and simple terminal alkenes participate in the reaction. Gin published an intramolecular cycloaddition where stereochemistry in the tether lead to good diasterofacial discrimination of the dipolarophile (Scheme 3.2, entry 4). However, there has been no systematic study of substitution in such systems.

Scheme 3.1.2 Intramolecular pyridinium oxide cycloaddition.
We began our investigations by preparing cycloaddition substrate 74. There are multiple synthetic strategies for preparing pyridinium oxides; however, we found the most convenient method was the substitution of alkyl mesylates with 3-hydroxypyridines. The pyridinium oxides was subjected under the published cycloaddition reaction conditions with no reaction in refluxing toluene, while heating to 210ºC in different solvents resulted in either no reaction or decomposition (Table 3.1.1, entry 1-3). Under the catalytic acid and base condition, there was no consumption of the starting material (Table 3.1.1, entry 4, 5). With the strong base, substrate was decomposed, and no desired product was obtained in the reaction with Lewis acid. (Table 3.1.1, entry 6,7). Under the condition which was heat the IRX-78 (OH form), we were able to yield cycloaddition product 75 in 60% yield with dr=4:1 (Table 3.1.1, entry 8). The major product of the reaction was the anticipated product, which positions the tether methyl substituent in an equatorial orientation. The structure of the major and minor diastereomers was confirmed by 2D–NMR methods (Scheme 3.1.3). This result is consistent with our prediction, in which substrate control arises from the methyl substituent in an equatorial position. After screening basic reaction conditions, we found that K$_2$CO$_3$ is a suitable reagent in this cycloaddition reaction to give the 83% yield dr=5:1, whereby the decomposition may happen because of the basicity of Cs$_2$CO$_3$ (Table 3.1.1, entry 9-13). Sequestration of the potassium counterion had no effect on the reaction yield (Table 3.1.1, entry 14). The reaction was largely insensitive to the carbonate counter-cation, and both Ag$_2$CO$_3$ (93% yield dr=6:1) and K$_2$CO$_3$ were effective in promoting the reaction (Table 3.1.1, entry 16,17). We found that polar solvents such as acetonitrile gave the best reaction rates, limited the formation of unwanted by products, and gave good selectivities for the major product. The best yields were obtained in butyronitrile at 130 ºC, and we settled on these as our standard conditions.
Table 3.1.1 Development of the intramolecular pyridinium oxide cycloaddition reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Toluene</td>
<td>210°C</td>
<td>no Reaction</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>ACN</td>
<td>210°C</td>
<td>no Reaction</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>DMSO</td>
<td>150°C</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>cat. HCl</td>
<td>ACN</td>
<td>160°C</td>
<td>no Reaction</td>
</tr>
<tr>
<td>5</td>
<td>cat. NaOH</td>
<td>ACN</td>
<td>160°C</td>
<td>no Reaction</td>
</tr>
<tr>
<td>6</td>
<td>NaOH</td>
<td>ACN</td>
<td>130-150°C</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>TiCl₄</td>
<td>ACN</td>
<td>130-150°C</td>
<td>no Reaction</td>
</tr>
<tr>
<td>8</td>
<td>IRX-78 OH form</td>
<td>ACN</td>
<td>130°C</td>
<td>60%, dr=4:1</td>
</tr>
<tr>
<td>9</td>
<td>TBAI</td>
<td>ACN</td>
<td>130°C</td>
<td>57%, dr=4:1</td>
</tr>
<tr>
<td>10</td>
<td>NEt₃</td>
<td>ACN</td>
<td>130°C</td>
<td>38%, dr=4:1</td>
</tr>
<tr>
<td>11</td>
<td>K₂CO₃</td>
<td>ACN</td>
<td>130°C</td>
<td>83%, dr=5:1</td>
</tr>
<tr>
<td>12</td>
<td>Cs₂CO₃</td>
<td>ACN</td>
<td>130°C</td>
<td>decomposition</td>
</tr>
<tr>
<td>13</td>
<td>K₂HPO₄</td>
<td>ACN</td>
<td>130°C</td>
<td>82%, dr=5:1</td>
</tr>
<tr>
<td>14</td>
<td>K₂CO₃, 18-C-6</td>
<td>ACN</td>
<td>130°C</td>
<td>75%, dr=5:1</td>
</tr>
<tr>
<td>15</td>
<td>K₂CO₃, AgOAc</td>
<td>ACN</td>
<td>130°C</td>
<td>88%, dr=5:1</td>
</tr>
<tr>
<td>16</td>
<td>Ag₂CO₃</td>
<td>ACN</td>
<td>130°C</td>
<td>93%, dr=6:1</td>
</tr>
<tr>
<td>17</td>
<td>Ag₂CO₃</td>
<td>BuCN</td>
<td>130°C</td>
<td>87%, dr=7:1</td>
</tr>
</tbody>
</table>

Table 3.1.1 Development of the intramolecular pyridinium oxide cycloaddition reaction.

Scheme 3.1.3 Conformation of the cycloaddition product

We next evaluated additional substrates to investigate the ability of the intramolecular cycloaddition to create other complex bicyclic products. Substitution on the dipolarophile and the pyridinium oxide dipole was well tolerated (Table 3.1.2). Halogen substituents as well as alkyl substitution are tolerated on the pyridinium oxide. Substrate 77 features an additional carbocycle and leads to polycyclic product 78. Moving the methyl substituent on the tether was possible, and 76 reacted to give good yields of the major product resulting from positioning of the methyl equatorial in the product. Substrate 92 includes two methyl substituents on the tether and cycloaddition leads to product 93, where both methyl groups are equatorial. In this
case the product ratio was very high, and we could not detect (NMR, TLC) a minor isomer. Conversely, diastereomeric substrate 94 reacts and is required to position one methyl group axial. The reaction was successful; however, as expected, the product isomer ratio was low (~3:1). These results demonstrate that the substitution on the molecular tether can control the stereochemistry of the cycloaddition. Unfortunately, cyclization of trisubstituted alkene dipolarophiles such as 96 and 98 were unsuccessful.

Table 3.1.2 Scope of the intramolecular pyridinium oxide cycloaddition reaction.
In all cases the product ratio was usually quite high, favoring a single major product with equatorial methyl substituent. All major products were separated and the isomer was characterized by 2D–NMR methods. In the case of 86, we were able to obtain x-ray crystallographic confirmation of the major product structure 87 (Scheme 3.1.4). Additionally, we isolated the minor product of the reaction, and found that it was structure 100, which is the result of the regioisomeric bond formation and positioning of the methyl substituent axial. Presumably, this avoids syn-pentane interactions between the halogen and methyl groups. Other than these two cases, we did not characterize the minor component of the product mixture.

Our original hypothesis was that the stereochemical outcome of the reaction was a result of kinetic control. Specifically, we anticipated that the transition state leading to the major product would be favored if the tether methyl was equatorial. This follows from Katritsky’s analysis in his seminal publication on the intermolecular reaction. However, we began to suspect the reaction may actually be under thermodynamic control. We noticed that the product ratios were somewhat variable, and more forcing conditions (higher temperatures, longer reaction times) generally gave superior product ratios. Finally, when the reaction was stopped prior to full consumption of the starting material, the product ratios tended to be lower.
Scheme 3.1.5 Study of the minor product in the cycloaddition reaction.

To unequivocally test whether the reaction was reversible, we isolated major product \textbf{87} and minor product \textbf{100}, and resubjected it to the reaction conditions respectively. Resubjecting compound \textbf{87} and compound \textbf{100} to the reaction conditions respectively resulted in equilibration to the same product ratio. This clearly demonstrates that this reaction is under thermodynamic control (Scheme 3.1.6).

Scheme 3.1.6 Study of the mechanism in the cycloaddition I.

We also wondered if the reaction was stereospecific with respect to dipolarophile substituents. We prepared geometrical isomers \textbf{101} and \textbf{103} and subjected them to our standard conditions (Scheme 3.7). \textit{E}-Isomer \textbf{101} reacted to give product \textbf{102}, and \textit{Z}-alkene isomer \textbf{103} gave \textbf{104}; the reaction is stereospecific with respect to the alkene substituents. This also suggests that although the reaction is reversible, it is likely proceeds with concerted bond formation. We observed that the cycloaddition of \textit{E}-configured \textbf{101} was a smooth transformation that occurred under our normal conditions. However, \textit{Z}-isomer \textbf{103} required longer reaction times. Moreover, the reaction yield was low, likely a result of the production of numerous other by
products. Analysis of crystal structure data for the related product 87 and models of 104 suggested that the pyrrolidine methyl substituent projects directly into the concave bicyclic structure leading to severe steric interactions. Such interactions would destabilize the transition state leading to this molecule, which in turn, would explain why more forcing conditions are required. Furthermore, these steric interactions would also explain the reluctance of trisubstituted alkenes in the cycloaddition reaction.

Scheme 3.1.7 Study of the mechanism in the cycloaddition II.

In conclusion, polycyclic nitrogenous architectures can be constructed by the regioselectivity and diastereoselectivity intramolecular pyridinium oxide cycloaddition reaction. In our investigation, the selectivity arises from the substrate control induced by the orientation of the molecular tether. Furthermore, this cycloaddition is concerted and under thermodynamic control. This methodology will be useful for the alkaloid synthesis to build up multiple bonds and control stereocenters in one step.

3.2. Application of cycloaddition of pyridinium oxide in total synthesis: Progress towards the total synthesis of himgaline

The rainforest tree *Galbulimima belgraveana* is distributed in Northern Astralgonistia and Papua New Guinea. In Papua New Guinea, people used Galbulimima bark as a traditional medicine. The bark was chewed and then swallowed with salt to reduce pain and fever, or it was mixed with leaves of *Homalomena* sp. to induce visions and a dream-like state. Likewise, people used Galbulimima bark in combination with tobacco leaves for the treatment of hair lice. The Galbulimima bark was found as a rich source of several complex alkaloids since 1965. A total of 28 Galbulimima
alkaloids have been isolated, of which 22 have structures which have been elucidated.28 According to their structural properties, Galbulimima alkaloids are divided into four classes (Figure 3. 2.1): (1) Class I can be represented by himbacine, which has shown potent muscarinic antagonist activity.29 Based on series structure-activity relationships (SAR) studies, derivatives of himbacine have been developed.30 Vorapaxar (SCH530348) was approved by FDA in 2014 as a treatment of acute coronary syndrome. Another class I compound (SCH205831) has shown strong antispasmodic activity.31, 32 (2) Class II can be represented by himandrine (15 members). (3) Class III is represented by GB13 and himgaline. (4) Some miscellaneous compounds belong to Class IV, like GB17. Synthetic chemists are interested in class I began with the biological properties. Despite the potentially high activity of class I, the pharmacological properties of class II—IV remain unexplored. We speculate that the difficulty to screen bioactivity of class II—IV Galbulimima alkaloids was due to the trace amount of these compounds. Although the more structurally complex molecules of class II—IV have received attention from synthetic chemists, the number of steps leads to low yields of these alkaloids. Based on the high potential of class I, the pharmacological properties are possible to be explored if the efficient synthetic route of class II—IV can be found. Himagaline has one of the most complicated structures of the Galbulimima alkaloids. The challenges include a hexacyclic ring system, nine contiguous chiral centers, a tertiary amine attached to three chiral centers, and few functional groups; these features make it the most difficult synthetic target of the Galbulimima alkaloids.
Shah and co-workers reported the first total synthesis of (–)-himgaline in 2006 (Scheme 3.2.1).\textsuperscript{33} Himgaline could be converted from GB13 by conjugate addition and hydrogenation. Hexacyclic intermediate \textbf{105} would be converted to GB13 via a decarboxylative intramolecular conjugate addition reaction, followed by a retro conjugate reaction. The intermediate \textbf{105} could be built from the pentacyclic intermediate \textbf{106}, which was from the tricyclic carboxylic acid \textbf{107}. Pentacyclic intermediate \textbf{106} was built from a diastereoselective intramolecular Diels-Alder reaction of precursor \textbf{108}. This route took 33 steps to finish and the overall yield was 0.3%.
Evans and co-workers reported a total synthesis of ent-himgaline at about the same time (Scheme 3.2.2). As in Shah’s synthetic route, they converted ent-GB13 to ent-himgaline. The ent-GB13 was made from imine 109 by enamine aldol cyclization. Multiple steps were required to convert imine 108 from 110, which was made by enantiopure trans decalin 111. The Evans auxiliary controlled the enantioselective intramolecular Diels–Alder reaction to give trans decalin 111 from the triene 112.

Synthesizing the unnatural enantiomer, the Evans group was able to elucidate the absolute stereochemistry of himgaline, which was previously unknown. This route is still a beautiful synthesis, although it took them 32 steps to finish and the unnatural enantiomer of himgaline was obtained in 0.9% yield.
Ma and co-workers reported a racemic synthesis of himgaline in 2011 (Scheme 3.2.3). As before, himgaline could be produced from GB13. Several steps including the key step, SmI$_2$-mediated carbonyl–alkene reductive coupling reaction of ketone 113, gave the GB13 from the pentacyclic intermediate. The carbonyl–alkene reductive coupling precursor 113 was made from silyl enol ether 115 and α,β-unsaturated ketone 114. This route took 25 steps to finish and the overall yield was 1.2%. It is a good strategy to build the pentacyclic intermediate by using a reductive coupling reaction.

The advantage of our strategy to synthesize himgaline is the use of our intramolecular oxide cycloaddition which could reduce the synthesis steps significantly.

Our first generation retrosynthetic plan is described in Scheme 3.2.4. Himgaline could be broken down to triketone 116 by global deoxygenation and deprotection. The hexacyclic ring 116 could be constructed by the keto enone ester 117 by Michael addition and reductive Claisen condensation. The intramolecular pyridinium oxide cycloaddition, which is the key step of this synthetic route, is expected to selectively give heterotricyclic intermediate 117. Br$_2$-mediated oxidative rearrangement of furanylamine 119 would form the 1,3-dipole 118, which is the pyridinium oxide cycloaddition precursor. The linear product 119 could be made by Wittig reaction,
Mitsunobu reaction and the epoxide opening reaction. Minimization of A\textsuperscript{1,3} strain would give the selective addition and condensation of the trisubstituted alkene. The only stereogenic center in the linear product 119 would be installed by Mitsunobu reaction of sulfonamide. 2,5- disubstituted furan could be installed by epoxide opening reaction.

According to our plan, we prepared the starting material for the Wittig reaction as depicted in Scheme 3.2.5. We reduced the lactone 120 to the acetal 121 with DIBAL. Bromination of methyl 2-methoxyacetate 122 by NBS gave bromide 123, and followed by the Wittig reaction with acetal 121 yielded the Mitsunobu reaction precursor 124 as an alcohol. For the other Mitsunobu reaction partner, we took the Ns protected furanylamine in the acidic condition in presence of methyl vinyl ketone to functionalize the C5 position of the furanylamine to obtain ketone 125. With this two reaction partners in hand, we tried this reaction with several Mitsunobu reaction conditions, but we did not identify suitable conditions.
Because of this result, we investigated other ways to form the C-N bond such as reductive amination. (Scheme 3.2.6) We treated alcohol 124 with Dess-Martin periodinane (DMP) to gain the corresponding ketone and followed by reductive amination with furanylamine in the presence of sodium cyanoborohydride to generate the anime 126 as a pyridinium oxide formation precursor. We tried to set up pyridinium oxide formation using Gin’s method, but it only showed the brominated compound 127. We thought that the second equivalent of bromine in Gin’s conditions could cause this undesired reaction, so we changed the reaction condition to only 0.8 equivalents of bromine. However, we were not able to observe our desired product. We also suspected that the relative electron rich alkene in amine 126 causes the undesired bromination reaction, so we tried to start with the simpler alkene which is the vinyl ester. The reaction was set up with vinyl ester 129 under the same reaction condition as we installed the furanylamine, but we obtained the undesired conjugated addition product 130 back. At this point, we were facing the problem that the previous chemists did not deal with, so it was important to find other ways to form the pyridinium oxide in our system.
Aggarwal mixed benzyl bromide with 3-hydroxypyridine to yield the pyridinium oxide bromine salt \(36\) (Scheme 3.2.7, entry 1). Coming up with a similar idea, we treated the alcohol \(131\) under mesylation condition to yield mesylate \(132\). The mesylate was stirred with 3-hydroxypyridine in acetonitrile at 130\(^\circ\)C to obtain the corresponding pyridinium oxide \(133\) successfully in good yield (Scheme 4.7, entry 2).
After having the pyridinium oxide \(133\) in hand, we started to run the key step of himgaline synthesis. The cycloaddition precursor \(133\) was treated under the standard reaction condition, but the starting material decomposed (Scheme 3.2.8). This result pushed us to investigate this intermolecular pyridinium cycloaddition reaction more in depth. First, we simplified the alkene and checked what the result was. The desired product was formed if the vinyl ester \(137\) was the starting material. This result showed that the diastereoselectivity and the regioselectivity of this intramolecular pyridinium oxide cycloaddition matched our expectations.

\[
\begin{align*}
\text{MeO}_2\text{C} & \text{OMe} \\
133 & \\
\text{HOO}_2\text{C} & \text{OMe} \\
137 & \\
\end{align*}
\]

Scheme 3.2.8 Study of the cycloaddition of the trisubstituted alkene I.

In order to figure out the intramolecular pyridinium oxide cycloaddition, more cycloaddition reactions were attempted. The monosubstituted alkene reacted very well in this reaction in 93% yield (Scheme 3.2.9). The 1,2-disubstituted alkene under the cycloaddition reaction condition only gave 51% yield. The 1,1,2-trisubstituted alkene was decomposed slowly under reaction condition. These results indicated the hindrance of the alkene played a very important rule in the intramolecular pyridinium oxide cycloaddition, and also implied the 1,1,2-trisubstituted alkene might not work in this reaction.
We found that the trisubstituted alkene does not generate the intramolecular dipolar pyridinium oxide cycloaddition product. We also found that the substitution of the pyridinium ring at position 2 does not yield cycloaddition product (Scheme 3.2.10). Based on these results we proposed our third generation retrosynthesis of himgaline. This new route has the tricyclic core structure of himgaline already installed and the end game is the functionalization of both α ester α keto-amino methynes.

Our retrosynthetic analysis of himgaline is outlined in Scheme 3.2.11. Himgaline could be obtained from peroxide 138 through aldol reaction and directed C-H oxygenation. The peroxide 138 should be available from the α-amino carbonyl 139 via a radical coupling reaction. Tetracyclic compound 139 should arise from hydroxypyridine and mesylate 140.
After the core structure of himgaline was successfully installed by the key step, we tried to construct the heterotetracyclic core of himgaline through Claisen condensation. The first successful reaction was the methylcuprate conjugate addition to the enone followed by Claisen condensation to give the heterotetracyclic core of himgaline (Scheme 3.2.12).

In the future, the functionalization of himgaline heterotetracyclic core to yield the natural product precursor is proposed in Scheme 3.2.13. The Claisen condensation will yield tetracyclic compound 139, followed by the radical coupling with alkyne-enone to form dienone 141. The treatment of 141 with oxygen with Co catalyst would produce peroxide 138 and the treatment with Cu catalyst should result in hydroxyenone 142. After its protection and reduction, we should obtain the aldol precursor 143 which would lead under basic condition to the hexacyclic compound 144. After the Barton-McCombie deoxygenation and Wolff-Kishner reduction compound 145 would be obtained. The subsequent deprotection and oxidation should yield himgaline precursor 146, whereas the conversion of it to himgaline is a known reaction.
If this route succeeds as we expect, we would be able to reduce the step count to 16. This is because of the methodology we discovered that belongs to a pericyclic reaction. The stereo and regio-selective intramolecular pyridinium oxide cycloaddition successfully forms two bonds and builds four stereocenters in a single step. This key cycloaddition reactions are particularly suitable to the challenge of preparing multiple rings with control of stereochemistry. It has been shown that the new methodology avoiding acid-base strategy would enhance the efficiency of the alkaloid synthesis.
4. Conclusion

In conclusion, alkaloids have been known for many years as difficult targets. They are important for human health and are difficult to synthesize. The difficulty in synthesizing them is mainly due to the properties of the nitrogen atom(s) in the compound. Hence, the common strategies that chemists have pursued to overcome this challenge was to use Lewis acid-base strategy. This strategy to the alkaloid syntheses either involved the protection of nitrogen atoms, the employment of unreactive nitrogen groups, or the installation of the nitrogen atom in the late stage of the total synthesis. It resulted in high step counts and low yields. Better solutions were provided by the use of radical or pericyclic reactions instead of Lewis acid-base reactions, which led to shorter synthesis and higher yields. As supportive evidence, the investigation of development in the strychnine syntheses over the years clearly shows the conclusion that the step count decreases as the amount of C-C bonds formed by radical or pericyclic reaction increases. This application of this feature is noticeable in the latest alkaloid synthetic approaches made by well-known chemists, which have the following two common features. Using radical or pericyclic reactions (avoiding Lewis acid-base reactions) leads to shorter routes and higher yields. In addition, the reduction in step count and improvement in yield is due to the development of new methodologies and reagents by organic chemists such as the radical and pericyclic reactions. These new C-C bond formation reactions, based on radical and pericyclic reactions, made the cascade possible and enabled the installation of two rings in one step.

In order to further expand the synthetic strategies for the alkaloid syntheses, we also developed a methodology in which the reductive synthesis of aminal radicals were utilized for the Carbon-Carbon bond formation. In our methodology we showed that the C-C bond formation by aminal radicals were successfully obtained from amidine or amidinium. Besides the traditional ways to overcome alkaloid syntheses, the new
methodologies have enriched the toolbox with more alternatives. Hence, it is important to develop new methodologies based on radical and pericyclic reactions to expand the toolbox for synthetic organic chemists. It is worthwhile to discover new methodologies or expand on existing strategies that can overcome the limitations and difficulties in the synthesis of alkaloids even further.

Furthermore, we were also interested in another alkaloid known as himgaline. For its synthesis we developed a pyridinium oxide cycloaddition reaction. We investigated the intramolecular pyridinium oxide cycloaddition reactions on its regioselectivity and diastereoselectivity and were able to successfully showcase the cycloaddition of pyridinium oxide in the progress towards the total synthesis of himgaline core structure.

We have successfully installed the himgaline core, which is the aza-tetracyclic ring system, in four steps. Our key step of the himgaline synthesis is the intramolecular pyridinium oxide cycloaddition which controlled four new stereocenters and formed two bonds in a single step. In addition, polycyclic nitrogenous architectures can be constructed by the regioselectivity and diastereoselectivity intramolecular pyridinium oxide cycloaddition reaction. These intramolecular pyridinium oxide cycloadditions have proven to be a useful tool for the successful polycyclic architecture construction such as in azatricyclo[4.4.1.0^{2,7}]undecanes. In our investigation, the selectivity arises from the substrate control induced by the orientation of the molecular tether. Furthermore, this cycloaddition is concerted and under thermodynamic control. This methodology will be useful for the alkaloid synthesis to build up multiple bonds and control stereocenters in one step. The facial diastereoselectivity and the
regioselectivity of the cycloaddition were described, and the cycloaddition was shown to be under thermodynamic control and stereospecific.


General Experimental Details:

All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. Flash column chromatography was carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with potassium permanganate, iodine, or vanillin stains. Toluene (PhMe) and methylene chloride (DCM) were dried by passage through activated alumina columns. Tetrahydrofuran (THF) was distilled from sodium and benzophenone and stored under an atmosphere of Ar. Butyl nitrite (BuCN) was distilled and stored under an atmosphere of Ar. Methyl acrylate and tert-butyl acrylate were purified by washing with aqueous NaOH, drying over MgSO4, and calcium hydride. These reagents were then distilled under vacuum prior to use. Acrylonitrile was distilled under vacuum prior to use. Samarium iodide solutions were prepared with THF distilled from sodium and benzophenone and stored under an atmosphere of argon with vigorous stirring. The concentrations of the samarium iodide solutions were determined by iodometric titration. All other reagents and solvents were used without further purification from commercial sources.

Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra (1H NMR and 13C NMR) were recorded in deuterated chloroform (CDCl3) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe and Bruker 400 MHz DPX-400 spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, br = broad, m = multiplet. FCC: flash column chromatography. Melting points were determined with a Cole–Parmer instrument and are uncorrected.
3-(3-benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile (47b) (general reductive alkylation procedure). To a solution of 3-benzylquinazolin-4(3H)-one (0.0327 g, 0.1390 mmol), NH₄Cl (0.0089 g, 0.166 mmol), and acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.46 mL, 0.3 M) was added a THF solution of SmI₂ (3.7 mL, 0.35 mmol) via syringe pump over a period of 1 hour. At this time, TLC indicated the consumption of 3-benzylquinazolin-4(3H)-one. The reaction mixture was diluted with half-saturated aqueous Rochelle salt. This biphasic mixture was extracted with ethyl acetate. The combined extracts were dried over MgSO₄ and concentrated to give known adduct 47b (0.0403 g, 0.1383 mmol, 99%) as a colorless oil.

methyl 3-(3-benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (47c). Following the general reductive alkylation procedure, 3-benzylquinazolin-4(3H)-one (0.0332 g, 0.141 mmol), CSA (0.0358 g, 0.154 mmol), methyl acrylate (0.065 mL, 0.70 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.45 mL, 0.35 mmol) to give known adduct 66 (0.0261 g, 0.080 mmol, 57%) as a colorless oil after purification by FCC (4:1 hexanes:EtOAc).

3-(4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile (50a). Following the general reductive alkylation procedure, 3-phenylquinazolin-4(3H)-one (0.0320 g, 0.144 mmol), NH₄Cl (0.0086 g, 0.158 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI₂ (4.4 mL, 0.36 mmol) to give 50a (0.0375 g, 0.135 mmol, 94%) as a colorless oil.

Data for 50a: Rf 0.40 (1:1 hexanes:EtOAc); mp = 155–156 °C; IR (thin film) 2929, 2246, 1638, 1496, 1154, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (dd, J = 7.7, 1.2 Hz, 1 H), 7.41 (m, 5 H), 7.33 (t, J = 7.7 Hz, 1 H), 7.41 (m, 5 H), 7.29 (m, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 5.20 (dt, J = 9.0, 4.5 Hz, 1 H), 4.72 (d, J = 4.5 Hz, 1 H), 2.36 (m, 2 H), 2.10 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃, DEPT) δ C 161.8, 143.6, 140.1, 118.5, 118.2; CH 134.0, 128.9, 129.5, 129.2, 127.4, 127.0, 121.0, 117.0; CH2 28.5, 13.7; HRMS (EI) calcd for C₁₇H₁₅N₃O [M⁺]: 277.1215, found 277.1227.

Methyl 3-(4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (50c). Following the general reductive alkylation procedure, 3-phenylquinazolin-4(3H)-one (0.0312 g, 0.140 mmol), CSA (0.0358 g, 0.154 mmol), methyl acrylate (0.07 mL, 0.70 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI₂ (4.4 mL, 0.36 mmol) to give 50c (0.0195 g, 0.0629 mmol, 45%) as a colorless oil after purification by FCC (4:1 hexanes:EtOAc).

Data for 50c: Rf 0.44 (1:1 hexanes:EtOAc); mp = 79–80 °C; IR (thin film) 2951, 1732, 1634, 1496, 1169, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 7.8 Hz, 1 H), 7.42 (m, 4 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.29 (m, 1 H), 6.91 (t, J = 7.6 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.19 (dd, J = 8.5, 3.8 Hz, 1 H), 3.60 (s, 3 H), 2.35 (m, 2 H),
2.22 (m, 1 H), 2.13 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), DEPT) δ C 173.3, 162.3, 144.8, 140.4, 117.4; CH 133.7, 129.3, 129.1, 127.1, 127.0, 119.8, 115.7, 71.3; CH2 29.7, 28.5; CH3 51.8; HRMS (ESI) calcd for C18H18N2O3 [M+H]: 310.1318, found 310.1304.

**tert-butyl 3-(4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 50b.**

*Following the general reductive alkylation procedure,* 3-phenylquinazolin-4(3H)-one (0.0313 g, 0.141 mmol), NH\(_4\)Cl (0.0083 g, 0.155 mmol), tert-butyl acrylate (0.11 mL, 0.71 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI\(_2\) (4.3 mL, 0.35 mmol) to give 50b (0.0367 g, 0.104 mmol, 74%) as a colorless oil after purification by FCC (3:1 hexanes:EtOAc).

Data for 50b: Rf 0.65 (1:1 hexanes:EtOAc); IR (thin film) 2977, 1724, 1685, 1495, 1152, 753 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.99 (dd, \(J = 7.7, 1.6\) Hz, 1 H), 7.42 (m, 4 H), 7.34 (ddd, \(J = 8.1, 7.6, 1.6\) Hz, 1 H), 7.29 (tt, \(J = 6.6, 2.1\) Hz, 1 H), 6.91 (t, \(J = 7.8\) Hz, 1 H), 6.73 (d, \(J = 8.1\) Hz, 1 H), 5.18 (dd, \(J = 8.4, 4.2\) Hz, 1 H), 2.28 (m, 2 H), 2.14 (m, 2 H), 1.37 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), DEPT) δ C 172.1, 162.3, 145.0, 140.5, 117.2, 81.0; CH 133.7, 129.3, 129.1, 127.2, 127.0, 119.7, 115.5, 71.4; CH2 31.1, 28.5; CH3 28.0; HRMS (ESI) calcd for C21H24N2O3Na[M+Na]: 375.1685, found 375.1674.

**methyl 3-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 48b.**

*Following the general reductive alkylation procedure,* quinazolin-4(3H)-one (0.0218 g, 0.149 mmol), CSA (0.0381g, 0.164 mmol), methyl acrylate (0.08 mL, 0.89 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI\(_2\) (3.8 mL, 0.37 mmol) to give 48b (0.0195 g, 0.083 mmol, 56%) as a colorless oil.

Data for 48b: Rf 0.25 (1:4 hexanes:EtOAc); IR (thin film) 2951, 1725, 1653, 1438, 1382, 1155, 756 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.88 (dd, \(J = 7.7, 1.4\) Hz, 1 H), 7.30 (ddd, \(J = 8.1, 7.3, 1.5\) Hz, 1 H), 6.85 (td, \(J = 7.5, 1.0\) Hz, 1 H), 6.66 (d, \(J = 8.0\) Hz, 1 H), 6.46 (s, 1 H), 5.05 (t, \(J = 4.6\) Hz, 1 H), 3.71 (s, 3 H), 2.64 (dt, \(J = 17.1, 6.6\) Hz, 1 H), 2.57 (dt, \(J = 17.1, 6.6\) Hz, 1 H), 2.12 (m, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), DEPT) δ C 173.9, 165.3, 147.2, 115.6, 81.1; CH 133.9, 128.5, 119.4, 114.8, 64.7; CH2 29.9, 28.1; CH3 52.1; HRMS (EI) calcd for C12H14N2O3 [M+] 234.1005, found 234.1016.

**tert-butyl 3-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 48c.**

*Following the general reductive alkylation procedure,* quinazolin-4(3H)-one (0.0238 g, 0.162 mmol), NH\(_4\)Cl (0.0096 g, 0.178 mmol), tert-butyl acrylate (0.12 mL, 0.81 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI\(_2\) (5.0 mL, 0.41 mmol) to give 48c (0.0289 g, 0.105 mmol, 65%) as a colorless oil after purification by FCC (1:3 hexanes:EtOAc).

Data for 48c: Rf 0.48 (1:2 hexanes:EtOAc); mp = 114–115 °C; IR (thin film) 2978, 2830, 1728, 1677, 1469, 1367, 1154, 757 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.86
(dd, J = 7.7, 1.4 Hz, 1 H), 7.28 (td, J = 7.6, 1.6 Hz, 1 H), 6.96 (s, 1 H), 6.82 (td, J = 7.5, 1.0 Hz, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 5.01 (t, J = 4.6 Hz, 1 H), 4.56 (s, 1 H), 2.55 (dt, J = 17.0, 7.0 Hz, 1 H), 2.45 (dt, J = 17.0, 6.7 Hz, 1 H), 2.01–2.13 (m, 2 H), 1.44 (s, 9 H); 13C NMR (100 MHz, CDCl₃, DEPT) δ C 172.8, 165.5, 147.4, 115.5, 81.1; CH 133.8, 128.4, 119.1, 114.7, 64.8; CH₂ 29.9, 29.6, CH₃ 28.3; HRMS (EI) calcd for C₁₅H₂₀N₂O₃Na [M+Na]: 299.1372, found 299.1379.

3-(3-(but-3-en-1-yl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 49a. Following the general reductive alkylation procedure, 3-(but-3-en-1-yl)quinazolin-4(3H)-one (0.0276 g, 0.138 mmol), NH₄Cl (0.0086 g, 0.160 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.46 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.7 mL, 0.35 mmol) to give 49a (0.0307 g, 0.120 mmol, 87%) as a colorless oil after purification by FCC (1:1 hexanes:EtOAc).

Data for 49a: Rf 0.31 (1:1 hexanes:EtOAc); IR (thin film) 2916, 2246, 1632, 1469, 1394, 759 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.92 (dd, J = 7.7, 1.4 Hz, 1 H), 7.32 (td, J = 7.6, 1.5 Hz, 1 H), 6.93 (t, J = 7.5, 1.0 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 5.84 (ddt, J = 17.0, 10.2, 6.9 Hz, 1 H), 5.12 (dd, J = 17.1, 1.6 Hz, 1 H), 5.07 (d, J = 10.1 Hz, 1 H), 4.72 (dd, J = 8.9, 3.8 Hz, 1 H), 4.54 (d, J = 13.9, 7.0 Hz, 1 H), 3.67 (s, 3 H), 2.92 (dt, J = 13.7, 7.1 Hz, 1 H), 2.15 (m, 1 H), 1.94 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃, DEPT) δ C 162.0, 143.2, 118.5; C H 134.8, 133.5, 128.6, 120.9, 117.1; CH₂ 117.5, 44.9, 32.9, 28.5, 13.6; HRMS (ESI) calcd for C₁₅H₁₈N₃O [M+H]: 256.1450, found 256.1446.

methyl 3-(3-(but-3-en-1-yl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 49c. Following the general reductive alkylation procedure, 3-(but-3-en-1-yl)quinazolin-4(3H)-one (0.0295 g, 0.147 mmol), CSA (0.0375 g, 0.162 mmol), methyl acrylate (0.07 mL, 0.78 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.6 mL, 0.37 mmol) to give 49c (0.0264 g, 0.0916 mmol, 62%) as a colorless oil after purification by FCC (3:1 hexanes:EtOAc).

Data for 49c: Rf 0.42 (2:1 hexanes:EtOAc); IR (thin film) 2976, 2926, 1733, 1632, 1468, 1370, 1168, 754 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, J = 7.8, 1.4 Hz, 1 H), 7.28 (td, J = 7.6, 1.5 Hz, 1 H), 6.87 (t, J = 7.5, 1.0 Hz, 1 H), 6.65 (d, J = 8.1 Hz, 1 H), 5.84 (ddt, J = 17.1, 10.2, 6.9 Hz, 1 H), 5.12 (dd, J = 17.2, 1.6 Hz, 1 H), 5.05 (d, J = 10.1 Hz, 1 H), 4.72 (dd, J = 8.9, 3.8 Hz, 1 H), 4.54 (d, J = 13.9, 7.0 Hz, 1 H), 3.67 (s, 3 H), 2.92 (dt, J = 13.7, 7.1 Hz, 1 H), 2.15 (m, 1 H), 1.94 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃, DEPT) δ C 173.3, 162.2, 144.3, 117.5; CH 135.1, 133.2, 128.5, 119.6, 115.7, 68.4; CH₂ 117.0, 44.8, 32.7, 29.6, 28.5; CH₃ 51.8; HRMS (ESI) calcd for C₁₆H₂₁N₂O₃ [M+H]: 289.1541, found 289.1552.

tert-butyl 3-(3-(but-3-en-1-yo)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 49b. Following the general reductive alkylolation procedure, 3-(but-3-en-1-yo)quinazolin-4(3H)-one (0.0289 g, 0.144 mmol), CSA (0.0375 g, 0.162 mmol), tert-butyl acrylate (0.07 mL, 0.76 mmol) in THF (0.50 mL, 0.3 M) were reacted with
a THF solution of SmI$_2$ (3.5 mL, 0.36 mmol) to give 49b (0.0364 g, 0.110 mmol, 77%) as a colorless oil after purification by FCC (3:2 hexanes:EtOAc).

Data for 49b: $R_f$ 0.68 (1:1 hexanes:EtOAc); IR (thin film) 2977, 2930, 1726, 1631, 1470, 1367, 1152, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.90 (dd, $J = 7.8, 1.3$ Hz, 1 H), 7.27 (td, $J = 7.7, 1.4$ Hz, 1 H), 6.85 (t, $J = 7.7$ Hz, 1 H), 6.65 (d, $J = 7.9$ Hz, 1 H), 5.84 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1 H), 5.11 (dd, $J = 17.1, 1.5$ Hz, 1 H), 5.05 (d, $J = 10.7$ Hz, 1 H), 4.70 (dd, $J = 8.8, 3.9$ Hz, 1 H), 4.59 (brs, 1 H), 4.20 (dt, $J = 13.9, 7.0$ Hz, 1 H), 2.90 (dt, $J = 14.1, 7.2$ Hz, 1 H), 2.41 (q, $J = 6.9$ Hz, 1 H), 2.09–1.91 (m, 2 H), 1.60 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 172.0, 162.2, 144.5, 117.3, 81.0; CH 135.1, 133.2, 128.4, 119.4, 115.4; CH$_2$ 117.0, 44.7, 32.7, 31.0, 28.6; CH$_3$ 28.0; HRMS (ESI) calcd for C$_{19}$H$_{27}$N$_2$O$_3$ [M+H]: 331.2022, found 331.2015.

3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 51a. Following the general reductive alkylation procedure, 2-methylquinazolin-4(3H)-one (0.0229 g, 0.141 mmol), NH$_4$Cl (0.0085 g, 0.155 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI$_2$ (3.6 mL, 0.35 mmol) to give 51a (0.0247 g, 0.115 mmol, 81%) as a white solid.

Data for 51a: $R_f$ 0.26 (1:2 hexanes:EtOAc); mp = 113–114 $^\circ$C; IR (thin film) 2927, 2249, 1655, 1486, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86 (dd, $J = 7.8, 1.4$ Hz, 1 H), 7.66 (s, 1 H), 7.33 (td, $J = 7.6, 1.5$ Hz, 1 H), 6.85 (t, $J = 7.5$ Hz, 1 H), 6.66 (d, $J = 8.0$ Hz, 1 H), 4.22 (s, 1 H), 2.67 (ddd, $J = 17.4, 8.8, 6.3$ Hz, 1 H), 2.55 (ddd, $J = 17.3, 8.7, 6.5$ Hz, 1 H), 2.20 (ddd, $J = 14.5, 8.7, 6.5$ Hz, 1 H), 2.09 (ddd, $J = 14.5, 8.7, 6.3$ Hz, 1 H), 1.60 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 164.8, 145.4, 119.6, 113.9, 69.4; CH 134.4, 128.2, 119.3, 114.9; CH$_2$ 37.3, 12.3; CH$_3$ 28.5; HRMS (ESI) calcd for C$_{12}$H$_{14}$N$_3$O [M+H]: 216.1137, found 216.1129.

methyl 3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 51c. Following the general reductive alkylation procedure, 2-methylquinazolin-4(3H)-one (0.0211 g, 0.130 mmol), CSA (0.0333 g, 0.143 mmol), methyl acrylate (0.04 mL, 0.65 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI$_2$ (3.6 mL, 0.35 mmol) to give 51c (0.0247 g, 0.115 mmol, 81%) as a white solid after purification by FCC (1:1 hexanes:EtOAc).

Data for 51c: $R_f$ 0.26 (1:2 hexanes:EtOAc); mp = 113–114 $^\circ$C; IR (thin film) 2927, 2249, 1655, 1486, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86 (dd, $J = 7.8, 1.3$ Hz, 1 H), 7.27 (td, $J = 7.7, 1.4$ Hz, 1 H), 6.85 (t, $J = 7.7$ Hz, 1 H), 6.65 (d, $J = 7.9$ Hz, 1 H), 5.84 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1 H), 5.11 (dd, $J = 17.1, 1.5$ Hz, 1 H), 5.05 (d, $J = 10.7$ Hz, 1 H), 4.70 (dd, $J = 8.8, 3.9$ Hz, 1 H), 4.59 (brs, 1 H), 2.41 (q, $J = 6.9$ Hz, 1 H), 2.09–1.91 (m, 2 H), 1.44 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 172.0, 162.2, 144.5, 117.3, 81.0; CH 135.1, 133.2, 128.4, 119.4, 115.4; CH$_2$ 117.0, 44.7, 32.7, 31.0, 28.6; CH$_3$ 28.0; HRMS (ESI) calcd for C$_{19}$H$_{27}$N$_2$O$_3$ [M+H]: 331.2022, found 331.2015.
6.57 (d, $J = 8.0$ Hz, 1 H), 6.30 (s, 1 H), 4.23 (s, 1 H), 2.55 (dt, $J = 14.7, 6.9$ Hz, 1 H), 2.44 (dt, $J = 16.9, 6.8$ Hz, 1 H), 2.11 (dt, $J = 14.7, 6.9$ Hz, 1 H), 1.99 (dt, $J = 14.8, 6.9$ Hz, 1 H), 1.53 (s, 3 H), 1.42 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 173.2, 164.4, 145.9, 114.0, 80.9, 70.0; CH 134.0, 128.3, 118.5, 114.5; CH$_2$ 36.4, 30.0; CH$_3$ 29.1, 28.0; HRMS (ESI) calcd for C16H23N2O3 [M+H]: 291.1709, found 291.1697.

3-(3-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 52a.

Following the general reductive alkylation procedure, 3-benzyl-2-methylquinazolin-4(3H)-one (0.0356 g, 0.142 mmol), NH$_4$Cl (0.0093 g, 0.174 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.47 mL, 0.3 M) were reacted with a THF solution of SmI$_2$ (4.7 mL, 0.36 mmol) to give 52a (0.0416 g, 0.136 mmol, 96%) as a white solid.

Data for 52a: R$_f$ 0.45 (1:1 hexanes:EtOAc); mp = 148–149 °C; IR (thin film) 3013, 2249, 1489, 1397, 1158, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98 (dd, $J = 8.0, 1.2$ Hz, 1 H), 7.36–7.25 (m, 6 H), 6.91 (dt, $J = 7.6, 1.0$ Hz, 1 H), 6.68 (d, $J = 8.0$ Hz, 1 H), 4.85 (d, $J = 16.0$ Hz, 1 H), 4.35 (d, $J = 16.0$ Hz, 1 H), 4.35 (s, 1 H), 2.36 (m, 2 H), 2.12 (m, 1 H), 1.86 (m, 1 H), 1.55 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 163.9, 143.8, 138.7, 119.2, 115.5, 73.4; CH 134.0, 128.9, 128.8, 127.4, 127.3, 119.8, 115.1; CH$_2$ 45.4, 34.5, 12.3; CH$_3$ 25.6; HRMS (ESI) calcd for C19H19N3ONa [M+Na]: 328.1426, found 328.1415.

methyl 3-(3-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 52c. Following the general reductive alkylation procedure, 3-benzyl-2-methylquinazolin-4(3H)-one (0.0321 g, 0.128 mmol), CSA (0.0328 g, 0.141 mmol), methyl acrylate (0.06 mL, 0.92 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI$_2$ (4.7 mL, 0.36 mmol) to give 52c (0.0199 g, 0.0588 mmol, 46%) as a white solid after purification by FCC (5:1 hexanes:EtOAc).

Data for 52c: R$_f$ 0.66 (1:1 hexanes:EtOAc); mp = 136–137 °C; IR (thin film) 2950, 1734, 1624, 1489, 1397, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (d, $J = 7.7$ Hz, 1 H), 7.35–7.20 (m, 6 H), 6.85 (t, $J = 7.7$ Hz, 1 H), 6.57 (d, $J = 8.1$ Hz, 1 H), 4.96 (d, $J = 15.8$ Hz, 1 H), 4.60 (d, $J = 15.8$ Hz, 1 H), 4.27 (s, 1 H), 3.59 (s, 3 H), 2.34 (m, 2 H), 2.12 (dt, $J = 14.7, 5.2$ Hz, 1 H), 2.02 (td, $J = 10.0, 5.1$ Hz, 1 H), 1.46 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$, DEPT) $\delta$ C 163.9, 143.8, 138.7, 119.2, 115.5, 73.4; CH 134.0, 128.9, 128.8, 127.4, 127.3, 119.8, 115.1; CH$_2$ 45.4, 34.5, 12.3; CH$_3$ 25.6; HRMS (ESI) calcd for C20H23N2O3 [M+Na]: 328.1426, found 328.1415.

tert-butyl 3-(3-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate 52b. Following the general reductive alkylation procedure, 3-benzyl-2-methylquinazolin-4(3H)-one (0.0331 g, 0.132 mmol), NH$_4$Cl (0.0080 g, 0.145 mmol), tert-butyl acrylate (0.10 mL, 0.66 mmol) in THF (0.50 mL, 0.3 M) were reacted with a THF solution of SmI$_2$ (3.4 mL, 0.33 mmol) to give 52b (0.0322 g, 0.0847 mmol, 64%) as a white solid.
Data for 52b: Rf 0.40 (3:1 hexanes:EtOAc); mp = 142–143 °C; IR (thin film) 2977, 2930, 1726, 1489, 1394, 1154, 754 cm−1; ¹H NMR (700 MHz, CDCl₃) δ 7.96 (d, J = 7.7 Hz, 1 H), 7.33–7.20 (m, 5 H), 7.22 (t, J = 7.3 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.56 (d, J = 7.7 Hz, 1 H), 5.00 (d, J = 15.8 Hz, 1 H), 4.54 (d, J = 15.9 Hz, 1 H), 4.40 (s, 1 H), 2.27 (m, 2 H), 2.10–1.99 (m, 1 H), 1.42 (s, 3 H), 1.38 (s, 9 H); ¹³C NMR (175 MHz, CDCl₃, DEPT) δ C 172.7, 164.2, 144.6, 139.0, 115.0, 80.8, 74.1; CH 133.6, 128.8, 128.5, 127.3, 126.9, 118.7, 114.2; CH₂ 45.2, 33.8, 30.2; CH₃ 27.9, 26.4; HRMS (ESI) calcd for C₂₀H₂₃N₂O₃ [M+H]: 339.1709, found 339.1693.

3-(2-(tert-butyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 53.

Following the general reductive alkylation procedure, 2-(tert-butyl)quinazolin-4(3H)-one (0.0280 g, 0.138 mmol), CSA (0.0366 g, 0.158 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.46 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.7 mL, 0.35 mmol) to give 153 (0.0124 g, 0.0482 mmol, 35%) as a white solid along with 0.0099 g of 2-(tert-butyl)quinazolin-4(3H)-one after purification by FCC (1:1 hexanes:EtOAc).

Data for 53: Rf 0.65 (1:2 EtOAc: Hexanes); IR (thin film) 3356, 2921, 2246, 1655 cm−1; ¹H NMR (700 MHz, CDCl₃) δ 7.79 (dd, J = 8.4, 1.4 Hz, 1 H), 6.73 (t, J = 7.7 Hz, 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 6.10 (s, 1 H), 4.09 (s, 1 H), 2.61–2.66 (m, 1 H), 2.53–2.58 (m, 1 H), 2.03–2.11 (m, 2 H), 1.03 (s, 9 H); ¹³C NMR (176 MHz, CDCl₃) δ C 164.1, 146.5, 134.9, 128.3, 120.0, 118.2, 12.8, 111.6, 43.2, 33.5, 29.9, 24.6, 12.8; HRMS (TOF MS ES+) calcd for C₁₅H₂₀N₃O [M+H]: 258.1606, found 258.1599.

3-(3-cyclopropyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 54a.

Following the general reductive alkylation procedure, 3-cyclopropylquinazolin-4(3H)-one (0.0261 g, 0.140 mmol), NH₄Cl (0.0086 g, 0.158 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.46 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.7 mL, 0.35 mmol) to give 54a (0.0340 g, 0.140 mmol, 99%) as a colorless oil.

Data for 54a: Rf 0.24 (1:1 EtOAc: Hexanes); IR (thin film) 3294, 2929, 2246, 1655 cm−1; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (dd, J = 8.0, 1.6 Hz, 1 H), 7.32 (td, J = 8.0, 1.6 Hz, 1 H), 6.90 (ddd, J = 8.0, 8.0, 0.8 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 4.81 (dd, J = 9.6, 4.0 Hz, 1 H), 2.69 (ddd, J = 9.6, 6.8, 4.0 Hz, 1 H), 2.46 (dd, J = 8.0, 6.4, 4.4 Hz, 1 H), 2.15–2.24 (m, 1 H), 2.01–2.10 (m, 1 H), 1.09–1.17 (m, 1 H), 0.79–0.89 (m, 2 H), 0.61–0.68 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ C 164.4, 143.4, 134.1, 128.6, 120.3, 118.9, 117.4, 116.4, 68.9, 28.5, 27.9, 13.8, 10.2, 6.0; HRMS (EI+) calcd for C₁₄H₁₅N₃O [M+H]: 241.12152, found 241.12128.

3-(3-cyclohexyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile 54b.

Following the general reductive alkylation procedure, 3-cyclohexylquinazolin-4(3H)-one (0.0338 g, 0.148 mmol), NH₄Cl (0.0089 g, 0.166 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.49 mL, 0.3 M) were reacted with a THF solution of SmI₂
(4.9 mL, 0.37 mmol) to give 54b (0.0409 g, 0.144 mmol, 97%) as a colorless oil after purification by FCC (3:1 hexanes:EtOAc).

Data for 54b: Rf 0.38 (1:1 EtOAc: Hexanes); IR (thin film) 3284, 2932, 2856, 2245, 1622 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.94 (dd, J = 7.7, 1.4 Hz, 1 H), 7.32 (td, J = 8.4, 1.4 Hz, 1 H), 6.95 (ddd, J = 8.4, 8.4, 1.4 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 4.82 (dd, J = 10.5, 2.8 Hz, 1 H), 4.46 (tt, J = 11.9, 3.5 Hz, 1 H), 2.34-2.44 (m, 2 H), 2.23-2.29 (m, 1 H) 1.78-1.92 (m, 6 H), 1.69 (d, J = 13.3 Hz, 1 H), 1.54 (qd, J = 11.9, 3.5 Hz, 1 H), 1.37-1.45 (m, 3 H), 1.14 (qt, J = 9.1, 4.2 Hz, 1 H); ¹³C (176 MHz, CDCl₃) δ C 161.8, 142.9, 133.4, 128.9, 120.8, 119.6, 118.9, 117.1, 63.2, 53.4, 31.8, 31.6, 30.2, 26.1, 25.9, 25.5, 14.0; HRMS (EI+) calcd for C₁₇H₂₁N₃O [M⁺]: 283.16847, found 283.16723.

3-(3-cyclopropyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile (54a).
Following the general reductive alkylation procedure, 3-cyclopropylquinazolin-4(3H)-one (0.0261 g, 0.140 mmol), NH₄Cl (0.0086 g, 0.158 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.47 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.7 mL, 0.35 mmol) to give 54a (0.0340 g, 0.140 mmol, 99%) as a colorless oil.

Data for 54a: Rf 0.24 (1:1 EtOAc: Hexanes); IR (thin film) 3294, 2929, 2856, 2246, 1636 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (dd, J = 8.0, 1.6 Hz, 1 H), 7.32 (td, J = 8.0, 1.6 Hz, 1 H), 6.90 (ddd, J = 8.0, 8.0, 0.8 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 4.81 (dd, J = 9.6, 4.0 Hz, 1 H), 2.69 (ddd, J = 9.6, 6.8, 4.0 Hz, 1 H), 2.46 (ddd, J = 8.0, 6.4, 4.4 Hz, 2 H), 2.15-2.24 (m, 1 H) 2.01-2.10 (m, 1 H), 1.09-1.17 (m, 1 H), 0.79-0.89 (m, 2 H), 0.61-0.68 (m, 2 H); ¹³C (100 MHz, CDCl₃) δ C 164.4, 143.4, 134.0, 128.6, 120.3, 118.9, 117.4, 116.4, 68.9, 28.5, 27.9, 13.8, 10.2, 6.0; HRMS (EI+) calcd for C₁₄H₁₅N₃O [M⁺]: 241.12152, found 241.12128.

3-(3-cyclohexyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanenitrile (54b).
Following the general reductive alkylation procedure, 3-cyclohexylquinazolin-4(3H)-one (0.0338 g, 0.148 mmol), NH₄Cl (0.0089 g, 0.166 mmol), acrylonitrile (0.05 mL, 0.76 mmol) in THF (0.49 mL, 0.3 M) were reacted with a THF solution of SmI₂ (3.7 mL, 0.35 mmol) to give 54b (0.0409 g, 0.144 mmol, 97%) as a colorless oil after purification by FCC (3:1 hexanes:EtOAc).

Data for 54b: Rf 0.38 (1:1 EtOAc: Hexanes); IR (thin film) 3284, 2932, 2856, 2245, 1622 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.94 (dd, J = 7.7, 1.4 Hz, 1 H), 7.32 (td, J = 8.4, 1.4 Hz, 1 H), 6.95 (ddd, J = 8.4, 8.4, 1.4 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 4.82 (dd, J = 10.5, 2.8 Hz, 1 H), 4.46 (tt, J = 11.9, 3.5 Hz, 1 H), 2.34-2.44 (m, 2 H), 2.23-2.29 (m, 1 H) 1.78-1.92 (m, 6 H), 1.69 (d, J = 13.3 Hz, 1 H), 1.54 (qd, J = 11.9, 3.5 Hz, 1 H), 1.37-1.45 (m, 3 H), 1.14 (qt, J = 9.1, 4.2 Hz, 1 H); ¹³C (176 MHz, CDCl₃) δ C 161.8, 142.9, 133.4, 128.9, 120.8, 119.6, 118.9, 117.1, 63.2, 53.4, 31.8, 31.6, 30.2, 26.1, 25.9, 25.5, 14.0; HRMS (EI+) calcd for C₁₇H₂₁N₃O [M⁺]: 283.16847, found 283.16723.

General procedure for synthesizing pyridinium oxide:
To a solution of the corresponding alcohol (1 eq) in DCM (0.2 M) at 0 °C was added Et3N (1.5 eq) and then methanesulfonyl chloride (1.5 eq). The mixture was stirred for 1 h at 0 °C and slowly warming up to room temperature for 3 hr before saturated aqueous NH4Cl solution was added. This mixture was extracted with DCM three times. The combined extracts were washed with brine and dried over Na2SO4 and concentrated. The mixture of the crude corresponding methylate (1 eq), 3-hydroxypyridine (2 eq) in BuCN (20 M) were heated up to 130 °C for 6 hr in sealed tube to give pyridinium oxide after purification by FCC (DCM:10%NH4OH in MeOH=1:0.08 to 1:0.15).

1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (74) Following the general reductive alkylation procedure, hex-5-en-2-ol40 (1 g, 10 mmol) in DCM (20 mL) at 0 °C was added Et3N (2.07 mL, 15 mmol) and then methanesulfonyl chloride (1.17 mL, 15 mmol). The mixture of the crude methylate (89 mg, 0.5 mmol), 3-hydroxypyridine (95 mg, 1 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 74 (68 mg, 67% two steps) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.06 to 1:0.12).

Data for 74: Rf 0.20 (1:0.1 DCM: 10%NH4OH in MeOH); IR (thin film) 3368, 3077, 2931, 1588, 1507, 1379 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.75 (t, J = 2.1, 1 H), 7.15 (dd, J = 8.8, 1.8 Hz, 1 H), 7.12 (dd, J = 8.8, 5.3 Hz, 1 H), 7.00 (d, J = 5.3 Hz, 1 H), 5.60 (ddt, J = 16.7, 10.5, 6.7 Hz, 1 H), 4.92 (d, J = 10.5 Hz, 1 H), 4.89 (d, J = 16.7 Hz, 1 H), 4.06 (dq, J = 8.8, 6.8 Hz, 1 H), 1.79–1.91 (m, 4 H), 1.48 (d, J = 6.8 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 170.1, 135.7, 134.5, 131.5, 126.8, 119.8, 116.7, 66.6, 35.6, 29.7, 21.8; HRMS (EI) calcd for C11H16NO [M+] : 178.1232, found 277.1238.

1-(3-methylpent-4-en-1-yl)pyridin-1-ium-3-olate (76) Following the general reductive alkylation procedure, 3-methylpent-4-en-1-ol41 (500 mg, 5 mmol) in DCM (25 mL) at 0 °C was added Et3N (1.05 mL, 7.5 mmol) and then methanesulfonyl chloride (0.6 mL, 75 mmol). The mixture of the crude methylate (165 mg, 1 mmol), 3-hydroxypyridine (340 mg, 4 mmol) in ACN (2 ml) were heated up to 100 °C for 10 hr in sealed tube to give 76 (165 mg, 75% two steps) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.1 to 1:0.12).

Data for 76: Rf 0.20 (1:0.1 DCM: 10%NH4OH in MeOH); IR (thin film) 3367, 3072, 2966, 1566, 1506 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.43 (s, 1 H), 7.30 (d, J = 9.3 Hz, 1 H), 7.23 (dd, J = 8.9, 4.9 Hz, 1 H), 7.00 (d, J = 4.9 Hz, 1 H), 5.67 (ddd, J = 17.3, 10.9, 7.7 Hz, 1 H), 5.12 (d, J = 11.1 Hz, 1 H), 5.01 (d, J = 17.3 Hz, 1 H), 4.11 (ddd, J = 13.3, 8.5, 5.2 Hz, 1 H), 4.02 (dd, J = 13.3, 7.9 Hz, 1 H), 2.20 (brs, 1 H), 2.00 (ddd, J = 16.3, 8.8, 5.2 Hz, 1 H), 1.92–1.85 (m, 4 H), 1.10 (d, J = 6.9 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 160.0, 141.0, 133.0, 131.8, 130.5, 128.0, 115.5, 68.4, 43.8, 36.0, 21.5, 21.2; HRMS (EI) calcd for C11H16NO [M+] : 178.1232, found 277.1236.
1-(cyclohex-3-en-1-ylmethyl)pyridin-1-ium-3-olate (78)  
Following the general reductive alkylation procedure, cyclohex-3-en-1-ylmethanol\(^42\) (1g, 10 mmol) in DCM (20 mL) at 0 °C was added Et\(_3\)N (2.07 mL, 15 mmol) and then methanesulfonyl chloride (1.17 mL, 15 mmol). The mixture of the crude methylate (89mg, 0.5 mmol), 3-hydroxypyridine (95mg, 1 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 78 (68mg, 67% two steps) after purification by FCC (DCM:10%NH\(_4\)OH in MeOH=1:0.06 to 1:0.12).

Data for 78:  \(R_f\) 0.20 (1:0.1 DCM:10%NH\(_4\)OH in MeOH); IR (thin film) 3368, 3077, 2931, 1588, 1563, 1507, 1379 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.75 (t, \(J = 2.1\), 1 H), 7.15 (dd, \(J = 8.8, 1.8\) Hz, 1 H), 7.12 (dd, \(J = 8.8, 5.3\) Hz, 1 H), 7.00 (d, \(J = 5.3\) Hz, 1 H), 5.60 (ddt, \(J = 16.7, 10.5, 6.7\) Hz, 1 H), 4.92 (d, \(J = 10.5\) Hz, 1 H), 4.89 (d, \(J = 16.7\) Hz, 1 H), 4.06 (dq, \(J = 8.8, 6.8\) Hz, 1 H), 1.79–1.91 (m, 4 H), 1.48 (d, \(J = 6.8\) Hz, 3 H); \(^1^3\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 170.1, 135.7, 134.5, 131.5, 126.8, 119.8, 116.7, 66.6, 35.6, 29.7, 21.8; HRMS (EI) calcd for C\(_{11}\)H\(_{15}\)NOCl [M+]: 178.1232, found 177.1238.

6-chloro-1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (80)  
Following the general reductive alkylation procedure, hex-5-en-2-ol\(^40\) (1g, 10 mmol) in DCM (20 mL) at 0 °C was added Et\(_3\)N (2.07 mL, 15 mmol) and then methanesulfonyl chloride (1.17 mL, 15 mmol). The mixture of the crude methylate (60mg, 0.34 mmol), 6-chloropyridin-3-ol (88mg, 0.68 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 80 (49mg, 48% two steps) after purification by FCC (DCM:10%NH\(_4\)OH in MeOH=1:0.06 to 1:0.08).

Data for 80 in acid:  \(R_f\) 0.28 (1:0.1 DCM:10%NH\(_4\)OH in MeOH); IR (thin film) 3390, 3076, 2934, 1581, 1499, 1374 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 9.47 (d, \(J = 2.3\), 1 H), 8.07 (dd, \(J = 8.6, 2.3\) Hz, 1 H), 7.72 (d, \(J = 8.6\) Hz, 1 H), 7.00 (d, \(J = 5.3\) Hz, 1 H), 5.71 (ddt, \(J = 16.4, 10.4, 6.4\) Hz, 1 H), 5.30 (tq, \(J = 6.8, 6.3\) Hz, 1 H), 5.03 (d, \(J = 11.6\) Hz, 1 H), 5.01 (d, \(J = 16.9\) Hz, 1 H), 2.07–2.22 (m, 4 H), 1.73 (d, \(J = 6.3\) Hz, 3 H); \(^1^3\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 158.9, 135.0, 134.9, 133.6, 132.1, 129.6, 117.3, 65.2, 35.4, 29.9, 21.0; HRMS (EI) calcd for C\(_{11}\)H\(_{15}\)NOCl [M+]: 212.0842, found 212.0832.

6-bromo-1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (82)  
Following the general reductive alkylation procedure, hex-5-en-2-ol\(^40\) (1g, 10 mmol) in DCM (20 mL) at 0 °C was added Et\(_3\)N (2.07 mL, 15 mmol) and then methanesulfonyl chloride (1.17 mL, 15 mmol). The mixture of the crude methylate (45mg, 0.25 mmol), 6-bromopyridin-3-ol (89mg, 0.68 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 82 (49mg, 48% two steps) after purification by FCC (DCM:10%NH\(_4\)OH in MeOH=1:0.06 to 1:0.08).

Data for 82 in acid:  \(R_f\) 0.22 (1:0.1 DCM:10%NH\(_4\)OH in MeOH); IR (thin film) 3404, 2978, 1578, 1494, 1374 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 2.5\), 1 H), 7.43 (d, \(J = 9.3\) Hz, 1 H), 7.72 (d, \(J = 8.6\) Hz, 1 H), 7.24 (dd, \(J = 9.6, 3.2\) Hz, 1 H),
5.72 (ddt, $J = 16.6, 10.4, 6.3$ Hz, 1 H), 5.03–5.01 (m, 3 H), 1.92–2.10 (m, 4 H), 1.67 (d, $J = 6.8$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 168.3, 136.5, 135.5, 133.2, 132.4, 116.9, 109.7, 65.6, 35.8, 29.8, 21.3; HRMS (El) calcd for C$_{11}$H$_{15}$NOBr $[M+]$: 256.0337, found 256.0324.

1-(hex-5-en-2-yl)-4-methylpyridin-1-ium-3-olate (84) Following the general reductive alkylation procedure, hex-5-en-2-ol$_{40}$ (1g, 10 mmol) in DCM (20 mL) at 0 °C was added Et$_3$N (2.07 mL, 15 mmol) and then methanesulfonyl chloride (1.17 mL, 15 mmol). The mixture of the crude methylate (89 mg, 0.5 mmol), 4-methylpyridin-3-ol (220 mg, 2 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 84 (50 mg, 48% two steps) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.08 to 1:0.12).

Data for 84 in acid: $R_f$ 0.22 (1:0.1 DCM:10%NH$_4$OH in MeOH); IR (thin film) 3384, 3079, 2980, 1561 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.26 (s, 1 H), 7.04 (d, $J = 5.5$ Hz, 1 H), 6.94 (d, $J = 6.3$ Hz, 1 H), 5.58 (ddt, $J = 16.6, 10.6, 6.3$ Hz, 1 H), 4.89 (d, $J = 10.6$ Hz, 1 H), 4.87 (d, $J = 16.6$ Hz, 1 H), 3.99 (tq, $J = 7.3, 6.8$ Hz, 1 H), 2.19 (s, 3 H), 1.75–1.87 (m, 4 H), 1.44 (d, $J = 6.8$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 169.3, 137.5, 135.8, 134.8, 129.3, 120.9, 116.7, 66.6, 35.7, 29.8, 21.8, 18.6; HRMS (El) calcd for C$_{12}$H$_{18}$NO $[M+]$: 192.1388, found 192.1378.

(E)-6-chloro-1-(7-ethoxy-7-oxohept-5-en-2-yl)pyridin-1-ium-3-olate (86) Following the general reductive alkylation procedure, ethyl (E)-6-hydroxyhept-2-enoate$_{43}$ (1g, 5.8 mmol) in DCM (11.6 mL) at 0 °C was added Et$_3$N (1.21 mL, 8.7 mmol) and then methanesulfonyl chloride (0.68 mL, 8.7 mmol). The mixture of the crude methylate (511 mg, 2.04 mmol), 6-chloropyridin-3-ol (531 mg, 4.09 mmol) in BuCN (0.1 mL) were heated up to 130 °C for 6 hr in sealed tube to give 86 (55 mg, 44% two steps) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.06 to 1:0.12).

Data for 86 in acid: $R_f$ 0.36 (1:0.1 DCM:10%NH$_4$OH in MeOH); IR (thin film) 3388, 3083, 2980, 1561, 1371 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 9.53 (S, 1 H), 8.05 (d, $J = 8.6$ Hz, 1 H), 7.73 (d, $J = 8.6$ Hz, 1 H), 6.82 (dt, $J = 14.4, 6.5$ Hz, 1 H), 5.80 (d, $J = 15.5$ Hz, 1 H), 5.27 (quint, $J = 6.7$ Hz, 1 H), 4.17 (q, $J = 7.0$ Hz, 2 H), 2.33 (quint, $J = 7.3$ Hz, 1 H), 2.27 (q, $J = 6.4$ Hz, 2 H), 2.21 (quint, $J = 7.3$ Hz, 1 H), 1.76 (d, $J = 6.8$ Hz, 3 H), 1.27 (d, $J = 7.4$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 165.8, 158.8, 144.5, 135.1, 133.6, 132.1, 129.7, 123.7, 65.0, 60.6, 34.7, 28.3, 21.0, 14.2; HRMS (El) calcd for C$_{14}$H$_{19}$NO$_3$Cl $[M+]$: 284.1053, found 284.1048.

(E)-6-bromo-1-(7-ethoxy-7-oxohept-5-en-2-yl)pyridin-1-ium-3-olate (88) Following the general reductive alkylation procedure, ethyl (E)-6-hydroxyhept-2-enoate$_{43}$ (1g, 5.8 mmol) in DCM (11.6 mL) at 0 °C was added Et$_3$N (1.21 mL, 8.7 mmol) and then methanesulfonyl chloride (0.68 mL, 8.7 mmol). The mixture of the crude methylate (25 mg, 0.1 mmol), 6-bromopyridin-3-ol (34 mg, 0.2 mmol) in BuCN (0.2 mL) were heated up to 130 °C for 6 hr in sealed tube to give 88 (14.4 mg, 37% two steps) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.06).
Data for 

88 in acid: RF 0.36 (1:0.1 DCM:10%NH4OH in MeOH); IR (thin film) 3396, 3056, 2981, 1711, 1493, 1369 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 9.62 (S, 1 H), 7.96 (d, \(J = 8.7\) Hz, 1 H), 7.90 (d, \(J = 8.7\) Hz, 1 H), 6.83 (dt, \(J = 15.7, 6.8\) Hz, 1 H), 5.80 (d, \(J = 15.9\) Hz, 1 H), 5.25 (quint, \(J = 7.0\) Hz, 1 H), 4.17 (q, \(J = 7.0\) Hz, 2 H), 2.35 (quint, \(J = 7.3\) Hz, 1 H), 2.27 (q, \(J = 6.4\) Hz, 2 H), 2.21 (quint, \(J = 7.3\) Hz, 1 H), 1.76 (d, \(J = 6.8\) Hz, 3 H), 1.27 (d, \(J = 7.4\) Hz, 3 H); 13C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 165.7, 159.2, 144.5, 134.6, 133.7, 133.2, 123.6, 123.3, 68.2, 60.5, 34.8, 28.2, 21.1, 14.2; HRMS (EI) calcd for C\(_{14}\)H\(_{19}\)NO\(_3\)Br [M\(^{+}\)]: 328.5048, found 328.5055.

1-((2S,4R)-4-methylhex-5-en-2-yl)pyridin-1-ium-3-olate (92) Following the general reductive alkylation procedure, (4R)-4-methylhex-5-en-2-ol\(^{44}\) (120 mg, 1.05 mmol) in DCM (5 mL) at 0 °C was added Et\(_3\)N (0.22 mL, 1.58 mmol) and then methanesulfonyl chloride (0.13 mL, 1.58 mmol). The mixture of the crude methylate (165 mg, 0.86 mmol), 3-hydroxypyridine (164 mg, 1.72 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 92 (105 mg, 55% two steps) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.06 to 1:0.1).

Data for 92: RF 0.25 (1:0.1 DCM: 10%NH4OH in MeOH); IR (thin film) 3388, 2979, 2935, 1728, 1579, 1496, 1374 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.95 (s, \(J = 1\) H), 8.39 (d, \(J = 5.0\) Hz 1 H), 7.80 (d, \(J = 6.8\) Hz, 1 H), 7.99 (d, \(J = 5.3\) Hz, 1 H), 5.36 (m 1 H), 5.26 (m, 1 H), 4.72 (quint, \(J = 7.6\) Hz, 1 H), 4.10 (quint, \(J = 7.2\) Hz, 1 H), 1.98–2.05 (m, 2 H), 1.95–1.89 (m, 2 H), 1.67 (d, \(J = 6.4\) Hz, 3 H), 1.57 (d, \(J = 6.6\) Hz, 3 H); 13C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 160.0, 141.0, 133.0, 131.9, 130.5, 128.0, 115.5, 68.4, 43.8, 36.0, 21.5, 21.2; HRMS (EI) calcd for C\(_{12}\)H\(_{18}\)NO [M\(^{+}\)]: 192.1388, found 192.1384.

(E)-1-(hept-5-en-2-yl)pyridin-1-ium-3-olate (101) Following the general reductive alkylation procedure, (E)-hept-5-en-2-ol\(^{45}\) (400 mg, 3.5 mmol) in DCM (17 mL) at 0 °C was added Et\(_3\)N (0.74 mL, 5.3 mmol) and then methanesulfonyl chloride (0.41 mL, 5.3 mmol). The mixture of the crude methylate (38 mg, 0.2 mmol), 3-hydroxypyridine (38 mg, 0.4 mmol) in BuCN (2 drops) were heated up to 130 °C for 6 hr in sealed tube to give 101 (27.5 mg, 55% two steps) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.08 to 1:0.15).

Data for 101: RF 0.20 (1:0.1 DCM:10%NH4OH in MeOH); IR (thin film) 3390, 3059, 2936, 1586, 1493, 1384 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.95 (s, \(J = 1\) H), 8.39 (d, \(J = 5.0\) Hz 1 H), 7.80 (d, \(J = 6.8\) Hz, 1 H), 7.99 (d, \(J = 5.3\) Hz, 1 H), 5.36 (m 1 H), 5.26 (m, 1 H), 4.72 (quint, \(J = 7.6\) Hz, 1 H), 4.10 (quint, \(J = 7.2\) Hz, 1 H), 1.98–2.05 (m, 2 H), 1.95–1.89 (m, 2 H), 1.67 (d, \(J = 6.4\) Hz, 3 H), 1.57 (d, \(J = 6.6\) Hz, 3 H); 13C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 159.1, 132.9, 132.6, 130.7, 128.5, 127.8, 127.7, 69.0, 36.5, 28.8, 21.8, 12.9; HRMS (EI) calcd for C\(_{12}\)H\(_{18}\)NO [M\(^{+}\)]: 192.1388, found 192.1384.
(Z)-1-(hept-5-en-2-yl)pyridin-1-ium-3-olate (103) Following the general reductive alkylation procedure, (Z)-hept-5-en-2-ol46 (140 mg, 1.23 mmol) in DCM (6.2 mL) at 0 °C was added Et3N (0.26 mL, 1.84 mmol) and then methanesulfonyl chloride (0.145 mL, 1.84 mmol). The mixture of the crude methylate (100 mg, 0.52 mmol), 3-hydroxypyridine (99 mg, 1.04 mmol) in BuCN (3 drops) were heated up to 130 °C for 6 hr in sealed tube to give 103 (75 mg, 62% two steps) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.06 to 1:0.12).

Data for 103: Rf 0.20 (1:0.1 DCM:10%NH4OH in MeOH); IR (thin film) 3382, 3024, 2919, 1567, 1505, 1507, 1372 cm⁻¹; 1H NMR (700 MHz, CDCl3) δ 7.44 (s, J = 1 H), 7.27 (m, 1 H), 7.20  (d, J = 8.8 Hz, 1 H), 7.99 (d, J = 5.3 Hz, 1 H), 5.52 (dq, J = 13.3, 7.0 Hz, 1 H), 5.27 (m, 1 H), 4.89 (d, J = 16.7 Hz, 1 H), 4.10 (quint, J = 7.2 Hz, 1 H), 1.83–1.98 (m, 4 H), 1.58 (d, J = 6.8 Hz, 3 H), 1.50 (d, J = 7.2 Hz, 3 H); ¹³C NMR (175 MHz, CDCl3) δ 170.3, 134.6, 134.6, 131.9, 127.3, 126.7, 126.5, 119.3, 66.8, 36.4, 23.0, 21.9, 12.9; HRMS (EI) calcd for C_{12}H_{18}NO [M+]: 192.1388, found 192.1386.

General procedure for the pyridinium oxide cycloaddition:

Procedure A: The mixture of the corresponding pyridinium oxide (1eq) and Ag₂CO₃ (1.1eq) in BuCN (0.1mL) was heated up to 130 °C for 36 hr in sealed tube and filtered by celite to give cycloaddition product after purification by FCC (DCM:10%NH₄OH in MeOH=1:0.04).

Procedure B: The mixture of the corresponding pyridinium oxide (1eq) and Ag₂CO₃ (1.1eq) in ACN (0.1M) was heated up to 130 °C for 24 hr in sealed tube and filtered by celite to give cycloaddition product after purification by FCC (DCM:10%NH₄OH in MeOH=1:0.04).

* Unstable compound, directly to next step.
** assigned by 2D-NMR (COSY, HSQC, HMBC).

(1S,4S,5S,6R,9aS)-4-methyl-1,3,4,9a-tetrahydro-2H,1,6-methanoquinolizin -7(6H)-one (75) Following the general reductive alkylation procedure A, 1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (35.4 mg, 0.2 mmol) and Ag₂CO₃ (83 mg, 0.22 mmol) in BuCN (2 mL) was heated up to 130 °C for 36 hr in sealed tube to give 75 (30.8 mg, 87% product ratio=7:1) after purification by FCC (pure EtOAc).

Data for 75: Rf 0.50 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 2933, 2860, 1694, 1507, 1386 cm⁻¹; ¹H NMR (700 MHz, CDCl3) δ 7.10 (dd, J = 9.5, 5.7 1 H), 5.87 (d, J = 9.5 Hz, 1 H), 3.75 (d, J = 7.4Hz, 1 H), 3.55 (d, J = 5.6 Hz, 1 H), 2.92 (tq, J = 11.6, 6.4 Hz, 1 H), 2.35 (t, J = 3.4 Hz, 1 H), 1.83 (dd, J = 13.5, 7.5 1 H), 1.77–1.71 (m, 2 H), 1.59 (ddd, J = 13.8, 6.7, 1.5 1 H), 1.47 (dt, J = 13.8, 5.3 1 H), 1.18–1.13 (m, 1 H), 1.04 (d, J = 6.4 Hz, 3 H); ¹³C NMR (175 MHz, CDCl3) δ 199.4, 151.2,
Following the general reductive alkylation procedure B, 1-(3-methylpent-4-en-1-yl)pyridin-1-ium-3-olate (60 mg, 0.34 mmol) and Ag$_2$CO$_3$ (103 mg, 0.37 mmol) in BuCN (3.4 mL) was heated up to 130 °C for 36 hr in sealed tube to give 77 (50 mg, 84% product ratio=10:1) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.02 to 0.04).

Data for 77: R$_f$ 0.4 (1:0.1 DCM: 10%NH$_4$OH in MeOH); IR (thin film) 2954, 2924, 1695, 1381 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.10 (dd, $J = 9.9$, 6.1 Hz, 1 H), 5.88 (d, $J = 9.9$ Hz, 1 H), 3.54 (d, $J = 7.6$ Hz, 1 H), 3.51 (d, $J = 6.1$ Hz, 1 H), 2.92-2.88 (m, 2 H), 2.12 (d, $J = 6.8$ Hz, 1 H), 1.92 (dd, $J = 13.7$, 7.6 Hz, 1 H), 1.87 (dt, $J = 11.8$, 5.7 Hz, 1 H), 1.41 (dd, $J = 13.6$, 6.8 Hz, 1 H), 1.37-1.33 (m, 1 H), 1.12-1.07 (m, 1 H), 0.88 (d, $J = 6.5$ Hz, 1 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 199.3, 151.5, 126.3, 69.8, 68.6, 53.4, 42.1, 35.0, 26.7, 26.2, 20.9; HRMS (EI) calcd for C$_{11}$H$_{16}$NO [M$^+$]: 178.1232, found 178.1223.

Following the general reductive alkylation procedure B, (S)-1-(cyclohex-3-en-1-ylmethyl)pyridin-1-ium-3-olate (19 mg, 0.1 mmol) and Ag$_2$CO$_3$ (30 mg, 0.11 mmol) in ACN (1 mL) was heated up to 130 °C for 24 hr in sealed tube to give 79 (11 mg, 58% product ratio=10:1) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.03 to 0.1).

Data for 79: R$_f$ 0.45 (DCM: 10%NH$_4$OH in MeOH=1:0.1); IR (thin film) 2960, 2922, 1696 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.17 (dd, $J = 9.7$, 6.2 Hz, 1 H), 5.96 (d, $J = 9.7$ Hz, 1 H), 3.60 (s, 1 H), 3.58 (d, $J = 6.2$ Hz, 1 H), 3.35 (s, 1 H), 3.22 (dd, $J = 14.4$, 4.0 Hz, 1 H), 2.79 (d, $J = 14.0$ Hz, 1 H), 2.32 (t, $J = 6.3$ Hz, 1 H), 2.25 (m, 1 H), 1.97 (dt, $J = 13.1$, 7.7 Hz, 1 H), 1.86-1.81 (m, 2 H), 1.74-1.69 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 199.5, 152.3, 126.2, 76.2, 69.0, 61.9, 38.8, 37.0, 30.4, 27.8, 27.2, 20.8; HRMS (EI) calcd for C$_{12}$H$_{18}$NO [M$^+$]: 190.1232, found 190.1232.

Following the general reductive alkylation procedure A, 6-chloro-1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (27 mg, 0.13 mmol) and Ag$_2$CO$_3$ (39 mg, 0.14 mmol) in BuCN (1.3 mL) was heated up to 130 °C for 12 hr in sealed tube to give 81 (21.9 mg, 80% product ratio=4:1) after purification by FCC (DCM:10%NH$_4$OH in MeOH=1:0.04 to 1:0.06).

Data for 81: R$_f$ 0.48 (1:0.1 DCM: 10%NH$_4$OH in MeOH); IR (thin film) 2940, 1710, 1606 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.11 (d, $J = 9.7$ Hz, 1 H), 5.92 (dd, $J = 9.3$, 1.4 Hz, 1 H), 3.80 (d, $J = 8.6$ Hz, 1 H), 3.38 (dq, $J = 13.5$, 6.5 Hz, 1 H), 2.48 (brs, 1 H), 2.34 (td, $J = 13.2$, 5.2 Hz, 1 H), 2.05 (dd, $J = 13.6$, 8.6 Hz, 1 H), 1.80 (ddd, $J = 13.6$, 6.6,
2.21 H), 1.62 (dt, J = 13.6, 5.2 1 H), 1.49 (dt, J = 14.8, 5.5 1 H), 1.19 (dd, J = 14.4, 6.0 1 H), 1.08 (d, J = 6.7 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 197.4, 153.8, 125.8, 89.9, 62.3, 51.0, 38.8, 30.8, 25.2, 24.5, 19.7; HRMS (EI) calcd for C11H15NOCl [M+]: 212.0842, found 212.0842.

(1S,4S,5R,6R,9aR)-9a-bromo-4-methyl-1,3,4,9a-tetrahydro-2H-1,6-methanoquinolinizin-7(6H)-one (83) Following the general reductive alkylation procedure B, 6-bromo-1-(hex-5-en-2-yl)pyridin-1-ium-3-olate (9.5 mg, 0.037 mmol) and Ag2CO3 (11.5 mg, 0.041 mmol) in ACN (0.4 mL) was heated up to 110 °C for 24 hr in sealed tube to give 82(5.3 mg, 56% product ratio=3:1) after purification by FCC (DCM:10%NH4OH in MeOH=1:0.03).

Data for 83: Rf 0.42 (1:0.075 DCM: 10%NH4OH in MeOH); IR (thin film) 2934, 2870, 1707, 1378 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.29 (d, J = 9.8 1 H), 5.82 (d, J = 9.5 Hz, 1 H), 3.73 (d, J = 8.5Hz, 1 H), 3.92 (tq, J = 13.1, 6.2 Hz, 1 H), 3.48 (q, J = 7 Hz, 1 H), 2.52 (t, J = 3.6 Hz, 1 H), 2.34 (td, J = 13.5, 7.5 1 H), 1.98 (dd, J = 14.7, 9.2 1 H), 1.78 (dd, J = 13.5, 7.0 1 H), 1.67 (dt, J = 13.8, 4.6 1 H), 1.56 (dt, J = 14.6, 5.4 1 H), 1.16 (dd, J = 13.2, 6.2 1 H), 1.07 (d, J = 6.8 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 198.0, 154.8, 125.3, 62.4, 53.4, 39.2, 30.3, 29.7, 26.9, 24.5, 20.0; HRMS (EI) calcd for C11H15NOBr [M+]: 254.0337, found 256.0341.

(1S,4S,5S,6R,9aS)-4,8-dimethyl-1,3,4,9a-tetrahydro-2H-1,6-methanoquinolinizin-7(6H)-one (85) Following the general reductive alkylation procedure A, 1-(hex-5-en-2-yl)-4-methylpyridin-1-ium-3-olate (19 mg, 0.1 mmol) and Ag2CO3 (31 mg, 0.11 mmol) in BuCN (1 mL) was heated up to 130 °C for 36 hr in sealed tube to give 85 (16.8 mg, 88% product ratio=8:1) after purification by FCC (pure EtOAc).

Data for 85: Rf 0.23 (pure EtOAc); IR (thin film) 2931, 1789, 1380 cm−1; 1H NMR (700 MHz, CDCl3) δ 6.82 (d, J = 6.2 1 H), 3.78 (d, J = 7.6 Hz, 1 H), 3.51 (d, J = 6.0 Hz, 1 H), 2.90 (dt, J = 12.3, 7.0 1 H), 2.30 (t, J = 3.1 Hz, 1 H), 1.81 (dd, J = 13.2, 7.2 1 H), 1.73 (s, 3 H), 1.51 (dd, J = 13.7, 6.8 1 H), 1.43 (dt, J = 14.0, 4.5 1 H), 1.19-1.12 (m, 1 H), 1.05 (d, J = 6.8 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 199.7, 146.7, 133.1, 69.1, 63.4, 57.6, 34.7, 30.4, 30.2, 25.9, 20.0, 14.6; HRMS (EI) calcd for C12H18NO [M+]: 192.1388, found 192.1385.

ethyl (1S,4S,5R,6R,9aS,10S)-9a-chloro-4-methyl-1,3,4,6,7,9a-hexahydro-2H-1,6-methanoquinolinizine-10-carboxylate (87) Following the general reductive alkylation procedure A, (E)-6-chloro-1-(7-ethoxy-7-oxohept-5-en-2-yl)pyridin-1-ium-3-olate (75mg, 0.017 mmol), Ag2CO3 (86 mg, 0.019mmol) was heated up to 130 °C for 36 hr in sealed tube to give 87 (64 mg, 85% product ratio=15:1) after purification by FCC (hexanes:EtOAc =1:3).

Data for 87: Rf 0.55 (1:0.1 DCM: 10%NH4OH in MeOH); IR (thin film) 2966, 2935, 1728, 1370 cm−1; 1H NMR (700 MHz, CDCl3) δ 7.04 (d, J = 9.6 1 H), 5.86 (d, J = 9.6 Hz, 1 H), 4.11 (d, J = 9.6 Hz, 1 H), 4.09-4.00 (m, 2H), 3.68 (tq, J = 12.8, 7.0 Hz,
Following the general reductive alkylation procedure A, (E)-6-bromo-1-(7-ethoxy-7-oxohept-5-en-2-yl)pyridinium-3-olate (23mg, 0.07 mmol), Ag₂CO₃ (21 mg, 0.077mmol) was heated up to 130 °C for 4 hr in sealed tube to give 89 (18.6 mg, 82% product ratio=7:1) after purification by FCC (DCM:10%NH₄OH in MeOH=1:0.02 to 0.04).

Data for 89:  Rₖ 0.52 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 2969, 2939, 1730, 1372 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.23 (d, J = 9.6 1 H), 5.76 (d, J = 9.6 Hz, 1 H), 4.09-4.00 (m, 3H), 3.66 (tq, J = 12.9, 6.6 Hz, 1 H), 3.20-3.17 (m, 2H), 2.40 (td, J = 13.9 , 5.8 Hz, 1 H), 1.75 (dt, J = 13.8 , 5.3 Hz, 1 H), 1.58-1.56 (m, 1 H), 1.18 (t, J = 7.5 Hz, 3 H), 1.09 (d, J = 6.4 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 193.6, 170.9, 154.6, 126.0, 85.3, 65.3, 61.5, 53.4, 48.9, 42.5, 26.5, 25.1, 19.9, 13.8; HRMS (EI) calcd for C₁₄H₁₉NO₃Br [M⁺]:328.5048, found 328.5037.

ethyl (1S,4S,5S,6R,9aS,10S)-4,9-dimethyl-7-oxo-1,3,4,6,7,9a-hexahydro-2H-1,6-methanoquinolizine-10-carboxylate (91) To a solution of the ethyl (E)-6-hydroxyhept-2-enoate (lig, 5.8 mmol) in DCM (11.6 mL) at 0 °C was added Et₃N (1.21 mL, 8.7 mmol) and then methanesulfonyl chloride (0.68 mL, 8.7 mmol). The mixture was stirred for 1 h at 0 °C and slowly warming up to room temperature for 3hr before saturated aqueous NH₄Cl solution was added. This mixture was extracted with DCM three times. The combined extracts were washed with brine and dried over Na₂SO₄ and concentrated. The mixture of the crude corresponding methylate (50mg, 0.2 mmol), 5-methylpyridin-3-ol (48mg, 0.4 mmol) in BuCN(2drops) were heated up to 130 °C for 6 hr in sealed tube to give pyridinium oxide after purification by FCC (DCM:10%NH₄OH in MeOH=1:0.06 to 0.12). The corresponding pyridinium oxide (13.2 mg, 0.05 mmol), Ag₂CO₃ (15 mg, 0.055 mmol) was heated up to 130 °C for 12 hr in sealed tube to give 90 (18.6 mg, 75% product ratio>20:1) after purification by FCC (hexanes:EtOAc =1:3).

Data for 91:  Rₖ 0.55 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 2966, 2931, 1723, 1699, 1371 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 5.65 (s, 1 H), 4.09 (d, J = 8.2 Hz, 1 H), 4.05-4.00 (m, 2H), 3.34 (s, 1 H), 3.07 (d, J = 7.9 Hz, 1 H), 3.01-2.97 (m, 2H), 2.00 (s, 1H), 1.86-1.82 (m, 2 H), 1.58-1.57 (m, 1 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.10 (d, J = 6.4 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 195.1, 171.8, 164.3, 124.3, 67.0, 61.1, 57.6, 49.3, 38.1, 30.1, 26.7, 20.9, 20.0, 13.9; HRMS (EI) calcd for C₁₅H₂₀NO₃ [M⁺]:264.1600, found 264.1589.
Following the general reductive alkylation procedure A, 1-((2S,4R)-4-methylhex-5-en-2-yl)pyridin-1-ium-3-olate (10mg, 0.052 mmol) and Ag₂CO₃ (16 mg, 0.059mmol) in BuCN (0.4 mL) was heated up to 130 °C for 36 hr in sealed tube to give 93 (7.9 mg, 79% product ratio>20:1) after purification by FCC (pure EtOAc).

Data for 93:  R₇0.50 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 2954, 2927, 2871, 1699, 1507, 1386 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.11 (dd, J = 9.5, 6.0 Hz, 1 H), 5.90 (d, J = 9.5 Hz, 1 H), 3.66 (d, J = 7.8 Hz, 1 H), 3.54 (d, J = 5.6 Hz, 1 H), 2.92 (tq, J = 11.9, 6.6 Hz, 1 H), 2.11 (d, J = 7.0 Hz, 1 H), 1.90 (tq, J = 12.0, 6.7 Hz, 1 H), 1.78 (dd, J = 13.4, 7.4 Hz, 1 H), 1.46 (dt, J = 13.8, 4.2 Hz, 1 H), 1.40 (ddd, J = 13.4, 6.7, 1.5 Hz, 1 H), 1.06 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 199.4, 151.6, 126.6, 69.6, 64.1, 57.2, 41.3, 35.0, 34.8, 25.9, 20.5, 19.6; HRMS (EI) calcd for C₁₂H₁₈NO [M⁺]: 192.1388, found 192.1389.

Following the general reductive alkylation procedure A, a solution of the (4S)-4-methylhex-5-en-2-ol (62.6 mg, 0.55 mmol) in DCM (1.1 mL) at 0 °C was added Et₃N (0.12 mL, 0.83 mmol) and then methanesulfonyl chloride (0.06 mL, 0.83 mmol). The mixture was stirred for 1 h at 0 °C and slowly warming up to room temperature for 1 hr before saturated aqueous NH₄Cl solution was added. This mixture was extracted with DCM three times. The combined extracts were washed with brine and dried over Na₂SO₄ and concentrated. The mixture of the crude corresponding methylate (90mg, 0.47 mmol), 3-hydroxypyridine (94 mg, 0.94 mmol) in BuCN(2drops) were heated up to 130 °C for 6 hr in sealed tube to give pyridinium oxide 94* (53 mg, 53% two steps) after purification by FCC (DCM:10%NH₄OH in MeOH=1:0.08 to 0.15). The corresponding pyridinium oxide (45 mg, 0.24 mmol), Ag₂CO₃ (72 mg, 0.26 mmol) was heated up to 130 °C for 36 hr in sealed tube to give 95 (32.3 mg, 72% product ratio=3:1:1) after purification by FCC (DCM:10%NH₄OH in MeOH =1:0.05).

Data for 95:  R₇0.48 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 2955, 2922, 1694, 1381 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.08 (dd, J = 9.6, 5.9 Hz, 1 H), 5.90 (dd, J = 9.5, 1.1 Hz, 1 H), 3.81 (d, J = 6.2 Hz, 1 H), 3.56 (d, J = 8.0 Hz, 1 H), 2.99 (tq, J = 14.2, 7.4 Hz, 1 H), 2.06 (d, J = 7.0 Hz, 1 H), 1.96 (dd, J = 14.0, 7.9 Hz, 1 H), 1.37 (dd, J = 13.6, 6.7, 2.0 Hz, 1 H), 1.21 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 199.4, 151.4, 126.7, 71.3, 61.8, 55.8, 41.9, 31.4, 31.3, 24.8, 20.8, 20.0; HRMS (EI) calcd for C₁₂H₁₈NO [M⁺]: 192.1388, found 192.1384.

Following the general reductive alkylation procedure A, (E)-6-chloro-1-(7-ethoxy-2-oxohept-5-en-2-yl)pyridin-1-ium-3-olate (75mg, 0.017 mmol), Ag₂CO₃ (86 mg, 0.019mmol) was heated up to 130 °C for 36 hr in sealed tube to give 100 (48 mg, 64% product ratio=2:1) after purification by FCC (hexanes:EtOAc =1:3).
Data for 100:  \( R_f \) 0.55 (1:0.1 DCM: 10%NH₄OH in MeOH); IR (thin film) 3039, 1714, 1601, 1369 cm⁻¹; \(^1\)H NMR (700 MHz, CDCl₃) \( \delta \) 7.37 (d, \( J = 9.8 \) 1 H), 5.88 (d, \( J = 9.8 \) Hz, 1 H), 4.14-4.09 (m, 2H), 3.92 (s, 1 H), 3.75 (dq, \( J = 13.0, 6.7 \) Hz, 1 H), 3.46 (dq, \( J = 14.4 \) Hz, 1 H), 2.84 (s, 1 H), 2.05 (dd, \( J_d = 13.0, 5.8, 2.0 \) Hz, 1 H), 1.86-1.75 (m, 5H), 1.30 (dd, \( J = 14.4, 5.9 \) Hz, 1 H), 1.25 (t, \( J = 6.8 \) Hz, 3 H), 1.23 (d, \( J = 7.2 \) Hz, 3 H); \(^{13}\)C NMR (175 MHz, CDCl₃) \( \delta \) 195.8, 169.9, 157.8, 126.9, 87.3, 72.4, 62.7, 61.5, 51.2, 39.0, 27.1, 22.2, 19.6, 14.1; HRMS (EI) calcd for C\(_{14}\)H\(_{19}\)NO\(_3\)Cl \([\text{M}+]: 284.1053\), found 284.1048.

\((1S,4S,5S,6R,9aR,10S)-4,10\text{-dimethyl-1,3,4,9a-tetrahydro-2H-1,6-methanoquinolizin-7(6H)-one} \) (102) Following the general reductive alkylation procedure A, \((E)-1-(hept-5-en-2-yl)pyridin-1-ium-3-olate \) (9mg, 0.05 mmol), Ag\(_2\)CO\(_3\) (15 mg, 0.055mmol), and trace of BHT in BuCN (0.5 mL) was heated up to 130 °C for 24 hr, then 150 °C for 24 hr in sealed tube to give 102 (4.6 mg, 51% product ratio=15:1) after purification by FCC (DCM:10%NH\(_4\)OH in MeOH=1:0.04 to 0.06).

Data for 102:  \( R_f \) 0.55 (1:0.1 DCM: 10%NH\(_4\)OH in MeOH); IR (thin film) 2966, 2931, 2862, 1693, 1507, 1383 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.17 (dd, \( J = 9.6, 5.9 \) 1 H), 5.99 (dd, \( J = 9.8, 1.0 \) Hz, 1 H), 3.86 (d, \( J = 7.9 \) Hz, 1 H), 3.42 (d, \( J = 6.2 \) Hz, 1 H), 2.99 (tq, \( J = 12.4, 7.0 \) Hz, 1 H), 2.34 (dq, \( J = 15.5, 8.0 \) Hz, 1 H), 2.03 (s, 1 H), 1.78 (dd, \( J = 13.4, 7.4 \) 1 H), 1.83-1.72 (m, 1H), 1.51 (dd, \( J = 13.8, 5.7, 1.2 \) 1 H), 1.24-1.19 (m, 1H), 1.09 (d, \( J = 6.4 \) Hz, 3 H), 0.96 (d, \( J = 7.7 \) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 198.5, 152.1, 129.2, 69.9, 69.4, 57.5, 42.0, 37.1, 30.9, 27.0, 20.0, 17.5; HRMS (EI) calcd for C\(_{12}\)H\(_{18}\)NO \([\text{M}+]: 192.1388\), found 192.1382.

\((1S,4S,5S,6R,9aR,10R)-4,10\text{-dimethyl-1,3,4,9a-tetrahydro-2H-1,6-methanoquinolizin-7(6H)-one} \) (104) Following the general reductive alkylation procedure A, \((Z)-1-(hept-5-en-2-yl)pyridin-1-ium-3-olate \) (9mg, 0.05 mmol), Ag\(_2\)CO\(_3\) (15 mg, 0.055mmol), and trace of BHT in BuCN (0.5 mL) was heated up to 130 °C for 24 hr, then 150 °C for 24 hr in sealed tube to give 104 (2.1 mg, 23% product ratio=8:1) after purification by FCC (DCM:10%NH\(_4\)OH in MeOH=1:0.04 to 0.06).

Data for 104:  \( R_f \) 0.55 (1:0.1 DCM: 10%NH\(_4\)OH in MeOH); IR (thin film) 2964, 2927, 2862, 1715, 1370 cm⁻¹; \(^1\)H NMR (800 MHz, CDCl₃) \( \delta \) 7.03 (dd, \( J = 9.6, 5.8 \) 1 H), 5.90 (d, \( J = 9.4 \) Hz, 1 H), 3.62 (d, \( J = 5.6 \) Hz, 1 H), 3.26 (brs, 1 H), 3.06 (tq, \( J = 13.4, 6.8 \) Hz, 1 H), 2.27 (m, 1 H), 2.04 (brs, 1H), 1.91-179 (m, 2H), 1.52 (m, 1H), 1.14 (m, 1H), 1.28 (d, \( J = 7.4 \) Hz, 3 H), 1.06 (d, \( J = 6.8 \) Hz, 3 H); \(^{13}\)C NMR (200 MHz, CDCl₃) \( \delta \) 199.5, 150.4, 127.0, 70.5, 70.1, 57.3, 36.4, 35.6, 30.9, 27.2, 26.4, 20.1, 11.2; HRMS (EI) calcd for C\(_{12}\)H\(_{18}\)NO \([\text{M}+]: 192.1388\), found 192.1384.
The Crystal data of compound 87

cu_osu41_0m.res created by SHELXL-2014/7

TITL cu_osu41_0m in P2(1)/c
CELL 1.54178 6.4248 10.6067 20.8894 90.000 94.550 90.000
ZERR 4.00 0.0002 0.0003 0.0006 0.000 0.002 0.000
LATT 1
SYMM -x, y+1/2, -z+1/2
SPAC C H N O Cl
UNIT 56 72 4 12 4
L.S. 10
ACTA
BOND $H
FMAP 2
PLAN 20
EQIV $1 -x+1, y+1/2, -z+1/2
HTAB C7 O1_$1
EQIV $2 -x, y-1/2, -z+1/2
HTAB C10 O2_$2
CONF
HTAB
SIZE 0.020 0.040 0.040
TEMP -100.000
WGHT 0.064800 0.430300
FVAR 0.16073
CL1 5 0.232430 0.254902 0.442254 11.00000 0.04015 0.03346 = 0.02804 -0.00749 0.0002 0.00095 0.00095
O1 4 0.546234 0.002240 0.237209 11.00000 0.02652 0.03695 = 0.04593 -0.00731 0.01357 0.00183
O2 4 -0.067373 0.205627 0.206522 11.00000 0.03832 0.03492 = 0.03022 0.00618 0.00129 0.00959
O3 4 0.081347 0.024128 0.178154 11.00000 0.04783 0.03549 = 0.02265 0.00212 0.00913
N1 3 0.317354 0.046685 0.373198 11.00000 0.01937 0.02449 = 0.02369 0.00043 -0.00010 -0.00030
C1 1 0.213380 0.170698 0.366949 11.00000 0.02305 0.02531 = 0.02347 -0.00319 0.00146 0.00099
C2 1 -0.012580 0.137285 0.341770 11.00000 0.02097 0.02978 = 0.02408 0.00048 0.00214 0.00374
C3 1 -0.119706 0.066302 0.394109 11.00000 0.01859 0.04282 = 0.02607 0.00034 0.00297 -0.00196
C4 1 -0.001422 -0.055019 0.413250 11.00000 0.02833 0.03562 = 0.00399 0.00392 0.00383 -0.00757
C5 1 0.234555 -0.033892 0.423911 11.00000 0.02753 0.03028 = 0.02253 0.00291 -0.00048 -0.00326
C6 1 0.355491 -0.156846 0.429415 11.00000 0.03387 0.03467 = 0.03427 0.00968 -0.00336 0.00116
C7 1 0.323289 0.251050 0.320566 11.00000 0.02398 0.02298 = 0.03265 0.00013 0.00074 -0.00288
C8 1 0.431592 0.199221 0.275925 11.00000 0.02198 0.02826 = 0.03543 0.00384 0.00534 -0.00334
C9 1 0.428854 0.060629 0.268977 11.00000 0.01850 0.02951 = 0.02760 0.00014 0.00154 0.0062
C10 1 0.263787 -0.001021 0.306948 11.00000 0.01923 0.02076 =
0.02588 -0.00003  0.00051  0.00018
C11 1  0.034603  0.047197  0.286814  11.00000  0.01873  0.02524 =
  0.02467  0.00106  0.00148  -0.00090
C12 1  0.007619  0.104469  0.220476  11.00000  0.01890  0.03097 =
  0.02582  0.00051  -0.00037  0.00018
C13 1  0.082967  0.066437  0.111999  11.00000  0.07931  0.05157 =
  0.02343  0.00686  0.00703  0.02118
C14 1  0.237895  -0.011623  0.080175  11.00000  0.07601  0.06209 =
  0.03644  0.00220  0.01778  0.00900
H2  2  -0.094570  0.212244  0.325395  11.00000  0.02576
H3A 2  -0.129425  0.123293  0.430674  11.00000  0.04077
H3B 2  -0.252887  0.048688  0.380051  11.00000  0.03710
H4A 2  -0.051138  -0.090565  0.452975  11.00000  0.02882
H4B 2  -0.032322  -0.114700  0.381345  11.00000  0.02253
H5  2  0.265526  0.010512  0.464810  11.00000  0.02370
H6A 2  0.318085  -0.200312  0.466930  11.00000  0.04077
H6B 2  0.332212  -0.210518  0.391125  11.00000  0.03220
H6C 2  0.501533  -0.141965  0.434038  11.00000  0.05303
H7  2  0.308647  0.340351  0.325211  11.00000  0.02943
H8  2  0.507163  0.248688  0.247729  11.00000  0.03704
H10 2  0.271308  -0.087640  0.304171  11.00000  0.01921
H11 2  -0.058661  -0.243732  0.285725  11.00000  0.02442
H13A 2  -0.054998  0.061897  0.093935  11.00000  0.06948
H13B 2  0.129278  0.149036  0.110572  11.00000  0.06971
H14A 2  0.207135  -0.105608  0.083051  11.00000  0.08440
H14B 2  0.244959  0.021120  0.034066  11.00000  0.08284
H14C 2  0.371780  0.012693  0.101737  11.00000  0.07268
HKL  4  1  1  0  0  0  1  0  0  0  1

REM cu_osu41_0m in P2(1)/c
REM R1 =  0.0371 for    2222 Fo > 4sig(Fo)  and  0.0422 for all    2498 data
REM    244 parameters refined using      0 restraints
END

WGHT      0.0632      0.4528

REM Instructions for potential hydrogen bonds
HTAB C7 O1_$1
HTAB C10 O2_$2

REM Highest difference peak  0.288, deepest hole -0.200, 1-sigma level  0.047
Q1  1  0.1482  0.0245  0.2949  11.00000  0.05  0.29
Q2  1  0.0108  0.0903  0.3131  11.00000  0.05  0.27
Q3  1  0.2776  0.0034  0.3978  11.00000  0.05  0.26
Q4  1  0.2835  0.2129  0.3456  11.00000  0.05  0.25
Q5  1  0.1188  0.0399  0.4226  11.00000  0.05  0.24
Q6  1  0.2726  0.1125  0.3742  11.00000  0.05  0.24
Q7  1  0.3359  0.0319  0.2890  11.00000  0.05  0.23
Q8  1  0.0936  0.1676  0.3603  11.00000  0.05  0.23
Q9  1  -0.0652  0.1013  0.3657  11.00000  0.05  0.22
Q10 1  0.3133  0.2192  0.2815  11.00000  0.05  0.21
Q11 1  0.4355  0.0504  0.3777  11.00000  0.05  0.20
Q12 1  0.4379  0.1299  0.2780  11.00000  0.05  0.20
Q13 1  0.0181  0.0778  0.2577  11.00000  0.05  0.19
| Q14 | 1 | 0.2914 | 0.0232 | 0.3449 | 11.00000 | 0.05 | 0.19 |
| Q15 | 1 | -0.0662 | 0.0024 | 0.3976 | 11.00000 | 0.05 | 0.17 |
| Q16 | 1 | 0.2113 | 0.2081 | 0.4002 | 11.00000 | 0.05 | 0.16 |
| Q17 | 1 | 0.2714 | 0.0818 | 0.1012 | 11.00000 | 0.05 | 0.16 |
| Q18 | 1 | 0.0075 | 0.1316 | 0.1024 | 11.00000 | 0.05 | 0.15 |
| Q19 | 1 | 0.2772 | -0.0985 | 0.4211 | 11.00000 | 0.05 | 0.15 |
| Q20 | 1 | 0.2973 | 0.1401 | 0.1130 | 11.00000 | 0.05 | 0.15 |