Intramolecular C-N Bond Formation: Reactivity and Selectivity of Iodine(III) Oxidants in the Generation of Carbamate-Derived Nitrenes

Alexander Wesley Bunnell
Bard College, ab0555@bard.edu

Follow this and additional works at: https://digitalcommons.bard.edu/senproj_f2019

Part of the Organic Chemistry Commons

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 4.0 License.

Recommended Citation
https://digitalcommons.bard.edu/senproj_f2019/52

This Open Access work is protected by copyright and/or related rights. It has been provided to you by Bard College's Stevenson Library with permission from the rights-holder(s). You are free to use this work in any way that is permitted by the copyright and related rights. For other uses you need to obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/or on the work itself. For more information, please contact digitalcommons@bard.edu.
INTRAMOLECULAR C-N BOND FORMATION: REACTIVITY AND SELECTIVITY OF IODINE(III) OXIDANTS IN THE GENERATION OF CARBAMATE-DERIVED NITRENES

Senior Project Submitted to
The Division of Science, Mathematics, and Computing
of Bard College

By
Alexander Wesley Bunnell

Annandale-on-Hudson, New York
December 2019
Acknowledgements

There are too many people that I would like to thank over the course of my time in the Hudson Valley.

Dad, thank you for supporting me in my decision to come to Bard. You did everything in your power to make sure that I remained at school. You worked and worked and worked and always managed to find ways to keep me up here. If it wasn’t for you, I’d probably be graduating from SCSU (no disrespect). Words can’t describe how much I appreciate everything that you’ve done for me. I love you. And I guess Zac and Jeremy too.

To Grandma, thank you for saving up money for me since I was born. You allowed me to experience my first year of college without having to worry about anything else. I know Grandpa would be proud of me and I love you both.

Mom, even though you never had the chance to really visit Bard or see any of my games, thank you for supporting me from afar. I love you and I miss you.

To my teammates and coaches, thank you for making sure I always had 30-something friends no matter the circumstances. You’ve brought me some of my favorite moments through the four years at Bard and I can’t wait to see what is in store for all of us. FV.

The same applies to all of my friends I have made over my four years at Bard. You opened me up to experiences and lifestyles which I never could have imagined that would happen.

Emma, thank you for always being there for me, allowing me to vent about this project. Hopefully, you’ll be around for me to continue to complain and vent about my chemistry woes. Just stop moving further and further away from me, please.

Lastly, thank you to everyone in the chemistry department for helping cultivate my passion for chemistry. This is especially true for you, Emily. You took me under your wing as an advisee as I came back from my break and ensured that I wouldn’t be left behind. Your energy and liveliness always inspired me to grow in and outside of the lab. Without your guidance, I’m not quite sure if I would have completed this project.
Table of Contents

Abstract
Introduction
Results and Discussion
Conclusions and Future Work
Experimental Methods
References
Appendix
Abstract

Nitrogen-containing compounds play a critical role in the world, ranging from Earth’s atmosphere to the backbone of amino acids, the ‘building blocks of life.’ Opioids like morphine and anti-cancer agents like mitomycin are just two examples of the plethora of naturally occurring, small molecules with carbon-nitrogen bonds, essential for potent bioactivity. Though ubiquitous in nature, small molecules with carbon-nitrogen bonds are often difficult to prepare in the laboratory. Arguably, the most efficient means to do this is through the use of nitrene intermediates. Nitrenes are neutral, monovalent, high-energy species that can be used for rearrangement and insertion into a variety of bonds, such as alkenes. Reactions reliant on the use of nitrenes often lack regiocontrol and selectivity. In this work, we investigate the formation of a nitrene intermediate by oxidation of carbamates using a hypervalent iodine oxidant and subsequent transfer to an alkene using a rhodium catalyst, resulting in a bicyclic three-membered ring containing nitrogen, known as an aziridine. Aziridines, in general, can then be used as a scaffold on which a variety of more complex, unique compounds can be synthesized. During the optimization of this process, we have learned that the identity of the hypervalent iodine oxidant is crucial, for which the current results are presented. We also report that suggest a bulkier, hypervalent iodine oxidant is most effective in nitrene generation and subsequent C-N bond formation.
I. Introduction

A. Nitrenes

Nitrogen, arguably, is one of the most important and essential building blocks for life as we know it. Not only does it form the basis for proteins, which all living things need to survive, but it is also needed by plants to grow and sustain life. Using the industrial Haber-Bosch process, the widespread availability of ammonia, a nitrogen-containing fertilizer, jumped. As a result, crop yields soared and allowed for the world’s population to skyrocket.¹

\[
\begin{align*}
N=\mathbf{N} & \quad + \quad 3\mathbf{H-H} \quad \rightarrow \quad 2\quad \mathbf{H-N} \quad \mathbf{H} \\
\end{align*}
\]

**Scheme 1:** Simplified equation of Haber-Bosch process

Due to nitrogen’s importance in life as we know it, the quest for the synthesis of uncomplicated and accessible nitrogen-containing bonds, specifically carbon-nitrogen bonds, is ever more crucial. Nitrene insertion reactions are arguably the most efficient method for the formation of these bonds. Generally, any type of radical reaction will react swiftly, but with little selectivity. Nitrene insertion reactions are no different, but with coordination to a metal complex, the generation and following reaction can be controlled.² Azides are typically the precursor of choice for the formation of nitrenes due to their “pre-oxidized” nature, benchtop stability, and release of harmless nitrogen gas as a byproduct of many reactions.

Nitrenes themselves are neutral, monovalent, electron-deficient nitrogen atoms with six valence electrons.³ These can be said to be “cousins” to the carbene, a neutral, divalent, electron-deficient carbon-containing species. Both species are isoelectronic and have similar synthetic applications with respect to carbon versus nitrogen usage. Like the carbene, there are two distinct
electron configurations in which the nitrene can exist, the triplet and singlet excited state. In the singlet excited state, two sets of nonbonding paired electrons occupy two separate orbitals. In the triplet excited state, two nonbonding electrons occupy one orbital, exhibiting anti-parallel spins, while the two other nonbonding electrons occupy two orbitals, exhibiting parallel spin. The free triplet nitrene is more thermodynamically favorable as it satisfies Hund’s rule, while the free singlet nitrene does not maximize the total spin of the system, disobeying Hund’s rule. As a result, free singlet nitrenes happen to be slightly more reactive than free triplet nitrenes, while free triplet nitrenes are more stable.

Scheme 2: Free singlet versus triplet nitrene configuration

Due to their reactive nature, nitrenes are an intermediate that will readily insert into varying bonds, such as C-H or C=C bonds to form C-H aminated products or aziridines, respectively. While in general, nitrenes will add directly to olefins to provide direct aziridination, the specific type of nitrene plays a role in the stereochemical consequences of the reaction. A singlet nitrene is able to insert into an alkene in a concerted mechanism. As the bonding lone pair of the nitrene attacks the electron-rich alkene, the alkene is simultaneously able to donate to the empty bonding orbital. The concurrent reaction is then diastereoselective, a highly sought-after characteristic of any synthetic route, providing a diastereopure aziridine (Scheme 3).
On the other hand, the free triplet nitrene has been shown to react following a stepwise, diradical reaction. Due to the fact that the triplet nitrene has two unpaired electrons in two separate bonding orbitals, one electron at a time reacts radically with the alkene. The lack of a concerted mechanism allows the alkene to undergo bond rotation (Scheme 4). As a result, the aziridine is afforded in a racemic mixture, a scenario in which the most contributing factor in stereoselectivity is whether the nitrene is singlet or triplet in nature.

B. Aziridines and Aziridination

As mentioned in the previous section, nitrenes can primarily either insert into a carbon-carbon pi bond or a carbon-hydrogen sigma bond. If the nitrene imbeds into the olefin, the resulting product is an aziridine. Pictured above, aziridines are three-membered nitrogen heterocycles. The simplest version, ethyleneimine, is water-soluble, odorless, and colorless. In nature, the aziridine has been most commonly found in particular species of the genus Streptomyces, a gram-positive bacterium. Two distinct categories of aziridine-containing compounds extracted from these bacteria have been characterized and shown to exhibit anti-cancer
uses, mitomycin and azinomycin. The compounds, specifically the ring-opening capability of the aziridines, act as powerful alkylating agents, which act to combat cancer by adding a methyl group to the guanine base of DNA. In turn, the DNA strands split open, preventing the cancerous cell from multiplying. Due to these discoveries, derivatives of these compounds have been synthesized and studied intensively for increased potency.

Figure 1: Structures of aziridine-containing anti-cancer medications

Besides aziridines being a critical piece of some anti-tumor medications, they also serve as important synthetic intermediates for the formation of a multitude of distinct functional groups. The ring strain from a three-membered ring is relatively high compared to rings of other sizes, which makes aziridines primed to undergo a myriad of ring-opening reactions, dependent on the reaction conditions. The aziridination and subsequent opening of the ring allow for facile and quick addition of a carbon-nitrogen bond and another, distinct functional group.
Scheme 5: Ring-opening reactions of aziridines

To generalize, there are five major ways to undergo an aziridination reaction. These reactions are either by addition to imines through a carbene or an ylide, from a 1,2 aminoalcohol or 1,2 aminohalide, a 1,2 azidoalcohol, an α-bromoacrylate, or a nitrene method. While all reactions have their own synthetic benefits and drawbacks, nitrene insertion reactions into an olefin are arguably the most efficient means of producing an aziridine, which is why they are of particular interest for the project at hand. In order to form a nitrene, particular compounds are utilized as nitrene precursors. These compounds are routinely referred to as “unoxidized” or “pre-oxidized”, based on the nature of the nitrogen. Routinely used pre-oxidized nitrene precursors are azides, which have long been studied in aziridination reactions. Although a majority of azides are acutely toxic, the benefit of working with azides includes the emission of nitrogen gas, which is harmless, when aziridination occurs and the relative bench stability of azides at room temperature. The azide is normally activated via photochemical or thermal means in order to form the nitrene. However, unoxidized nitrene precursors have gained popularity in the creation of nitrenes and are particularly...
the focus of our research. Carbamates and sulfamates, specifically, have been of interest in the past twenty years for the formation of aziridines (Figure 2). In short, the unoxidized precursor is oxidized \textit{in situ} to form the nitrene (singlet or triplet) and then reacts with the olefin to undergo aziridination. A deeper, mechanistic investigation into nitrene generation will be discussed in subsequent sections.

![Figure 2: Two unoxidized nitrene precursors](image)

**Figure 2: Two unoxidized nitrene precursors**

The Du Bois lab made a sizeable impact in the field of aziridination through the development of conditions originally created to study C-H amination reactions via sulfamate esters. This created a set of conditions that, within the past 20 years, have primarily been used and tested to investigate aziridination with hypervalent iodine oxidants. These conditions, at a minimum, included a hypervalent iodine oxidant and a rhodium catalyst.

![Scheme 6: Du Bois intermolecular aziridination](image)

**Scheme 6: Du Bois intermolecular aziridination**

Concurrently, the Dauban lab was focused on aziridination of sulfamate esters with slightly different reaction conditions, testing if the reaction could be carried out intramolecularly. Instead of a rhodium catalyst, a copper catalyst was utilized, as well as iodosylbenzene, the simplest known hypervalent iodine oxidant. Both labs reported isolated aziridine yields in the 90% range, establishing that aziridination of sulfamate esters could be accomplished by deploying multiple synthetic systems. Carbamates, on the other hand, played second fiddle to sulfamate esters in terms
of C-H amination and aziridination reactions, as they typically require the usage of higher catalyst loadings and reaction temperatures than the sulfamate esters.\textsuperscript{11} It was not until the Padwa lab delved into carbamates that the substrate entered the intramolecular aziridination conversation. Using very similar conditions to Du Bois, the group showed that intramolecular aziridination from carbamates was feasible, reporting a 75\% isolated yield of the aziridine product.\textsuperscript{12} That product could then react with a nucleophile to open the aziridine with isolated yields in the 80\% range.

Scheme 7: Padwa intermolecular aziridination with carbamates\textsuperscript{12}

C. Hypervalent Iodine Reagents

The very crux of the creation of these reactive nitrone species that were used for aziridination reactions in the Du Bois, Padwa, and Dauban labs were the hypervalent iodine reagents that were briefly mentioned before. When learning about the element iodine, it is generally not the focus of any undergraduate course, other than the fact that it is a halide, makes one bond, and that it is a good leaving group, particularly in S\textsubscript{N}2 type reactions. However, hypervalent iodine reagents lend themselves to breaking any preexisting stereotypes that the halides may have. Hypervalent iodine reagents are compounds in which iodine is bonded to three or even five other species, breaking the traditional valency rules for p-block elements. The element is able to do this because of its large size. A three-center-four electron (L-I-L) bond can be formed with the 5p orbital of iodine with the orbitals of the other ligands, in lieu of pi-bonding that takes place in lighter p-block elements.\textsuperscript{13} It is also the large size of iodine that allows these compounds to act similarly to other transition metal species in terms of reactivity. Compared to these transition
metal species, hypervalent iodine compounds are environmentally benign and inexpensive\textsuperscript{14}, making them an ever-growing area of study. A majority of these iodine(III) reagents can be synthesized with relative ease and are bench stable, making them uncomplicated to work with.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Common $\lambda^3$-Iodanes}
\end{figure}

Hypervalent iodine reagents, importantly, serve as the means to oxidize sulfamates or carbamates \textit{in situ} to produce nitrenes for aziridination or C-H amination reactions. While iodosylbenzene (PhIO) has been extensively used in these types of reactions\textsuperscript{11,15}, (diacetoxyiodo)benzene [PhI(OAc)\textsubscript{2}] is the common choice of oxidant for these reactions. Due to the overlap between the 5p orbital of the iodine and orbitals on the ligand, the hypervalent bond formed is polarizable and weaker than a normal covalent bond between two atoms\textsuperscript{13}. This allows the hypervalent iodine reagent to easily undergo ligand exchange with the carbamate or sulfamate ester to form an iminoiodinane, a nitrene-containing species.
In the scheme above, one equivalent of the iminoiodinane and two equivalents of acetic acid are formed. The acetic acid byproduct is of concern in these aziridination reactions, as the acid could cause the aziridine to open up, decreasing the efficiency of the reaction if preventative measures are not taken (i.e.: the addition of molecular sieves\textsuperscript{15} or a weak base such as magnesium oxide\textsuperscript{10}). It is that acetate group, or more broadly, the ligands of the hypervalent iodine reagents that are of particular interest in this project. The effect that these different hypervalent iodine reagents have in relation to aziridination and C-H amination reactions has been fairly unexplored, with this project hopefully adding to the knowledge that is available.

**D. Rhodium Catalyst**

The last component to these aziridination reactions that has not been discussed is the use of a rhodium catalyst. Rhodium, element 45, is typically found when mining platinum or nickel, and generally has its use in catalytic converters in automobiles, reducing nitrogen oxides in exhaust. While the identity of the rhodium species in different reaction conditions may change, the most commonly used compound for aziridination is dirhodium tetraacetate, Rh\textsubscript{2}(OAc)\textsubscript{4}. Rh\textsubscript{2}(OAc)\textsubscript{4} is a dimer that can be characterized as a “paddlewheel” compound. Each of the four acetate ligands are attached to the four faces of the rhodium atoms, giving the “paddlewheel” moniker. Each of the rhodium atoms exhibits octahedral geometry and a bond length of 2.39 Å between the two metal atoms.\textsuperscript{16}
As the figure above shows, these catalysts have an open axial site on the sides of the molecule. Solvents, substrates, and other compounds can coordinate to this site. When a species does coordinate to the site, the oxidation state of one of the rhodium atoms can increase, which can be easily be spotted by a change in color from a forest green to a brick red. Specifically, these types of carboxylate-derived rhodium catalysts serve to function to stabilize a free nitrene. As mentioned before, nitrenes are a highly reactive species and could, without much chemoselectivity, lead to unwanted products or even decompose. However, by coordinating to the site, the nitrene is stabilized due stabilizing pi orbital interactions, helping to ensure the appropriate reaction occurs.

The process by which this happens first starts with the formation of the iminiodinane (Scheme 8). The formation of the iminiodinane is reported to be the rate-determining step. Once that formation takes place and the addition of the rhodium catalyst is completed, a metal-phenyliodinane entity is created. Rapidly after the creation of the metal-phenyliodinane, iodobenzene leaves due to an increase in entropy, leaving the metal-nitrene species. It is this metal-nitrene complex that reacts with the olefin to undergo aziridination. The complex must be stable enough for the nitrene to exist when the olefin is presented, but not too stable as to allow the reaction to occur.
While an acetate ligand has been used most predominantly in the current literature surrounding aziridination reactions, it is not the only available rhodium dimer. Due to the facile nature of ligand exchange of the catalyst, numerous ligands could be employed, which can affect whether a reaction proceeds to form an aziridine or C-H amination product.

**E. Advances in Intramolecular Aziridination of Unoxidized Nitrene Precursors**

Since the initial publication of the seminal articles in the field of carbamate-derived nitrenes via hypervalent iodine oxidants, there has been much work done either directly modifying the classic Du Bois conditions or developing novel conditions with the basis of a metal catalyst, hypervalent iodine species, and a carbamate substrate.

Humphries et al., in 2006, published a deeper investigation into the aziridination of homoallylic carbamates mediated by a rhodium catalyst and hypervalent iodine oxidant, a substrate not touched upon by Padwa. Using the Du Bois conditions and the same substrate which this senior project is primarily focused on, Humphries achieved a 45% isolated yield of aziridine product and 19% of a C-H amination product.

**Scheme 9: Coordination of metal-nitrene**

**Scheme 10: Humphries-adapted Du Bois reaction**
The aziridination reaction was diastereoselective and dependent on the *cis* or *trans* nature of the olefin, meaning that each isomer would only yield one set of enantiomers. Humphries then shifted from Du Bois conditions to Padwa-like conditions, applying the usage of iodosylbenzene instead of PhI(OAc)₂. However, the traditional usage of Rh₂(OAc)₄ was replaced with other “paddlewheel” dirhodium catalysts, like Rh₂(Oct)₄ and Rh₂(S-TBSP)₄. The weak electron-donating carboxylate ligands like octanoate and S-TBSP contributed to the shift in yield of products to favor aziridination in various other homoallylic carbamate substrates. In their optimization reactions under these Padwa conditions, they lastly found that for any reaction to occur with the homoallylic car bamates, there must be a rhodium catalyst present, even under thermal heating.

Work by Moriarty et al. and Deng et al., however, show that metal-free aziridination using pre-oxidized nitrene precursors and hypervalent iodine oxidants is possible. Not unlike the Du Bois group and their original focus on C-H amination reactions, the Moriarty group had focused on an analogous reaction, cyclopropanation. Comparable to aziridination reactions, those cyclopropanation reactions occurred both in and without the presence of a metal catalyst, such as rhodium or copper. The same approach led to the investigation of metal-free aziridinations of sulfonamides with the usage of iodosylbenzene, a source of protons, and 4 Å molecular sieves in dichloromethane, DCM. Different sulfonamide substrates led to bicyclic or tricyclic aziridine structures in conversion upwards of 100%, with conformationally rigid systems found to be more favored substrates for aziridination. However, a different explanation of how the reaction proceeded was warranted for this new finding. In fact, two possibilities are presented. First, iodosylbenzene could be reduced by the source of protons added into the reaction, leaving a
positively-charged iodine species with two bonds. This species and the nitrogen of the sulfonamide then would attack the olefin, resulting in the formation of water, iodobenzene, and the aziridine.

Conversely, the sulfonamide can react with the iodosylbenzene reversibly to form an iminoiodinane and water, the same process as a metal-catalyzed reaction. From there the iminoiodinane can react directly with the olefin to form the aziridine. This direct reaction is thought to form via a 2+2 addition reaction,\textsuperscript{20} shown by Scheme 11 below. Essentially, the 2+2 addition bypasses the need for a metal catalyst to act as a stabilizing force for the nitrene species.

\textbf{Scheme 11: 2+2 Addition of an iminoiodinane}

Work done by Deng et al. took the successful methodology discovered by Moriarty and applied it to allylic carbamates. No matter the steric or electronic differences of the allylic carbamate, the iodosylbenzene/molecular sieve combination afforded pure diastereoselective aziridines in yields around 95\%.\textsuperscript{19} These reactions also had the added bonus of being experimentally easy to perform, only needing to undergo basic filtration to recover the aziridine.

In addition to rhodium and metal-free aziridination reactions of sulfamates and carbamates, silver-mediated reactions have recently garnered interest for their versatility. Specifically, the Schomaker group has capitalized on the potential of silver-catalyzed aziridination reactions. Using the same homoallylic carbamate that Humphries had first shown could undergo aziridination via Du Bois conditions, Schomaker was able to “tune” the silver catalyst by the changing of the respective ligands in a way that would yield aziridine product in high enantiomeric excess.\textsuperscript{21} Previous studies in the group had shown that a low coordination silver complexes would favor
aziridination and higher coordination silver complexes would favor C-H amination products. With this in mind, they screened silver salts and separate nitrogen-chelating ligands in conjunction with iodosylbenzene to optimize the reaction conditions. The combination of yield, enantiomeric excess, and price lead to AgClO₄ and a tert-butyl-containing bis(oxazoline) ligand to be sufficient for substrate screenings.

Scheme 12: Silver-catalyzed aziridination

In a later paper written by the group, the reasons for the tunability of this reaction is explored. The silver species with one ligand happens to favor aziridination, where the species with two ligands favors C-H amination in the same substrate. Through both computational and mechanistic studies, both types of silver catalyst were shown to create an electronically similar nitrene, meaning that the nitrene species itself is not responsible for the chemoselectivity. Rather, it is the steric surroundings surrounding nitrene species that determines whether an aziridination or C-H amination reaction moves forward. These silver-catalyzed reactions have also shown to be effective with allenic carbamates as nitrene precursors. Allenic carbamates can undergo aziridination via a rhodium catalyst in conjunction with a hypervalent iodine oxidant, yet the success often depends on the substitution of the substrate. Robertson et. al showcased that principle, with Du Bois like conditions yielding at most a 20% isolated yield of the aziridine. Unsurprisingly, once again the Schomaker group saw that the silver catalyst and BOX ligand significantly improved yields, regardless of the substitution of the substrate.
The work done by Schomaker is closely tied in with work done by Zhang et al. Both groups provide how the influence of ligands can sway the reaction to either provide aziridines or C-H amination products. Zhang provides computational and experimental studies of three rhodium catalysts [Rh$_2$(OAc)$_4$, Rh$_2$(NHCOCF$_3$)$_4$, Rh$_2$(NCH$_3$CHO)$_4$] under classic Du Bois conditions and studied whether C-H amination or aziridination was favored with a sulfamate ester substrate. What both aspects of the study showed was that while Rh$_2$(OAc)$_4$ showed no real preference, Rh$_2$(NHCOCF$_3$)$_4$ clearly favored aziridination and Rh$_2$(NCH$_3$CHO)$_4$ overwhelmingly underwent C-H amination. The studies showed that weak electron-donor catalysts would promote aziridination, like Rh$_2$(NHCOCF$_3$)$_4$. Rhodium catalysts, with this work, could then be designed with both the substrate and desired product in mind to ensure efficiency.

F. Previous Work

Work done previously in the McLaughlin lab has focused on the aziridination of benzylic and phenylic carbamates via Du Bois derived conditions. Using a synthetic pathway put forward by Fletcher$^{25}$, Atuk$^{26}$ performed aziridination trials from the substrate below (Scheme 13).

![Scheme 13: Pathways for Atuk’s reaction](image)

In a novel approach, the reaction was facilitated using microwaves as a source of heat. The microwave-mediated aziridination attempts gave impure aziridine product in a yield of 30%, even after optimization trials changed the catalyst loading, the temperature of the microwave, and the identity of the metal catalyst. The carbamate substrate was not fully consumed under any of those
conditions. While $^1$H NMR did show characteristic signs of aziridination, with peaks ranging from 2.5 - 4.0 ppm, there was also a peak at 10.5 ppm. This peak was thought to be characteristic of an aldehyde, which excessive oxidation of the carbamate will produce. Although the by-products of these reactions were not characterized, it is believed that acetic acid, a byproduct of iminooiodinane formation, opened the aziridine ring, decreasing overall yield of the reactions.

Lasky$^{27}$ similarly was concerned with benzylic carbamate substrates, although instead of a terminal alkene at the 2-position on the benzene ring, an ester was purposefully included to provide a more substituted and electron-rich group that could possibly react with the electrophilic nitrene species. Once again, employing Du Bois based conditions, a mixture of cis/trans isomers in the carbamate substrate yielded a 10% yield of diastereomeric aziridine isomers as a crude product.

Scheme 14: Microwave-mediated aziridination of benzylic carbamate

Full characterization was achieved of the aziridine products. $^1$H NMR showed a retention in the ratio of diastereomers, alluding to the fact that this process most likely proceeds via a concerted, singlet nitrene intermediate. From that point, the phenylic version of the carbamate substrate in Scheme 14 was synthesized and used for further aziridination optimization reactions. Instead of a slightly-strained seven-member bicyclic aziridine species, a more favorable six-membered ring would prevail. Two trials in the microwave, following the same procedure as the benzylic carbamate, showed decomposition of the starting material. It was hypothesized that the carbamate reacted immediately with the rhodium catalyst, which was supported by the color change of green to red almost instantaneously. $^1$H NMR kinetic trials were then run, where the
type of hypervalent iodine oxidant was adjusted and addition of Rh$_2$(OAc)$_4$ was controlled and varied. No definitive aziridine product was isolated, yet growth of peaks in a similar chemical shift to the aziridine products formed with the benzylic carbamate gave promise to the notion that aziridine product was formed, especially with PIFA [(PhI(OCOCF$_3$)$_2$] used. Further research on the phenylic carbamate synthesized by Lasky done by Bunnell and Lee showed that PhI(OPiv)$_2$ in conjunction with Rh$_2$(OAc)$_4$, was promising as an oxidant for aziridination, as crude product indicated the formation of aziridine product.

**G. Substrate Design and Other Considerations**

The further optimization of reactions previously performed by Atuk and Lasky provided a potential avenue for the exploration into the field of carbamate-derived nitrenes. However, the substrates previously used lacked a site to undergo C-H amination, another possible reaction pathway. The possible C-H amination product, in both projects, would consist of highly-strained or large rings, which simply would not be formed to do thermodynamic unfavorability. The substrates previously investigated also involved multiple step syntheses to achieve the nitrene precursor. As a result, a carbamate substrate that could undergo either aziridination or C-H amination, along with an easier synthetic route was ideal for this project.

![Figure 5: New substrate design for investigation of hypervalent iodine oxidant effect](image)

Due to the success of [Bis(acyloxy)iodo]arenes in Lasky’s previous work,$^{27}$ they were a logical starting point in determining the effect of the oxidant. Other bench-top stable hypervalent iodine oxidants were also of interest due to the ease of working with them. Lastly, a simple substrate design would allow for more investigative work to be done on the effect of the oxidant.
within the scope of aziridination versus C-H amination, making this particular substrate ideal for these studies.
II. Results and Discussion

A. Synthesis of Cis and Trans Carbamates 1 and 3

Before the core investigation was to be studied, the syntheses of 1 and 3 were needed. Again, this particular group of substrates were chosen due to the various routes the reaction could proceed. Compared to the seven-step syntheses of both benzylic and phenyllic carbamates prepared by Lasky, the one-step syntheses of both isomers were relatively simple, meaning more investigative work could be done with regard to the hypervalent iodine reagent.

Scheme 15

The formation of both 1 and 3 is the same, with the only difference being the corresponding alcohol that was used as the starting material. The procedure used for carbamate formation was adapted from Schomaker et al.24 This reaction occurs in a two-step process. First, trichloroacetyl isocyanate, a more electrophilic isocyanate, is attacked by the alcohol. Then, a base-catalyzed hydrolysis reaction with potassium carbonate facilitates the formation of 1 or 3, dependent on the cis or trans alcohol that was used as the starting material. Substrate 1 was formed in 80% yield, while 3 was formed in quantitative yield.
B. NMR Kinetic Trials of Nitrogen-Insertion Reactions

The successful formation of 1 allowed for the process and optimization of intramolecular nitrogen-insertion reactions to begin. Previous work that had been done by Lasky, Lee, and myself on the phenylic carbamate had indicated that if a reaction occurred, it happened rapidly. This is thought so because when the rhodium catalyst was added to a solution containing the carbamate, a rapid color change from forest green to brick red occurs. Although aziridination was thought to have transpired, isolation attempts were unsuccessful. Due to the swiftness of the reaction, the best course of action was thought to be monitoring the reaction via $^1$H NMR. The reaction was monitored every forty seconds for an hour and forty minutes with the hopes that peak consumption of the starting material and peak growth of any product would be seen.
Table 1: NMR Scale Screening

As Table 1 shows, all eight screenings run and monitored by NMR resulted in no reaction whatsoever. After the first four trials were run, the temperature at which the experiments happened at were steadily increased in hope to, at the very least, decompose the starting material. Nevertheless, four separate oxidants, with and without the presence of Rh₂(OAc)₄, failed to provide the conditions needed for any type of reaction to occur. These conclusions were made after analyzing the ¹H NMR spectra for each set of reaction conditions. Specifically, the peaks of interest in each spectrum were the ones signed to the alkene protons of the carbamate. Only the cis-carbamate, 1, was used in these trials, meaning the peaks of interest were located at 5.51 and 5.32 ppm. While the product of C-H insertion could have alkene peaks of similar shifts, the aziridination product would not, meaning if the aziridine had formed, the alkene peaks would shrink and eventually disappear. Yet, the peaks remained the same integration throughout the reaction period. Even though no internal standard was used, a combination of the relatively stable integration of
the starting material peaks in addition to none of the other starting material peaks decreasing or disappearing signaled no reaction had taken place. Another piece of evidence is that no new peaks formed. The lack of reactivity is thought to have occurred due to reasons such as a lack of stirring and the relatively mild conditions that the experiments were performed under.

Figure 6

C. Oxidant Screenings

Although NMR scale screening reactions were unsuccessful, there were more changes that could be made to increase the likelihood of a reaction materializing. Once again, inspiration and success derived from previous works would shape this project. The reaction conditions were changed slightly to involve the usage of a microwave as a source of heating, as well as continuously stirring the reaction solution while heating took place.
Table 2: Oxidant Screening Trials

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Heating</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)$_2$</td>
<td>µwave</td>
<td>28% isolated yield</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OPiv)$_2$</td>
<td>µwave</td>
<td>36% isolated yield</td>
</tr>
<tr>
<td>3</td>
<td>PIFA</td>
<td>µwave</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Iodosodilactone</td>
<td>µwave</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Koser’s Reagent</td>
<td>µwave</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Reaction conditions: substrate (0.75 mmol), oxidant (1.2 eq), Rh$_2$(OAc)$_4$ (4 mol%), solvent (DCM, 10 mL), time (1 hr), temperature (50ºC)

The aziridine product was fully characterized via $^1$H, $^{13}$C, COSY, HSQC, and NOESY NMR. Just as before with the NMR trials, the main indication that aziridination took place was the lack of the alkene proton peaks present in the carbamate species. While not all of the carbamate substrate was consumed during the reaction, the isolated product no longer had peaks at 5.51 and
5.32 ppm, meaning that the product formed did not have an alkene, likely forming the aziridine product. The added presence of two sets of diastereotopic protons (i/j, k/l), confirmed by COSY and HSQC, indicated the formation of a six-membered ring had taken place (Figure 6).

**Figure 6:** Characterization of 2 through $^1$H NMR

While the assignment of protons and carbons was relatively straightforward for the aziridine product, the stereochemistry determination was not. There were no NOESY correlations in the spectrum, leaving no hard evidence behind to comfortably assume stereochemistry. Yet based on previous work done in the investigation of nitrene insertion reactions, it is likely that this process occurs through a singlet nitrene. Based on the $^1$H spectrum for 2, there is just one set of peaks in the sample. Therefore, the reaction is diastereoselective. Mechanistic studies have shown that the singlet nitrene often inserts through a concerted mechanism due to the ability of the nitrene to attack the $\pi^*$ orbital of the alkene and receive of electrons from the alkene by the empty orbital. These studies corroborate the hypothesis that the reaction takes place via the insertion of a singlet
nitrene, again, due to the set of enantiomers that preferentially form from the corresponding carbamate.

Scheme 17: Aziridination Mechanism for 2

While both PhI(OAc)₂ and PhI(OPiv)₂ resulted in the yield of aziridines, it is noticeable that the pivalic species produces a higher return than the acetic species. Some explanation may come in the decreased nucleophilicity of the leaving pivalate group over the acetate group. Due to the steric bulk of the tert-butyl group, the pivalate group is slower in reacting with the substrate, nitrene, or rhodium catalyst than the acetate group. A lack of side reactions leaves more material available for aziridination. Once again, further explanations in the efficacy of the hypervalent iodine oxidants are available in the section titled “Electrochemical Trends” (Section F, pg 32).

D. Further Optimization Reactions in the Synthesis of 2

With the highest yield of the oxidant screening trials only at 36% aziridine, the search for more suitable conditions was desired.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp (ºC)</th>
<th>Heating</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>Iodosodilactone</td>
<td>1.2</td>
<td>DMSO</td>
<td>50</td>
<td>µwave</td>
<td>1</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>Koser’s Reagent</td>
<td>1.2</td>
<td>DMSO</td>
<td>50</td>
<td>µwave</td>
<td>1</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>PhI(OPiv)$_2$</td>
<td>1.2</td>
<td>CH$_2$Cl$_2$</td>
<td>80</td>
<td>µwave</td>
<td>1</td>
<td>21% yield</td>
</tr>
<tr>
<td>4</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>PhI(OPiv)$_2$</td>
<td>1.2</td>
<td>CH$_2$Cl$_2$</td>
<td>50</td>
<td>thermal</td>
<td>1</td>
<td>26% yield</td>
</tr>
<tr>
<td>5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>PhI(OPiv)$_2$</td>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>50</td>
<td>µwave</td>
<td>2</td>
<td>47% yield</td>
</tr>
<tr>
<td>6</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>PhI(OPiv)$_2$</td>
<td>4.2</td>
<td>CH$_2$Cl$_2$</td>
<td>50</td>
<td>µwave</td>
<td>6</td>
<td>21% yield</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>PhI(OPiv)$_2$</td>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>50</td>
<td>µwave</td>
<td>2</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Reaction conditions: substrate (0.75 mmol), Rh$_2$(OAc)$_4$ (4 mol%), solvent (10 mL)

All yields reported are isolated yields

**Table 3: Optimization Trials of 1**

Two trials first involved the usage of iodosodilactone and Koser’s reagent in a dimethyl sulfoxide, DMSO, to ensure complete dissolution of the oxidant. However, no reaction occurred. Focus shifted to the usage of PhI(OPiv)$_2$, as it was the most promising oxidant. Time, equivalence, temperature, method of heating, and addition of the rhodium catalyst were all investigated (Table 3). It is worth noting that even with these variables being altered, there was seemingly no increase in the conversion of the C-H insertion product. In regard to aziridination, time and equivalence of the oxidant added played the largest role in increasing the isolated yield. An increase in temperature slightly lowered the yield from the original conditions from 26% to 21%, indicating that a sizable increase in temperature may decompose the aziridine, assuming that the quality of lab work was consistent throughout each trial. The method of heating, either microwave or thermal, does not significantly change the yield of the reaction. While the reactions monitored by NMR showed no product formation under thermal heating, the simple addition of a stir bar helps drive
the reaction by promoting a homogenous reaction mixture. Although previous work by Lasky, Moriarty, and Deng was promising in the field of metal-free aziridination, this particular substrate is not available for metal-free aziridination. Moriarty had success with sulfamate esters and did not work with carbamates, while Deng had success with allylic carbamates, but with iodosylbenzene as the oxidant, not any other hypervalent iodine oxidants. Lastly, it is worth noting that both time and equivalence of the oxidant added improves the isolated yield of the aziridine, but the conditions seem to “peak” after two hours in the microwave and three equivalents of PhI(OPiv)$_2$. The addition of two equivalents of PhI(OPiv)$_2$ every two hours for six hours does slightly increase the yield, but a similar problem is observed with these conditions as the temperature is increased. It appears that after two hours, the aziridine may begin to decompose in solution, decreasing isolated yield. Therefore, the best conditions studied so far for aziridination of 2 are three equivalents of PhI(OPiv)$_2$ stirred in a microwave vial for two hours at 50ºC in the presence of Rh$_2$(OAc)$_4$ (Scheme 18).

![Scheme 18](image)

E. Aziridination Trials with Trans-Carbamate 3

With conditions proven to induce aziridination in carbamate substrate 1, the plan was then to move on to its geometric isomer 3 to study how the stereochemistry of the reaction is affected. As mentioned in the first section of the discussion, synthesis of the trans-carbamate 3 was facile and followed the same mechanism as cis-carbamate 1. The first reaction using this substrate was to then utilize the same conditions that provided the highest isolated yield for aziridine to see
if the same conditions applied. Intriguingly, an aziridine was not the product formed through this reaction (Scheme 19).

![Scheme 19](image)

Scheme 19

This novel product, 4, was characterized by $^1$H, $^{13}$C, COSY, HSQC, HMBC, and NOESY NMR. The characteristic peak that confirms that 4 is the product is the tert-butyl peak at 1.22 ppm. Based on integration the peak on the $^1$H spectrum, COSY, and HSQC correlations, it is clear that the pivalate group, which was the byproduct of nitrene formation, had inserted into the carbamate species. Once again, this reaction is diastereoselective, with NOESY spectrum being inconclusive of one diastereomer over another.

At first glance, it appears that this product is fashioned from an aziridine. The formation of this aziridine is similar to the mechanism proposed in Scheme 17, with the only change being the stereochemistry of the aziridine due to the starting geometry of carbamate 3. From this aziridine, the pivalate group or pivalic acid may attack the highly-strained aziridine, opening the ring (Scheme 20). This hypothetical aziridine is more strained than species 3 because of the ethyl and six-membered ring being on opposite faces of the aziridines, causing a twisted type of aziridine more prone for nucleophilic attack.
Another possible mechanism for the formation of 4 does not involve the creation of an aziridine at all. Instead, a zwitterionic intermediate is the key feature of this mechanism. Once the carbamate is oxidized to the nitrene, the electron-rich alkene attacks the nitrene, which, due to its unsatisfied octet, is considered electrophilic. During this process, a zwitterionic species is formed, with the nitrogen carrying a negative formal change and the carbon of the alkene closest to the carbamate group being the carbocation. Now, the pivalate or pivalic acid can attack nucleophilically attack the carbocation, resulting in 4 (Scheme 21). While both are possible mechanisms (Schemes 20 and 21), there is no presence of aziridine in the crude NMR of any trials performed. The lack of evidence leads us to believe that the pivalate group is intercepting our proposed zwitterionic intermediate before aziridine formation. A NMR kinetic trial would be useful in the determination if the aziridine is formed but, just like with cis-carbamate 1, it is possible that no reaction will occur in the NMR tube while one will take place in a microwave.
Further trials were run with 3 in order to isolate and characterize the hypothetical aziridine. Time of reaction and equivalence of PhI(OPiv)₂ were shortened and lowered, but 4 was still the only isolated product. In another twist of fate, PhI(OAc)₂ may play a role in whether or not C-H amination products form with substrate 3. Crude ¹H NMR seems to indicate that two products form, the ring-opened species with an acetate group instead of the pivalate group in 4, and a C-H amination product. As of the end of this project, two products were isolated but not fully characterized. Further characterization is needed to verify the identity of these products and to possibly provide a novel method of C-H amination with particular substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Equiv.</th>
<th>Heating</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(OAc)₄</td>
<td>PhI(OPiv)₂</td>
<td>3</td>
<td>µwave</td>
<td>2</td>
<td>22% isolated yield</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>PhI(OPiv)₂</td>
<td>3</td>
<td>µwave</td>
<td>2</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(OAc)₄</td>
<td>PhI(OPiv)₂</td>
<td>1.2</td>
<td>µwave</td>
<td>1</td>
<td>19% isolated yield</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(OAc)₄</td>
<td>PhI(OPiv)₂</td>
<td>1.2</td>
<td>µwave</td>
<td>0.5</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OAc)₄</td>
<td>PhI(OAc)₂</td>
<td>3</td>
<td>µwave</td>
<td>2</td>
<td>Uncharacterized products</td>
</tr>
<tr>
<td>6</td>
<td>Rh₂(OAc)₄</td>
<td>PIFA</td>
<td>3</td>
<td>µwave</td>
<td>2</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Reaction conditions: substrate (0.75 mmol), Rh₂(OAc)₄ (4 mol%), CH₂Cl₂ (10 mL), 50°C

Table 3: Aziridination Trials with 3 as Substrate
F. Electrochemical Trends

Organic chemistry textbooks all across the globe preach that sterics and electronics are the major contributing factors in the viability of a reaction. Sterics were casually mentioned in the success of PhI(OPiv)$_2$ for aziridination due to the attenuated nucleophilicity of the tert-butyl group, but not much else can be said about the other oxidants and their lack of efficacy. Electronic factors were the next crossroad in the determination of any sort of tendency with the hypervalent iodine oxidants. Specifically, the redox potential of all substrates involved were measured in hopes of finding a trend in the reactivity of the oxidants.

The reduction or oxidation potential was first determined with respect to the direction of voltage sweep. IUPAC convention states that as voltage is changed from low to high potential, oxidation takes place, with the opposite being true for reduction of the substrate. The values of either event were then determined from the redox potential of ferrocene, a reliable internal standard for cyclic voltammetry, as zero volts. Knowing that the carbamates and rhodium catalyst should be oxidized, and that the oxidants should be reduced, the corresponding peaks were easily picked from the cyclic voltammogram.
Both carbamate species, 1 and 3, had the greatest values, followed by the rhodium catalyst, PhI(OPiv)$_2$, iodosodilactone, PhI(OAc)$_2$, and PIFA and Koser’s reagent, with similarly, low reduction potentials. These values, to a large extent, nicely correlate with the results of all optimization trials performed. PhI(OPiv)$_2$ is the most reactive oxidant, and under mild conditions yields new product. PhI(OAc)$_2$ is closely behind PhI(OPiv)$_2$, which explains a lowered yield in aziridine and other possible products with both carbamates. The closer in value that the reduction potential of the oxidant is to the oxidation value of Rh$_2$(OAc)$_4$, the higher likelihood of a reaction yielding aziridine is to occur. The same cannot be said about iodosodilactone, with a reduction potential basically similar to that of PhI(OPiv)$_2$. If the trend is to be taken literally, then iodosodilactone should be a prime candidate for aziridination under the conditions tested. Yet, a lack of solubility in most solvents and stubbornness of the acetate-like ligand dissociate from both the iodine and benzene ring far more contributes to the lack of reactivity than the reduction potential.
potential. The cause of this trend is not highly understood, but nevertheless extremely promising in the search for hypervalent iodine oxidants for a particular carbamate substrate.
III. Conclusions and Future Work

In this project, novel microwave-mediated methodologies for the formation of aziridine 2 were discovered, along with the serendipitous discovery of product 4 under those same conditions. Full characterization of both 2 and 4 showed that both reactions happened diastereoselectively, but failed to confirm if the reaction was enantioselective. Likely, the formation of 2 prevails through a singlet nitrene species due to the retention of stereochemistry, while 4 forms through a zwitterionic intermediate. Cyclic voltammetry allowed for the creation of a trend that supports the claim that the closer in value the reduction potential of the hypervalent iodine oxidant to the oxidation potential of the rhodium catalyst and carbamate substrate, the more reactive the conditions will be. Further research should both reproduce the outcomes of the experiments, as well as broaden the substrate scope to see if these conditions apply to other conjugated or substituted homoallylic carbamate substrates (Figure 7).

![Figure 7](image-url)

The most promising conditions for aziridination consist of three equivalents of PhI(OPiv)$_2$ and four-mole percent of Rh$_2$(OAc)$_4$ dissolved in DCM and microwaved at 50ºC for two hours. The discovery of the electrochemical trend may allow for the mixing and matching of rhodium catalysts and hypervalent iodine oxidants to the corresponding carbamate to give even greater isolated yields of aziridine.

Additional experiments with carbamate substrate 3 may consist of NMR kinetic trials to explore the synthesis of an aziridine and the opening mechanism which it may follow, in addition
to performing the reactions at lower temperatures and decreasing the equivalency of the oxidant and rhodium catalyst.

![Heterocyclic Hypervalent Iodide Oxidant Examples](image)

**Figure 8: Heterocyclic Hypervalent Iodide Oxidant Examples**

Lastly, the exploration into heterocyclic oxidants is tantalizing due to the lack of research done with these compounds in the field of carbon-nitrogen bond formation. Iodosodilactone is a similar structure to these heterocyclic compounds and lacked any success, but there is only one way to be certain. Additionally, an investigation into iodine(V) compounds and iodosobenzene (PhIO) is worth the effort, although the handling of these compounds may be slightly too dangerous for undergraduate work. Needless to say, anyone that decides to continue this project has plenty of avenues to explore and probe.
IV. Experimental Methods

General Methods:

All reactions were conducted in oven-dried glassware under inert argon conditions unless otherwise noted. $^1$H and $^{13}$C spectra were analyzed with a Varian 400 MHz Magnetic Nuclear Resonance Spectrometer. CDCl$_3$ was referenced to 7.26 (H) and 77.0 ppm (C) and CD$_2$Cl$_2$ was referenced to 5.32 (H) and 53.84 ppm (C). Microwave reactions were carried out in a CEM Discover SP® using closed, snap-cap reaction vials. Thin-layer chromatography was performed on 60-mesh silica plates purchased from Sorbent Technologies (XHL, UV254, 250 μm) and purification was accomplished using a CombiFlash® (Teledyne Isco) R$_f$ 150 and NextGen 300+ Chromatography Systems on RediSep Rf Gold® normal-phase silica columns.

All reagents were purchased from Sigma-Aldrich unless otherwise noted. Rh$_2$(OAc)$_4$ was purchased from Pressure Chemicals Company. Iodosodilactone was purchased from Toyko Chemical Industry. Anhydrous solvents were dried over 3 Å molecular sieves and kept under an inert atmosphere. This process was performed as described as Williams and Lawton.\textsuperscript{27}
(Z)-hex-3-en-1-yl carbamate: In a 250 mL round-bottom flask equipped with a stir bar, cis-3-hexenol (1.18 mL, 9.98 mmol) was added and dissolved in dichloromethane (20 mL) and cooled to 0°C. Trichloroacetyl isocyanate (1.43 mL, 11.98 mmol) was added dropwise. The reaction was allowed to warm to room temperature (25°C) and stir for 4.5 hours. The reaction was monitored by TLC and showed consumption of the starting material. Solvent was removed through rotary evaporation. Potassium carbonate (0.998 mmol, 0.138 g) was added to the flask and placed under argon. Methanol (17 mL) was added to the flask and allowed to stir for 13.5 hours. TLC showed the presence of a product, in which the reaction was quenched with ammonium chloride, extracted with dichloromethane, dried over MgSO$_4$, and rotovapped, which yielded 2.98 g of crude (Z)-hex-3-en-1-yl carbamate. The crude product was then dissolved in dichloromethane (200 mL), 1 M sodium hydroxide aqueous solution (100 mL), and stirred vigorously for 30 minutes. The solution was extracted with dichloromethane, dried over MgSO$_4$, and concentrated under reduced pressure. The product was purified via silica gel chromatography (50:50 hexanes/ethyl acetate) to yield (Z)-hex-3-en-1-yl carbamate as a thick oil with a yellow hue (1.14 g, 7.96 mmol, 80% yield). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 5.58 – 5.44 (m, 1H), 5.32 (m, 1H), 4.58 (s, 2H), 4.06 (t, $J = 6.9$ Hz, 2H), 2.44 – 2.32 (m, 2H), 2.20 – 1.98 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 157.02, 134.70, 123.90, 64.85, 27.17, 20.76, 14.36.
**General Procedure for $^1$H NMR Kinetic Aziridination Trials**

![Diagram](image1.png)

Into an oven-dried J. Young NMR tube, (Z)-hex-3-en-1-yl carbamate (28.6 mg, 0.2 mmol) in 0.75 mL of DCM-d was added. In a separate vial, a hypervalent iodine reagent (0.24 mmol) and, if the trial called for catalyst, Rh$_2$(OAc)$_4$ (3.53 mg, 0.008 mmol) were dissolved in 0.75 mL of DCM-d. A standard $^1$H NMR was taken of the starting material. The J. Young NMR tube was then ejected from the NMR machine. The 0.75 mL of the oxidant/catalyst containing DCM-d was injected rapidly into the tube, inverted once, and inserted back into the same slot which the tube was originally ejected from. Scans were immediately taken of the solution with the following parameters: number of scans - 4, relaxation delay - 7 seconds, acquisition time - 3 seconds, pre-acquisition delay - 0 seconds, array size - 150. In all trials, no reaction occurred.

**General Procedure A of Microwave-Mediated Reactions of (1)**

![Diagram](image2.png)

Into a clean, 10 mL microwave vial equipped with a stir bar, (Z)-hex-3-en-1-yl carbamate (107.39 mg, 0.75 mmol), dirhodium tetraacetate (13.26 mg, 0.03 mmol), and oxidant (0.9 mmol) were added. Dry DCM (10 mL) was added to the vial and equipped with a cap. The reaction was run for one hour at 50ºC. The reaction solution was then filtered through a silica pipette column. A TLC was then taken of the solution. Regardless of the outcome of the TLC, the solution was
concentrated under reduced pressure. A crude NMR was taken of the solution. If the reaction was deemed successful, the reaction mixture was purified via flash column chromatography (20:80 hexanes/ethyl acetate).

\[(6S,7R)-7\text{-ethyl-3-oxa-1-azabicyclo}[4.1.0]heptan-2\text{-one} + (6R,7S)-7\text{-ethyl-3-oxa-1-azabicyclo}[4.1.0]heptan-2\text{-one}:
\]

General Procedure A was followed, with Phl(OPiv)\(_2\) (365.63 mg) as the oxidant. The reaction mixture was purified to yield compounds (2) as a white solid (36.42 mg, 0.27 mmol, 36% yield). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 4.39 (ddd, \(J = 12.1, 10.5, 2.2\) Hz, 1H), 4.33 (ddd, \(J = 10.5, 4.8, 1.7\) Hz, 1H), 2.86 (ddd, \(J = 9.0, 6.9, 4.9\) Hz, 1H), 2.60 (dt, \(J = 8.4, 5.1\) Hz, 1H), 2.18 (ddt, \(J = 14.7, 6.9, 2.0\) Hz, 1H), 1.87 (dqd, \(J = 14.4, 7.3, 5.4\) Hz, 1H), 1.48 (dddt, \(J = 14.7, 12.1, 9.0, 4.9\) Hz, 1H), 1.31 – 1.16 (m, 1H), 1.10 (t, \(J = 7.3\) Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 158.54, 67.78, 43.94, 37.14, 18.98, 18.96, 10.79.

\[
\text{General Procedure A was followed, with Phl(OAc)}\(_2\) (289.89 mg) as the oxidant. The reaction mixture was purified to yield compounds (2) (29.60 mg, 0.21 mmol, 28% yield).
General Procedure A was followed, with PhI(OPiv)$_2$ (365.63 mg) as the oxidant and the temperature of the reaction maintained at 80°C. The reaction mixture was purified to yield compounds (2) (21.80 mg, 0.15 mmol, 21% yield).

Into a dried 50 mL round-bottom flask equipped with a stir bar, (Z)-hex-3-en-1-yl carbamate (107.39 mg, 0.75 mmol), dirhodium tetraacetate (13.26 mg, 0.03 mmol), and PhI(OPiv)$_2$ (365.63 mg, 0.9 mmol) were added. Dry DCM (10 mL) was added to the flask and allowed to stir at 50°C in a water bath for one hour. The reaction solution was then filtered through a silica pipette column. A TLC was then taken of the solution and concentrated under reduced pressure. The crude mixture was then purified via flash column chromatography (20:80 hexanes/ethyl acetate) to yield compounds (2) (27.60 mg, 0.20 mmol, 26% yield).
Into a clean, 10 mL microwave vial equipped with a stir bar, (Z)-hex-3-en-1-yl carbamate (107.39 mg, 0.75 mmol), dirhodium tetraacetate (13.26 mg, 0.03 mmol), and PhI(OPiv)$_2$ (914.09 mg, 2.25 mmol) were added. Dry DCM (10 mL) was added to the vial and equipped with a cap. The reaction was run for two hours at 50ºC. The reaction solution was then filtered through a silica pipette column. A TLC was then taken of the solution and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography (20:80 hexanes/ethyl acetate) to yield compounds (2) (50.0 mg, 0.35 mmol, 47% yield).

Into a clean, 10 mL microwave vial equipped with a stir bar, (Z)-hex-3-en-1-yl carbamate (107.39 mg, 0.75 mmol), dirhodium tetraacetate (13.26 mg, 0.03 mmol), and PhI(OPiv)$_2$ (365.63 mg, 0.9 mmol) were added. Dry DCM (10 mL) was added to the vial and equipped with a cap. The reaction was run for six one-hour intervals, with a TLC taken every hour to monitor the reaction. Every two hours, an additional equivalent of PhI(OPiv)$_2$ was added (304.70 mg, 0.75 mmol) to try and drive the reaction forward. After six hours, the reaction was filtered through a silica pipette column and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography (20:80 hexanes/ethyl acetate) to yield compounds (2) (50.0 mg, 0.35 mmol, 47% yield).
chromatography (20:80 hexanes/ethyl acetate) to yield compounds (2) (22.4 mg, 0.16 mmol, 21% yield).

\[
\text{\textit{(E)}-hex-3-en-1-yl carbamate: Into a dried, 250 mL round-bottom flask, trans-3-hexenol (1.18 mL, 9.98 mmol) was dissolved in dry DCM (20 mL), purged with argon, and cooled to 0°C. Trichloroacetyl isocyanate (1.43 mL, 11.98 mmol) was added dropwise. The reaction was allowed to rise to room temperature. The reaction was monitored via TLC and concentrated under reduced pressure after five and a half hours. Potassium carbonate (138 mg, 0.998 mmol) and methanol (17 mL) was added to the flask and allowed to stir for 21 hours, after which TLC showed consumption of starting material. The reaction was quenched with ammonium chloride, extracted with DCM, and dried with magnesium sulfate. The reaction mixture was concentrated under reduced pressure. The crude product was then dissolved in DCM (200 mL) and 1 M aqueous sodium hydroxide solution and stirred vigorously for 30 minutes. The mixture was extracted with DCM, dried with magnesium sulfate, and concentrated once again under reduced pressure. Compound (3) was recovered in quantitative yield as a white solid.} \]

\[
\text{\textit{\textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \delta 5.54 (m, 1H), 5.41 – 5.26 (m, 1H), 4.55 (s, 2H), 4.05 (t, J = 6.9 Hz, 2H), 2.29 (qq, J = 6.8, 1.2 Hz, 2H), 1.99 (dtdd, J = 8.7, 7.4, 6.3, 1.4 Hz, 2H), 0.95 (t, J = 7.5 Hz, 3H). \textit{\textsuperscript{13}C NMR (101 MHz, Chloroform-\textit{d}) \delta 156.84, 135.01, 124.01, 64.85, 32.16, 25.59, 13.68.}}}
\]
(65,75)-7-ethyl-3-oxa-1-azabicyclo[4.1.0]heptan-2-one + (6R,7R)-7-ethyl-3-oxa-1-azabicyclo[4.1.0]heptan-2-one:

Into a clean, 10 mL microwave vial equipped with a stir bar, (E)-hex-3-en-1-yl carbamate (107.39 mg, 0.75 mmol), dirhodium tetraacetate (13.26 mg, 0.03 mmol), and PhI(OPiv)2 (914.09 mg, 2.25 mmol) was added and allowed to stir for two hours at 50ºC in the microwave. The reaction mixture was filtered through a silica pipette column and a TLC was taken. The mixture was concentrated under reduced pressure. The reaction was purified through flash column chromatography to yield compounds (4) as white solid (40 mg, 0.16 mmol, 22% yield). 1H NMR (400 MHz, Chloroform-d) δ 5.75 – 5.69 (s, 1H), 4.90 (ddd, J = 7.1, 5.9, 4.3 Hz, 1H), 4.36 (dt, J = 11.2, 4.1 Hz, 1H), 4.26 – 4.15 (m, 1H), 3.70 – 3.63 (m, 1H), 2.00 – 1.84 (m, 2H), 1.64 (dq, J = 9.2, 7.3 Hz, 2H), 1.22 (t, J = 1.4 Hz, 12H), 0.93 (td, J = 7.4, 2.2 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 183.30, 178.47, 154.48, 74.42, 65.21, 53.68, 39.20, 27.28, 27.23, 22.70, 22.35, 9.92.

General Procedure A was followed with compound (3) as the starting material and PhI(OPiv)2 as the oxidant (365.63 mg). The crude product was purified via flash column chromatography (20:80 hexanes/ethyl acetate) to yield compounds (4) (34.8 mg, 0.14 mmol, 19% yield).
V. References


(25) Fletcher, M. H. From Aziridines to Daffodils : Development of an Oxidative Insertion for the Synthesis of Isoquinolone Derivatives. 2012,


Appendix
H NMR Spectrum of (1)
$^{13}$C NMR Spectrum of (1)
HSQC Spectrum of (1)
$^1$H NMR Spectra of (2)
$^{13}$C NMR Spectrum of (2)
COSY NMR Spectrum of (2)
HSQC Spectrum of (2)
NOESY Spectrum of (2)
$^1$H NMR Spectrum of (3)
$^{13}$C NMR Spectrum of (3)
COSY Spectrum of (3)
HSQC Spectrum of (3)
$^1$H NMR Spectrum of (4)
$^{13}$C NMR Spectrum of (4)
COSY Spectrum of (4)
HSQC Spectrum of (4)
HMBC Spectrum of (4)
NOESY Spectrum of (4)
Cyclic Voltammogram of (1)
Cyclic Voltammogram of (3)
Cyclic Voltammogram of PhI(OPiv)₂
Cyclic Voltammogram of PhI(OAc)$_2$
Cyclic Voltammogram of PIFA
Cyclic Voltammogram of Iodosodilactone
Cyclic Voltammogram of Koser’s Reagent
Cyclic Voltammogram of Rh$_2$(OAc)$_4$