The Synthesis and Applications of $N$-Alkenyl Aziridines

by

Nicholas A. Afagh

A thesis submitted in conformity with the requirements for the degree of Master of Science

Department of Chemistry
University of Toronto

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Abstract

N-alkenyl aziridines are a unique class of molecules that do not behave as typical enamines as a result of the inability of the nitrogen atom lone-pair of electrons to delocalize. The attenuated nucleophilicity of these enamines presents opportunities for the selective functionalization and reactivity not available to classical enamines. An operationally simple and mild copper-mediated coupling has been developed that facilitates the preparation of a broad range of N-alkenyl aziridines not available through existing methods. The preparation and reactivity of highly-functionalized N-alkenyl aziridines are reported. Also reported is the application of the chemoselective amine/aldehyde/alkyne (A^3) multicomponent coupling involving amphoteric aziridine aldehydes as the aldehyde component. This coupling allows access to propargyl amines with pendent aziridine functionality.
Acknowledgments

First and foremost, I would like to thank my supervisor, Professor Andrei K. Yudin for his continuous support and encouragement over the past two years. His wealth of knowledge and profound insight into all matters chemistry made for many interesting discussions. In addition, I would like to thank all the members of the Yudin group past and present with whom I have had the distinct pleasure of working alongside and shared many late evenings. In particular I would like to thank Mr. Igor Dubovyk, Ms. Naila Assem, and Mr. Ben Rostein who have become wonderful friends and contributed to a great working environment filled with stimulating discussion and comedic relief. Most importantly, I would like to thank my parents, sister and all of the rest of my family for their love, support, and kind words without which this would not have been possible.
This thesis is dedicated to my family
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1 The Synthesis and Reactivity of a Diverse Class of $N$-Vinyl/Alkenyl Aziridines

1.1 Introduction

Enamines are long established and powerful enol synthons in the toolbox of organic chemists that have found applications in diverse sub-disciplines of organic chemistry.\(^1\) The simplest enamine of a carbonyl compound was prepared in 1921 by Meyer and Hopf who synthesized dimethylvinylamine through the pyrolysis of choline.\(^2\) Clearly, a more general method that accommodated diversity in the substitution pattern of the resulting enamine was necessary. To this end, Mannich and Davidsen provided the general method for the synthesis of enamines that, with some minor modification, has persisted and is commonly used today.\(^3\) The condensation between a secondary amine and an aldehyde or a ketone in the presence of an acid catalyst and a water scavenger yields the desired enamines (Scheme 1-1).

\(\text{Scheme 1-1}\)

\(\text{Meyer, K. H., Hopf, H., Ber., 1921, 54, 2274.}\)
\(\text{Mannich, C., Davidsen, H., Ber., 1936, 69, 2106.}\)
While versatile for many applications, this route is plagued by several drawbacks including the lack of regioselectivity with respect to the introduction of the unsaturated bond and generally low functional group tolerance. Other viable alternatives to condensation chemistry include the nucleophilic substitution reaction of amines with appropriate electrophiles and metal-catalyzed or mediated reactions which will be discussed shortly.

Typically, enamines behave as C-nucleophiles through delocalization of the nitrogen electron pair into the $\pi^*$ of the alkene to generate a nucleophilic carbon at the $\beta$-position that is capable of attacking an electrophile. This reaction generates a transient iminium ion that is generally hydrolyzed upon workup returning the carbonyl compound. (Scheme 1-2)

Such a reactivity profile is predicated upon the ability of the nitrogen atom to undergo quaternization. This is not an issue with the vast majority of secondary amines as they can tolerate quaternization and an appreciable quantity of the iminium species exists in equilibrium to facilitate reaction with electrophiles. However, if nitrogen quaternization is thermodynamically unfeasible then any enamine derived from the parent amine should display a unique reactivity profile uncommon to most ‘classical’ enamines. In theory, this can be accomplished by restricting the ability of the lone pair to delocalize and form an iminium ion. The unavailability of the lone pair would dramatically decrease nucleophilicity of the enamine. This presents interesting opportunities to study the chemoselectivity$^4$ of such species. For instance, would the enamine behave as a typical

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alkene or can conditions be developed under which the nucleophilicity of the enamine can be harnessed? Moreover, is it possible to control these pathways? Exploring these questions requires the judicious choice of a suitable parent amine that would confer the desired properties to the resulting enamine.

N-H aziridines are unusual secondary amines with the nitrogen lone pair displaying considerably more s-character than the corresponding acyclic parent amine as evidenced by the \( pK_{\text{aH}} \) values of the corresponding acids. For instance, the \( pK_{\text{aH}} \) of dimethylamine is 10.7 while that of ethyleneimine, the simplest aziridine, is approximately 7.9, a nearly 1000-fold difference in basicity (Scheme 1-3).

The 60° bond angles of ethyleneimine deviate considerably from the ideal 109.5° resulting in a great deal of angle strain as in the comparable cyclopropane and oxirane molecules. These properties should reduce the enamine character of an enamine that incorporates an aziridine as the amine component. The increased nitrogen s-character should diminish the ability of the lone pair to delocalize. Moreover, the resulting transient iminium species formed upon N-quaternization would be highly strained and unstable (Scheme 1-3). Therefore, these non-classical enamines should behave as if the enamine functionality is ‘masked’ on thermodynamic grounds allowing for the possibility of new and unique reactivity.

**Scheme 1-3**

- high degree of s-character
- highly strained
- negligible \( K_{eN} \) value
These properties of aziridines were recently exploited in an analogous fashion in the synthesis of dimeric unprotected amino aldehydes.\(^5\) In this case, reduction of aziridine esters using DIBAL led to diastereoselective homodimerization of the corresponding aziridine aldehydes rather than condensation products through iminium ion formation (Scheme 1-4). The resistance of aziridines to iminium ion formation precludes the possibility of synthesizing \(N\)-alkenyl aziridines through condensation type chemistry. Consequently, other routes to these fundamentally interesting molecules must be devised.

### Scheme 1-4

While a great deal of consideration has been given to the synthesis of C-vinyl aziridines, comparably little effort has been spent in the development of efficient routes to \(N\)-alkenyl aziridines.\(^6\) The methods that do exist suffer from numerous limitations, including being limited in scope to only a few examples and are generally low yielding. Thus, an in depth exploration into their synthetic potential necessitates the development of practical, high-yielding, and scalable protocols for their preparation. The existing routes to \(N\)-alkenyl aziridines will now be briefly reviewed.

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1.2 Synthetic Routes to $N$-Alkenyl Aziridine

1.2.1 $N$-Alkenyl Aziridines via Propiolates

Arguably the simplest synthesis of $N$-alkenyl aziridines involves the nucleophilic addition of N-H aziridines to propiolates. For instance, addition of aziridine 1 to ethyl propiolate in an alcoholic solution of ethanol resulted in the formation of the $E$ and $Z$ isomers of the corresponding $N$-alkenyl aziridine in a 40/60 ratio\(^7\) (Scheme 1-5). When ethylene imine was subjected to the same reaction conditions, a similar $E/Z$ ratio (42/58) of the product aziridinoacrylic acid ethyl ester was obtained in 73\% overall yield. The reaction of ethylene imine (2) with DMAD in MeOH gave the reverse stereoselectivity giving the product in 76\% yield with an $E/Z$ ratio of 67/33.\(^8\) Interestingly, it was noted that the stereoselectivity of the reaction was strongly solvent dependent. A dramatic example of this solvent dependence is the reaction between ethyleneimine and DMAD in DMSO which resulting in product formation in 75\% yield with the $E/Z$ ratio increased to 5:95. While this is an effective and operationally simple procedure, the requirement of an electron poor acetylene places strict limitations on the functional groups which can be appended on the alkene.


Reinhoudt and co-workers reported another route to $N$-alkenyl aziridines through the 1,3-dipolar cycloaddition reaction of cyclic nitrones 3 with DMAD to generate bicyclic intermediates 4 which undergo rearrangement\(^9\) (Scheme 1-6). The driving force for the rearrangement reaction which involves a concerted [1,3]-sigmatropic shift of the N-atom is reported to be the cleavage of the weak N-O bond and concomitant formation of the carbonyl functionality. As in the addition of aziridines to propiolates, this methodology relies on highly activated acetylenes which again places restrictions on the substitution pattern of the olefin.

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1.2.2 N-Alkenyl Aziridine via the Pyrolysis of Δ²-Triazolines

Hassner reported that the pyrolysis of Δ²-triazolines either in refluxing toluene or by flash vacuum pyrolysis under neat conditions at 250 ºC results in the formation of N-alkenyl aziridines (Scheme 1-7). The Δ²-triazolines were prepared by reacting vinyl azides with sulfoxonium ylides. While the N-alkenyl aziridines could be prepared in good yields, the very high reaction temperatures make this approach impractical.

Scheme 1-7

flash vacuum pyrolysis yields:

\[ R^1 = \text{Ph, } R^2 = \text{Me}, \quad 93\% \]
\[ R^1 = \text{n-Bu, } R^2 = \text{H}, \quad 93\% \]
\[ R^1 = \text{H, } R^2 = \text{t-Bu}, \quad 94\% \]
\[ R^1 = R^2 = -(\text{CH}_2)_6, \quad 91\% \]

1.2.3 N-Alkenyl Aziridine From N-Acyl Aziridines

In 1987, Baldwin reported the isolation of N-alkenyl aziridines as byproducts in the ring opening reactions of aziridine-1,2-dicarboxylates with Wittig reagent.\textsuperscript{11} Treating activated N-acyl aziridines with stabilized Wittig reagents in toluene at 50ºC resulted in the formation of two regioisomeric ylides and an N-alkenyl aziridine in low yield and as a mixture of E/Z stereoisomers (Scheme 1-8).

The Peterson olefination reaction is a common way to generate olefins from α-silyl carbanions and a ketone or aldehyde.\textsuperscript{12} This olefination reaction was successfully applied to the synthesis of 2-aminoalkenyl sulfides in the reaction between the α-silyl carbanion 1-lithio-1-phenylthiomethyltrimethylsilane (5) with an N-acyl aziridine at 0 ºC in THF resulted in the formation of the product N-alkenyl aziridine as an 80:20 distribution of stereoisomers in 87% overall yield (Scheme 1-9).

1.2.4 Synthesis via Nucleophilic Alkenylic Substitution

Another common method of synthesizing N-alkenyl aziridines is via nucleophilic displacement of halogens from electron poor, activated alkenes. When the E- and Z-isomers of methyl-3-bromo-4,4-dimethoxy-2-butenoate (6a/6b) were treated with ethyleneimine, the corresponding N-alkenyl aziridines were obtained in good yields with retention of stereochemistry via a Michael addition-elimination process involving the aziridine and bromide ion respectively\(^\text{13}\) (Scheme 1-10).

![Scheme 1-10](image_url)

Cis-β-chloroacrylic esters, cis-chloroacrylonitriles and phenyl cis-chloroalkenyl ketones are also suitable alkene donors and react with retention of stereochemistry.\(^\text{14}\) The same is true for the trans stereoisomers of these alkenes which gave the corresponding trans isomers of the alkenylated aziridines (Scheme 1-11). If instead, a typical secondary amine such as dimethyl amine is subjected to the same reaction conditions, the trans isomer of the alkenylated aziridine would be obtained exclusively regardless of the stereochemistry of the donor alkene prior to the reaction. Thus, in the case of cis alkenes, isomerization from the initial cis adduct to the thermodynamically more stable trans configuration occurred through what is believed to be a zwitterionic intermediate. Such an


isomerization is not possible in the case of \textit{N}-alkenyl aziridines for reasons highlighted earlier in this chapter. These unique properties of aziridines permit the transmission of stereochemical information from starting materials to products. However, like the previous examples, this methodology is once again limited by the requirement for a highly activated alkene.

Scheme 1-11

![Scheme 1-11](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Stereochemistry of Starting Material</th>
<th>% cis in product</th>
<th>% trans in product</th>
</tr>
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<tr>
<td>CO$_2$Et</td>
<td>cis</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>CO$_2$Et</td>
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<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Ts</td>
<td>trans</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>CN</td>
<td>&gt; 97% cis</td>
<td>&gt;97</td>
<td>&lt;3</td>
</tr>
<tr>
<td>CN</td>
<td>trans</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

1.2.5 Palladium Catalyzed Alkenylation of Aziridines

Yudin and co-workers showed that conditions developed by Barluenga and co-workers\textsuperscript{15} for the intermolecular Pd-catalyzed coupling of primary and secondary amines with alkenyl bromides to form imines and enamines, respectively, were suitable for the preparation of \textit{N}-alkenyl aziridines.\textsuperscript{16} For instance, the reaction between cyclohexeneimine (7) and \textit{a}-bromostyrene catalyzed by Pd$_2$(dba)$_3$ (2 mol\%) with BINAP (6 mol \%) as a ligand in toluene overnight at 90° resulted in the formation of the corresponding \textit{N}-alkenyl aziridine in 22\% yield after purification by flash chromatography or 69\% yield after purification by Kugelrohr distillation (Scheme 1-12).


While effective for the synthesis of N-alkenyl aziridine without recourse to electron-withdrawing groups, the reported yields were only satisfactory in most cases (Figure 2). Moreover, the conditions were not tolerant of certain aziridines or alkenyl bromide combinations. For instance, aziridines with appended ketones were not tolerated, presumably due to chelation between the aziridine nitrogen, ketone oxygen and Pd catalyst that retards the catalytic cycle. Long chain aliphatic alkenyl bromides such as 2-bromo-1-decene were also unsuitable coupling partners. Low boiling alkenes such as 2-bromoethene also proved unsuccessful. The catalytic cycle for this process is believed to involve the initial oxidative addition of the alkenyl bromide to the Pd(0) complex generating a Pd(II) intermediate. Coordination of the aziridine and deprotonation by base leads to
an amino alkenylated Pd(II) intermediate that reductively eliminates generating the product N-alkenyl aziridine and regenerating the catalytically active Pd(0) species (Figure 3).

To address some of the limitations imposed by the Pd-catalyzed procedure, a Cu-catalyzed procedure developed for the N-arylation of aziridines was successfully adapted to the N-alkenylation reaction involving aziridines and boronic acids as alkenyl bromide surrogates. Although gains were made with respect to functional group compatibility, the yields were significantly lower than in the Pd-catalyzed process reducing the viability of this process as a general tool for N-alkenyl aziridine synthesis. It was found that Cu(OAc)$_2$ (10 mol %) and myristic acid (20 mol %) in toluene at room temperature were the optimal conditions for this transformation. For instance, using 2,4,6-trivinylcyclotriboroxane (9) as a vinyl boronic acid surrogate, aziridine 8 was N-alkenylated but only in 30% yield (Scheme 1-13). Two other examples were also reported, however both were relatively low yielding. Unfortunately, even under prolonged reaction times, aziridines with pendent ketones were not suitable as coupling partners.
1.2.6 *N*-Alkenyl Aziridines from *N*-Allyl Aziridines

*N*-allyl aziridines have been shown to undergo isomerization to the corresponding enamines in the presence of Rh-hydride catalysts.\(^\text{17}\) Interestingly, the isomerization was selective for *Z*-enamine formation in contrast to the conventional isomerization of *N*-allyl amines which yields the thermodynamically more stable *E*-enamines. For instance, in the presence of 5 mol % Rh\((\text{CO})(\text{PPh}_3)_3\), allyl aziridine was isomerized to the enamine with an *Z/E* selectivity of 95:5 (Scheme 1-14).

Computational studies by Tantillo and co-workers\textsuperscript{18} indicate that the selectivity determining step in the catalytic cycle occurs just prior to reductive elimination and is governed by an $\text{N}_{\text{l.p.}} \rightarrow \sigma^*_{\text{CH}}$ interaction. The process is believed to begin with hydrometallation of the allylic olefin to generate intermediate A. Rotation about the Rh-C bond then generates an aza-metallocyclobutane (B) which breaks open to generate C which displays the critical $\text{N}_{\text{l.p.}} \rightarrow \sigma^*_{\text{CH}}$ interaction that weakens the C-H bond priming it for $\beta$-hydride elimination to generate the Z-enamine.

Figure 4

1.3. Applications of $N$-Vinyl Aziridines in Synthesis

Ketene $S,N$-acetals can also be subjected to nucleophilic attack and displacement of methanethiol (MeSH) in a reaction analogous to the nucleophilic displacement of bromides from activated alkenes described earlier in this chapter. This methodology has been used in the synthesis of the spiropyrrolidinyl oxindole alkaloids coerulescine and horsfiline.\textsuperscript{19} Initial displacement of MeSH on ketene $S,N$-acetal 11 by ethyleneimine leads to vinyl aziridine 12 which is subjected to an iodide-induced rearrangement to the spiropyrrline-2-oxindole (13). Reduction with Raney Ni yields

\textsuperscript{18} Siebert, M R., Yudin, A. K., Tantillo, D. J., \textit{Unpublished results}.
the desired alkaloids (Scheme 1-15). It is important to note that the success of the key step of this synthesis, the iodide-induced rearrangement, is contingent on the presence of a strong electron-withdrawing group such as the conjugated ketone that can support the ring opened product.

Yudin and co-workers have shown that $Z$-enamines derived from $N$-allyl aziridines undergo an intriguing cycloaddition reaction in the presence of DMAD upon heating.\(^\text{17}\) (Scheme 1-16) The resulting cyclobutene cycloadduct (14) was isolated in 60% yield as exclusively the cis stereoisomer. Quantum chemical calculations revealed that the mechanism likely proceeds through a step-wise process beginning with the initial attack of the enamine double bond onto DMAD to generate a zwitterionic intermediate.\(^\text{20}\) This intermediate is short lived which prevents bond rotation and scrambling of stereochemistry which would lead to the more stable trans isomer.

Interestingly, changing the substituents on the aziridine ring led to a different reactivity manifold. When monocyclic $N$-alkenyl aziridines were employed, the products of a non-regioselective formal [3+2] cycloaddition were isolated. Steric congestion around the aziridine was an impediment to this reaction (Scheme 1-17A). Simply heating the same aziridine at 135 °C triggered a [1,5]-hydrogen shift to generate an imine (Scheme 1-17B). While the latter transformation is not synthetically relevant, it provides insight into the reaction pathways available to $N$-alkenyl aziridines.

Gin and co-workers reported in interesting strain-release formal [3,3] rearrangement of a divinyl aziridine species analogous to the well-documented vinyl cyclopropane rearrangement in their synthesis of the anti-Leukemia alkaloid (-)-Deoxyharringtonine.\textsuperscript{21} In this synthesis, an $N$-vinyl/C-aryl species undergoes a formal [3,3] rearrangement to generate an azepine species that is

then carried forward to the desired product. Heating the divinyl aziridine in the presence of Cs$_2$CO$_3$ triggers the desired rearrangement (Scheme 1-18). The N-vinyl aziridine itself is synthesized through the familiar addition-elimination procedure that necessitates the presence of an electron-withdrawing group.

Scheme 1-18

1.4 Formulation of the Research Question

The preceding examples have demonstrated that the synthesis of N-alkenyl aziridines remains challenging and is subject to numerous limitations. For instance, many procedures rely on the presence of an activated alkenyl halides or acetylenes which limit the placement of functional groups on the alkene portion. Moreover, the requirement for strong electron-withdrawing substituents on both alkenyl halides and acetylenes further limits the scope of tolerable functional groups. In the Pd-catalyzed process, the requirement for elevated temperatures precludes the use of low molecular weight alkenyl bromides limiting the availability of the N-alkenyl aziridines bearing simpler alkene. Even in cases with higher molecular weight alkenyl bromides, the yields of the resulting N-alkenyl aziridines are relatively low. A solution to the problem of low molecular weight alkenyl bromides was found using the copper-catalyzed procedure, however, the yields were dramatically lower in these cases rendering this methodology wholly inefficient. Thus, a general,
functional group tolerant, mild and high yielding procedure still does not exist. In order to fully explore the synthetic potential of these unique enamines, such a procedure must be developed to enable rapid access to sufficient quantities of a diverse array of N-alkenyl aziridines. Our goal was therefore to develop such a method from lessons learned in the Pd- and Cu-catalyzed syntheses of N-alkenyl aziridines developed in our laboratories.

1.5 Cu-mediated synthesis of N-alkenyl aziridines

At the onset of these studies, both Cu and Pd systems were evaluated for their potential as the more suitable methodology to further investigate. Copper was chosen for several reasons. First, copper is significantly cheaper than palladium, immediately making it more attractive. In addition, copper (II) is generally much more tolerant of air and moisture than palladium making it more attractive from the perspective of operational simplicity. Moreover, copper has been shown to effect the desired transformation under mild conditions while the analogous palladium system required heating to 90°C for a prolonged period of time. This was seen as an impediment to the use of thermally sensitive alkenes and N-H aziridines. Thus, we chose to further investigate a copper-mediated protocol.

Our investigation began by examining the state of the art at the time which involved the use of a catalytic quantity of Cu(OAc)₂ (10 mol %) and myristic acid (20 mol %), 1 equivalent of the base 2,6-lutidine and toluene as the solvent. At room temperature, this procedure reportedly resulted in a 30% yield of the alkenylated product (see Scheme 1-13). Aziridine 16 was chosen as the model substrate since it is readily available in a high yielding two step procedure from ethyl 3-phenyl glycidate 15. Moreover, the aziridine is activated by both ester and phenyl groups making it an ideal substrate to test. Testing on an activated and therefore sensitive aziridine is critical as it is a measure of mildness of the methodology. Aziridine 16 was prepared by treating commercially available ethyl 3-phenyl glycidate 15 with NaN₃ to generate the azido alcohol which was then treated with PPh₃ to form the aziridine through a mitsunobu-like ring closure²² (Scheme 1-19).

Vinyl boronic acid surrogate 2,4,6-trivinylcyclotriboroxane (17) was used as the alkenyl donor and was synthesized according to a slightly modified literature procedure\textsuperscript{23} in high yield by treating B(OMe)$_3$ with vinyl magnesium bromide at low temperature followed by quenching with dilute aqueous HCl. Dehydration was performed using pyridine to generate the 2,4,6-trivinylcyclotriboroxane-pyridine complex which was purified by Kugelrohr distillation (Scheme 1-20).

When 16 was treated under the reported conditions, the alkenylated product (18) was recovered in a mere 15% yield after 4 days at room temperature (Scheme 1-21). Crude $^1$H-NMR indicated approximately 18% conversion with most of remainder of the mass balance accounted for by starting material. The remainder were unidentified byproducts.

Failure to achieve adequate conversion after nearly a week called for a re-examination of each individual component of the reaction in order to optimize conditions. It was noted that the N-alkenyl aziridines are highly sensitive to acid. The addition of a dilute solution of acetic acid or hydrochloric acid to 18 resulted in nearly complete destruction of the vinyl aziridine after only 10 minutes. The result was an intractable mixture of oligomers that was shown to be composed of 2- and 3-mers of the parent aziridine by ESI-MS. To avoid any compromise in yield by virtue of acid-catalyzed product decomposition, the myristic acid catalyst which is believed to protonate the acetate ligand on copper, releasing acetic acid and opening a vacant coordination site on copper was removed. Unfortunately, only a slight increase in yield to 18% was noted after a reaction time of 4 days. A great deal of effort has been invested into devising protocols for the coupling of amines with boronic acids. One such protocol was developed by Chan and Lam for the coupling of heterocyclic amines with aryl boronic acids and employs a superstoichiometric amount of copper (II) acetate to achieve good conversions24 (Scheme 1-22).

---

Employing these same conditions for the coupling of our aziridine with the cycloboroxane led to an increase in yield to 43% after a reaction time of 4 days. Encouraged by this result, a comprehensive screening of various copper catalysts, ligands, solvents and reagent proportions was undertaken. Among the various sources of copper, Cu(OAc)$_2$ proved to be far superior (Table 1, Entry 7). It was noted that the solubility of Cu(OAc)$_2$ in dichloromethane was the highest amongst the sources of copper, a possible rationale for its improved performance. (Table 1) It was also noted that there was no difference in conversion when using 1 equivalent of Cu(OAc)$_2$ compared to using 1.5 equivalents (Table 1, Entry 4). However, under catalytic conditions, a sharp decline in conversion was observed (Table 1, Entries 8-11).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper Source</th>
<th>Conversion$^a$</th>
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<tr>
<td>1</td>
<td>CuCl$_2$</td>
<td>10%</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>CuBr$_2$</td>
<td>10%</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>CuO</td>
<td>&lt;5%</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$</td>
<td>50%</td>
<td>1.5</td>
</tr>
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</table>

$^a$ Conversion was determined after 4 days at room temperature.
<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>Conversion</th>
<th>Equivalent</th>
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<td>Cu(OTf)₂</td>
<td>30%</td>
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<td>CuI</td>
<td>&lt;5%</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂</td>
<td>50%</td>
<td>1.0</td>
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</tr>
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<tr>
<td>11</td>
<td>Cu(OAc)₂</td>
<td>13%</td>
<td>0.10</td>
</tr>
</tbody>
</table>

a Conversion of starting material to product. The remainder was unreacted starting material. Assessed by crude \(^1\)H-NMR.

It has been shown that the Chan-Lam coupling of aryl boronic acids with phenols fails in the absence of an amine base. The amine base is posited to play two possible roles. Amines could function as ligands for the organocopper intermediates and/or proton acceptors, although the exact role is not yet clear.\(^{25}\) A screening of some amine bases was conducted to determine the most suitable base (Table 2). In the presence of two equivalents of the surveyed bases, pyridine performed the best (Table 2, Entry 2) while non-aromatic or large and bulky aromatic bases performed quite poorly. Gratifyingly, increasing the number of equivalents to three resulted in a dramatic increase in conversion to from 50% to 79% after stirring for 4 days (Table 2, Entry 9). Increasing the amount of pyridine even further to 5 and 10 equivalents resulted in a marginal increase in conversion (Table 2, Entries 10 and 11). However, this increase comes at the cost of using large quantities of extremely toxic pyridine, thus it was concluded that using only 3 equivalents offered the best compromise between conversion and safety. It is important to note that 2,4,6-trivinylcyclotriboroxane is already complexed to 1 equivalent of pyridine, which likely accounts for the small degree of conversion achieved in the absence of any exogenous base (Table 2, Entry 1).

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conversion&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Equivalents of Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Base</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td><img src="base1.png" alt="Image" /></td>
<td>50%</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td><img src="base2.png" alt="Image" /></td>
<td>35%</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td><img src="base3.png" alt="Image" /></td>
<td>26%</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td><img src="base4.png" alt="Image" /></td>
<td>39%</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td><img src="base5.png" alt="Image" /></td>
<td>&lt;5%</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td><img src="base6.png" alt="Image" /></td>
<td>&lt;5%</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td><img src="base7.png" alt="Image" /></td>
<td>42%</td>
<td>1.0</td>
</tr>
<tr>
<td>9</td>
<td><img src="base8.png" alt="Image" /></td>
<td>79%</td>
<td>3.0</td>
</tr>
<tr>
<td>10</td>
<td><img src="base9.png" alt="Image" /></td>
<td>80%</td>
<td>5.0</td>
</tr>
</tbody>
</table>
McKinley and O’Shea have demonstrated the critical importance of the pyridine base complexed to the cyclotriboroxane core during their investigation of the Cu(OAc)$_2$-mediated coupling of phenols with aryl and vinyl boronic acids to generate arylated and vinylated phenols respectively (Scheme 1-23).

To explore the significance of the cyclotriboraxane species in solution, trials were conducted with both free and dehydrated boronic acids. Phenylboronic acid was used as a surrogate for vinyl boronic acid due to the difficulties associated with the isolation of the polymerization-prone free vinylboronic acid. Three independently synthesized boronic acid equivalents A, B and C were prepared. The reaction of the phenol in the absence of pyridine with substrate 4-phenylphenol resulted in a very low 7% conversion to 4-phenylbiphenyl ether (Table 3, Entry 1). When Cs$_2$CO$_3$ (1 equivalent) was introduced as the base, the product conversion improved to 35% (Table 3, Entry 2). Similarly, B gave poor conversion (5%) in the absence of base indicating that whether the boronic acid is cyclic or acyclic is not of great importance. The conversion improved to 60% when an equivalent of cesium carbonate was employed in the reaction with Y (Table 3, Entries 3 and 4). Interestingly, the reaction of C in the absence of base gave a good product conversion (93%) (Table

---

\[ \text{Conversion of starting material to product. The remainder was unreacted starting material. Assessed by crude } ^{1} \text{H-NMR.} \]
3, Entry 5). When the reaction was carried out using cesium carbonate the reaction reached completion (Table 3, Entry 6). Taken together, these results suggest that the pyridine-coordinated cycloboroxanes have an important role to play in achieving good conversions. In our experiments, this notion is supported by the experimental observation that pyridine proved to be the base of choice and exogenous pyridine may help increase the lifetime of these species in solution. It is well known that tetracoordinate boron species are critical to a successful transmetalation step in the catalytic cycles of other metal catalyzed reactions such as the Suzuki-Miyaura coupling. Thus, it is possible that the tetracoordinated boron species predisposes these complexes to transmetalation, facilitating the reaction.

**Table 3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td>Cs$_2$CO$_3$</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>Cs$_2$CO$_3$</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Z</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>Z</td>
<td>Cs$_2$CO$_3$</td>
<td>99</td>
</tr>
</tbody>
</table>

The next obstacle to overcome in the optimization step was to achieve good conversions after a reasonable time period. Although 79% conversion is reasonable, a reaction time of 4 days was a significant hindrance. Therefore, a variety of solvents and solvent mixtures were screened to determine whether changing the solvent had any significant effect on the reaction outcome. (Table 4) Gratifyingly, a 1:1 mixture of CH₂Cl₂:DMSO resulted in a significant rate enhancement and yielded 80% conversion in 9 hours, a significant improvement over the previous efforts (Table 4, Entry 6). The reaction time could be reduced to 6 hours if the temperature was increased to 40 ºC (Table 4, Entry 7). It was noted that under these conditions, after reaching approximately 50% conversion (after 3 hours, monitored by GC) the reaction mixture changed colour from a greenish blue, the characteristic colour of Cu(II) salts, to a dark brown characteristic of Cu(0) and the reaction rate decreased significantly. When the air in the reaction vial was replaced with an oxygen atmosphere, the solution changed colour once again to greenish blue after 5 minutes of vigorous stirring and for the first time, 100% conversion was observed. Thus, it became clear that oxidation of copper by O₂(g) was critical for achieving full conversion. To further explore this, the reaction was conducted in air, under a nitrogen atmosphere and under an atmosphere of pure oxygen from the onset. In air, the conversion stops at 80% while under a nitrogen atmosphere only 24% conversion was achieved (Table 4, Entry 6). Remarkably, when the reaction was performed under O₂ at 40 ºC, 100% conversion was achieved in only 2.5 hours (Table 4, Entry7). The product was isolated by flash column chromatography leading to an isolated yield of 95%. Increasing the temperature beyond 40 ºC had deleterious effects on the yield as a result of decomposition of the sensitive N-alkenyl aziridine to a series of unidentified byproducts. The role of DMSO in the rate-acceleration is not quite clear. Using a catalytic amount of DMSO (10 mol %) results in a sluggish reaction that did not reach completion which suggested that DMSO was not acting as a ligand for copper. However, Cu(OAc)₂ did appear to have improved solubility in the equimolar co-solvent mixture relative to the neat solvents. The greater effective concentration of Cu(OAc)₂ in solution may be the key to the rate acceleration.
**Table 4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion</th>
<th>Atmosphere/Temperature</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>50%</td>
<td>Air/r.t.</td>
<td>4 d</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>7%</td>
<td>Air/r.t.</td>
<td>4 d</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>12%</td>
<td>Air</td>
<td>4 d</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>&lt;5%</td>
<td>Air</td>
<td>4 d</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>32%</td>
<td>Air</td>
<td>4 d</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂:DMS (1:1)</td>
<td>80%</td>
<td>Air/r.t.</td>
<td>9 h</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂:DMS (1:1)</td>
<td>80%</td>
<td>Air/40 °C</td>
<td>6 h</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂:DMS (1:1)</td>
<td>24%</td>
<td>N₂/40 °C</td>
<td>4 d</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂:DMS (1:1)</td>
<td>100%</td>
<td>O₂/40 °C (95% yield)</td>
<td>3 h</td>
</tr>
</tbody>
</table>
On the basis of experimental observations and literature accounts of similar transformations, the following mechanism for this transformation is proposed (Figure 5). Initially, coordination of the N-H aziridine occurs to the Cu-center followed by deprotonation with pyridine to generate pyridinium acetate and the Cu-aziridine species. In contrast to earlier reports the rely on myristic acid to protonate an acetate ligand to free up a coordination site for the aziridine, in this case a base-promoted proton shuttle is operative which avoids the generation of potentially harmful acetic acid (HOAc). Next, transmetalation of the vinyl moiety from boron to copper occurs. Kerins and O’Shea propose the transmetalation may occur through intermediates such as I and II which implicate tetracoordinated boron species. After transmetalation, the resulting species can then undergo oxidation from a Cu$^{II}$ species to a Cu$^{III}$ species by molecular oxygen which can undergo rapid reductive elimination to generate the product and a Cu$^{I}$ species. Cu$^{I}$ can be re-oxidized back to Cu$^{II}$ by O$_2$ to facilitate another coupling reaction. Alternatively, reductive elimination can occur from a Cu$^{II}$ species to generate the product and Cu$^{0}$.

Figure 5
Under these optimized conditions, a variety of aryl and alkyl substituted alkenyl boronic acids proved to be suitable coupling partners and provided the products in good to excellent yields (Scheme 1-24). Alkenyl boronic acids substituted at both the α and β positions were tolerated.

Most alkenyl boronic acids can be introduced into the reaction as the free boronic acids which presumably react as is, or undergo dehydration in the presence of pyridine to form the cyclotriboroxane and then participate in coupling. However, in certain cases this was not a viable option. For instance, α-methyl alkenyl boronic acid 19 is highly unstable and prone to polymerization. It was prepared by treating isoprenyl magnesium bromide with trimethyl borate at -
78 °C in THF, followed by quenching with dilute aqueous HCl. Concentrating the reaction mixture inevitably led to polymerization. The reagent was introduced as a solution in THF in an attempt to circumvent this problem, but unfortunately none of the desired N-alkenyl aziridine was obtained. It is likely that even as a dilute solution, 19 does not survive for long under the reaction conditions. The solution to this problem was found in the cyclodehydration strategy. After quenching with HCl, pyridine was added to a dilute solution of 19 in Et₂O and the reaction stirred for 4 hours. Concentration and distillation afforded the cyclodehydration product as a white solid (20) which performed exceptionally well under the vinylation reaction conditions allowing isolation of the α-methylated N-alkenylated aziridine 21 in 89% yield (Scheme 1-25).

Scheme 1-25

Other aziridines were also examined to determine the extent to which the substitution pattern influenced reactivity. Benzyl aziridine 22 was prepared by first converting L-phenyl alanine to the
corresponding ethyl ester followed by NaBH₄-mediated reduction to the alcohol. Ring closure of the amino alcohol to form the aziridine was carried out under Mitsunobu conditions (Scheme 1-26). This aziridine was a good candidate for vinylation and the reaction proceeded smoothly to give the product in 81% yield although the reaction time was somewhat longer.

Scheme 1-26

The serine-derived aziridine 23 prepared by the esterification of serine with SOCl₂/n-PrOH followed by ring closure under Mitsunobu conditions was also a suitable candidate for vinylation. In this case, the simple vinyl aziridine can be prepared in good yield under the optimized conditions in only 6 hours (Scheme 1-27).
The symmetrical aziridine-2,3-dicarboxylate ethyl ester was also a suitable candidate for the alkenylation reaction. A variety of N-alkenylated aziridines were synthesized to showcase the tolerance of this protocol. The aziridine itself was prepared from diethyl tartrate via the synthetic scheme outlined in Scheme 1-28. Diethyl tartrate was treated with SOCl₂ to form the cyclic sulfite which was then subjected to ring opening with NaN₃ and finally PPh₃-mediated ring closure to generate the aziridine functionality. This aziridine was then subjected to several vinyl boronic acids under the optimized conditions yielding the corresponding N-alkenyl aziridines.

Scheme 1-28

![Scheme 1-27](image)
While many vinylboronic acids participated in the coupling without any problems, certain derivates did not lead to any conversion. For instance, using chloro allyl boronic acid 25 did not result in any formation of the desired vinyl aziridines. Activated vinylboronic acid 24 prepared by the hydroboration of methyl propiolate also failed. Similarly, not all aziridines performed well (Scheme 1-29).

Both C-vinyl and C-alkynyl aziridines were also not tolerated (Scheme 1-30). Background reactions revealed that these particular aziridines were not stable in the presence of Cu(OAc)$_2$ and decomposed quickly to a complex mixture of unidentified products. The $N$-alkenylated product of C-
alkenyl and C-alkynyl aziridines\textsuperscript{27} remains of considerable interest especially in the case of the former which would allow for the synthesis of divinyl aziridines, synthetically challenging substrates that can undergo facile [3,3] rearrangement to generate azepines.

\begin{center}
\textbf{Scheme 1-30}
\end{center}

After having firmly established a high yielding, operationally simple protocol to enable rapid access to \textit{N}-alkenyl aziridines, the focus of this project shifted to an exploration of the general chemistry of \textit{N}-alkenyl aziridines and to the preparation of vinyl aziridines with pendent functionality that could potentially participate in a variety of intramolecular transformations to generate larger rings.

\textsuperscript{27} C-alkynyl aziridine obtained from Zhi He, Ph.D. candidate in the Yudin group.
1.6 Synthetic Applications of \( N \)-Alkenyl Aziridines

We explored a variety of metal and non-metal catalyzed reactions of \( N \)-alkenyl aziridines. These efforts are described below.

1.6.1 Lewis-Acid Catalyzed Rearrangement

Lectka and co-workers have shown that \( N \)-acyl aziridines can undergo a rearrangement to form oxazolines in the presence of azaphilic Lewis acids.\(^\text{28}\) Of all the Lewis acids tested, \( \text{Cu(OTf)}_2 \) proved was the most successful delivering the oxazolines in 80-89% yield. When the same procedure was carried out with \( N \)-alkenyl aziridines, no product formed (Table 5). We then tested a variety of other Lewis acids to no avail. In most cases, concentration of the reaction mixture after the disappearance of starting material by TLC led to the isolation of a mixture of oligomers consisting of 2-4 “mers” of N-H aziridine adducts (characterized by MS) with no desired rearrangement product. In cases where polymerization did not occur at room temperature, starting material could be recovered. However, heating the mixture inevitably resulted in polymer formation.

Table 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid (10 mol %)/Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃OEt₂ (r.t., THF)</td>
<td>Polymerization</td>
</tr>
<tr>
<td>2</td>
<td>BF₃OEt₂ (-78 ºC, THF)</td>
<td>Polymerization</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)₂ (r.t., DME/THF)</td>
<td>N. R.</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂ (reflux, DME/THF)</td>
<td>Polymerization</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)₃ (r.t., CH₂Cl₂)</td>
<td>Polymerization</td>
</tr>
<tr>
<td>6</td>
<td>Ag(OTf) (r.t., CH₂Cl₂)</td>
<td>N. R.</td>
</tr>
<tr>
<td>7</td>
<td>Yb(OTf)₃ (r.t., CH₂Cl₂)</td>
<td>Polymerization</td>
</tr>
</tbody>
</table>

1.6.2 Heck Reaction

*N*-alkenyl aziridines were reacted with 4-nitrophenyl iodide in the presence of various Pd catalyst precursors and ligands in an attempt to generate Heck addition products. In all cases, no conversion was observed by ESI-MS or crude NMR. Even after prolonged heating (7 days), no trace of addition products was observed (Scheme 1-31).
After not observing any intermolecular Heck reaction, we considered the possibility on an intramolecular Heck reaction instead. An intramolecular Heck reaction would also generate a new ring, highlighting the synthetic utility of these N-alkenyl aziridines. We considered a number of routes to a substrate bearing an aryl-halogen bond in close proximity to the alkene. Our first proposed route involved reductive amination from the aziridine aldehyde dimers developed in our laboratory.\textsuperscript{29} Phenyl aziridine aldehyde was prepared by reduction of the corresponding phenyl aziridine ester with DIBAL-H at -78 °C. While the reductive amination with aniline is known to proceed smoothly, when we employed the same protocol with 2-bromoaniline, we observed no conversion. The more nucleophilic alkylated 2-bromoaniline was also unsuccessful alluding to the possibility that the bromine atom of 2-bromoaniline created an unfavorable steric environment for reductive amination (Scheme 1-32).

The next route we considered involved N,N'-Dicyclohexylcarbodiimide (DCC) mediated amide bond formation. Treating ethyl-3-phenyl glycinate with KOH at 0 °C in EtOH generated the potassium carboxylate salt in 92% yield. This salt was then treated with DCC at 0 °C in CH₂Cl₂ and the same aniline derivates as in the previous case (Scheme 1-33). Again, we found that no reaction occurred. Had amide bond formation occurred smoothly, we would have proceeded with azide opening of the epoxide and PPh₃-mediated ring closure to form the aziridine which could have been alkenylated.
We then turned our attention to developing conditions for the preparation of the acid chloride derived from potassium phenyl glycidate and the possibility that the resulting highly electrophilic species might allow for the synthesis of the desired scaffold. When the salt was treated with COCl₂ at -40 °C, the acid chloride was cleanly formed. Treatment of the acid chloride with iodophenol at room temperature proceeded to give the ester in 65% yield. Unfortunately, when the phenyl ester was subsequently treated with NaN₃ to open the epoxide, only iodophenol was recovered (Scheme 1-34). Therefore, the general approach of coupling the salt with an amine or alcohol to generate an amide or ester respectively was abandoned.
Ultimately, we discovered that the Darzens reaction was an excellent means by which to generate the desired epoxide in high yield.\textsuperscript{30} The Darzens reaction generates an epoxide by the treatment of a carbonyl compound and an α-chloroester with a strong base. We found that that treatment of a solution of 2-bromobenzaldehyde and ethyl chloroacetate with $t$-BuOK at 0 ºC in THF led to the formation of bromoaryl epoxide 26 in 87\% yield. Standard NaN$_3$ opening and PPh$_3$ ring closure generated aziridine 27 in 64\% yield over 2 steps. Finally, alkenylation under optimized conditions afforded the desired $N$-alkenyl aziridine (28) in excellent yield with no indication of any undesired byproducts of inter- or intramolecular N-arylation (Scheme 1-35). Thus, the optimized conditions are also completely chemoselective for $N$-alkenylation over $N$-arylation, a common reaction catalyzed by Cu(OAc)$_2$.

![Scheme 1-35](image)

This substrate was subjected to the same Heck conditions as before but unfortunately none of the desired product could be detected (Scheme 1-36) Since the starting material was recovered nearly quantitatively, it is likely that oxidative addition into the sterically encumbered C$_{aryl}$-Br bond is difficult and necessitates the use of more active Pd catalysts. This continues to be an area of active investigation in our laboratories.

\textsuperscript{30} Darzens, G., Compt. Rend. 1905, 141, 766.
1.6.3 Alkene/Enyne Metathesis

With the hope of generating new strained rings, we turned our attention to intramolecular olefin metathesis with N-alkenyl aziridines (Figure 6). The first challenge was designing suitable substrates for this reaction.

We began by exploring the possibility of performing a metal-halogen exchange reaction with epoxide 26 followed by trapping with an allyl source. Using t-BuLi to perform the metal
halogen exchange and trapping with allyl bromide and allyl acetate led mainly to the recovery of 29 and the starting material, even at room temperature (Scheme 1-37). We observed the same trend with both the N-H aziridine and the N-alkenyl aziridines under the same conditions.

We then opted for a different route starting from 2-bromobenzaldehyde. To this end, 2-bromobenzaldehyde was treated with the Wittig salt Ph₃PMeBr and strong base to generate 1-bromo-2-vinylbenzene 30 in 31% yield. Treating 30 with n-BuLi and DMF gave aldehyde 31 in 61% yield. When 31 was subjected to Darzens’ conditions, a complex reaction mixture resulted with only a small amount of the desired product detectable by crude NMR (Scheme 1-38).
Finally, a successful route to the desired alkenyl aziridine was realized using aziridine 32 developed earlier in our laboratories. To prepare 32, 4-pentenoic acid was treated with oxalyl chloride to generate the corresponding acid chloride which then treated with EtOH to form ethyl 4-pentenoate in quantitative yield. DIBAL reduction to the aldehyde followed by BF₃OEt₂-mediated aldol-type condensation with 1-phenyl-1-trimethylsilyloxyethylene gave the aldol product in 89% yield. The β-ketoalcohol was dehydrated to form the α,β-unsaturated ketone in 95% yield by treatment with TsOH in toluene. Conjugate addition with NH₂OMe followed by treatment with freshly prepared NaOMe yielding the aziridine 32 in 74% yield. Application of the standard alkenylation protocol gave the N-alkenylated aziridine 33 in 69% yield (Scheme 1-39). Interestingly, application of the previous state-of-the-art Pd- and Cu-catalyzed alkenylation protocols failed to produce any N-alkenylated aziridine indicating a marked improvement in the methodology.
Scheme 1-39

$N$-alkenyl aziridine 33 was subjected to three different Ru-based metathesis catalysts under a variety of conditions. Unfortunately, the desired cyclized product was not observed in any of these cases (Scheme 1-40). Tertiary amines are understood to be challenging substrates for metathesis since the nitrogen lone pair can coordinate to Ru and inactivate the catalyst.\textsuperscript{31}

However, a number of literature reports demonstrate that in certain cases tertiary amines are tolerated. In our case, the problem could have two origins. Either the aziridine nitrogen is coordinating to Ru and deactivating the catalyst or the enamine is stereoelectronically unsuitable for metathesis. To probe this possibility, we prepared the N-allylated aziridine 34 by Pd-catalyzed aziridine allylation (Scheme 1-41).
When treated with Grubbs-Hoveyda II catalyst, 34 did not cyclize indicating that the likely culprit in both cases is nitrogen lone pair coordination to ruthenium and not the stereoelectronic nature of the alkene. With the advent of new generation Mo-based methathesis catalysts by Schrock and Hoveyda specifically designed to handle molecules bearing tertiary amines, the possibility of metathesis remains and will be fully explored in the near future.

We also explored the possibility of enyne metathesis with N-alkenyl aziridines. Again, this necessitated the preparation of a unique substrate. A Sonogashira coupling between 2-bromobenzaldehyde and 1-hexyne gave 2-(hex-1-ynyl)benzaldehyde in 81% yield, which was then reacted with chloroethyl acetate under Darzens’ conditions to generate ethyl 3-(2-(hex-1-ynyl)phenyl)oxirane-2-carboxylate in 66% yield. Azide ring opening and PPh₃-mediated ring closure delivered the aziridine in 62% yield without any issues arising from intramolecular alkyne-azide cycloaddition. Application of the standard alkenylation protocol gave the N-alkenyl aziridine 35 in excellent yield (Scheme 1-42). To our dismay, treating the alkynyl vinyl aziridine 35 with different Ru-metathesis catalysts did not result in any conversion to the desired product. Instead, starting material was cleanly recovered. Despite the fact that metathesis was not successful, N-alkenyl aziridines 33 and 35 still hold a great deal of synthetic promise and variety of reactions including reductive cyclizations and radical reactions remain to be explored and will be the subject of intense investigation.
Scheme 1-42

47% yield

66% yield

62% yield over 2 steps

35% yield

Grubbs I (10 mol %)
CH₂Cl₂, 40 °C
N.R.

Grubbs II (10 mol %)
CH₂Cl₂, 40 °C
or
Toluene, 80 °C
N.R.

Grubbs-Hoveyda II (10 mol %)
CH₂Cl₂, 40 °C
or
Toluene, 80 °C
N.R.
1.6.4 Preparation of an N-Alkenyl Aziridine Aldehyde

We became interested in the possibility of preparing an N-alkenyl aziridine aldehyde because of the synthetic potential of such a compound. From this starting point, one could envisage a variety of [3,3]-type reactions. For instance, Claisen rearrangements could occur from the aldehyde or imine to form 7-membered rings. A Wittig reaction would convert the aldehyde to an alkene to form a divinyl aziridine that could participate in an electrocyclization to form an azepine. Such a substrate is also ideally suited for intramolecular hydroacylation reactions to generate bicycles. These intriguing possibilities led us to consider routes to such a molecule. Our studies began by attempting to selectively reduce the ester functionality of 18 to an aldehyde. Common reducing agents such as DIBAL, NaBH₄ and LiAlH₄ all proved to be unsuitable (Scheme 1-43). All of these reducing agents resulted in very complex reaction mixtures consisting of mainly the over-reduced alcohol and what are believed to be ring-opened products.

To avoid the problem of over-reduction, we then turned our attention to Weinreb amides which form a very stable metal-chelate species after the amide is attacked by a single equivalent of hydride, resulting in resistance to over-reduction. Collapse of this intermediate upon workup gives an aldehyde. The desired Weinreb amide was prepared by a literature procedure developed in our laboratories beginning from potassium phenyl glycidate. N,N'-Dicyclohexylcarbodiimide (DDC) mediated amide bond formation with N,O-dimethylhydroxyl amine proceeded smoothly to give the Weinreb amide in 67% yield. Aziridine formation by standard techniques also proceeded smoothly.
to give the desired aziridine in 70% over two steps. N-alkenylation then generated N-methoxy-N-methyl-3-phenyl-1-vinylaziridine-2-carboxamide 36 in 79% yield (Scheme 1-44).

Scheme 1-44

When 36 was treated with DIBAL at -78ºC, a small amount of aldehyde could be detected by crude NMR, but incomplete conversion and the appearance of unwanted byproducts led us to abandon this reducing agent. A similar problem arose when 36 was treated with Schwartz’s reagent (Cp)₂Zr(H)Cl which is known to be highly chemoselective for the reduction of amides in the presence of a variety of other functional groups. However, we were pleased to discover that treating 36 with LiAlH₄ at -40 ºC in THF resulted in complete and very clean conversion to the corresponding aldehyde (Scheme 1-45). Although crude NMR indicated complete conversion with no other byproducts, the aldehyde could only be isolated in 12% yield likely as a result of its instability to conventional chromatography. To the best of our knowledge, this is a unique instance in the literature where an aldehyde and an enamine can co-exist in the same molecule without undergoing condensation chemistry. This presents a unique opportunity to investigate the orthogonal reactivity of these two functional groups which will be the focus of continuing doctoral studies.
Scheme 1-45

\[
\begin{align*}
\text{DIBAL} & \quad \text{Toluene, -78 °C} \\
\text{Cp}_2\text{Zr(H)Cl} & \quad \text{THF, r.t.} \\
\text{LiAlH}_4 & \quad \text{THF, -40 °C}
\end{align*}
\]

complex reaction mixture

100% conversion
12% isolated yield
1.7 Experimental

General Information: Anhydrous toluene and dimethylformamide (DMF) was purchased and used as received. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon. CH2Cl2 was distilled from CaH2 under argon. All other solvents including TFE (2,2,2, trifluoroethanol) and acetonitrile were of reagent grade quality.

Chromatography: Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel and thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm) and Iodine stain.

Nuclear magnetic resonance spectra: 1H NMR and 13C NMR spectra were recorded on Varian Mercury 300 or 400 MHz spectrometers. 1H NMR spectra were referenced to TMS (0 ppm) and 13C NMR spectra were referenced to CDCl3 (77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ds, doublet of singlets; dd, doublet of doublets; ddd, doublet of doublet of doublets; bt, broad triplet; td, triplet of doublets; tdd, triplet of doublets of doublets.

trans-3-Phenylaziridine-2-carboxylic acid ethyl ester

The title compound was synthesized according to a literature procedure. To a mixture of 3-phenyloxirane-2-carboxylic acid ethyl ester (9.6 ml, 55 mmol) and 183 ml of EtOH in a flame-dried two-necked flask equipped with a water condenser and magnetic stirring rod was added NaN3 (10.73 g, 165 mmol) and ammonium chloride (8.83 g, 165 mmol). The reaction mixture was brought to 65 °C and stirred for 5 hours at which point TLC analysis showed that the reaction was complete. The mixture was filtered and concentrated under reduced pressure. The crude 1H NMR showed that the product of nucleophilic opening of the epoxide by azide was pure enough to carry over to the next step. In a flame-dried two-neck flask fitted with a water condenser and equipped with a magnetic
stirring bar was added the product from above (12.93 g, 55 mmol) dissolved in 183 ml of acetonitrile. The reaction mixture was brought to 40 °C, at which point PPh₃ (16 g, 61 mmol) was added at a controlled rate to avoid rapid evolution of N₂. The reaction was then brought to 83 °C and stirred for 5 hours. The reaction mixture was then cooled and concentrated under reduced pressure. The crude mixture was then dissolved in 5% EtOAc in pentane and filtered. The filtrate was concentrated and subsequently dissolved in pentane and placed in the freezer overnight (-15 °C). Any resulting precipitate that formed was filtered off and the filtrate was concentrated under reduced pressure and subjected to silica gel column chromatography to yield a pale yellow oil in 61% over two steps.

¹H NMR (200 MHz, CDCl₃) δ: 7.36-7.25 (m, 5H), 4.25 (m, 1.2 Hz, 2H), 3.25 (s, 1H), 2.58 (s, 1H), 1.89 (bs, 1H), 1.31 (t, J = 7 Hz, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃) δ: 171.6, 137.8, 128.3, 127.6, 126.1, 61.6, 40.2, 39.3, 14.0 ppm.

2,4,6-Trivinylcyclotriboroxane-Pyridine Complex

The title compound was synthesized according to a slightly modified literature procedure.³² A solution of trimethyl borate (10 mL, 89.2 mmol) in dry THF (75 mL) was cooled to -78 °C under N₂ in a dry ice-acetone bath. Vinylmagnesium bromide (50 mL of a 1.0 M solution in THF, 50.0 mmol) was added dropwise over 1 h and the reaction stirred for a further 1 h. Hydrochloric acid (1 M, 25 mL) was added over 30 min and the solution removed from the cooling bath and allowed to warm to room temperature. Brine (20 mL) was added, the solution was extracted with diethyl ether (4 x 50 mL), and the combined extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated under reduced pressure to 25 mL. The diethyl ether solution was treated with pyridine (10 mL) and stirred at room temperature for 4 h. The solvents were evaporated

under reduced pressure to give a pale yellow oil. Distillation under reduced pressure (95 °C, 1.0 Torr) gave the product as a white solid 3.5 g, 85% yield, mp 46-47 °C.

^1^H NMR (CDCl3): 5.78-5.86 (m, 3H), 5.93-6.07 (m, 6H), 7.54-7.59 (m, 2H), 7.94-8.01 (m, 1H), 8.79-8.81 (m, 2H).

^1^3^C NMR (CDCl3): 125.3, 131.5, 138.0 (broad) 140.1, 145.1.

^1^1^B NMR (CDCl3): 17.68.

**Standard Protocol for the synthesis of N-alkenyl aziridines**

To a flame-dried 2-dram vial equipped with a magnetic stir bar under and atmosphere of O₂ was added anhydrous Cu(OAc)_2 (18.1 mg, 0.10 mmol). Anhydrous CH₂Cl₂ (0.250 mL) and anhydrous DMSO (0.250 mL) were successively added and the mixture stirred under all of the Cu(OAc)_2 dissolves in solution (approximately 5 min.) Then, aziridine (1 mmol) was added and the reaction stirred for a further 15 minutes. Boronic acid (3 mmol) was then added followed by pyridine (3 mmol) and the reaction mixture was placed in an oil bath maintained at a constant temperature of 40 °C. After reaction completion, as judged by TLC (generally 2.5-5 h), the reaction mixture is cooled to room temperature, diluted with saturated NH₄Cl_(aq) and extracted 4x with CH₂Cl₂ 5 mL, dried over Na₂SO₄ and concentrated. The crude oil is purified by flash chromatography on silica gel.

(±)-ethyl 3-phenyl-1-vinylaziridine-2-carboxylate

![Chemical Structure](image)

Alkenylation performed using standard protocol. Title compound isolated in 95% yield.

^1^H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.28 (m, 5H), 6.22 (dd, J=15.2, 8.0, 1H), 4.67 (d, J=15.2, 1H), 4.57 (d, J=8.0, 1H), 4.29 – 4.19 (m, 2H), 3.51 (d, J=2.6, 1H), 2.97 (d, J=2.6, 1H), 1.31 (t, J=7.2, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 168.3, 142.3, 136.0, 128.6, 128.2, 127.1, 100.4, 61.6, 47.1, 44.6, 14.4.$

(±)-ethyl 1-((E)-2-cyclohexylvinyl)-3-phenylaziridine-2-carboxylate

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{CO}_2\text{Et}
\end{array}
\]

Alkenylation performed using standard protocol. Title compound isolated in 87% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.38 – 7.24$ (m, 5H), 5.85 (d, $J=13.6$, 1H), 5.15 (dd, $J=13.7$, 7.4, 1H), 4.29 – 4.17 (m, 2H), 3.46 (d, $J=2.6$, 1H), 2.92 (t, $J=10.0$, 1H), 1.98 – 1.86 (m, 1H), 1.75 – 1.56 (m, 4H), 1.31 (t, $J=7.1$, 3H), 1.28 – 1.00 (m, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 168.3, 133.6, 128.5, 128.1, 127.7, 125.0, 105.6, 61.4, 47.5, 45.3, 38.6, 33.8$ (d, $J=12.1$), 26.2 (d, $J=7.2$), 14.5 (s).

(±)-ethyl 3-phenyl-1-styrylaziridine-2-carboxylate

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{CO}_2\text{Et}
\end{array}
\]

Alkenylation performed using standard protocol. Title compound isolated in 82% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.37 – 7.29$ (m, 5H), 7.25 – 7.19 (m, 4H), 7.13 (m, 1H), 6.70 (d, $J=13.5$, 1H), 6.15 (d, $J=14.0$, 1H), 4.31 – 4.19 (m, 2H), 3.62 (d, $J=2.6$, 1H), 3.07 (d, $J=2.7$, 1H), 1.30 (t, $J=7.1$, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 168.2, 136.7, 136.5, 135.9, 128.7$ (d, $J=6.2$), 128.4, 127.1, 126.4, 125.6, 118.0, 61.7, 47.7, 45.4, 14.4.
(±)-ethyl 3-phenyl-1-(prop-1-en-2-yl)aziridine-2-carboxylate

\[
\text{Ph} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

Alkenylation performed using standard protocol. Title compound isolated in 89% yield.

\[^1\text{H} \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta = 7.36 - 7.26 \ (m, 5H), \ 4.36 \ (dd, J=6.3, 5.6, 2H), \ 4.28 - 4.19 \ (m, 2H), \ 3.58 \ (d, J=2.4, 1H), \ 3.01 - 2.98 \ (m, 1H), \ 1.71 \ (d, J=0.7, 3H), \ 1.34 - 1.27 \ (m, 3H)\].

\[^{13}\text{C} \text{ NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta = 168.5, \ 149.2, \ 136.4, \ 128.6, \ 128.1, \ 126.9, \ 96.1, \ 77.5, \ 77.2, \ 76.9, \ 61.5, \ 46.7, \ 44.3, \ 20.6, \ 14.4\].

(±)-ethyl 1-((E)-hept-1-enyl)-3-phenylaziridine-2-carboxylate

\[
\text{Ph} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

Alkenylation performed using standard protocol. Title compound isolated in 93% yield.

\[^1\text{H} \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta = 7.45 - 7.14 \ (m, 5H), \ 5.88 \ (d, J=13.6, 1H), \ 5.27 - 5.13 \ (m, 1H), \ 4.30 - 4.17 \ (m, 2H), \ 3.47 \ (d, J=2.7, 1H), \ 2.94 \ (d, J=2.7, 1H), \ 2.05 - 1.88 \ (m, 2H), \ 1.36 - 1.20 \ (m, 9H), \ 0.88 \ (m, J=3H)\].

\[^{13}\text{C} \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta = 168.4, \ 135.4, \ 128.5, \ 128.1, \ 127.3, \ 119.0, \ 115.2, \ 61.4, \ 47.5, \ 45.2, \ 31.4, \ 29.8 \ (d, J=10.3), \ 22.6, \ 14.4, \ 14.2\].
2,4,6-Triisopropenylcyclotriboroxane-Pyridine Complex

![Chemical structure](image)

Title compound isolated in 84% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.88 – 8.80$ (m, 2H), $8.01$ (tt, $J=7.6$, 1.6, 1H), $7.60$ (ddd, $J=7.6$, 5.3, 1.3, 2H), $5.68$ (d, $J=3.3$, 3H), $5.46$ (d, $J=2.3$, 3H), 1.80 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 144.2$, 140.2, 125.0, 124.8, 105.3, 20.8.

(S)-2-benzylaziridine

![Chemical structure](image)


**Reduction:** To a solution of L-phenyl alanine (16.5 g, 100 mmol) in 400 mL of absolute EtOH was added slowly SOCl$_2$ (10 mL, 137.5 mmol). After the addition was complete, the flask was equipped with a water cooled condenser and the contents were refluxed for 3 hours. The reaction mixture was cooled to room temperature and the excess SOCl$_2$ and EtOH were removed by rotary evaporation. The crude ethyl ester hydrochloride salt was dissolved in 250 mL of 1:1 EtOH:H$_2$O and added slowly to a solution of NaBH$_4$ in 250 mL of 1:1 EtOH:H$_2$O. This mixture was refluxed for 4 hours and then cooled to room temperature. 50 mL of 1 M NaOH was added to quench the reaction. The EtOH was removed by rotary evaporation and the solution was extracted 4x with EtOAc, dried over MgSO$_4$ and concentrated. The crude white solid was dissolved in a minimum amount of hot EtOAc.
and cold hexanes were added until the product precipitated out. The amino alcohol product was collected by vacuum filtration in 88% yield.

**Ring Closure:** To a flame-dried flask equipped with a magnetic stir bar was added the amino alcohol (2 g, 13.23 mmol) and anhydrous toluene (65 mL). To this solution was added PPh$_3$ (3.46 g, 13.23 mmol). The reaction mixture was cooled to 0 °C and DIAD (2.75 mL, 13.23 mmol) was added slowly via syringe pump over a period of 30 minutes. The solution was allowed to slowly warm to room temperature and then the flask was equipped with a water cooled condenser and the contents refluxed for 15 hours. The reaction mixture was then cooled to room temperature and the toluene was removed by rotary evaporation. A solution of 5% EtOAc in hexanes was added to the crude oil and the contents vigorously stirred which caused PPh$_3$O to precipitate out of solution. The contents of the flask were cooled to 0 °C and stirred for a further 30 min before filtering to remove precipitated PPh$_3$O. The solution was concentrated to afford a crude oil which was purified by Kulgelrohr distillation (125 °C, 1 torr) giving the pure aziridine as a colourless oil in 55% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.35 – 7.19 (m, 5H), 2.81 (dd, $J$=14.4, 6.0, 1H), 2.67 (dd, $J$=14.4, 6.0, 1H), 2.23 (m, 1H), 1.83 (d, $J$=5.7, 1H), 1.46 (d, $J$=3.5, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 129.0, 128.6, 126.5, 105.3, 40.3, 31.1, 25.0.

(S)-2-benzyl-1-vinylaziridine

![Chemical Structure](image)

Alkenylation performed using standard protocol. Title compound was isolated in 81% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.35 – 7.19 (m, 5H), 6.31 (dd, $J$=15.1, 7.8, 1H), 4.46 – 4.39 (m, 1H), 4.36 (d, $J$=7.8, 1H), 2.77 (m, 2H), 2.01 (ddd, $J$=12.4, 6.1, 3.5, 1H), 1.91 (d, $J$=3.3, 1H), 1.81 (d, $J$=6.1, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 148.1, 139.4, 128.9, 128.6, 126.5, 99.1, 40.0, 39.1, 33.4.
(S)-propyl aziridine-2-carboxylate

To a flame-dried flask equipped with a magnetic stir bar was added serine (10 g, 95 mmol) followed by n-propanol (200 mL) and the solution was cooled to -10 °C with the aid of an ice/salt-water bath. SOCl₂ (7.64 g, 100 mmol) was added slowly along the sides of the flask via syringe pump and the reaction was heated to 70 °C for 4 hours until ESI MS indicated the disappearance of starting material and the formation of product was complete. The reaction mixture was cooled to room temperature at which point cold hexanes was added which caused precipitation of the product as a hydrochloride salt. The salt was filtered and dried under high vacuum (0.1 torr). To serine propyl ester hydrochloride was added sufficient NH₄OH(aq) to cause all of the salt dissolve forming the free base (~5 mL). The serine propyl ester was isolated by extraction with CH₂Cl₂ followed by drying over MgSO₄, filtration and concentration of the solution. To a flame dried flask equipped with a magnetic stir bar was added serine propyl ester (4.71 g, 26 mmol) and dry CH₂Cl₂ (160 mL) and the solution was cooled to -10 °C with the aid of a salt water/ice bath. PPh₃ (6.81 g, 26 mmol) was added and the solution stirred for 10 minutes. A solution of DIAD (95%, 5.39 mL, 26 mmol) was added slowly along the walls of the vessel over a period of 30 minutes. The solution was allowed to warm to room temperature slowly and stirred at room temperature for 20 h. The reaction mixture was then cooled and concentrated under reduced pressure. The crude mixture was then dissolved in 5% EtOAc in pentane and filtered. The filtrate was concentrated and subsequently dissolved in pentane and placed in the freezer overnight (-15 °C). Any resulting precipitate that formed was filtered off and the filtrate was concentrated under reduced pressure and subjected to Kugelrohr distillation (90-95 °C, 1 torr) giving the product as a clear colourless oil in 76% yield.

¹H NMR (300 MHz, CDCl₃) δ = 4.20 – 4.06 (m, 2H), 2.53 (s, 1H), 2.00 (s, 1H), 1.86 (s, 1H), 1.70 (m, J=14.3, 7.0, 2H), 0.97 (t, J=7.4, 3H).

¹³C NMR (100 MHz, CDCl₃) δ = 169.7, 67.4, 29.2, 27.5, 22.1, 10.5.
(S)-propyl 1-vinylaziridine-2-carboxylate

\[ \text{N} \quad \text{O} \quad \text{O} \quad \text{H} \]

Alkenylation performed using standard protocol. Title compound isolated in 74% yield.

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \delta = 6.33 \text{ (dd, } J=15.1, 7.9, 1\text{H}), 4.58 \text{ (dd, } J=15.1, 0.6, 1\text{H}), 4.51 \text{ (d, } J=7.8, 1\text{H}), 4.21 - 4.04 \text{ (m, } 2\text{H}), 2.50 - 2.43 \text{ (m, } 1\text{H}), 2.38 \text{ (dd, } J=3.0, 1.8, 1\text{H}), 2.03 \text{ (dd, } J=6.2, 1.6, 1\text{H}), 1.77 - 1.61 \text{ (m, } 2\text{H}), 1.01 - 0.90 \text{ (m, } 3\text{H}). \]

\[ ^13\text{C NMR (100 MHz, CDCl}_3 \delta = 170.0, 145.9, 100.4, 66.9, 36.5, 33.4, 21.9, 10.2. \]

(2R,3R)-diethyl aziridine-2,3-dicarboxylate

\[ \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \]

The title compound was prepared using a literature method.\textsuperscript{33} In a round bottom flask equipped with a Teflon coated magnetic stirring bar and pressure equalizing addition funnel was placed L-diethyl-tartrate (17.73 g, 86 mmol). The reaction was cooled to 0°C and then SOCl\textsubscript{2} (7.3 ml, 100 mmol) was added dropwise through the addition funnel over a period of 15 minutes. After the addition was complete, 20 drops of anhydrous DMF were added to the reaction mixture and the vessel was first allowed to warm to room temperature, and then it was heated at 50°C for 30 minutes. The reaction was allowed to cool back to room temperature and N\textsubscript{2} was bubbled through for 1 hour in order to remove excess SOCl\textsubscript{2} and liberated acidic components. The mixture was then concentrated using rotary evaporator at 50°C to remove residual SOCl\textsubscript{2}, then further concentrated under high vacuum to afford the cyclic sulfite as a pale yellow oil. The cyclic sulfite (21.67 g, 86 mmol) was then dissolved in 50 ml of anhydrous DMF. NaN\textsubscript{3} (16.77 g, 258 mmol) was then added to the solution and the reaction was allowed to stir for 24 hours. 50 ml of CH\textsubscript{2}Cl\textsubscript{2} and 60 ml of water were then added to the

reaction, and stirred for 2 hours. The aqueous phase was extracted three times with CH$_2$Cl$_2$ and the collected organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the azido alcohol in 95% yield (18.87 g, 81.7 mmol) over two steps as a yellow oil, which was pure by NMR and carried over to the next step. The azido alcohol (18.87 g, 81.7 mmol) was dissolved into 400 ml of anhydrous DMF and cooled to 0°C. PPh$_3$ (22.5g, 85.79 mmol) was added in portions over a period of 30 minutes. The reaction vessel was then allowed to warm to room temperature and stirred at this temperature of 90 minutes. The reaction vessel was then warmed to 85°C and stirred until completed by TLC. The reaction was then concentrated under reduced pressure and purified by flash column chromatography to afford the title compound as a pale yellow oil in 76% yield (11.8 g).

$^1$H NMR (CDCl$_3$, 400MHz) δ: 4.30 (m, 4H), 2.87 (dd, $J = 9.2$ Hz, 3.2 Hz, 2H), 1.82 (bt, $J = 9.2$ Hz, 1H), 1.31 (dt, $J = 10.4$ Hz, 7.2 Hz, 6 H) ppm.

$^{13}$C NMR (CDCl$_3$, 50MHz) δ: 170.6, 168.9, 62.4, 61.8, 36.3, 35.5, 14.2 ppm.

(2R,3R)-diethyl 1-vinylaziridine-2,3-dicarboxylate

Alkenylation performed using standard protocol. Title compound isolated in 89% yield.

$^1$H NMR (300 MHz, CDCl$_3$) δ = 6.18 (dd, $J = 15.1$, 8.0, 1H), 4.70 (d, $J = 15.2$, 1H), 4.62 (d, $J = 8.0$, 1H), 4.33 – 4.14 (m, 4H), 3.16 (s, 2H), 1.38 – 1.23 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ = 167.3, 140.8, 101.6, 62.0, 42.1, 14.3.

(2R,3R)-diethyl 1-(prop-1-en-2-yl)aziridine-2,3-dicarboxylate

Alkenylation performed using standard protocol. Title compound isolated in 86% yield.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 4.39$ (dd, $J=10.0, 4.1$, 2H), $4.30 - 4.14$ (m, 4H), $3.20$ (d, $J=1.5$, 2H), $1.79 - 1.73$ (m, 3H), $1.30$ (dd, $J=8.3, 5.9$, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 167.5, 147.7, 97.0, 62.0, 41.7, 20.4, 14.3$.

*(2R,3R)-diethyl 1-styrylaziridine-2,3-dicarboxylate*

![Diethyl 1-styrylaziridine-2,3-dicarboxylate](image)

Alkenylation performed using standard protocol. Title compound isolated in 79% yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 7.28 - 7.10$ (m, 5H), $6.65$ (d, $J=13.9$, 1H), $6.19$ (d, $J=13.9$, 1H), $4.33 - 4.15$ (m, 4H), $3.26$ (s, 2H), $1.30$ (t, $J=7.1$, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta = 167.3, 136.1, 134.9, 128.7, 126.8, 125.8, 119.4, 62.1, 42.8, 14.3$.

*(2R,3R)-diethyl 1-((E):hept-1-enyl)aziridine-2,3-dicarboxylate*

![Diethyl 1-((E):hept-1-enyl)aziridine-2,3-dicarboxylate](image)

Alkenylation performed using standard protocol. Title compound isolated in 88% yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 5.86$ (d, $J=13.5$, 1H), $5.35 - 5.19$ (m, 1H), $4.29 - 4.14$ (m, 4H), $3.11$ (s, 2H), $1.96$ (q, $J=6.7$, 2H), $1.41 - 1.17$ (m, 12H), $0.87$ (t, $J=6.7$, 3H).

$^{13}$C NMR (75 MHz, cdcl$_3$) $\delta = 167.5, 133.9, 120.6, 61.8, 42.7, 31.3, 29.7, 29.6, 22.6, 14.3, 14.2$. 
(±)-ethyl 3-(2-bromophenyl)oxirane-2-carboxylate

![Chemical Structure](image)

To a flame-dried flask equipped with a magnetic stir bar was added 2-bromobenzaldehyde (2.66 g, 14.4 mmol), ethyl chloroacetate (2 mL, 18.7 mmol) and anhydrous THF (45 mL). The reaction mixture was cooled to 0 ºC and a t-BuOK (1.0 M solution in THF, 18.8 mL, 18.8 mmol) was added dropwise via syringe pump over a period of 1 h. The reaction mixture was allowed to slowly warm to room temperature and then stirred overnight. After reaction was complete (monitored by TLC), the reaction mixture was quenched with the addition of water and extracted 3x with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated to a crude yellow oil. The crude oil was purified by flash column chromatography giving the product as a pale yellow oil in 87% yield.

¹H NMR (400 MHz, CDCl₃) δ = 7.56 (dd, J=8.0, 1.1, 1H), 7.35 – 7.29 (m, 1H), 7.26 – 7.17 (m, 2H), 4.37 – 4.36 (m, 1H), 4.35 – 4.28 (m, 2H), 3.35 (s, 1H), 1.37 – 1.31 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 168.0, 135.0, 132.6, 130.1, 127.9, 126.5, 122.8, 62.0, 57.9, 56.3, 14.3.

(±)-ethyl 3-(2-bromophenyl)aziridine-2-carboxylate

![Chemical Structure](image)

To a mixture of ethyl 3-(2-bromophenyl)oxirane-2-carboxylate (1.42 g, 5.24 mmol) and 20 mL of EtOH in a flame-dried two-necked flask equipped with a water condenser and magnetic stirring rod was added NaN₃ (1.02 g, 15.7 mmol) and ammonium chloride (0.84 g, 15.7 mmol). The reaction mixture was brought to 78 ºC and stirred for 8 hours at which point TLC analysis showed that the reaction was complete. The mixture was filtered and concentrated under reduced pressure. The crude ¹H NMR showed that the product of nucleophilic opening of the epoxide by azide was pure enough to carry over to the next step. In a flame-dried two-neck flask fitted with a water condenser and equipped with a magnetic stirring bar was added the product from above (1.4 g, 4.46 mmol)
dissolved in 15 ml of acetonitrile. The reaction mixture was brought to 40ºC, at which point PPh₃ (1.28g, 4.9 mmol) was in a controlled manner to avoid rapid evolution of N₂. The reaction was then brought to 83 ºC and stirred for 7 hours. The reaction mixture was then cooled and concentrated under reduced pressure. The crude mixture was then dissolved in 5% EtOAc in pentane and filtered. The filtrate was concentrated and subsequently dissolved in pentane and placed in the freezer overnight (-15 ºC). Any resulting precipitate that formed was filtered off and the filtrate was concentrated under reduced pressure and subjected to silica gel column chromatography to yield a pale yellow oil in 64% over two steps.

¹H NMR (400 MHz, CDCl₃) δ = 7.53 (dd, J=8.0, 1.0, 1H), 7.36 (dd, J=7.7, 1.7, 1H), 7.32 – 7.24 (m, 1H), 7.14 (td, J=7.7, 1.8, 1H), 4.38 – 4.22 (m, 2H), 3.48 (dd, J=9.4, 2.4, 1H), 2.46 (dd, J=7.9, 2.4, 1H), 1.87 (t, J=8.4, 1H), 1.37 – 1.29 (m, 3H).


[Image of molecular structure]

Alkenylation performed using standard protocol. Title compound isolated in 94% yield.

¹H NMR (400 MHz, cdcl₃) δ = 7.58 – 7.53 (m, 1H), 7.33 – 7.27 (m, 2H), 7.20 – 7.13 (m, 1H), 6.37 – 6.27 (m, 1H), 4.70 (dd, J=15.2, 0.6, 1H), 4.58 (d, J=8.0, 1H), 4.35 – 4.17 (m, 2H), 3.73 (d, J=2.6, 1H), 2.86 (d, J=2.7, 1H), 1.37 – 1.27 (m, 3H).

1-bromo-2-vinylbenzene

[Image of molecular structure]

To a flame-dried flask equipped with a magnetic stir bar was added Ph₃PCH₃Br (17.86 g, 50 mmol) and anhydrous THF (50 mL). The resulting suspension was cooled to 0 ºC and n-BuLi (1.6 M
solution in hexanes, 31.25 mL, 50 mmol) was added dropwise over a period of 30 minutes. The solution was allowed to stir for a further 30 minutes. Then, 2-bromo benzaldehyde was added dropwise over 15 minutes and the solution was allowed to warm to room temperature. Once the reaction was complete (monitored by TLC), water was added slowly to quench any residual n-BuLi. The mixture was extracted 3x with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated to a crude yellow oil. The crude oil was purified by flash column chromatography giving the product as a pale yellow oil in 31% yield.

¹H NMR (400 MHz, CDCl₃) δ = 7.53 (dd, J=7.9, 1.4, 2H), 7.29 – 7.23 (m, 1H), 7.12 – 7.01 (m, 2H), 5.68 (dd, J=17.4, 1.1, 1H), 5.39 – 5.30 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 137.7, 136.0, 133.1, 129.3, 127.7, 127.0, 123.8, 116.9.

2-vinylbenzaldehyde

To a flame-dried flask equipped with a magnetic stir bar was added 2-vinylbenzaldehyde (2.5 g, 13.7 mmol) and anhydrous THF (20 mL). The reaction mixture was cooled to −78 °C and n-BuLi (1.6 M solution in hexanes, 8.61 mL, 13.7 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred for an addition 30 minutes at −78 °C. Then, a solution of DMF (1 mL) in THF (5 mL) was added dropwise ensuring that the temperature remained below −70 °C at all times. The resulting mixture was stirred for an additional 50 minutes at −78 °C and then allowed to warm to room temperature over a period of 1 hour. The reaction mixture was then poured into brine and extracted 3x, with EtOAc, dried over Na₂SO₄, filtered and concentrated to a crude oil. The crude oil was purified by flash column chromatography to give the title compound as a pale yellow oil in 61% yield.

¹H NMR (400 MHz, CDCl₃) δ = 10.30 (s, 1H), 7.86 – 7.81 (m, 1H), 7.59 – 7.56 (m, 2H), 7.55 – 7.50 (m, 1H), 7.43 (ddd, J=13.2, 6.6, 4.0, 1H), 5.79 – 5.62 (m, 1H), 5.60 – 5.45 (m, 1H).
**ethyl pent-4-enoate**

![Structure of ethyl pent-4-enoate]

To a flame-dried flask equipped with a magnetic stir bar was added 4-pentenoic acid (10 g, 0.1 mol). The neat acid was cooled to 0 °C and oxalyl chloride (9.45 mL, 0.11 mol) was added along the walls of the vessel over a period of 30 minutes. The reaction was stirred for a further 1h at which point crude NMR indicated complete conversion to the acid chloride. Absolute EtOH (17.5 mL, 0.3 mol) was then added slowly at 0 °C. After the addition was complete, the reaction was allowed to warm to room temperature and then stirred for an addition 3 h until crude NMR indicated that complete conversion had been achieved. Excess EtOH was removed by rotary evaporation and the crude oil subjected to Kugelrohr distillation (1 torr, 80 °C) to give the title compound as a clear, colourless oil in quantitative yield.

**(±)-3-(but-3-enyl)aziridin-2-yl)(phenyl)methanone**

![Structure of (±)-3-(but-3-enyl)aziridin-2-yl)(phenyl)methanone]

To a mixture of ethyl 4-pentenoate (10 g, 78 mmol) and toluene (100 mL), 1.5 M DIBAL in toluene (57 mL, 86 mmol) was slowly added at –78 °C, and the mixture was stirred for 1 hour at –78 °C. To this reaction mixture, THF (240 mL), boron trifluoride diethyl ether (11 mL, 86 mmol), and 1-phenyl-1-trimethylsilyloxyethylene (16.5 g, 86 mmol) were successively added at –78 °C, and the reaction mixture was allowed to warm up to around 0 °C with stirring. After completion (judged by TLC), 1N HCl (240 g), cooled in the ice bath, was added into the reaction mixture. The mixture was separated into two layers and the water layer was extracted with toluene (50 mL). The combined organic layers were washed with water (150 mL) and dried over sodium sulfate. The solvent was removed in vacuo and the aldol product was obtained as crude yellow oil (16.2 g). A mixture of this aldol (18.0 g), p-toluenesulfonic acid hydrate (16.7 g, 88 mmol), and toluene (200 mL) was heated to
40 °C for 4 hours. After completion (judged by TLC), sodium sulfate was added to the reaction mixture, filtered, and the solid residue was washed with toluene (40 mL). The solvent was removed from the filtrate in vacuo and α,β-unsaturated ketone was obtained as crude yellow oil (15.5 g). A mixture of the α,β-unsaturated ketone (15.5 g), 12% NH$_2$OMe in ethanol (33 g, 84 mmol), and ethanol (100 mL) was heated to gentle reflux for 4 hours. After completion (judged by TLC), the solvent was removed in vacuo. The residue was added to DMF (100 mL), and this solution was added to a mixture of sodium methoxide (9.3 g, 172 mmol) and DMF (250 mL) at room temperature and the reaction mixture was stirred for 1 hour. CH$_2$Cl$_2$ (1000 mL) and water (670 mL) were added to the reaction mixture, separated to two layers, and the water layer was extracted with CH$_2$Cl$_2$ (670 mL). The combined organic layers were washed with water (330 mL) and dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography to give 9.2 g.

$^1$H NMR (CDCl$_3$, 300MHz): δ 8.00-8.03 (m, 2H), 7.58-7.64 (m, 1H), 7.48-7.53 (m, 2H), 5.76-5.90 (m, 1H), 4.95-5.06 (m, 2H), 3.27 (br, 1H), 2.11-2.29 (m, 4H), 1.65-1.72 (m, 2H).

$^{13}$C NMR (CDCl$_3$, 75MHz): δ 197.3, 137.7, 136.3, 133.9, 129.0, 128.4, 115.6, 42.9, 40.0, 32.8, 31.5.

(±)-3-(but-3-enyl)-1-vinylaziridin-2-yl)(phenyl)methanone

Alkenylation performed using standard protocol. Title compound isolated in 94% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 8.07 – 8.00 (m, 2H), 7.64 – 7.57 (m, 1H), 7.54 – 7.47 (m, 2H), 6.26 (dd, $J$=15.2, 8.0, 1H), 5.84 (ddt, $J$=16.9, 10.2, 6.6, 1H), 5.06 (ddd, $J$=17.1, 3.3, 1.6, 1H), 4.99 (ddd, $J$=10.2, 2.9, 1.2, 1H), 4.61 (d, $J$=15.2, 1H), 4.55 (d, $J$=8.0, 1H), 3.41 (d, $J$=2.6, 1H), 2.68 (td, $J$=6.3, 2.7, 1H), 2.35 – 2.19 (m, 2H), 1.74 (dt, $J$=13.9, 6.9, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 194.7, 142.9, 137.5, 137.4, 133.6, 128.9, 128.4, 115.8, 100.76, 47.0, 45.5, 31.9, 29.8.
(±)-1-allyl-3-(but-3-ynyl)aziridin-2-yl(phenyl)methanone

\[
\begin{align*}
\text{N} & \quad \text{Ph} \\
\text{O} & \\
\end{align*}
\]

To a flame-dried Schlenk flask equipped with a magnetic stir bar were added Pd-allyl chloride dimer (1 mol %, 7 mg, 0.0191 mmol) and Xantphos (2 mol %, 25 mg, 0.0372 mmol) in a N\textsubscript{2} filled glovebox. The Schlenk tube was sealed with a rubber septum and removed from the glovebox. Anhydrous THF (5 mL) and the reaction mixture stirred for 10 minutes. Then, aziridine (0.38 mg, 1.88 mmol) and allyl acetate (0.22 mL, 2.06 mmol) were added and the reaction was stirred under N\textsubscript{2} overnight. Water was added and the reaction mixture was extracted 3x with Et\textsubscript{2}O, the organic extracts dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated to a yellow oil. The crude oil was purified by flash column chromatography giving the title compound in 79% yield.

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 8.05 – 7.96 \text{ (m, 2H)}, 7.59 \text{ (dd, } J=10.5, 4.3, 1H), 7.48 \text{ (dd, } J=10.4, 4.7, 2H), 5.91 – 5.76 \text{ (m, 2H)}, 5.16 – 4.94 \text{ (m, 4H)}, 3.39 \text{ (d, } J=2.9, 1H), 3.31 \text{ (ddd, } J=20.3, 12.1, 3.7, 2H), 2.47 \text{ (ddd, } J=7.1, 5.5, 3.0, 1H), 2.26 – 2.14 \text{ (m, 2H)}, 1.65 \text{ (dt, } J=21.7, 7.4, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta = 172.1, 139.5, 131.9, 128.0, 127.4, 124.9, 61.8, 39.3, 39.2, 31.0, 22.2, 19.4, 14.4, 13.8.

2-(hex-1-ynyl)benzaldehyde

\[
\begin{align*}
\text{O} & \\
\end{align*}
\]

The title compound was synthesized according to a literature procedure. To a triethylamine solution (30 mL) of Pd(PPh\textsubscript{3})\textsubscript{4} (374 mg, 0.3 mmol) and CuI (123 mg, 0.6 mmol) was added 2-bromobenzaldehyde (3 g, 16.2 mmol), and the reaction mixture was cooled to 0 °C. After stirring for 5 min, to this solution was added hexyne (1.6 g, 19.4 mmol) slowly in a period of 30 min, and the mixture was warmed to 50 °C with stirring for 6 h. The resulting mixture was filtered through a short
The crude product was purified by flash column chromatography on silica gel to afford the title compound as a colourless oil in 81% yield.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \] \[ \delta = 10.54 \text{ (d, } J=0.8, \text{ 1H)}, 7.93 – 7.85 \text{ (m, 1H), 7.56 – 7.47 \text{ (m, 2H), 7.43 – 7.34 \text{ (m, 1H), 2.49 \text{ (t, } J=7.0, \text{ 2H), 1.68 – 1.58 \text{ (m, 2H), 1.56 – 1.44 \text{ (m, 2H), 0.97 \text{ (t, } J=9.2, \text{ 3H).}}}}

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \] \[ \delta = 192.4, 136.2, 133.8, 133.5, 128.0, 127.1, 120.8, 98.3, 76.5, 30.8, 22.3, 19.5, 13.8.\]

\((\pm)\)-ethyl 3-(2-(hex-1-ynyl)phenyl)oxirane-2-carboxylate

\[ \text{To a flame-dried flask equipped with a magnetic stir bar was added 2-(hex-1-ynyl)benzaldehyde (670 mg, 3.6 mmol), ethyl chloroacetate (0.425mL, 4 mmol) and anhydrous THF (10 mL). The resulting solution was cooled to 0°C and } t\text{-BuOK (1.0 M solution in THF, 4 mL, 4 mmol) was added dropwise over a period of 1 hour. The solution was allowed to slowly warm to room temperature and was stored overnight. After reaction was complete (monitored by TLC), the reaction mixture was quenched with the addition of water and extracted 3x with CH}_2\text{Cl}_2, \text{ dried over Na}_2\text{SO}_4, \text{ filtered and concentrated to a crude yellow oil. The crude oil was purified by flash column chromatography giving the title compound as a clear colourless oil in 66% yield.}

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \] \[ \delta = 7.39 \text{ (m, 1H), 7.29 – 7.23 \text{ (m, 2H), 7.19 – 7.13 \text{ (m, 1H), 4.53 \text{ (d, } J=1.8, \text{ 1H), 4.35 – 4.22 \text{ (m, 2H), 3.40 \text{ (d, } J=1.8, \text{ 1H), 2.44 \text{ (dd, } J=6.8, \text{ 2H), 1.60 – 1.53 \text{ (m, 2H), 1.46 \text{ (m, 2H), 1.37 – 1.30 \text{ (m, 3H), 0.94 \text{ (t, } J=7.3, \text{ 3H)}}}}}

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \] \[ \delta = 168.4, 136.8, 132.1, 128.4, 128.1, 124.0, 123.6, 96.3, 61.8, 56.7 \text{ (d, } J=12.9), 31.8, 30.9, 22.2, 19.3, 14.3, 13.7.\]
(±)-ethyl 3-(2-(hex-1-ynyl)phenyl)aziridine-2-carboxylate

![Chemical structure](image)

To a mixture of ethyl 3-(2-(hex-1-ynyl)phenyl)oxirane-2-carboxylate (450 mg, 1.65 mmol) and 10 mL of EtOH in a flame-dried two-necked flask equipped with a water condenser and magnetic stirring rod was added NaN₃ (321 mg, 4.95 mmol) and ammonium chloride (0.265 mg, 4.95 mmol). The reaction mixture was brought to 65 ºC and stirred for 6 hours at which point TLC analysis showed that the reaction was complete. The mixture was filtered and concentrated under reduced pressure. The crude ¹H NMR showed that the product of nucleophilic opening of the epoxide by azide was pure enough to carry over to the next step. In a flame-dried two-neck flask fitted with a water condenser and equipped with a magnetic stirring bar was added the product from above (333 mg, 1.06 mmol) dissolved in 10 ml of acetonitrile. The reaction mixture was brought to 40 ºC, at which point PPh₃ (290 mg, 1.1 mmol) was added at a controlled rate to avoid rapid evolution of N₂. The reaction was then brought to 83 ºC and stirred for 7 hours. The reaction mixture was then cooled and concentrated under reduced pressure. The crude mixture was then dissolved in 5% EtOAc in pentane and filtered. The filtrate was concentrated and subsequently dissolved in pentane and placed in the freezer overnight (-15 ºC). Any resulting precipitate that formed was filtered off and the filtrate was concentrated under reduced pressure and subjected to silica gel column chromatography to yield the title compound as a pale yellow oil in 62% over two steps.

(±)-ethyl 3-(2-(hex-1-ynyl)phenyl)-1-vinylaziridine-2-carboxylate

![Chemical structure](image)

The title compound was prepared using standard protocol. Product isolated in 92% yield.
**1H NMR (400 MHz, CDCl$_3$)** $\delta = 7.43 - 7.37$ (m, 1H), 7.27 – 7.17 (m, 3H), 6.34 – 6.25 (m, 1H), 4.73 – 4.65 (m, 1H), 4.56 (d, $J=8.0$, 1H), 4.30 – 4.18 (m, 2H), 3.92 (d, $J=2.6$, 1H), 2.90 (d, $J=2.6$, 1H), 2.43 (t, $J=7.1$, 2H), 1.61 – 1.54 (m, 2H), 1.52 – 1.41 (m, 2H), 1.31 (t, $J=7.1$, 3H), 0.97 – 0.91 (m, 3H).

**13C NMR (101 MHz, CDCl$_3$)** $\delta = 167.8$, 142.3, 137.8, 131.8, 127.6, 127.5, 125.5, 124.0, 99.8, 95.9, 77.9, 61.1, 45.8, 44.0, 30.7, 22.0, 19.2, 14.2, 13.5.

(±)-**N-methoxy-N-methyl-3-phenyloxirane-2-carboxamide**

Dicyclohexylcarbodiimide (2.05 g, 10 mmol) was added to a solution of potassium 3-phenylglycidate (2.02 g, 10 mmol) in anhydrous dichloromethane (10 mL) under nitrogen at 0 °C. N,O-Dimethylhydroxylamine hydrochloride (970 mg, 10 mmol) was added, and the mixture was warmed to room temperature and stirred overnight. After 20 h, the solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 5% acetone/dichloromethane, affording the amide as a white gum in 67% yield.

**1H NMR (CDCl$_3$, 300 MHz):** $\delta$ 7.38–7.31 (m, 5H), 4.09 (d, $J=1.8$ Hz, 1H), 3.93 (br s, 1H), 3.72 (s, 3H), 3.28 (s, 3H).

**13C NMR (CDCl$_3$, 75 MHz):** $\delta$ 167.5, 135.6, 128.7, 128.6, 125.8, 62.1, 57.6, 55.5, 32.6.

(±)-**N-methoxy-N-methyl-3-phenylaziridine-2-carboxamide**

Sodium azide (564.4 mg, 8.68 mmol) and ammonium chloride (464.3 mg, 8.68 mmol) were added to a solution of (±)-**N-methoxy-N-methyl-3-phenyloxirane-2-carboxamide** (600 mg, 2.89 mmol) in methanol (20 mL). The mixture was refluxed for 5 hours and then concentrated by evaporation, and
poured into a 1:1 mixture of ethyl acetate and water. The aqueous layer was extracted 3x with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated to yield a yellow oil, which was carried to the following step without purification. Triphenylphosphine (788 mg, 3.00 mmol) was added in small portions to a stirred solution of the azido alcohol intermediate (723.3 mg, 2.89 mmol) in acetonitrile (15 mL). Evolution of nitrogen gas was observed. The mixture was stirred for 45 minutes at ambient temperature before refluxing for 4 hours, after which no starting material remained. The solvent was evaporated *in vacuo*, the residue was diluted with 5% ethyl acetate/hexanes, and the precipitate of triphenylphosphine oxide was filtered. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography, eluting with 15% acetone/dichloromethane, to yield the title compound as a pale yellow gummy solid (424 mg, 70% over two steps).

1H NMR (CDCl₃, 300 MHz): δ 7.32–7.25 (m, 5H), 3.69 (s, 3H), 3.28 (s, 3H), 3.11 (dd, J=7.5, 1.8 Hz, 1H), 3.00 (d, J=7.1, 1H), 2.04 (m, 1H, NH).

13C NMR (CDCl₃, 75 MHz): δ 170.4, 138.4, 128.4, 127.5, 126.1, 61.9, 40.0, 37.5, 32.8.

(±)-N-methoxy-N-methyl-3-phenyl-1-vinylaziridine-2-carboxamide

The title compound was prepared using standard protocol. Product isolated in 79% yield.

1H NMR (300 MHz, CDCl₃) δ = 7.38 – 7.26 (m, 5H), 6.23 (dd, J=15.2, 8.0, 1H), 4.66 (d, J=15.2, 1H), 4.55 (d, J=8.0, 1H), 3.76 (s, 3H), 3.59 (d, J=2.6, 1H), 3.43 (s, 1H), 3.26 (s, 3H).
(±)-3-phenyl-1-vinylaziridine-2-carbaldehyde

To a flame-dried flask equipped with a magnetic stir bar was added (±)-N-methoxy-N-methyl-3-phenyl-1-vinylaziridine-2-carboxamide (50 mg, 0.21 mmol) and anhydrous THF (5 mL). The solution was cooled to -40°C with the aid of an ethylene glycol/CO$_2$ bath. LiAlH$_4$ (25 mg, 0.64 mmol) was added in one portion and the reaction mixture was stirred for 2 hours until complete by TLC. H$_2$O (1 mL) and EtOAc (5 ml) were added slowly to quench the reaction. The mixture was extracted 3x with EtOAc, dried over sodium sulfate and concentrated in vacuo. The crude oil was purified by silica gel chromatography (%5 EtOAc in hexanes) to give the title compound in 12% yield.

$^1$H NMR (400 MHz, cdcl$_3$) $\delta =$ 9.27 (dd, $J$=6.6, 3.6, 1H), 7.38 – 7.29 (m, 5H), 6.46 (dd, $J$=15.2, 8.0, 1H), 4.80 (dd, $J$=15.2, 0.8, 1H), 4.63 (t, $J$=4.8, 1H), 3.68 (d, $J$=2.4, 1H), 3.00 – 2.89 (m, 1H).
2 Aldehyde/Amine/Alkyne (A$_3$) Coupling of Amphoteric Amino Aldehydes

2.1 Introduction

The nucleophilic addition of acetylides to aldehydes, ketones, and imines has attracted a great deal of attention as a powerful method for the construction of enantioenriched propargylic alcohols and amines. Nucleophilic metal acetylides can be easily prepared by using a variety of methods, but must generally be prepared in a separate pot prior to the reaction with an electrophile or generated in situ. The reason for this is the sensitivity of the unsaturated carbon-heteroatom bonds to the harsh reagents required to generate the metal acetylides. To overcome this limitation, the Carreira research group reported that Zn(OTf)$_2$ can catalyze the addition of terminal acetylenes to aldehydes in a one-pot process that precludes the need for preformation of the zinc acetylide. 

Scheme 2-1

![Scheme 2-1](image)

Remarkably, this highly selective deprotonation process is also tolerant of air and moisture, a feature not displayed by other systems. A variety of propargylic alcohols derived from aliphatic aldehydes could be synthesized in high yields and up to 99% ee by using 20 mol% Zn(OTf)$_2$ (Scheme 36). In the same year, Wei and Li demonstrated that this reaction could be carried out in

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water by using a RuCl$_3$/In(OAc)$_3$ catalyst system.$^{37}$ Extending these conditions for additions to imines proved unsuccessful. In 2002, Li reported the three-component coupling of an aldehyde, amine, and acetylene that chemoselectively delivered the corresponding propargyl amine, albeit in racemic form, without any trace of the propargyl alcohol.$^{38}$ Interestingly, this was achieved by changing the catalytic system to RuCl$_3$/CuI. The origin of the chemoselectivity is believed to be the inability of the indium(III) center to coordinate and activate the imine in water. The softer copper(I) ions were more effective in this regard. An enantioselective route to propargylamines in which a RuCl$_3$/CuI-PyBox catalyst system was employed delivered enantioenriched propargyl amines in high yields and enantiomeric excesses, although it was limited in scope to aromatic aldehydes, acetylenes, and anilines.$^{39}$

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**Figure 7**

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More recently, copper(I) complexes with pinap and quinap systems have been developed by the research groups of Carreira\textsuperscript{40} and Knochel\textsuperscript{41} for the three-component coupling of aldehydes, amines, and acetylenes. The reaction tolerated enolizable aldehydes and aliphatic amines/acetylenes (Scheme 37). Interestingly, challenging primary propargyl amines can be easily accessed by using the method developed by Carreira and co-workers. Once again, complete chemoselectivity was observed for the addition of acetylene to the aldehyde-derived iminium species, with no detectable addition to the aldehyde. These reactions deliver propargylamines as the sole products in high yields and ee values and do not require a RuCl\textsubscript{3} co-catalyst.

2.2 Application of Aziridine Aldehydes in the A\textsuperscript{3} Coupling

We became interested in the application of this technology to the aziridine aldehyde dimers developed in our laboratory. Although the aziridine aldehydes are isolated as dimeric molecules with no trace of free aldehyde observable by NMR, under the appropriate conditions they do react as monomers. This also presented us with an interesting opportunity to study the chemoselectivity of the reaction between an amine, the aziridine aldehyde and an alkyne. For instance, we were interested in whether the rate of iminium ion formation would be rapid enough to avoid any addition of the metal-acetylide to the aldehyde. One could envisage several equilibrium processes that could lead to a variety of different outcomes.

To this end, of commonly used catalysts for the A³ coupling of an enantiomerically pure leucine-derived aziridine aldehyde with phenyl acetylene and piperidine were screened. The results are presented in Table 6. In general, silver salts performed poorly in toluene at high temperatures giving a mixture of products (detected by ESI MS and TLC). In trifluoroethanol (TFE), a solvent known to facilitate reactivity of the free aldehyde, no reaction was observed with silver salts. Zinc salts performed better in toluene at 100°C and gave cleaner reaction mixtures but complete conversion could not be achieved even after prolonged reaction times (2 days). Gratifyingly, we discovered that 10 mol % Zn(OAc)₂ in TFE at room temperature gave complete conversion to a single product as a 1:1 mixture of diastereomers isolated in 95% yield combined yield after 18 hours at room temperature.
Table 6

<table>
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<tr>
<th>Entry</th>
<th>Catalyst (10 mol%)</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Result</th>
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<td>1</td>
<td>AgI</td>
<td>100 ºC</td>
<td>Toluene</td>
<td>Incomplete, not clean</td>
</tr>
<tr>
<td>2</td>
<td>AgCl</td>
<td>100 ºC</td>
<td>Toluene</td>
<td>Incomplete, not clean</td>
</tr>
<tr>
<td>3</td>
<td>AgBr</td>
<td>100 ºC</td>
<td>Toluene</td>
<td>Incomplete, not clean</td>
</tr>
<tr>
<td>4</td>
<td>AgI</td>
<td>r.t.</td>
<td>TFE</td>
<td>No conversion</td>
</tr>
<tr>
<td>5</td>
<td>AgCl</td>
<td>r.t.</td>
<td>TFE</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>AgBr</td>
<td>r.t.</td>
<td>TFE</td>
<td>No conversion</td>
</tr>
<tr>
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<td>Toluene</td>
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</tr>
<tr>
<td>9</td>
<td>Zn(OAc)₂</td>
<td>100 ºC</td>
<td>Toluene</td>
<td>Incomplete, clean</td>
</tr>
<tr>
<td>10</td>
<td>ZnBr₂</td>
<td>r.t.</td>
<td>TFE</td>
<td>Incomplete, clean</td>
</tr>
<tr>
<td>11</td>
<td>ZnCl₂</td>
<td>r.t.</td>
<td>TFE</td>
<td>Incomplete, clean</td>
</tr>
<tr>
<td>12</td>
<td>Zn(OAc)₂</td>
<td>r.t.</td>
<td>TFE</td>
<td>Complete, 95% yield, 18h</td>
</tr>
</tbody>
</table>

Only the product of addition of the metal-acetylide to the iminium species derived from the condensation between the aldehyde and piperidine was isolated (path c). Path a is also unfavorable on the basis of the highly strained iminium ion intermediate which confers chemoselectivity to this reaction that allows for the selection between two different secondary amines. Addition of the metal-acetylide to the aldehyde was also not observed in this case (path b). Efforts are currently underway
in our laboratories to explore the reactivity of these densely functionalized scaffolds. In addition, we are exploring methods for achieving enantioselective addition of the metal-acetylide to the aldehyde to generate enantiomerically enriched aziridine-containing propargyl amines in high yields.
2.3 Experimental

Aziridine aldehyde (70mg, 0.24 mmol), phenyl acetylene (98 mg, 0.95 mmol) and piperidine (66mg, 0.64 mmol) were added to a 2 dram vial and dissolved in TFE (1.5 ml). The reaction mixture was stirred overnight. When complete (monitored by ESI-MS) the reaction mixture was concentrated and loaded directly onto silica gel and purified via flash chromatography.

Title compound isolated in 47% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.46 – 7.38 (m, 2H), 7.35 – 7.27 (m, 3H), 4.20 – 3.98 (m, 1H), 2.78 (d, $J$=4.5, 2H), 2.53 (d, $J$=4.7, 2H), 1.96 (s, 1H), 1.90 (td, $J$=6.3, 3.1, 1H), 1.78 (tt, $J$=13.3, 6.6, 1H), 1.69 – 1.56 (m, 4H), 1.49 – 1.36 (m, 3H), 1.30 – 1.18 (m, 1H), 1.01 – 0.92 (m, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 132.0, 128.5, 128.4, 122.7, 105.0, 88.6, 61.3, 51.3, 42.4, 38.62, 27.5, 26.3, 24.4, 23.1, 22.7.

Title compound isolated in 46% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.45 – 7.40 (m, 2H), 7.33 – 7.28 (m, 3H), 3.65 (s, 1H), 2.80 – 2.70 (m, 2H), 2.57 (d, $J$=4.9, 2H), 2.04 (d, $J$=4.6, 1H), 1.97 (s, 1H), 1.82 (td, $J$=13.4, 6.7, 1H), 1.64 (dq, $J$=11.8, 5.9, 4H), 1.47 (dd, $J$=11.4, 5.7, 2H), 1.34 (t, $J$=6.4, 2H), 0.98 (dd, $J$=6.6, 1.2, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 132.0, 128.5, 128.4, 123.0, 87.4, 84.1, 62.0, 51.4, 42.7, 38.0, 27.5, 26.2, 24.5, 23.0, 22.8.