STUDIES IN AZIRIDINE-ALLYLSILANE CHEMISTRY: EXTENSION OF SCOPE

DISSERTATION

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By

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ABSTRACT

We have been interested in developing methodology for the synthesis of alkaloids and other heterocycles that could serve as potential drug candidates. In this regard, we have discovered a method that could serve as a general and useful procedure for the synthesis of these molecules. Specifically, we can convert an aziridine-allylsilane to either the $\gamma$-amino olefin, the silylated azabicycle, or the desilylated azabicycle. $\gamma$-Amino olefins and silylated azabicycles have served as useful precursors in our synthesis of the rauwolfia alkaloid (-)-yohimbane and bicyclic proline analogs.

In an effort to extend the scope of our methodology, the synthesis and intramolecular cyclizations of C-2 aziridine-allylsilanes were examined. Due to an initial failure in our traditional allylsilane-organocuprate / N-Ts-aziridine methanol approach, a new converse strategy for the synthesis of C-2 aziridine-allylsilanes was developed. The coupling of a nucleophilic aziridine with an electrophilic allylsilane highlights the converse strategy of C-2 aziridine-allylsilane synthesis. The Suzuki cross-coupling reaction of olefinic aziridines is not only an effective route for the synthesis of C-2 aziridine-allylsilanes, but for other substituted aziridines as well. This represents the first example of a palladium coupling reaction applied to an aziridine-containing
molecule and proves complementary to other methods of aziridine synthesis utilizing organocuprate reagents.

We observed that connection of C-2 of an allylsilane to a tethered aziridine ring yields exocyclic $\gamma$-amino olefins and desilylated azabicyclo[2.2.1]-systems upon cyclization with BF$_3$•OEt$_2$. Furthermore, manipulation of a specific exocyclic $\gamma$-amino olefin provided access to an azabicyclo[3.3.1]nonane. This methodology should be useful for the preparation of natural products and pharmacologically active agents containing these bicyclic heterocyclic systems.

With intentions of applying our methodology to the synthesis of natural products and studying the effect of a substituted tether on the diastereoselectivity of intramolecular C-3 aziridine-allylsilane cyclizations, a C-3 aziridine-allylsilane containing a methyl substituent on the tether was envisioned based on a proposed retrosynthesis of (+)-$\alpha$-skytanthine. The target aziridine-allylsilane was synthesized via Suzuki cross-coupling of a known allylsilane-vinyl iodide with a chiral aziridine-olefin containing the key methyl substituent. The chiral aziridine-olefin stemmed from transformation of a known amino acid in good yield and high optical purity.

Unfortunately the diastereoselectivity of products resulting from the cyclization of a tether-substituted C-3 aziridine-allylsilane did not improve. In fact, the tether-substituted aziridine-allylsilane offered an additional mode of cyclization that was not seen in our previous cyclizations of C-3 aziridine-allylsilanes. A hydroboration-oxidation / Mitsunobu reaction sequence was performed on select $\gamma$-amino olefin cyclization products to form 3-azabicyclo[4.3.0]nonane and 2-azabicyclo[3.3.1]nonane frameworks. One of the 3-azabicyclo[4.3.0]nonanes synthesized represents the tosylated analog of a known natural product, nor-$\alpha$-skytanthine.
Dedicated to the memory of Mary Lapinsky (1912 – 2002)
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VITA

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Research Publication

1. S.C. Bergmeier, D.J. Lapinsky, R.B. Free and D.B. McKay, “Ring E analogs of
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FIELDS OF STUDY

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CHAPTER 1

REACTIVITY OF AZIRIDINES AND ALLYLSILANES

1.1. Introduction

Alkaloids represent a group of structurally diverse natural products that can possess a wide variety of biological activities. Man has taken advantage of some of these activities and used them for beneficial medicinal purposes. However, there are a number of problems associated with obtaining alkaloids for therapeutic use, be it their minute quantity in nature, difficulty of isolation, or rarity of supplying source. As a result, we have often sought other methods for obtaining these valuable entities. Organic synthesis has played a pivotal role as an alternative source to gain access to these invaluable compounds.

Although alkaloids are often structurally complex in nature, a simpler nitrogen-containing heterocycle can often represent the pharmacophore of alkaloids. Organic synthesis plays a role in the preparation of structurally simpler analogs that are minimized in complexity yet retain the important biological activity. As a result, general methodology for the synthesis of alkaloids and other nitrogen-containing heterocycles continues to be of immense importance to the pharmaceutical sciences. In this regard, our lab has discovered a method that could serve as a general and useful procedure for the synthesis of these molecules. Specifically, an aziridine-allylsilane (1.1) can be converted to the $\gamma$-amino olefin (1.2), the silylated azabicycle (1.3), or the
desilylated azabicycle (1.4) (Scheme 1.1). Simpler compounds 1.2 and 1.3 have served as instrumental intermediates toward our synthesis of the more complex rauwolfia alkaloid (-)-yohimbane\(^1\) (1.5) and bicyclic proline analogs (1.6).\(^2\)

\[
\begin{align*}
\text{1.1} & \quad \text{Lewis acid} \\
\text{1.2} & \quad \text{NH} \\
\text{1.3, X = -SiR}_3 & \quad \text{or-} \\
\text{1.4, X = -H} & \\
\text{1.5} & \\
\text{1.6} & \quad \text{CO}_2\text{H} \\
& \quad \text{NH•HBr}
\end{align*}
\]

Scheme 1.1: Intramolecular aziridine-allylsilane methodology.

In order to understand the formation and stereochemistry of products resulting from the intramolecular cyclizations of aziridine-allylsilanes, it is important to first understand the reactivity of each of the moieties involved in the reaction.

1.2. General reactivity of allylsilanes

Allylsilanes are well known nucleophilic reagents for both regio- and stereoselective formation of carbon-carbon bonds.\(^3-8\) Scheme 1.2 highlights the potential reaction pathways that
can occur when a nucleophilic allylsilane (1.7) reacts with an electrophile (1.8) in the presence of a Lewis acid (LA). When compared to other nucleophilic allylmetal reagents such as allylstannanes, the advantages of allylsilanes are multifold. The inherent allylic stability of allylsilanes allows them to be carried though a multi-step synthesis and reacted at the appropriate point in time to provide either allylated (1.10) or annulated (1.12, 1.13) products. Another powerful advantage of organosilicon chemistry is the ability of certain types of silyl groups to be oxidized to alcohols (e.g. 1.14).9,10

Scheme 1.2: Reaction pathways of allylsilanes.
1.2.1. Sakurai reactions of allylsilanes

The reaction of an allylsilane (1.7) with an electrophile (1.8) to produce the allylated product (1.10) is typically referred to as a Sakurai reaction (Scheme 1.2). Scheme 1.3 shows an example of allyltrimethylsilane (1.16) reacting with an aldehyde (1.15) via a Sakurai reaction mechanism. The mechanism of allylsilanes as nucleophiles is often classified via an \textit{anti-S_{E'}} (substitution – elimination) mode of addition. Lewis acid activation of the electrophile (1.17) followed by nucleophilic attack of the $\pi$ bond of the allylsilane produces the $\beta$-silyl carbocation 1.18. The crucial influence on the reactivity pattern of allylsilanes is the very high stabilization that silicon provides for $\beta$-carbocations. This stabilization is primarily due to hyperconjugation with the Si-C bond. The $\beta$-silyl carbocation (1.18) can then undergo an elimination reaction to provide homoallylic alcohol 1.19.

While the example depicted in Scheme 1.3 represents an intermolecular Sakurai reaction, the reaction can also proceed intramolecularly. For example, Weinreb and co-workers recently used a stereocontrolled intramolecular spirocyclization reaction of an allylsilane with an N-acyl iminium ion (1.20) (Scheme 1.4). This reaction was reported as a key step in the synthesis of the marine tunicate alkaloid lepadiformine (1.22).
Scheme 1.3: An example of an intermolecular Sakurai reaction with mechanism.

Scheme 1.4: Intramolecular Sakurai reaction of an allylsilane with an N-acyl iminium ion.
1.2.1.1. Stereochemical control in allylsilane reactions

Allylsilanes traditionally react with electrophiles with \textit{anti} stereoselectivity. Scheme 1.5 shows an example where examining reactive conformations of allylsilanes explains the stereochemical results of an intermolecular reaction. The preferred reaction conformation for allylsilanes is conformation A. This conformation has the $\alpha$-silyl hydrogen eclipsing the allylsilane double bond while the electrophile approach is \textit{anti} to the bulky silyl group.\textsuperscript{17-19} However, this conformation is somewhat influenced by the size of the olefin substituent \textit{cis} to the silyl group. If this substituent is relatively small (i.e. a hydrogen), a second reacting conformation (B) can exist.\textsuperscript{20} A remaining factor that affects the stereoselectivity of these reactions is the size of the R group $\alpha$ to the silyl group. In this particular example,\textsuperscript{21} the preference for conformation A, and hence epoxide 1.24, increases with the size of the R group due to the unfavorable steric interaction pictured in conformation B. We will later see how reactive conformations of aziridine-allylsilanes can be used to understand the stereochemical outcome of their intramolecular reactions.
1.2.1.2. Intermolecular reactions of aziridines with allylsilanes

There are numerous reports that review the intermolecular reactions of allylsilanes with a variety of electrophiles.\textsuperscript{7,8,22-24} While our work focuses on the intramolecular reaction between an aziridine and an allylsilane, few reports exist on the intermolecular variant. Scheme 1.6 shows an experiment conducted by Taddei and co-workers which reacts allyltrimethylsilane (1.16) intermolecularly with a phenyl-substituted aziridine (1.26).\textsuperscript{25} This work was reported after our initial report on the intramolecular reaction of an aziridine with an allylsilane.\textsuperscript{26} The reaction gave a mixture of the Sakurai olefin product 1.29 and [3+2]-annulation product 1.30 in 36% and 44% yield respectively. In this reaction, the allylsilane attacked the more-substituted carbon of the
aziridine ring, presumably due to a greater polarization of the more-substituted C-N bond when a
three-membered ring electrophile is coordinated with a Lewis acid. We will see later that the
intramolecular reactions of aziridine-allylsilanes proceed in a similar manner. It should be noted
that Taddei’s work on the intermolecular reactions of aziridines with allylsilanes is limited in that
reactions were only successful with phenyl-aziridine ring substrates.

![Scheme 1.6: An intermolecular reaction between an aziridine and an allylsilane.](image-url)
1.2.2. [3+2]-Annulation reactions of allylsilanes

An alternative reaction pathway of allylsilanes is a [3+2]-annulation reaction. A proposed mechanism of this reaction is shown in Scheme 1.7. The mechanism suggests that β-silyl carbocations (1.9) can undergo siliranium ion formation. This new intermediate (1.31) can be attacked at either position of the ring by a nucleophile to give the corresponding cycloadduct. Nucleophilic attack at C$_2$ results in the [2+2]-adduct 1.13, while attack at C$_1$ produces the [3+2]-adduct 1.12. It should be noted that despite the plausibility of this explanation, theoretical calculations do not support the existence of siliranium ions in solution.$^{27,28}$

![Scheme 1.7: [2+2] and [3+2] reaction mechanisms of allylsilanes via siliranium ions.](image-url)
Lambert and co-workers have suggested an alternative reaction mechanism for the [3+2]-annulation reaction of allylsilanes (Scheme 1.8).\textsuperscript{27,28} The mechanism is highlighted by a 1,2-silyl shift of β-silyl carbocation 1.9 to produce intermediate 1.32. This new cationic intermediate can be trapped with an inherent nucleophile to produce the [3+2]-adduct 1.12.

While the nature of the silyl shift mechanism is still the subject of many debates, the unique feature of intermediates 1.9 and 1.32 is that there is no rotation around the C$_1$-C$_2$ single bond. This thought could be used to explain the highly stereoselective result that occurs upon ring closure.\textsuperscript{29} Traditionally, the nucleophilic attack of these cations takes place anti to the silicon.

Scheme 1.8: 1,2-Silyl shift mechanism leading to [3+2]-adducts.
1.2.2.1. Intermolecular [3+2]-annulation reactions of allylsilanes

The [3+2]-annulation reaction of allylsilanes has been used in an intermolecular fashion with a variety of electrophiles,\textsuperscript{30-34} including carbonyl compounds,\textsuperscript{35} imines,\textsuperscript{36} and \(\alpha,\beta\)-unsaturated carbonyls.\textsuperscript{32,37,38} The example provided in Scheme 1.9 shows the [3+2]-annulation reaction of allylsilane 1.34 with 1-acetylcyclohexene (1.33).\textsuperscript{33} The stereochemical result of the reaction is thought to derive from addition of the allylsilane via a synclinal arrangement (1.35). Subsequent cyclization by intramolecular nucleophilic attack of the titanium enolate at the siliranium ion 1.36 leads to the chiral product 1.37.

1.2.2.2. Intramolecular [3+2]-annulation reactions of allylsilanes

Outside of our lab, few reports exist on the intramolecular variation of the [3+2]-annulation reaction of allylsilanes.\textsuperscript{39,40} The reaction shown in Scheme 1.10 is an example of an intramolecular [3+2]-annulation involving an allylsilane tethered to a diketone (1.38). Schinzer and co-workers reported this reaction as a key step in their synthesis of triterpenoids.\textsuperscript{39} Cyclic ether 1.40 is formed by an initial 1,2-silyl shift of \(\beta\)-silyl carbocation 1.39 followed by trapping of the Lewis acid-complexed alkoxide.
Scheme 1.9: Intermolecular [3+2]-annulation reaction of an allylsilane with a $\alpha,\beta$-unsaturated ketone.

Scheme 1.10: Intramolecular [3+2]-annulation of an allylsilane-diketone.
1.2.2.3. The effect of silicon in the annulation reactions of allylsilanes

The nature of the silyl group plays an important role in the reaction pathways of allylsilanes.\(^4^1\) Allylsilanes containing small silyl groups (i.e. Me\(_3\)Si) typically react via the Sakurai i/elimination pathway (Scheme 1.11). This is due to the inability of smaller groups on the silicon to impede the approach of nucleophiles that trigger the elimination reaction. As a result, chemists have used bulkier groups on the silicon (e.g. PhMe\(_2\)Si,\(^3^0,4^2\) TrMe\(_2\)Si,\(^4^3\) i-Pr\(_3\)Si,\(^4^1\) Ph\(_3\)Si,\(^4^4\) i-Pr\(_2\)PhSi,\(^4^5\) t-BuPh\(_2\)Si\(^4^6\)) in an attempt to impede the approach of nucleophiles and slow down the rate of the elimination step. This strategy increases the probability of allylsilanes to react via the annulation pathways.

![Scheme 1.11: The effect of silicon in the annulation reactions of allylsilanes.](image)

The nature of the silyl group also plays an important role in whether it can be oxidized to a hydroxyl group.\(^9,1^0\) For this transformation to be possible, at least one of the groups on the silicon must have a phenyl group. The power of this reaction lies in the ability to provide functionality to the annulated products of allylsilanes, a strategy that has been often seen in the
synthesis of complex natural products.\textsuperscript{9,10} For example, Angle and El-Said utilized this transformation as a key step (i.e. conversion of 1.44 to 1.45) in their reported synthesis of (-)-allomuscarine (1.46a) and (+)-epimuscarine (1.46b) (Scheme 1.12).\textsuperscript{47} It should be noted that in this allylsilane reaction a nucleophile other than the Lewis acid-complexed alkoxide intercepted the β-silyl carbocation intermediate. As we shall see later, this versatile transformation was also used in our reported synthesis of bicyclic proline analogs.\textsuperscript{2}

\begin{equation}
\text{SiR}_3 = \text{SiMe}_2\text{CHPh}_2
\end{equation}

\textbf{Scheme 1.12: Use of }-\text{SiR}_3 \text{ to } -\text{OH} \text{ transformation in a natural product synthesis.}
1.3. General reactivity of aziridines

Section 1.2 provided a brief review of the reactivity of the allylsilane partner in our methodology. Let us now turn our attention towards the reactivity of the aziridine partner.

Aziridines represent a chemical class of compounds characterized by a strained three-membered nitrogen-containing ring. They are similar to epoxides in that their chemistry is dominated by ring-opening reactions with a host of nucleophiles.\textsuperscript{48-52} The reactivity displayed by aziridines depends on the substitution of the nitrogen and the reaction conditions utilized. Sulfonyl, phosphinyl, acyl, alkyl, and carbamate groups have been used as traditional substituents on the aziridine nitrogen.

1.3.1. Ring-opening reactions of activated aziridines with nucleophiles

Scheme 1.13 depicts the ring-opening reactions of activated aziridines (1.47) in the presence of a nucleophile. Activated aziridines contain an electron-withdrawing group (EWG) on the nitrogen that can stabilize negative charge once the ring is opened by a nucleophile.

\[
\begin{align*}
\text{EWG} & = -\text{SO}_2\text{R}, -\text{COR}, -\text{CO}_2\text{R}, \text{POR}_2 \\
\text{Scheme 1.13: Nucleophilic attack on an activated aziridine.}
\end{align*}
\]
1.3.1.1. Intermolecular reactions of activated aziridines with nucleophiles

Scheme 1.14 shows a few examples of activated aziridines being attacked by various nucleophiles. The most popular activating groups in the chemistry of aziridines are the $N$-arenesulfonamides. These aziridines (1.50, $R = -\text{Ts}$) can be opened with organocuprate reagents regioselectively with attack at the less-hindered carbon of the aziridine ring to produce products such as 1.51. Likewise $N$-phosphinyl aziridines (1.50, $R = -\text{POPh}_2$) can react in a similar manner. One particular advantage of the phosphinyl group when compared to the arenesulfonamides is the ease with which they can be deprotected under mildly acidic conditions.

Acyl and carbamoyl groups are another popular class of functionality that can activate an aziridine for nucleophilic attack. However, there are potential limitations with using these groups. There are a few reports of nucleophilic attack at the carbonyl of the activating group rather than the aziridine ring. For example, treatment of $N$-benzoyl aziridine 1.52 with $n$-BuLi resulted in no aziridine ring-opened products. Instead, ketone 1.54 was the major product of the reaction (80%). It should be noted that provided the appropriate $N$-acyl group and reaction conditions, nucleophilic attack on the aziridine ring is possible. We have reported the opening of an oxazolidinone-activated aziridine (1.55) with a variety of nucleophiles.

In addition to carbon nucleophiles, heteroatom nucleophiles such as $\text{Ph}_3\text{P}$ and hydrides have been used in ring-opening reactions of aziridines. Reaction of aziridine-methyl ester 1.57 with histidine (1.58) is an example of how amino groups can be used as nucleophiles in the reactions of aziridines.
Scheme 1.14: Examples of intermolecular ring-opening reactions of activated aziridines with nucleophiles.

1.3.1.2. Intramolecular reactions of activated aziridines with nucleophiles

There is only one report of an intramolecular reaction between an activated aziridine ring and a nucleophile. Rapoport and co-workers reported the intramolecular cyclization of an enolate...
tethered to an N-arenesulfonamide aziridine (1.60) (Scheme 1.15). The product 1.61 would be considered a valuable precursor in the synthesis of carbocyclic nucleosides.

Scheme 1.15: Intramolecular reaction of an activated aziridine with an enolate.

1.3.2. Lewis acid-promoted ring-opening reactions of activated and unactivated aziridines

An alternative mode of ring opening of aziridines involves the use of protic or Lewis acids (Scheme 1.16). Initial complexation of a Lewis acid to the aziridine nitrogen (1.63) enables both activated (R₁ = electron-withdrawing group) and unactivated (R₁ = alkyl) aziridine rings to become susceptible to nucleophilic attack at either position of the aziridine ring.
Scheme 1.16: Lewis acid-promoted ring-opening reactions of aziridines.

1.3.2.1. Lewis acid-promoted intermolecular reactions of activated and unactivated aziridines with nucleophiles

Scheme 1.17 gives some examples of activated and unactivated aziridines being promoted by Lewis acids for intermolecular attack by nucleophiles. Some activated aziridines are simply not active enough to undergo nucleophilic ring opening and thus require the use of acid activation for a reaction to occur. There also exists the possibility that the requisite nucleophile is inherently weak, prompting one to use Lewis acid promotion in order to achieve success. Such is the case with indole 1.66 reacting with activated aziridine 1.67. It was found that Zn(OTf)$_2$ catalysis was essential for product formation to occur.$^{70,71}$

In addition to carbon nucleophiles,$^{72}$ there are a number of examples involving the use of heteroatom nucleophiles (e.g. alcohols,$^{73}$ thiols, amines) coupled with Lewis acid promotion of the aziridine ring. Selected examples include the reaction of unactivated disubstituted aziridine

\[ R_1 = \text{EWG} \quad \text{(activated aziridine)} \]
\[ R_1 = \text{alkyl} \quad \text{(unactivated aziridine)} \]
1.69 with PhSH in the presence of BF₃•OEt₂ to produce the amino acid derivative 1.70, while activated aziridine 1.71 was opened with benzylamine and Yb(OTf)₂ to yield diamino product 1.72.

![Scheme 1.17: Examples of Lewis acid-promoted openings of aziridines.](image)

1.3.2.2. Azaphilic vs. oxaphilic Lewis acids in aziridine reactions

The choice of Lewis acid can play a crucial role in the results of a nucleophile reacting with an aziridine. This is no more apparent then in the example provided in Scheme 1.18. Lectka and co-workers showed that N-acyl aziridine 1.73 could undergo distinctive ring-opening.
reactions dependent on the type of Lewis acid used. The use of an oxophilic Lewis acid (Ti(OiPr)$_2$, Yb(biphenol)OTf) resulted in nucleophilic ring opening to give product 1.74, while rearrangement products 1.75 were observed with azaphilic Lewis acids (Zn(OTf)$_2$, Sn(OTf)$_2$, Cu(OTf)$_2$).

![Scheme 1.18](image)

**Scheme 1.18: The effect of Lewis acid type on the nucleophilic opening of an aziridine.**

It is clear from the reactions described in Section 1.3 that the type of substituent on the aziridine nitrogen, the substitution pattern of the aziridine, and the choice of Lewis acid employed are all important factors that can affect the outcome a nucleophile reacting with an aziridine.
1.4. Intramolecular reactions of aziridines with allylsilanes

Our lab has been developing two modes of intramolecular cyclization between aziridines and allylsilanes (Scheme 1.19). The first mode involves treatment of aziridine-allylsilanes (1.1) with greater than a stoichiometric amount of BF₃•OEt₂ to provide access to carbocycles containing a γ-amino olefin unit (1.2). This cyclization reaction mode proceeds via the Sakurai reaction pathway. The second mode of cyclization involves treatment of aziridine-allylsilanes with a catalytic amount of BF₃•OEt₂ to provide silylated azabicycles (1.3) via the [3+2]-annulation pathway.

Scheme 1.19: BF₃•OEt₂-catalyzed intramolecular cyclization modes of aziridine-allylsilanes.

1.4.1. Intramolecular Sakurai reaction of aziridine-allylsilanes to form γ-amino olefins

1.4.1.1. Reaction mechanism of γ-amino olefin formation

Scheme 1.20 shows the intramolecular Sakurai reaction mechanism of aziridine-allylsilanes (1.1) to produce carbocycles containing a γ-amino olefin unit (1.2). BF₃•OEt₂ initially coordinates to the aziridine ring nitrogen, thereby activating the aziridine ring for nucleophilic
attack by the π bond of the allylsilane (1.78). The attack occurs in a $S_N2$ fashion preferentially at
the more-substituted carbon of the aziridine ring, presumably due to a greater polarization of the
more-substituted C-N bond when a three-membered ring electrophile is coordinated with a Lewis
acid. The resulting β-silyl carbocation (1.79) is stabilized via hyperconjugation with the C-Si
bond.\textsuperscript{14,15} Cationic intermediate 1.79 can then undergo an elimination reaction to provide γ-
amino olefin 1.2.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node[draw, shape=rectangle, rounded corners] (A) at (0,0) {\textbf{1.1}, $n = 1, 2$};
\node[draw, shape=circle, rounded corners] (B) at (2,0) {\textbf{1.78}, $n = 1, 2$};
\node[draw, shape=circle, rounded corners] (C) at (4,0) {\textbf{1.79}, $n = 1, 2$};
\node[draw, shape=rectangle, rounded corners] (D) at (2,-2) {\textbf{1.2}, $n = 1, 2$};
\draw[->, thick] (A) -- (B) node[midway, above] {$\text{BF}_3\cdot\text{OEt}_2$};
\draw[->, thick] (B) -- (C);\draw[->, thick] (C) -- (D) node[midway, above] {$\text{Nu}^-$};\draw[->, thick] (D) -- (A) node[midway, below] {$-\text{SiR}_3$};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.20: Mechanism of γ-amino olefin formation.}
1.4.1.2. Synthesis of carbocyclic γ-amino olefins via intramolecular cyclization of aziridine-allylsilanes

We have reported the intramolecular cyclization reaction of aziridines with allylsilanes to stereoselectively produce disubstituted cyclopentanes and cyclohexanes containing a γ-amino olefin unit (Scheme 1.21). Treatment of racemic aziridine-allylsilane 1.80a with 300 mol% of BF₃•OEt₂ produced a 2.6 : 1 mixture of 1.81a to 1.81b in 84% yield. The major isomer was shown to be the cis isomer 1.81a via nOe studies. The yield for the cyclization of aziridine-allylsilane 1.80b proved equally successful (90%). However, in this case the major isomer was shown to be the trans isomer 1.82b. The ratio of diastereomeric products for this reaction was shown to be 2.7 : 1 (1.82b : 1.82a). The diastereomeric ratios for the cyclization products were obtained via ¹H NMR integration values for the protons representing the methylamino group.

Scheme 1.21: Synthesis of carbocyclic γ-amino olefins.
1.4.1.3. Stereochemical rationale for the formation of γ-amino olefin carbocycles

The results of the reactions in Scheme 1.21 prove very interesting in that the five-membered ring forms primarily the cis isomer, while the six-membered ring forms primarily the trans isomer. We suggest that the results of these reactions can be explained by depicting the aziridine-allylsilanes in reactive chair-like conformations.

Scheme 1.22 shows the stereochemical rationale for the formation of five-membered carbocycles 1.81a and 1.81b via chair-like conformations of aziridine-allylsilane 1.80a. The formation of the major cis isomer 1.81a could be rationalized via conformation A, which depicts both the aziridine and allylsilane in an equatorial orientation. This arrangement reduces the unfavorable steric interactions predicted for conformations C and D. Synclinal transition states (allylsilane equatorial) are preferred over antiperiplanar transition states (allylsilane axial) in the intramolecular reactions of allylsilanes. A possible explanation for this preference could be the unfavorable $A^{(1,3)}$ interaction between the allylic protons of the allylsilane and the axial hydrogen of the forming ring when the allylsilane is in an axial orientation.77,78 The alternative diaxial arrangement of the aziridine and allylsilane shown in conformation B would seem to exclude any product formation due to the presence of unfavorable steric interactions. Attack of the allylsilane at the internal carbon of the aziridine ring in an $S_N^2$ fashion produces intermediate 1.83, which undergoes elimination to produce the cis isomer 1.81a with protons $H_a$ and $H_b$ oriented on the same side.

Conformations C and D could be used to explain the formation of the minor trans isomer 1.81b (Scheme 1.22). These conformations show either the aziridine or allylsilane adopting an
equatorial orientation. Nevertheless, the unfavorable steric interactions in both of these conformations make them less favorable when compared to conformation A. The orientations of protons H\textsubscript{a} and H\textsubscript{b} in conformations C and D are on opposite sides, which accounts for the \textit{trans} relationship of substituents in the minor product \textit{1.81b}.

The formation of the six-membered carbocycles \textit{1.82a} and \textit{1.82b} can also be rationalized via chair-like conformations of aziridine-allylsilane \textit{1.80b} (Scheme 1.23). The formation of the major \textit{trans} isomer \textit{1.82b} could arise through conformation E, which orients both the aziridine and allylsilane in an equatorial arrangement. Once again, unfavorable steric interactions can be accounted for in conformations G and H\textsuperscript{77,78} while diaxial representation of the aziridine and allylsilane in conformation F represses product formation arising by this conformation. The organization of protons H\textsubscript{a} and H\textsubscript{b} on opposite sides in conformation E accounts for the \textit{trans} relationship of substituents in \textit{1.82b}.

\textit{Cis} isomer \textit{1.82a} could arise through conformations G or H (Scheme 1.23). These conformations depict either the aziridine or allylsilane in an equatorial orientation. However, due to the steric interactions present in these conformations, the formation of the \textit{trans} fused carbocycle \textit{1.82b} predominates. Conformations G and H show the arrangement of protons H\textsubscript{a} and H\textsubscript{b} on the same side, which accounts for the \textit{cis} relationship of substituents in product \textit{1.82a}.
Scheme 1.22: Stereochemical rationale for the formation of five-membered carbocycles containing a γ-amino olefin unit.
Scheme 1.23: Stereochemical rationale for the formation of six-membered carbocycles containing a γ-amino olefin unit.
1.4.1.4. The effect of various nitrogen activating groups on the intramolecular Sakurai reaction of aziridine-allylsilanes

The intramolecular cyclization of aziridine-allylsilane \(1.80b\) proceeded in good yield (90%), but rather moderate results in terms of diastereoselectivity (2.7 : 1 ratio of \textit{trans} \(1.82b\) to \textit{cis} \(1.82a\)) (Scheme 1.21). One of the goals of our group is to improve the diastereoselectivity of the intramolecular aziridine-allylsilane reaction.

Given our hypothesis that aziridine-allylsilanes react intramolecularly via chair-like conformations, biasing the population distribution of reactive conformations could potentially reflect a change in the formation of one diastereomer over another. Since the populations of reactive chair-like conformations of aziridine-allylsilanes are mainly governed by steric considerations, one could think of changing several variables in this regard to potentially change the diastereoselectivity of the reaction. Some examples might include using different Lewis acids for complexation or changing the substitution pattern of the aziridine-allylsilane.

Dr. Susan Donaldson investigated the cyclizations of aziridine-allylsilanes containing various nitrogen activating groups in order to learn the effect of this variable on the diastereoselectivity and yield of the intramolecular Sakurai reaction (Scheme 1.24).\(^79\) The differentially substituted aziridines \((1.91)\) were prepared by sodium naphthalenide deprotection\(^80\) of \(N\)-Ts-aziridine-allylsilane \((R)-1.80b\) followed by reprotection of the free \(N\)-H-aziridine with the activating group of choice. The aziridine-allylsilanes \((1.91)\) were then cyclized using 300 mol\% of \(BF_3\cdot\text{OEt}_2\) for 1 hour at 0\(^\circ\)C then warmed to room temperature overnight. The results for the
synthesis and cyclization of these aziridine-allylsilanes to olefin products (1.92) are shown in

Scheme 1.24.

<table>
<thead>
<tr>
<th>R</th>
<th>yield</th>
<th>cyclization product</th>
<th>yield</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Ts</td>
<td>NA</td>
<td>1.82</td>
<td>90%</td>
<td>2.7 : 1</td>
</tr>
<tr>
<td>1.91a</td>
<td>80%</td>
<td>1.92a</td>
<td>47%*</td>
<td>2 : 1</td>
</tr>
<tr>
<td>1.91b</td>
<td>91%</td>
<td>1.92b</td>
<td>60%*</td>
<td>2 : 1</td>
</tr>
<tr>
<td>1.91c</td>
<td>71%</td>
<td>1.92c</td>
<td>96%</td>
<td>2.3 : 1</td>
</tr>
<tr>
<td>1.91d</td>
<td>67%</td>
<td>1.92d</td>
<td>50%*</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>1.91e</td>
<td>56%</td>
<td>1.92e</td>
<td>17%*</td>
<td>1 : 1</td>
</tr>
<tr>
<td>1.91f</td>
<td>52%</td>
<td>1.92f</td>
<td>36%</td>
<td>1 : 1</td>
</tr>
<tr>
<td>1.91g</td>
<td>59%</td>
<td>1.92g</td>
<td>55%</td>
<td>1 : 1</td>
</tr>
<tr>
<td>1.91h</td>
<td>78%</td>
<td>1.92h</td>
<td>93%</td>
<td>2 : 1</td>
</tr>
</tbody>
</table>

*10 -25% of desilylated bicycle also formed

Scheme 1.24: The effect of various nitrogen activating groups on the intramolecular Sakurai reaction of aziridine-allylsilanes.
The cyclizations of \( p \)-nitrobenzenesulfonyl aziridine (1.91c) and diphenylphosphinyl aziridine (1.91h) gave only olefin products (1.92) in excellent yield with \( \text{trans} : \text{cis} \) ratios of \( \sim 2 : 1 \). The other \( N \)-arenesulfonamide aziridines (1.91a and 1.91b) cyclized to give olefin products in moderate yield and diastereoselectivity while contaminated with desilylated azabicycle. The formation of these desilylated azabicycles will be discussed in Chapter 3. One should note that none of the aziridines examined produced better diastereoselectivity than the tosylated analog (\( R \)-1.80b). In fact, the use of carbonyl activating groups (1.91e-g) provided olefin products (1.92e-g) of lower yield and diastereoselectivity.

The poor diastereoselectivity of the acyl derivatives when compared to the arenesulfonyl derivatives could be explained by the size of the activating group and its effect on conformation I (Scheme 1.25). Recall that conformation I has the aziridine ring oriented axially while the allylsilane is oriented equatorially. Subsequent ring closure of this conformation produces the \textit{cis} product. The size difference between the acyl and sulfonyl derivatives in Scheme 1.24 may be related to the \( A \) values for a methanesulfonyl group and an acetate. The \( A \) value for a methanesulfonyl group on a cyclohexane ring is 2.5 kcal/mol\(^81\) while an acetate is only 1.02 – 1.52 kcal/mole.\(^82\) The values indicate that conformation I could better tolerate an acyl-activating group versus a sulfonyl on an axial aziridine. As a result, more \textit{cis} products are formed with the acyl groups and the diastereoselectivity evens out at \( \sim 1 : 1 \).
1.4.2. Intramolecular [3+2]-annulation reaction of aziridine-allylsilanes to form silylated azabicycles

When the crude reaction mixtures of the reactions shown in Scheme 1.21 were subjected to closer examination, the presence of a small quantity (< 5%) of another product was noted. This product still contained the trimethylsilyl group, but no traces of aziridine remained. It was postulated that the minor component was a compound such as 1.3, which is the product of an intramolecular [3+2]-annulation (Scheme 1.26). Upon further investigation, it was found that using a catalytic amount of BF₃•OEt₂ could give the [3+2]-product 1.3 (R = Me) as the major product, albeit in poor yield (20 – 40%).
Scheme 1.26: [3+2]-Annulation reaction of aziridine-allylsilanes to form silylated azabicycles.

Scheme 1.27: [3+2] Reaction mechanism to silylated azabicycles.
1.4.2.1. Reaction mechanism of silylated azabicycle formation

Scheme 1.27 shows how aziridine-allylsilanes 1.1 react via a [3+2]-annulation mechanism to produce silylated azabicycles 1.3. The reaction proceeds through the identical β-silyl carbocation 1.79 described in Section 1.4.1.1, however this time the cation is trapped by the sulfonamide nucleophile to form the silylated azabicycle 1.3.

1.4.2.2. Synthesis of silylated azabicycles via intramolecular [3+2]-annulation of aziridine-allylsilanes

As we saw in Section 1.2.2, the [3+2]-annulation reaction between allylsilanes and electrophiles has been successfully used in the synthesis of a diversity of cyclic molecules.\textsuperscript{30-34} It should be noted that a number of other silanes (most prominently triisopropyl) can be retained in the [3+2]-annulation reaction.\textsuperscript{41} As previously mentioned in Section 1.2.2.3, the use of allylsilanes containing small groups on the silicon (e.g. trimethylsilyl) typically results in an elimination reaction. Alternatively, bulkier groups on the silicon have been used to block the approach of incoming nucleophiles and reduce the rate of elimination. Also, the use of alternative silyl groups containing at least one phenyl group on the silicon can be oxidized to a hydroxyl group,\textsuperscript{9,10} thus providing future functionality to silylated annulated products. With these thoughts in mind, our group examined a series of aziridine-allylsilanes containing a phenyldimethylsilyl group in the [3+2]-annulation mode.\textsuperscript{2}
The cyclizations of epimeric aziridine-allylsilanes 1.94 and 1.97 were carried out using a catalytic amount of BF$_3$•OEt$_2$ (15 mol%) at 0°C for 30 minutes (Scheme 1.28). In each case, the major product of the reaction was the formation of a diastereomerically pure silylated 5-5 azabicycle (1.95 and 1.98) in moderate yield. The reactions were also contaminated with the corresponding γ-amino olefins 1.96 and 1.99, but these products could be removed by column chromatography. It should be noted that changing the silyl group from trimethylsilyl to phenyldimethylsilyl significantly improved the yield of silylated azabicycle formation.

Synthesis of silylated 6-5 azabicycles was accomplished using epimeric aziridine-allylsilanes 1.100 and 1.104 (Scheme 1.29). Even though identical reaction conditions were used (i.e. 15 mol% BF$_3$•OEt$_2$, 0°C, 30 min.), substrates 1.100 and 1.104 provided different product
ratios. The more flexible nature of the 6-5 bicycle system allows for the generation of either a cis or trans ring junction. However, in both cases the trans ring isomer (1.102 and 1.106) was the major product. Once again, the reaction mixtures were contaminated with the corresponding γ-amino olefins 1.103 and 1.107 in ca. 25% yield and 1.5 : 1 trans : cis ratio. The stereochemistry of the silylated bicycle products was assigned by nOe spectroscopy.

Scheme 1.29: Synthesis of 6-5 silylated azabicycles.

1.4.2.3. Stereochemical rationale for the formation of silylated azabicycles

The formation of the major cis silylated 5-5 azabicycle 1.98 could be rationalized by aziridine-allylsilane 1.97 adopting reactive chair conformation J, which orients both the aziridine and allylsilane equatorially (Scheme 1.30). This conformation minimizes the unfavorable steric
interactions seen in conformations K through M, where either the aziridine or allylsilane are oriented axially. Once again, synclinal transition states (allylsilane equatorial) are preferred over antiperiplanar transition states (allylsilane axial) in the intramolecular reactions of allylsilanes. A possible explanation for this preference could be the unfavorable A(1,3) interaction between the allylic protons of the allylsilane and the axial hydrogen of the forming ring when the allylsilane is in an axial orientation.77,78 It is highly unlikely that product formation proceeds through reaction conformation K, which depicts both the aziridine and the allylsilane in the energetically unfavorable axial orientation.

The highly stereoselective nature of the second ring closer could be explained by the fact that β-silyl carbocations do not rotate around the single bond between C-1 and C-2.3-8,30-34 Also, nucleophile approach must take place anti to the silicon. As a result, the cis olefin geometry of the allylsilane is retained in the cyclization product 1.98 (i.e. protons Hb and Hc are on the same side). Cationic intermediates 1.110 and 1.111 can not undergo the second ring closure and could explain the formation of olefin product 1.99 via elimination.
Scheme 1.30: Stereochemical rationale for the formation of silylated 5-5 azabicycles.
The formation of the major *trans* silylated 6-5 azabicycle 1.106 could be explained by aziridine-allylsilane 1.104 adopting reactive chair-like conformation N (Scheme 1.31). Once again, this reactive conformation places both the aziridine and the allylsilane in the energetically favorable equatorial orientation. However, due to the longer tether between the reacting partners, protons H<sub>a</sub> and H<sub>b</sub> are now on opposite sides, which accounts for the *trans* ring junction in product 1.106. As seen with the 5-5 bicycles, the *cis* olefin geometry of the starting allylsilane is retained in the final product 1.106 (i.e. protons H<sub>b</sub> and H<sub>c</sub> are on the same side). Once again, this is due to the nature of the hyperconjugation and the *anti* approach of the sulfonamide nucleophile towards β-silyl carbocation 1.112.

The formation of the minor *cis* silylated 6-5 azabicycle 1.105 could take place via aziridine-allylsilane 1.104 in conformation P or Q (Scheme 1.31). These conformations show either the aziridine or the allylsilane in an equatorial orientation. However, due to the steric interactions present in these conformations, they are not favored when compared to conformation N. The notion that any product results through conformation O is highly unlikely due to the unfavorable diaxial relationship of the reacting moieties.
Scheme 1.31: Stereochemical rationale for the formation of silylated 6-5 azabicycles.
1.5. Applications of intramolecular aziridine-allylsilane methodology in the synthesis of biologically important molecules

To demonstrate the synthetic utility of intramolecular aziridine-allylsilane methodology, our group has transformed selected products of the cyclization reactions into some biologically important molecules.

1.5.1. Aziridine-allylsilane-mediated total synthesis of (-)-yohimbane

We have reported the total asymmetric synthesis of (-)-yohimbane (1.5a) and ent-alloyohimbane (1.5b) via intramolecular aziridine-allylsilane methodology (Scheme 1.32).\textsuperscript{1} Treatment of optically pure aziridine-allylsilane (\textit{R})-1.80b with BF\textsubscript{3}•OEt\textsubscript{2} provided a 2.8 : 1 \textit{trans} to \textit{cis} mixture of aminomethyl-substituted carbocycle 1.82 in excellent yield (94%). Alkylation of the tosylamide with mesylate 1.116 followed by oxidation of the olefin provided ester 1.118. Tosyl removal with sodium naphthalenide\textsuperscript{80} resulted in the formation of lactam 1.119 in 77% yield. The lactam was converted to (-)-yohimbane (1.5a) and ent-alloyohimbane (1.5b) by a Bischler-Napieralski reaction. The synthesis provided (-)-yohimbane (1.5a) in eight steps and 24% overall yield from optically pure aziridine-allylsilane (\textit{R})-1.80b.
Scheme 1.32: Aziridine-allylsilane-mediated synthesis of (-)-yohimbane.
1.5.2. Synthesis of bicyclic proline analogs using a formal [3+2] intramolecular aziridine-allylsilane cycloaddition reaction

We have also reported the synthesis of bicyclic proline analogs (1.6) via intramolecular aziridine-allylsilane methodology (Scheme 1.33).2 Proline analogs have potential biological utility as analgesics, enzyme inhibitors, and peptidomimetics. A representative example of the reaction sequence employed to synthesize these analogs is given by the conversion of silylated azabicycle 1.95 to amino acid 1.6a. The identical reaction sequence was applied to the synthesis of analogs 1.6b-d starting from the corresponding silylated azabicycle.

The silylated azabicycle was first oxidized to the corresponding alcohol (e.g. 1.120) using mercuric acetate with acetic and peracetic acids.83 The alcohol was further oxidized to the corresponding carboxylic acid (e.g. 1.121) using RuCl₃•H₂O and sodium periodate.84 Final removal of the tosyl group from the nitrogen using 32% HBr / AcOH and phenol85 provided the bicyclic proline analog (e.g. 1.6a) in good yield.
1.6. Chapter summary

The intramolecular reaction of an aziridine with an allylsilane proves to be a versatile reaction that can provide simple products such as \( \gamma \)-amino olefin carbocycles and silylated azabicycles. These products can serve as key building blocks in the synthesis of alkaloids and other nitrogen-containing heterocycles. By understanding the individual reactivity of allylsilanes as nucleophiles and aziridines as electrophiles, one can understand the formation and stereochemistry of products that result from intramolecular aziridine-allylsilane methodology.
CHAPTER 2

SYNTHESIS OF AZIRIDINES AND ALLYLSILANES

2.1. Introduction

An interesting facet of aziridine-allylsilane methodology is the synthesis of the reactive substrates. Aziridine-allylsilanes appear as structurally simple molecules. However, given the inherent ability of allylsilanes to react with electrophiles, acids, and halogens, coupled with the reactivity of aziridines with acids and nucleophiles, makes the synthesis of the reactive substrates in fact a formidable assignment. To formulate a successful approach to the synthesis of these substrates, it is important to understand how the reactive moieties can be constructed on an individual basis. In this regard, brief reviews will be given on the general methods used to synthesize allylsilanes and aziridines. The chapter will conclude by reviewing the successful approaches to aziridine-allylsilane synthesis.

2.2. General methods for the synthesis of allylsilanes

Due to their sustained presence as valuable nucleophiles, a number of review articles on the preparation and reactivity of allylsilanes have been written.\textsuperscript{6,24,86,87} The following sections
will highlight general methods for the preparation of allylsilanes in light of their tremendous potential as reagents and intermediates in organic synthesis.

2.2.1. Synthesis of allylsilanes via a Wittig reaction

The Wittig reaction of either a ketone or an aldehyde (2.1) with (2-trimethylsilylethyliedene)triphenylphosphorane (2.2a) or other ylides (2.2b, 2.7) has been a popular approach to the synthesis of terminally substituted allylsilanes (2.3) (Scheme 2.1). However, some drawbacks of the method include the lack of E/Z stereocontrol, difficulty in preparing allylsilanes with substituents at C-1, and synthesis of the requisite ylides. Some representative examples of the strategy include the reaction of cyclohexanone (2.4) with Wittig reagent 2.2a and the formation of 2-alkoxy-carbonyl-substituted allylsilane 2.8 via ylide 2.7.
Scheme 2.1: Wittig approach to allylsilane synthesis.

2.2.2. Synthesis of allylsilanes via transition metal-catalyzed cross-coupling reactions

Transition metal-catalyzed coupling of silyl enol ethers,\textsuperscript{90} enol phosphates,\textsuperscript{91} vinyl and aryl halides,\textsuperscript{92} and vinyl triflates\textsuperscript{93} with requisite Grignard or related reagents has been a useful strategy for the synthesis of allylsilanes. For example, enol phosphates (2.11) can be prepared by adding diethylchlorophosphate (2.10) to lithium enolates of ketones (Scheme 2.2).

Subsequent transition metal-catalyzed coupling in the presence of trimethylsilylmethyl magnesium halide (2.12) produces the allylsilane (2.13, 2.15).\textsuperscript{91} Alternatively, the palladium-catalyzed coupling of alkenyl triflates (2.16) with tris(trimethylsilylmethyl)aluminum is noted for its
ability to tolerate reactive functionality. As a result, this particular coupling strategy has been used for the synthesis of a diversity of functionalized allylsilanes (2.17).93

\[
\begin{align*}
\text{R}^1 \text{R}^2 \text{R}^3 \xrightarrow{\text{1. LDA}} (\text{EtO})_2 \text{P} \xrightarrow{\text{2. (EtO)}_2 \text{Cl}} \text{R}^1 \text{R}^2 \text{R}^3 \xrightarrow{\text{2.12} \text{Me}_3 \text{Si} \xrightarrow{\text{MgX}} \text{catalyst}} \text{R}^1 \text{R}^2 \text{R}^3
\end{align*}
\]

Scheme 2.2: Transition metal cross-coupling routes to allylsilanes.

2.2.3. Synthesis of allylsilanes via allylic alcohols, carbonyl compounds, and hexamethyldisilane

The direct conversion of allylic alcohols (2.18) to terminally-substituted allylsilanes (2.21) by way of hexamethyldisilane represents a powerful strategy in allylsilane synthesis (Scheme 2.3).94 The reaction typically begins with conversion of the alcohol (2.18) to the alkoxide (2.19)
using methyllithium. Subsequent exposure of the alkoxide to hexamethyldisilane in HMPT gives the allylsilane 2.21 in one pot. It is believed the reaction proceeds through an $S_{n}2'$ pathway of trimethylsilylanion reacting with an in situ-generated silyl ether (2.20). A representative example is the conversion of allylic alcohol 2.22 to allylsilane 2.23 in good yield.\textsuperscript{94} Once again, a potential drawback of this strategy is the lack of $E$/$Z$ stereocontrol.

$$\begin{align*}
R_1\text{OH} &\xrightarrow{\text{MeLi, 0}^\circ\text{C}} R_1\text{OLi} \\
&\xrightarrow{(\text{Me}_3\text{Si})_2 \text{Et}_2\text{O : HMPT (1 : 4)}} 80^\circ\text{C, 24 h.} \quad \text{Me}_3\text{Si}^+ \\
\text{Me}_3\text{Si}^- \\
\end{align*}$$

```
R
\text{MeLi, 0}^\circ\text{C}
\text{R}_1\text{OLi}
\text{2.19}
\\
\text{(Me}_3\text{Si})_2
\text{Et}_2\text{O : HMPT (1 : 4)}
80^\circ\text{C, 24 h.}
\text{Me}_3\text{Si}^+
\text{R}_1\text{SiMe}_3
\text{2.21}
```

Scheme 2.3: One-pot conversion of allylic alcohols to allylsilanes using hexamethyldisilane.

### 2.2.4. Synthesis of allylsilanes via hydrosilylation reactions

Allylsilanes can be synthesized via transition metal-catalyzed hydrosilylation of 1,3-dienes via proceeding in a 1,4 fashion (Scheme 2.4). However, the regio-, stereo-, and enantioselectivity of this process proves difficult to control. A representative example of this
strategy is the conversion of diene 2.24 to allylsilane 2.25 in good yield (95%), but very low enantioselectivity (1-25% ee). In another interesting reaction sequence, a protocol involving trichlorosilane, copper(I) chloride, and triethylamine was used to convert allylic bromide 2.26 into an intermediate allylic trichlorosilane (2.27). Subsequent exposure of the trichlorosilane to excess methyllithium provided allyltrimethylsilane 2.28.

Scheme 2.4: Synthesis of allylsilanes via hydrosilylation reactions.
2.2.5. Synthesis of allylsilanes via reductive elimination of β-hydroxy sulfones and β-hydroxy selenides

Terminal allylsilanes can be made from aldehydes and ketones by reductive elimination of β-hydroxy sulfones (2.33) through their corresponding mesylates (Scheme 2.5). In general, 1-lithio-2-(trimethylsilyl)ethyl phenyl sulfone (2.31) reacts with carbonyl compounds (2.32) to generate an alcohol (2.33) that is mesylated. The crude mesylates are subjected to reductive elimination using Na-Hg to provide $E$/$Z$ allylsilanes 2.21.

![Scheme 2.5: Allylsilanes via reduction of β-hydroxy sulfones.](image)

Likewise, β-hydroxy selenides (e.g. 2.37) can be reductively eliminated to provide terminal $E$-allylsilanes (Scheme 2.6). The requisite selenides can made by Grignard or aldol addition to an α-seleno aldehyde (2.35). Excess mesyl chloride or $N,N'$-carbonyldiimidazole...
is typically used to carry out the elimination step. A notable feature of this particular strategy is the ability to introduce allylsilane functionality $\alpha$ to a carbonyl. A representative example is given by the conversion of enolate 2.36 to allylsilane-ketone 2.38.$^{98}$

**Scheme 2.6: Allylsilanes via elimination of $\beta$-hydroxy selenides.**

2.2.6. Synthesis of allylsilanes via reagents containing silicon-metal bonds

$(\text{PhMe}_2\text{Si})_2\text{CuLi},^{99} (\text{PhMe}_2\text{Si})_2\text{Cu(CN)}\text{Li}_2,^{100-102} \text{and } \text{Me}_3\text{SiCu}^{103-105}$ are reagents containing Si-Cu bonds that have been used in the synthesis of allylsilanes. $(\text{PhMe}_2\text{Si})_2\text{Cu(CN)}\text{Li}_2$ appears to be the most versatile of these reagents with numerous examples of substitution and addition reactions involving a range of electrophiles (e.g. allylic acetates, $^{102}$ urethanes, $^{106}$ chlorides, $^{107}$ and allenes$^{108}$). One particularly interesting reaction is the Michael-type addition of $(\text{PhMe}_2\text{Si})_2\text{Cu(CN)}\text{Li}_2$ to $\alpha,\beta$-unsaturated esters (2.39) (Scheme 2.7).
The resulting enolates from this reaction can be protonated or alkylated to afford products 2.40 functionalized at either the $\beta$ or $\alpha$ and $\beta$ positions. The corresponding esters 2.40 can be reduced with LiAlH$_4$ and subjected to Grieco dehydration to provide a wide range of allylsilanes (2.41).\textsuperscript{109}

![Scheme 2.7: Synthesis of allylsilanes via Michael addition of (PhMe$_2$Si)$_2$Cu(CN)Li$_2$.](image)

Another method for the synthesis of unsymmetrically-substituted allylsilanes also stems from the Michael addition of (PhMe$_2$Si)$_2$Cu(CN)Li$_2$ to $\alpha,\beta$-unsaturated esters (2.42) (Scheme 2.8).\textsuperscript{110} After addition of the organocuprate, the esters are subjected to an aldol condensation with an aldehyde of choice to produce a $\beta$-hydroxy ester. The acid 2.43 becomes available after hydrogenolysis ($R^2 = Bn$) or cleavage ($R^2 = allyl$) of the ester. Acid 2.43 can then undergo decarboxylative elimination in the presence of dimethylformamide dimethyl acetal in refluxing chloroform in an anti-stereospecific manner to provide $Z$-allylsilanes 2.45. Syn-decarboxylation of
Acid 2.43 involves initial formation of a β-lactone (2.44) followed by refluxing in collidine to give E-allylsilanes 2.45.

\[
\begin{align*}
\text{SiPhMe}_2 & \quad \text{reflux} \quad 5 \text{ h} \\
\text{(E)-2.45} \\
\text{PhSO}_2\text{Cl} & \quad \text{Py} \\
0^\circ \text{C}, 12 \text{ h.}
\end{align*}
\]

\[
\begin{align*}
\text{SiPhMe}_2 \\
\text{reflux, 5 h.}
\end{align*}
\]

Scheme 2.8: Allylsilanes from α,β-unsaturated esters via decarboxylative elimination.

Allylsilanes can also be generated by silylcupration of allenes. A representative example is given in Scheme 2.9. Treatment of allene 2.46 with (PhMe₂Si)₂Cu(CN)Li₂ at −78°C for 1 hour provided allylsilane 2.47 in good yield (93%), but moderate stereoselectivity (\(E/Z = 3:1\)).
Even though \((\text{PhMe}_2\text{Si})_2\text{Cu(CN)Li}_2\) has proven to be a reagent of choice, it does have some potential drawbacks. For instance, the phenyldimethylsilyl moiety in \((\text{PhMe}_2\text{Si})_2\text{Cu(CN)Li}_2\) generates \(\text{PhMe}_2\text{SiH}\) or \(\text{PhMe}_2\text{SiOH}\) as nonvolatile byproducts of the requisite allylsilane reaction. For this reason, mixed cuprates \((\text{PhMe}_2\text{Si})\text{MeCu(CN)Li}_2\) and \((\text{Me}_3\text{Si})\text{MeCu(CN)Li}_2\) have been developed. These reagents selectively transfer the \(\text{R}_3\text{Si}\)-moiety and eliminate or minimize silicon-containing byproducts to improve reaction efficiency.

There are several examples \(\text{Me}_3\text{SiCu}\) reacting with primary allylic halides or sulfonates to give a variety of allylsilanes in good yield. For a selected example, the reaction of \(\text{Me}_3\text{SiCu}\) with allylic chloride \(\text{2.48}\) was a useful step in the synthesis of (+)-tricyclohexaprenol (Scheme 2.10).
Scheme 2.10: An allylsilane via Me$_3$SiCu reaction with an allyl chloride.

Me$_3$SiLi can silylate primary allylic halides to yield terminal E-allylsilanes.$^{103-105}$ However, it appears this route gives complicated mixtures of products at times and is limited to cases where reactive functional groups are not present. Nonetheless, successful transformations can occur given the appropriate reaction conditions. For example, reaction of allylic chloride 2.50 with Me$_3$SiLi provided allylsilane 2.51 in good yield (78%) (Scheme 2.11).

Scheme 2.11: Allylsilanes via Me$_3$SiLi.

2.2.7. Synthesis of allylsilanes via organocuprates

$\alpha$-Silylated organocuppper reagents Me$_3$SiCH$_2$Cu, Me$_3$SiCH(R)Cu, (Me$_3$SiCH$_2$)$_2$CuMgCl, and (Me$_3$SiCH$_2$)$_2$CuLi have been used to synthesize functionally-substituted allylsilanes.$^{113-116}$ Me$_3$SiCH$_2$Cu is a recommended reagent for the conversion of $\alpha$-acetylinic and –allenic oxiranes,
and α-methanesulfinates or disulfinates into 1,3-substituted products.\textsuperscript{113} The α-silylated organocopper reagents can also add to alkynes. The representative example in Scheme 2.12 shows (Me\textsubscript{3}SiCH\textsubscript{2})\textsubscript{2}CuMgCl reacting with alkynyl-ester 2.52. Aqueous quench of the reactive intermediate 2.53 produced the functionalized allylsilane 2.54 in excellent yield and moderate stereoselectivity.\textsuperscript{113} One should note that the addition of α-silylated organocuprates to alkynes produces the intermediate vinyl cuprates that can be reacted with a variety of electrophiles.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme2.12.png}
\end{center}

**Scheme 2.12: Allylsilanes via α-silylated organocuprates.**

Another beneficial strategy to allylsilane synthesis is the organocuprate-mediated γ-coupling of silylated allylic alcohols using (methylphenylamino)tributylphosphonium iodide (Scheme 2.13).\textsuperscript{117} This process has the advantage in the ease with which various unsymmetrically-substituted allylsilanes can be made in a predictable fashion with \(E\)-selective geometry. A representative example is the conversion of silylated allylic alcohol 2.58 to allylsilane 2.59 in good yield.
2.2.8. Synthesis of allylsilanes via organoalanes

Organoalanes can also represent valuable intermediates in allylsilane synthesis. For example, stereo- and regioselective hydroalumination of 1-[chloromethyl(dimethyl)silyl]-1-alkyne (2.60) with DIBAL-H yields aluminoalkene 2.61 (Scheme 2.14). Subsequent treatment of 2.61 with methylolithium provides β-lithioallylsilane 2.62 as an attractive intermediate for terminal E-allylsilane synthesis. In addition to protonolysis of intermediate 2.62, carbon electrophiles may be introduced in the presence of transition metal catalysts.
2.2.9. Synthesis of allylsilanes via organocerium reagents

This particular strategy involves the use of carboxylic acid derivatives as functional precursors of allylsilanes. For example, addition of trimethylsilylmethylmagnesium chloride to an ester (2.64, X = OR\(^1\))\(^{120,121}\) produces intermediate bis(\(\beta\)-silyl)alcohol 2.65, which upon deoxysilylation provides access to allylsilanes of type 2.66 (Scheme 2.15). Lactones\(^{122}\) and acid chlorides\(^{123}\) have also served as useful substrates in this protocol. However, the overall yields for these reactions are not very high and esters of \(\alpha\)-branched carboxylic acids do not react at all.\(^{120}\) The use of trimethylsilylmethylcerium dichloride has significantly improved these reactions with a wide variety of esters,\(^{124,125}\) while analogous conversion of acid chlorides appears to be less general.\(^{126}\) Scheme 2.15 also shows the reaction of lactone 2.67 with trimethylsilylmethylcerium dichloride to give allylsilane-alcohol 2.68 in 74\% yield.\(^{124}\)
2.2.10. Synthesis of allylsilanes via silylated olefin isomerization

[Rh(COD)(PPh₃)₂]PF₆ and [Ir(COD)(PPh₃)₂]PF₆ have been used as isomerization catalysts for the stereo- and regiocontrolled synthesis of allylsilanes from silylated olefins.¹²⁷ The iridium(I) catalyst has been recommended for more complete E-selectivity in product formation.¹²⁸ A selected example in Scheme 2.16 shows the isomerization of silylated olefin 2.69 to allylsilane 2.70 in excellent yield and moderate stereoselectivity.

Scheme 2.16: Allylsilanes via isomerization of silylated olefins.
2.2.11. Synthesis of allylsilanes from propargylsilanes and allylsilanes

Further manipulation of readily available allyl- and propargylsilanes is another strategy in the synthesis of functionalized allylsilanes. Treatment of 3-bromo-2-(trimethylsilylmethyl)propene (2.71) with bis(1,5-cyclooctadiene)nickel(0) in toluene at ambient temperature gave crystalline \( \pi \)-allylnickel halide complex 2.72 in 87% yield after 30 minutes. Exposure of the complex to organic halides in DMF or HMPT at room temperature provided access to a variety of functionalized allylsilanes.\(^{129}\) For example, reaction of complex 2.72 with the \( \alpha \)-chloro ketone 2.73 provided the allylsilane-ketone 2.74 in excellent yield (Scheme 2.17).

![Scheme 2.17: \( \pi \)-Allylnickel complex-mediated synthesis of functionalized allylsilanes.](image)

Vinylmagnesium and vinyllithium reagents such as Me\(_3\)SiCH\(_2\)CH(MgBr)CH\(_2\),\(^{130}\) Me\(_3\)SiCH\(_2\)CHMgBr,\(^{131}\) Me\(_3\)SiCH\(_2\)CH(Li)CH\(_2\),\(^{132,133}\) and PhMe\(_2\)SiCH\(_2\)CH(Li)CH\(_2\)\(^{134}\) have been reported in the synthesis of functionalized allylsilanes. A representative example is shown in Scheme 2.18. Treatment of epoxide 2.75 with Me\(_3\)SiCH\(_2\)CH(MgBr)CH\(_2\) and Cul provided the allylsilane-alcohol 2.76 in good yield (85%).\(^{130}\)

61
Propargylsilanes have also been used as starting materials in the synthesis of functionalized allylsilanes. Representative examples are shown in Scheme 2.19. 1-Ethoxy-3-trimethylsilyl-1-propyne (2.77) represents a valuable source for the stereo- and regioselective synthesis of a host of α-ethoxycarbonylallylsilanes (2.78). The reaction proceeds with aldehydes, ketones, and acetals in the presence of TiCl₄.¹³⁵,¹³⁶ Propargylsilane (2.79) has also found valuable use in the synthesis of functionalized allylsilanes. Zirconium-catalyzed carboalumination of propargylsilane has provided access to a variety of β,γ-disubstituted allylsilanes (e.g. 2.81).⁹²
2.2.12. Synthesis of allylsilanes via Diels-Alder and ene reactions

Due to the availability of silylated 1,3-dienes, the Diels-Alder reaction has been used as a strategy to provide functionalized allylsilanes.\textsuperscript{137-139} For example, the Diels-Alder reaction of silylated diene \textsuperscript{2.82} provided allylsilane \textsuperscript{2.84}, which was used as a key intermediate in the synthesis of (+)-shikimic acid (\textsuperscript{2.85}) (Scheme 2.20).\textsuperscript{137}

Scheme 2.20: Diels-Alder approach to functionalized allylsilanes.
An intramolecular ene reaction has been reported as a general method for the synthesis of cis-1,2-disubstituted cyclopentanoid allylsilanes (Scheme 2.21). The reactions feature the use of activated 1,6-dienes (2.86) containing a homoallylsilane unit as the ene donor. The use of this reaction strategy provided key allylsilane intermediate 2.87 in the total synthesis of (+)-hirsutene (2.88).

![Scheme 2.21: Synthesis of a functionalized allylsilane via an ene reaction.](image)

### 2.2.13. Synthesis of allylsilanes via allylic organometallics

Silylation of an allylic organometallic is probably the simplest way to make an allylsilane. However, the strategy is limited to cases were reactive functional groups are not present. A representative example is the conversion of terpene 2.89 to allylsilane 2.90 (Scheme 2.22).
Scheme 2.22: Allylsilanes via allylic organometallics.

As we have seen, there are numerous methods for the synthesis of allylsilanes to couple to the expanding growth of allylsilane chemistry. Close examination of these synthetic methods is an important step in the development of successful strategies for the synthesis of allylsilanes tethered to aziridine rings.

2.3. General methods for the synthesis of aziridines

As we saw in Chapter 1, the ability of aziridines to participate in highly stereo- and regioselective ring-opening reactions makes them of great value in organic synthesis. As a result, the synthesis of aziridines has been reviewed on several occasions. It should be noted that for all intents and purposes the methods to prepare achiral and enantiopure aziridines are identical.

2.3.1. Synthesis of aziridines from amino alcohols

Aziridines can stem from 1,2-amino alcohol precursors via conversion of the hydroxyl functional group into a good leaving group (LG) (Scheme 2.23). Either an amide...
anion or the lone pair of an amine can cause an intramolecular nucleophilic displacement to yield the aziridine ring (2.93).

\[
\begin{align*}
R & \quad R' \\
\text{NH}_2 & \quad \text{LG} \\
\end{align*}
\]

\[
\begin{align*}
R & \quad R' \\
\end{align*}
\]

Scheme 2.23: General synthesis of aziridines from amino alcohols.

While this strategy is efficient for simple amino alcohols, tertiary alcohols tend to eliminate to give olefin products rather than cyclized aziridines. The ring closure is generally stereospecific and relies on the ability of the leaving group and amine to adopt a trans coplanar relationship.

In addition to 2-haloamines, more recent methods involve the conversion of the hydroxyl group of amino alcohols into powerful leaving groups such as oxyphosphonium species. For example, treatment of amino alcohols with PPh₃ plus either Br₂,¹⁴⁵ CCl₄,¹⁴⁶-¹⁴⁸ or DEAD¹⁴⁹ has been a widely used method to effect aziridine ring closure. Additionally, other phosphorus reagents such as diphenylphosphinic chloride¹⁵⁰ and diethoxytriphenylphosphine¹⁵¹ can be employed in the reaction.

Enantiomerically pure 1,2-amino alcohols are often obtained via reduction of commercially available enantiopure 2-amino acids (2.94), or the amino alcohols themselves are
commercially available (Scheme 2.24). In order to avoid the problem of water-soluble metal complexes of amino alcohols resulting from the reduction of amino acids, the reduction of $N$-Ts amino acids (2.95) has been suggested and applied to the synthesis of a wide variety of 2-substituted $N$-Ts aziridines (2.97).$^{152}$

Unluckily, this method can not be applied to the synthesis of $N$-acyl or $N$-carbamoyl aziridines (2.98).$^{153}$ In these cases, formation of a 5-membered oxazolonium intermediate 2.100 is favored over aziridine ring formation (Scheme 2.25).
The synthesis of \(N\)-Boc aziridines (2.103) from amino alcohols has required temporary amine protection. In particular, the use of a trityl protecting group has been efficient (Scheme 2.26).\(^{154}\) \(N\)-Tr amino alcohols (e.g. 2.101) are typically tosylated then refluxed with \(\text{Et}_3\text{N}\) in THF to give the corresponding \(N\)-Tr aziridine (e.g. 2.102), which can be deprotected under acidic conditions and reprotected with a Boc group. However, Baldwin and co-workers have reported an improved synthesis of \(N\)-Boc aziridines via a one-pot activation / cyclization of amino alcohols (e.g. 2.104) using diethoxytriphenylphosphine (DTPP).\(^{151}\) One should note that a potential limitation associated with DTPP use is its explosive nature.

\[
\begin{align*}
&\text{BnO}_2\text{C} \quad \text{OH} \\
&\quad \text{NTr} \\
&\text{1) TsCl, pyridine} \\
&\quad \text{2) Et}_3\text{N} \\
&\quad \text{BnO}_2\text{C} \quad \text{NHTrH} \\
&\text{1) TFA} \\
&\quad \text{2) Boc}_2\text{O} \\
&\quad \text{BnO}_2\text{C} \quad \text{NBocH} \\
&\text{58%} \\
&\text{80%}
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2\text{N} \quad \text{OH} \\
&\text{CO}_2\text{Bn} \\
&\text{1) DTPP, toluene, 24 h.} \\
&\quad \text{2) Boc}_2\text{O, DMAP, MeCN} \\
&\quad \text{CO}_2\text{Bn} \\
&\quad \text{BocN} \\
&\quad \text{2.103b} \\
&\quad \text{25-69% over 2 steps}
\end{align*}
\]

**Scheme 2.26: Synthesis of \(N\)-Boc aziridines.**

### 2.3.2. Synthesis of aziridines from epoxides

The ability of azide ion to regiospecifically open epoxides has been exploited for the synthesis of aziridines.\(^{155,156}\) The azide moiety of the first formed azido-alcohol (e.g. 2.106)
can be reduced with triphenylphosphine in a Staudinger reaction to produce an imino phosphorane, which proceeds to an oxazaphospholane intermediate (e.g. 2.107). Thermal-induced cyclization of the oxazaphospholane intermediate provides the aziridine. A representative example of this strategy is shown in Scheme 2.27. 157,158

Scheme 2.27: Synthesis of aziridines from epoxides via a Staudinger reaction.

The conversion of chiral epoxides (e.g. 2.109) to chiral aziridines (e.g. 2.113) can also result from the formation of chiral episulfonium intermediates (e.g. 2.111) (Scheme 2.28). The
reaction proceeds with an overall retention in configuration resulting from double inversion of sequential $S_n2$ reactions.\textsuperscript{159}

Scheme 2.28: Synthesis of an $N$-Ts aziridine via an episulfonium intermediate.

2.3.3. Synthesis of aziridines from alkenes

Scheme 2.29 shows a reaction sequence analogous to the azide opening / Staudinger sequence involving cyclic sulfates \textsuperscript{2.115}. These intermediates can be obtained from asymmetric dihydroxylation of alkenes.\textsuperscript{160} There are two pathways for the conversion of the cyclic sulfate intermediates (2.115) into aziridines (2.117, 2.119). They both involve two consecutive nucleophilic displacement reactions with the final displacement being intramolecular.
Scheme 2.29: Aziridine synthesis via cyclic sulfates.

Scheme 2.30: Aziridines via an asymmetric Gabriel-Cromwell reaction.
The addition of bromine to alkenes can produce 1,2-dibromoalkanes (e.g. \(2.121\)), which can be transformed into aziridines upon treatment with an amine.\(^{161}\) Scheme 2.30 shows the synthesis of \(N\)-alkyl aziridines (\(2.125\)) via an asymmetric Gabriel-Cromwell reaction of primary amines with an enantiomerically pure 2-bromocarboxylate (\(2.122\)).

Aziridines can also be synthesized via sulfilimines (Scheme 2.31).\(^{162,163}\) The reaction involves the addition diphenylsulfilimine (\(2.127\)) to an electron-deficient alkene (\(2.126\)) followed by base-induced elimination of diarylsulphide to give the aziridine (\(2.129\)).

Scheme 2.31: Synthesis of aziridines via sulfilimines.

Nitrene addition to alkenes has become a popular method for the synthesis of aziridines (Scheme 2.32). The reaction is conceptually similar to the epoxidation of alkenes using peracids. The addition of free nitrenes to an alkene is generally not stereocontrolled due to the rapid interconversion of singlet (\(2.130\)) and triplet (\(2.133\)) nitrene states. As a result, mixtures of \(cis\) (\(2.132\)) and \(trans\) (\(2.137\)) aziridines can be formed.\(^{164,165}\)
2.3.4. Synthesis of aziridines from azirines

Azirines are unsaturated aziridines that can represent intermediates for aziridine synthesis. They are typically prepared from oximes (2.138) either via a Neber reaction \(^{166}\) or by treatment with a Grignard reagent.\(^{167}\) A representative example of the synthesis of azirines (2.139) and aziridines (2.140) via a Neber reaction is shown in Scheme 2.33.\(^{168}\)
2.3.5. Synthesis of aziridines from imines

Imines are also valuable intermediates in the synthesis of aziridines. In the aza-Darsens route to aziridines, the imine initially acts as an electrophile at carbon and subsequently as a nucleophile at nitrogen. α-Haloester enolates are the most popular anions for this reaction, which produces aziridine-2-carboxylic acid derivatives. Scheme 2.34 shows the general reaction
strategy and a representative example. Reaction of \( N \)-trimethylsilyl imine 2.146 with the enolate of an \( \alpha \)-chloroester (2.147) provides aziridine 2.148.\(^{169}\)

2.4. Synthesis of aziridine-allylsilanes

Our group has developed several successful strategies for the synthesis of aziridine-allylsilanes based on an initial understanding of the reactivity and general synthetic methods of the individual moieties.

2.4.1. Synthesis of aziridine-allylsilanes via metal nitrenoids

Our lab initially employed an olefin / nitrenoid route for the synthesis of aziridine-allylsilanes (Scheme 2.35).\(^{26}\) In this synthetic strategy, a monoprotected diol (2.149) was first oxidized to the aldehyde, then treated with Ph\(_3\)PCH\(_2\) to provide an olefin (2.150). The olefins were then subjected to Cu(CH\(_3\)CN)\(_4\)ClO\(_4\)-catalyzed aziridination using PhINTs.\(^{170}\) The silyl protecting group of 2.151 was removed with \( n \)-Bu\(_4\)NF to give the corresponding alcohol in good yield. Subsequent TPAP / NMO oxidation provided the aziridine-aldehydes 2.152a and 2.152b in 86% and 82% yield respectively. A final Wittig reaction using Ph\(_3\)PCHCH\(_2\)SiMe\(_3\)\(^{88}\) produced the target aziridine-allylsilanes 1.80 in 30 to 40% yield. Aziridine opening by the Wittig reagent could explain the poor yields for the final step.\(^{64}\)
(a) For 2.149a: PCC, CH₂Cl₂, 78%. For 2.149b: (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78°C, 82%.
(b) Ph₃CH₃I, n-BuLi, -78°C to rt, 2.150a, 85%; 2.150b, 80%.
(c) PhINTs, CuClO₄(CH₃CN)₄, 2.151a, 61% (considering recovered olefin); 2.151b, 49% (considering recovered olefin).
(d) n-Bu₄NF (150 mol%), THF, 0°C, n = 1, 75%; n = 2, 76%.
(e) TPAP, NMO, 2.152a, 86%; 2.152b, 82%.
(f) Ph₃CH₃I, nBuLi, 0°C to rt, n-BuLi, -78°C, ICH₂SiMe₃, 1.80a, 36%; 1.80b, 33%.

Scheme 2.35: Aziridine-allylsilanes via olefin / nitrenoid route.

2.4.2. Synthesis of aziridine-allylsilanes via epoxides

This particular strategy involves initial formation of an allylsilane-epoxide (2.155) followed by manipulation of the epoxide ring into an aziridine (Scheme 2.36). To accomplish this task, monoprotected alcohol 2.149b was first oxidized to the aldehyde under Swern conditions then treated with the Ph₃PCHCH₂SiMe₃ to provide allylsilane 2.153 in good overall yield. The hydroxyl protecting group was removed with n-Bu₄NF and oxidation provided allylsilane-aldehyde 2.154 in 70% yield over two steps. Subsequent conversion of the aldehyde into an epoxide was
accomplished using a trimethylsulfoxonium ylid\textsuperscript{172} to give allylsilane-epoxide \textit{2.155}. Opening of the epoxide with NaN\textsubscript{3} followed by treatment with Ph\textsubscript{3}P provided target aziridine-allylsilane \textit{2.157} in varying yields of 25 – 65%.

\begin{center}
\textbf{Scheme 2.36: Synthesis of aziridine-allylsilanes via an allylsilane-epoxide.}
\end{center}

\textbf{2.4.3. Synthesis of aziridine-allylsilanes via N-Ts-aziridine methanols}

The strategies depicted in Sections 2.4.1 and 2.4.2 were beneficial to our group in providing racemic aziridine-allylsilanes. However, the availability of scalemic chiral aziridine-
allylsilanes (2.158) was desired for the application of our methodology in the synthesis of biologically important molecules.\(^1\)\(^2\) To accomplish this task, a strategy was developed involving the nucleophilic attack of chiral \(N\)-Ts-aziridine methanols (2.159) with organometallic allylsilane reagents (2.160) (Scheme 2.37).

![Scheme 2.37: Retrosynthesis of chiral aziridine-allylsilanes via \(N\)-Ts-aziridine methanols.]

The inherent chiral center in \(N\)-Ts-aziridine methanols 2.159 stems from the use of commercially available (S)-serine (2.161) as a chiral starting material (Scheme 2.38).\(^{173}\) (S)-Serine was esterified using MeOH / HCl then tosylated to provide alcohol 2.162 in 75% yield. The free hydroxyl was protected as the \(tert\)-butyldimethylsilyl ether before reduction of the methyl ester using LiBH\(_4\). The aziridine ring was formed by a Mitsunobu reaction of alcohol 2.164 to provide 2.159a in 88% yield. Deprotection of the silyl ether to the free alcohol followed by tosylation produced ditosylate 2.159b in good overall yield.
Scheme 2.38: Synthesis of N-Ts-aziridine methanols.

The synthesis of the organometallic allylsilane reagents 2.160 stem from the generation of allylsilane-iodides, which can readily undergo lithium-halogen exchange to produce a nucleophilic species.\(^1,\)\(^2\) The examples provided in Scheme 2.39 show the nickel-catalyzed ring opening of either dihydrofuran (2.165a) or dihydropyran (2.165b) with PhMe\(_2\)SiCH\(_2\)MgCl\(^{174}\) to provide allylsilane-alcohols 2.166\(^{175,176}\). These ring-opening reactions work equally well with commercially available Me\(_3\)SiCH\(_2\)MgCl to provide the trimethylsilane derivatives. Tosylation of the alcohol followed by NaI displacement provided the key iodides 2.167a and 2.167b in 81% and 90% yield over two steps.
Two different methods can be used to form the requisite chiral aziridine-allylsilanes (i.e. 2.158).\textsuperscript{1,2} The first method involves the use of ditosylate aziridine 2.159b (Scheme 2.40). As mentioned previously, allylsilane-iodides 2.167 can undergo lithium-halogen exchange followed by transmetallation in the presence of CuI. The subsequent organocopper species attacks the less-substituted carbon of aziridine 2.159b to generate intermediate 2.168, which closes to the aziridine ring upon tosyl displacement by the sulfonamide nucleophile. The advantage of this pathway is the formation of optically pure aziridine-allylsilanes (1.97 and 1.104) in a single step from a chiral aziridine. The disadvantage appears to be that lower yields are observed upon scale-up of the reaction.
An alternative stepwise approach can be used to synthesize requisite chiral aziridine-allylsilanes (Scheme 2.41).\textsuperscript{1,2} Once again, the organocuprate originates from iodides 2.167 in an identical manner. However this time they are reacted with N-Ts aziridine methanol 2.159a to provide ring-opened products 2.169. Deprotection with $n$-Bu$_4$NF followed by Mitsunobu ring closure provided aziridine-allylsilanes 1.97 and 1.104 in 85% and 76% yield from the silyl ether. While this strategy involves two additional steps, the advantage is that the procedures are amenable to larger scale.
Scheme 2.41: Stepwise synthesis of aziridine-allylsilanes.

2.5. Chapter summary

As we have seen, there are numerous methods for the synthesis of allylsilanes and aziridines as individual moieties. These synthetic methods along with the reactivity patterns of aziridines and allylsilanes must be considered in order to develop a successful aziridine-allylsilane synthetic strategy. Our lab has developed two linear routes for the synthesis of racemic aziridine-allylsilanes, an olefin / nitrenoid route and an allylsilane-epoxide route. The synthesis of chiral aziridine-allylsilanes can be accomplished via nucleophilic attack of chiral $N$-Ts-aziridine methanols with organometallic allylsilane reagents.
3.1. Introduction

As we saw in Chapter 1, the intramolecular reaction between an aziridine and an allylsilane can represent a powerful method for the synthesis of $\gamma$-amino olefin carbocycles and silylated azabicycles. These simple products can represent key building blocks in the synthesis of larger and more complex molecules such as alkaloids. However, the development of intramolecular aziridine-allylsilane methodology at this point in time is still in its early stages. Much work can be done to expand and improve the methodology. By synthesizing and studying simple model reaction systems to understand the methodology at its roots, one could potentially apply the acquired knowledge to the successful synthesis of a complex target.

3.1.1. C-3 vs. C-2 aziridine-allylsilanes

In an effort to broaden the scope and knowledge base of intramolecular aziridine-allylsilane methodology, we felt changing the connectivity point between the aziridine and the allylsilane could produce synthetically useful products. Previous to the work of this dissertation, our lab has only focused on the synthesis and reactivity of aziridine-allylsilanes containing C-3
connectivity. That is, the aziridine ring is tethered through a methylene chain and connected to C-3 of the allylsilane (1.1) (Scheme 3.1).

![Scheme 3.1: C-3 versus C-2 aziridine-allylsilanes.](image)

Chapter 1 revealed that cyclization of C-3 aziridine-allylsilanes 1.1 in the Sakurai reaction mode produced 1,2-disubstituted carbocycles containing a γ-amino olefin unit (1.2), while cyclization in the [3+2]-annulation mode produced silylated azabicyclo[x.3.0]-systems (1.3) (Scheme 3.1). Another product that can be obtained from the cyclization of aziridine-allylsilanes with this connectivity are desilylated azabicyclo[x.3.0]-systems (1.4). The formation of these desilylated azabicycle compounds will be discussed in detail later in this chapter.
Changing the connection point of the aziridine tether to C-2 of the allylsilane (e.g. 3.1) could result in the formation synthetically useful products when these substrates are cyclized under Lewis acid conditions (Scheme 3.1). Given the reactivity patterns of C-3 aziridine-allylsilanes (1.1), treatment of aziridine-allylsilanes with C-2 connectivity (3.1) could potentially lead to the isolation of 1,3-disubstituted carbocycles containing an exocyclic γ-amino olefin (3.2), silylated azabicyclo[x.2.1]-systems (3.3), or desilylated azabicyclo[x.2.1]-systems (3.4).

3.1.2. Intramolecular reactions of C-2 allylsilane-epoxides

Given their similarities as reactive three-membered ring electrophiles, the chemistry of aziridines is often compared to epoxides. However, one should note that the chemistry of aziridines does not exactly mimic that of epoxides. Aziridines in general are somewhat less reactive than epoxides and can often show incongruous degrees of regio- and stereoselectivity.

There are a number of intramolecular cyclization examples of C-2 allylsilane-epoxides that would support the undertaking of an aziridine variant. Selected examples of Lewis acid-promoted intramolecular cyclizations of C-2 allylsilane-epoxides are given in Scheme 3.2.
Scheme 3.2: Examples of intramolecular C-2 allylsilane-epoxide cyclizations.
Fredj and co-workers cyclized C-2 allylsilane-epoxide 3.5 to exocyclic olefin 3.6 as a key reaction step in their enantiospecific synthesis of a taxol A-ring building unit.\textsuperscript{177} Weiler and co-workers carried out a similar type of cyclization with allylsilane-epoxide 3.7.\textsuperscript{178} The monocyclic product 3.9 was converted to (+)-karahana ether (3.10) in two additional steps. The cyclization of epoxy allylsilane 3.11 was examined with several Lewis acids under a variety of solvent and temperature conditions.\textsuperscript{179} It was found that excess Lewis acid (500 mol\%) was required due to competing complexation with the sulfone oxygens. One should note that optimized conditions only provided 30\% yield of the product alcohol 3.12. While the previous reaction examples involve the use of BF\textsubscript{3}•OEt\textsubscript{2} as the Lewis acid catalyst, Molander and co-workers reported the combination of Sn\textsuperscript{4+} Lewis acid-catalysis and fluoride-induced nucleophilic assistance to facilitate ring opening of an intermediate allylsilane-epoxide (3.15).\textsuperscript{180}

The examples of intramolecular C-2 allylsilane–epoxide cyclizations depicted in Scheme 3.2 offer unique reaction behavior when compared to our previous work with C-3 aziridine-allylsilanes. In all the examples provided, the allylsilane attacked the terminal carbon of the epoxide ring and not the internal position. This type of ring opening was not seen in the cyclizations of C-3 aziridine-allylsilanes (1.1). These aziridine substrates always provided ring-opened products resulting from attack of allylsilane at the internal carbon of the aziridine. Likewise, C-3 allylsilane-epoxides react in a similar manner to their aziridine counterpart via attack of the allylsilane at the internal position.\textsuperscript{181} Furthermore, there are no C-2 allylsilane-epoxide cyclization examples in the literature with either three or four carbon tethers separating the reacting moieties. Therefore, cyclization studies of C-2 aziridine-allylsilanes (3.1) could prove
worthwhile for not only the determination of reaction products, but also to draw conclusions about reactivity for comparison with C-2 allylsilane-epoxides and C-3 aziridine-allylsilanes (1.1).

3.1.3. Potential applications of intramolecular C-2 aziridine-allylsilane methodology

The potential cyclization products (3.2 – 3.4) of intramolecular C-2 aziridine-allylsilane methodology could be useful in either total or analog synthesis of complex natural products and pharmacologically active agents. For example, azabicyclo[x.2.1]-systems are present in a number of natural products and biologically active agents (Scheme 3.3).

Scheme 3.3: Examples of natural products and pharmacologically active agents containing an azabicyclo[x.2.1]-system.
Securinine (3.17) is an alkaloid from the Securinega family that contains an azabicyclo[3.2.1]-system and possesses CNS biological activity as a GABA receptor antagonist (Scheme 3.3).\textsuperscript{182} Azaprophen (3.18) and (-)-aphanorphine (3.19) have inherent 6-azabicyclo[3.2.1]octane frameworks. Azaprophen is a potent muscarinic antagonist that represents a lead compound in the development of agents for the treatment of Alzheimer’s disease,\textsuperscript{183} while (-)-aphanorphine was recently isolated from the freshwater blue-green alga \textit{Aphanizomenon flos-aquae}.\textsuperscript{184}

Additionally, 2-azabicyclo[2.2.1]heptanes could be representative targets for application of intramolecular C-2 aziridine-allylsilane methodology (Scheme 3.3). Malpass and co-workers have reported the synthesis of novel epibatidine isomers (3.20) as potent nicotinic acetylcholine receptor antagonists,\textsuperscript{185} while Takeda and co-workers synthesized azabicycloalkane 3.21 as a lead compound displaying a good mixture of analgetic and narcotic antagonist activities.\textsuperscript{186}

The proposed exocyclic \(\gamma\)-amino olefin products (3.2) resulting from C-2 aziridine-allylsilane methodology could also be used as key intermediates in the synthesis of complex organic targets. For example, appropriate manipulation of olefin 3.2b could provide access to 3-azabicyclo[3.3.1]nonanes, which represents the key bicyclic system in a number of natural products.\textsuperscript{187-192} A representative example of potential application of C-2 aziridine-allylsilane methodology to MLA (3.23) is depicted in Scheme 3.4.
Our group has shown interest in the synthesis of analogs of the diterpene alkaloid methyllycaconitine (MLA) (3.23) (Scheme 3.4), which is the most potent nonpeptide nicotinic acetylcholine receptor antagonist currently known and is reported to selectively act at $\alpha_7$ nicotinic receptors. Thomas et al. reported the synthesis of a 1,5-disubstituted-6-azabicyclo[3.2.1]octane (3.22) in order to explore the effect of ring E contraction on nicotinic acetylcholine receptor antagonist activity of MLA (3.23). Proposed azabicycles 3.3b and 3.4b, $X = -\text{SiMe}_3$, $3.4b, X = -\text{H}$.
3.4b, which could result from the intramolecular cyclization of aziridine-allylsilane 3.1b, contain the same bicyclic ring system seen in alcohol 3.22. Furthermore, appropriate manipulation of proposed olefin 3.2b could lead to the inherent azabicyclo[3.3.1]nonane (3.24) present within the AE rings of MLA (3.23).

To conclude, expanding our methodology to include C-2 aziridine-allylsilanes should prove very valuable to the organic and medicinal chemistry communities. By studying reactive model systems of C-2 aziridine-allylsilanes (i.e. 3.1), we could understand what products can form from these substrates and compare their reactivity to C-2 allylsilane-epoxides and our previous work with C-3 aziridine-allylsilanes. The value of the proposed products (i.e. 3.2 – 3.4) lies in their potential application as key building blocks in the synthesis of natural products or pharmacologically active agents.

3.2. Synthesis of C-2 aziridine-allylsilanes

The first major task in studying intramolecular C-2 aziridine-allylsilane methodology is the synthesis of reactive substrates 3.1. As we saw in Chapter 2, there are a host of methods available for the synthesis of aziridines and allylsilanes as individual entities. By understanding these synthetic methods and the reactivity associated with the individual moieties, our group developed several strategies for the synthesis of C-3 aziridine-allylsilanes (see Section 2.4). The most attractive of these strategies is the nucleophilic attack of N-Ts-aziridine methanols with nucleophilic allylsilane reagents to produce chiral aziridine-allylsilanes.1,2,173 Given the success of this synthetic strategy with C-3 aziridine-allylsilanes and our interest in MLA (3.23) (Scheme
3.4), the synthesis of C-2 aziridine-allylsilane 3.1b was envisioned through the allylsilane-cuprate / N-Ts-aziridine methanol route.

3.2.1. Attempted synthesis of C-2 aziridine-allylsilane 3.1b using the allylsilane-cuprate / N-Ts-aziridine methanol strategy

A retrosynthesis of C-2 aziridine-allylsilane (R)-3.1b using the allylsilane-cuprate / N-Ts-aziridine methanol strategy is given in Scheme 3.5. Aziridine-allylsilane (R)-3.1b could be made via reaction of N-Ts-aziridine methanol 2.159 with an organocuprate reagent derived from organolithium 3.25. We saw in Section 2.4 that the preparation of N-Ts-aziridine methanols 2.159 stem from the use of commercially available (S)-serine (2.161) as a starting material. Therefore, the only remaining piece that would need to be made is the organometallic allylsilane 3.25. Also discussed in Section 2.4 was the notion that allylsilane-alcohols could be transformed into allylsilane-iodides, which can readily undergo lithium-halogen exchange to produce a nucleophilic species. Therefore, organolithium 3.25 could potentially be made via lithium-halogen exchange of iodide 3.26, which could stem from transformation of allylsilane-alcohol 3.27. It should be noted that the preparation of allylsilane-alcohol 3.27 is reported.195
Scheme 3.5: Retrosynthesis of C-2 aziridine-allylsilane (R)-3.1b via the allylsilane-cuprate / N-Ts-aziridine methanol strategy.

Allylsilane-alcohol 3.27 was prepared from commercially available homoallylic alcohol 3.28 by the known method (Scheme 3.6).\textsuperscript{195} Deprotonation of alcohol 3.28 using excess $n$-BuLi and chlorotrimethylsilane quench provided silyl ether 3.29 in 96% crude yield. Subsequent hydrolysis of the crude silyl ether using aqueous 1N H$_2$SO$_4$ gave allylsilane-alcohol 3.27 in 45% yield from homoallylic alcohol 3.28. However, all attempts to synthesize a halogenated allylsilane (3.26, 3.31, and 3.32) that could be converted to either an organolithium (3.25) or Grignard reagent were unsuccessful. Several methods were examined for the conversion of alcohol 3.27 to a halogenated species (3.26, 3.31, and 3.32). While attempted tosylation of alcohol 3.27 gave products of protodesilylation and decomposition, the corresponding mesylate 3.30 could be made in quantitative yield. However, attempted displacement of mesylate 3.30 with NaI to give iodide
proved unsuccessful. Furthermore, strategies for the direct conversion of alcohol 3.27 to either bromide 3.31 or chloride 3.32 via oxyphosphonium species also failed.

Upon closer examination, compounds 3.26 and 3.31-3.32 could prove to be inherently unstable (Scheme 3.7). Along with protodesilylation, these compounds could potentially undergo elimination to form a stable conjugated diene (3.33). Furthermore, subjection of diene 3.33 to acid conditions could give a highly stabilized allylic and 3-silyl carbocation (3.34). As a result of these chemical features, the requisite synthesis of compounds 3.26 and 3.31-3.32 proved troublesome and thus a new strategy for the synthesis of aziridine-allylsilane 3.1b was
investigated. However, one should note that organolithium reagent 3.25 has been prepared by reductive lithiation of a phenylsulfide.\textsuperscript{196}

\[
\begin{align*}
3.26, \ X = I \\
3.31, \ X = Br \\
3.32, \ X = Cl
\end{align*}
\]

Scheme 3.7: Instability of halogenated allylsilanes 3.26 and 3.31-3.32.

3.2.2. Converse approach to the synthesis of C-2 aziridine-allylsilanes. Coupling of a nucleophilic aziridine with an electrophilic allylsilane.

With thoughts of synthesizing C-2 aziridine-allylsilane 3.1\textsuperscript{b} and expanding the methods of substituted aziridine preparation, a converse synthetic strategy to aziridine-allylsilanes was envisioned (Scheme 3.8). Our lab has traditionally synthesized aziridine-allylsilanes (e.g. 1.1) via the coupling of a nucleophilic allylsilane 3.35 (e.g. organocuprate 2.160) with an electrophilic aziridine 3.36 (e.g. N-Ts-aziridine methanols 2.159). However, the converse strategy of a nucleophilic aziridine with an electrophilic allylsilane could also hold true in the synthesis of aziridine-allylsilanes.

Scheme 3.8 shows a retrosynthesis of C-2 aziridine-allylsilane 3.1\textsuperscript{b} via the converse strategy. The retrosynthesis is highlighted by two types of potential carbon-carbon bond formation, either the coupling of a \(sp^3\) nucleophilic aziridine (3.38) with a \(sp^3\) electrophilic
allylsilane (3.37), or the coupling of a $sp^3$ nucleophilic aziridine (3.40) with a $sp^2$ electrophilic allylsilane (3.39).

![Scheme 3.8: Traditional versus converse approach to aziridine-allylsilane synthesis.](image)

At first glance, the plausibility of nucleophilic aziridine species 3.38 and 3.40 to be successfully generated and coupled to electrophilic allylsilanes 3.37 and 3.39 appears highly unlikely. This is due to the potential reaction of the nucleophilic portion of the molecule with the aziridine ring. However, recent developments in the Suzuki cross-coupling reaction has enabled the coupling of $sp^3$ and $sp^2$ hybridized carbons to $sp^2$ hybridized carbons (as well as $sp^3$...
to \(sp^3\)^197 with the added feature of tolerability to a wide variety of functional groups present in either coupling partner. The tremendous versatility of this reaction has allowed its application to the synthesis of a large variety of compounds.198-200

3.2.2.1. The \(\beta\)-alkyl Suzuki-Miyaura cross-coupling reaction

Due to its tremendous versatility and application in organic synthesis, the \(\beta\)-alkyl Suzuki-Miyaura cross-coupling reaction has been reviewed on several occasions.198-200 The reaction is distinguished from other Suzuki-Miyaura cross-coupling reactions in that a \(sp^3\) alkyl borane (as opposed to a vinyl or aryl borane) is coupled to a vinyl or aryl halide, triflate, or enol phosphate in the presence of a base and Pd(0) catalyst (Scheme 3.9).

\[
\begin{align*}
\text{R} & \quad \text{1)} \quad 9-\text{BBN} \\
& \quad \text{2)} \quad \text{Pd}^0, \text{base, R}^1\text{X} \\
\hline
\text{R} & \quad \text{R}^1 \\
\hline
\text{3.41} & \quad \text{3.42} \\
\end{align*}
\]

\(R^1 = \text{aryl, vinyl} \)
\(X = \text{I, Br, Cl, OTf, OP(O)(OR)^2}\)

**Scheme 3.9: The \(\beta\)-alkyl Suzuki-Miyaura cross-coupling reaction.**

Other cross-coupling methods for C\((sp^3)\)-C\((sp^3)\) bond formation are available and have been reviewed.201 However, the advantages of the \(\beta\)-alkyl Suzuki-Miyaura cross-coupling lies in the versatile and mild methods for the synthesis of the alkyl borane component, the ease of
incorporation of nontransferable boron ligands, the controllable toxicity of the boron-derived by-products, and the tolerance of water as a beneficial additive.

The $sp^3$ alkyl borane component of the Suzuki reaction can originate via hydroboration of the corresponding olefin\(^{202}\) (Scheme 3.10) or by alkylation of a boron-based electrophile with an alkyllithium or Grignard reagent (Scheme 3.11)\(^{203}\). The most popular approach is the hydroboration protocol because the alkyl boranes can be generated chemo-, regio-, and diastereoselectively. The hydroboration route features formation of the terminal alkyl borane regioisomer due to anti-Markovnikov addition. The rate of hydroboration is governed by steric and electronic factors with electron-rich unhindered olefins reacting the fastest.

\[
\begin{align*}
R-H & \quad \overset{9\text{-BBN}-H}{\longrightarrow} \quad R-BR_3 \\
\text{3.41} & \quad \text{3.43}
\end{align*}
\]

\[
\begin{align*}
R-H & \quad \overset{[\text{RhCl}(\text{PPh}_3)_{3}]}{\longrightarrow} \quad R-BR_3 \\
\text{3.41} & \quad \text{3.44} \quad \text{3.45}
\end{align*}
\]

Scheme 3.10: Hydroboration strategies to alkyl boranes.
As with other cross-coupling reactions, the Suzuki-Miyaura reaction is thought to proceed through a catalytic cycle involving sequential oxidative addition, transmetalation, and reductive elimination steps. The general Suzuki-Miyaura catalytic cycle is shown in Scheme 3.12.

The rate-limiting step in the catalytic cycle is often the oxidative addition step. Alkenyl, alkynyl, allyl, benzyl, aryl, and alkyl halides may participate in the reaction under the appropriate conditions. Aryl and 1-alkenyl halides activated by electron-withdrawing groups tend to be more reactive in the oxidative addition when compared to electron-donating groups. It has been suggested that the order of reactivity for the electrophilic partner is $I \gg Br > OTf > Cl$.\textsuperscript{204} However, the nature of the organoborane, coupling partner, palladium catalyst, and base all influence the overall cross-coupling rate.\textsuperscript{205-209}
Scheme 3.12: General Suzuki-Miyaura catalytic cycle.

Both PdCl$_2$(dppf) and Pd(PPh$_3$)$_2$ have been found to be efficient catalysts for the $\beta$-alkyl Suzuki-Miyaura coupling when used in catalytic amounts. Additionally, complexes containing an electron-rich Pd$^0$ center, or precursors thereof, can function as catalysts for the reaction.$^{200}$ A typical problem found in the coupling reactions of organometallic compounds that are $sp^3$ carbon-metalated and possess $\beta$-hydrogens is the tendency for the alkyl-palladium complex to undergo $\beta$-hydride elimination instead of reductive elimination.$^{210}$ The bis(diphenylphosphino)ferrocene ligand in PdCl$_2$(dppf) is thought to favor reductive elimination by enforcing a cis arrangement between the vinyl and alkyl groups on the square-planar Pd$^\text{II}$ complex. As a result, this catalyst is most effective if the reductive elimination is part of the rate-determining step in the coupling. Additionally, other ligands have been suggested for promoting the reductive elimination process,$^{207}$ while others can affect the rate of oxidative addition.$^{211-213}$
The choice of base is also important in the application of the β-alkyl Suzuki-Miyaura coupling. The role of the base has been proposed to be involved in several steps of the catalytic cycle, most notably the transmetalation. Stronger bases (NaOH, NaOMe) have been shown to perform well in THF / H2O systems, while weaker bases (K2CO3, K3PO4) appear to be more successful in DMF. Miyaura and co-workers suggested that the role of the base (‘OR3) was to increase the nucleophilicity of the alkylboranes by coordinating with the boron atoms, thereby triggering transfer of the alkyl group (R3) from boron to palladium to make complex 3.55 (Scheme 3.13). It has also been suggested that the halide or triflate on species 3.52 can be displaced by the base (‘OR3) to give the more reactive complex 3.57 prior to transmetalation.

The influence of the borane substituents can also have an effect on the coupling reaction. In general, electron-rich unhindered organoboranes and electron-poor vinyl or aryl halides or triflates are the most reactive partners for the coupling reaction. 9-BBN-H is the most commonly used hydroborating reagent for the reaction. However disiamylborane, dicyclohexylborane, and borane can also be used. The transmetalation rate of a primary alkyl group on boron is faster than a secondary alkyl group. One should note there are no literature examples of β-alkyl Suzuki couplings involving secondary alkyl boranes. In addition to alkyl hydroborating reagents, alkyl boronic esters have also been shown to be valuable substrates in the Suzuki reaction.
3.2.2.1.1.  Representative examples of the β-alkyl Suzuki-Miyaura cross-coupling reaction supporting the converse strategy

The β-alkyl Suzuki-Miyaura coupling has been successful employed using a wide variety of aryl and vinyl electrophiles while tolerating the presence of reactive functional groups in either coupling partner. However, there is only one example in the literature in which an epoxide ring is present in either coupling partner (Scheme 3.14). The coupling of the β-alkyl-9-BBN species derived from epoxy-olefin 3.59 with bromide 3.60 gave the expected coupled product 3.61 in 52% yield while contaminated with 30% of diol 3.62 resulting from epoxide opening with K₂CO₃. This reaction suggests that an aziridine variant could potentially tolerate a β-alkyl Suzuki-Miyaura coupling (i.e. coupling of 3.39 with 3.40) though the possibility of aziridine ring hydrolysis still exists. One should note that another potential problem associated with the β-
alkyl Suzuki-Miyaura coupling of an aziridine variant could be palladium-catalyzed ring opening.215

\[
\begin{align*}
\text{3.59} & \xrightarrow{\text{1) 9BBN}} \text{1) 9BBN} \\
& \xrightarrow{\text{2) PdCl}_2(dppf) (3 \text{ mol}\%)} \text{PdCl}_2(dppf) (3 \text{ mol}\%) \\
& \xrightarrow{\text{K}_2\text{CO}_3 (2 \text{ eq.})} \text{K}_2\text{CO}_3 (2 \text{ eq.}) \\
& \xrightarrow{\text{DMF-THF, 50°C}} \text{DMF-THF, 50°C} \\
\text{3.60} & \xrightarrow{\text{Br}} \text{3.60} \\
\end{align*}
\]

\[\text{3.61, 52\%}\]

\[\text{3.62, 30\%}\]

Scheme 3:14: Suzuki coupling in the presence of an epoxide.

The \(\beta\)-alkyl Suzuki reaction has also been used in the synthesis of non-natural \(\alpha\)-amino acids (Scheme 3.15). Organoborane homoalanine anion equivalent 3.65 can be coupled to a number of olefinic, aromatic, and heteroaromatic halides.216,217 Subsequent removal of the protecting oxazolidine unmasked a range of non-natural amino acids (3.67). Likewise, protected allylglycine (3.68) has been hydroborated and the intermediate organoborane employed in Suzuki coupling reactions.218 Given that enantiomerically pure amino acids are popular starting materials for the synthesis of aziridines (see Sections 2.3.1 and 2.4.3), these examples support the potential synthesis of substituted aziridines via a Suzuki cross-coupling route.
3.2.2.2. Synthesis of racemic C-2 aziridine-allylsilane 3.1b and substituted aziridines via a β-alkyl Suzuki-Miyaura cross-coupling route

Given the supportive examples of the β-alkyl Suzuki-Miyaura cross-coupling reactions provided in the previous section, a more detailed retrosynthesis of C-2 aziridine-allylsilane 3.1b can be given via the converse strategy (Scheme 3.16).
Scheme 3.16: Retrosynthesis of aziridine-allylsilane 3.1b via a Suzuki cross-coupling route.

The Suzuki cross-coupling of bromide 3.70 (i.e. electrophilic allylsilane) with organoborane 3.71 (i.e. nucleophilic aziridine) highlights the converse strategy retrosynthesis. The allylsilane partner (2-bromoallyl)trimethylsilane (3.70) is commercially available or can be prepared via a reported method.219 The aziridine partner 3.71 could arrive via hydroboration of olefin 3.72, which potentially stems from transformation of commercially available allylglycine (3.73). With these thoughts in mind, the Suzuki cross-coupling route to racemic aziridine-allylsilane 3.1b was investigated. One should note that an intramolecular Heck reaction has been used in the presence of an aziridine ring.220 Other than this report, Suzuki or similar types of reactions have not been carried out with an aziridine ring present in the molecule.
Racemic aziridine-olefin 3.72 was conveniently prepared from commercially available allylglycine (3.73) (Scheme 3.17). Treatment of amino acid 3.73 with MeOH / HCl followed by tosylation provided diprotected amino acid 3.74 in 80% yield from allylglycine. Reduction of the ester with LiBH₄ followed by Mitsunobu ring closure provided target aziridine 3.72.

![Chemical reaction diagram]

(a) MeOH, AcCl (500 mol%), reflux, 24 h.
(b) TsCl (110 mol%), Et₃N (250 mol%), CH₂Cl₂, rt, 24 h, 80% (two steps).
(c) NaBH₄ (300 mol%), LiCl (300 mol%), EtOH:THF (2:1), rt, 24 h, 80%.
(d) Ph₃P (110 mol%), DEAD (110 mol%), THF, rt, 16 h, 82%.


As mentioned previously, (2-bromoallyl)trimethylsilane (3.70) is commercially available, but rather expensive. Alternative to purchasing this reagent, it was prepared on a large scale via the reported method of Trost and co-workers (Scheme 3.18). Commercially available 2,3-dibromopropene (3.76) was reacted with trichlorosilane and triethylamine in the presence of copper(I) chloride to give intermediate trichlorosilane 3.77, which was converted to allyltrimethylsilane 3.70 in one pot upon treatment with methylmagnesium bromide. We carried out this reaction on a 310 mmol scale to provide 42 grams of bromide 3.70 (71% yield).
Scheme 3.18: Large scale preparation of (2-bromoallyl)trimethylsilane (3.70).

With both coupling partners in hand, the Suzuki strategy to racemic C-2 aziridine-allylsilane 3.1b was initiated (Scheme 3.19). Olefin 3.72 was treated with 9-BBN followed by (2-bromoallyl)trimethylsilane (3.70) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ under standard Suzuki cross-coupling conditions. We were pleased to find that the coupling provided the target C-2 aziridine-allylsilane 3.1b in 58% yield.$^{221,222}$ The success of this reaction supports the converse strategy to aziridine-allylsilane synthesis. It also confirms the successful generation and utilization of organoborane-aziridine 3.71.

Given the success of this initial reaction, the Suzuki cross-coupling route could be very useful for the preparation of substituted aziridines, especially those in which the desired organometallic reagent (such as organolithium 3.25) is not readily available or one in which the aziridine is not amenable to the type of ring-opening reaction we have typically employed.1,2,173 With these thoughts in mind, the coupling of olefin 3.72 was examined with a variety of vinylic and aryl halides (Scheme 3.20).222

In general, olefin 3.72 was treated with 120 mol% of 9-BBN as the hydroborating reagent. The progress of the hydroboration was followed by TLC and typically after 4 hours at room temperature no alkene remained. The organoborane was then coupled with the vinyl or aryl halide of choice using 3 M aqueous K3PO4 (210 mol%) as the base, PdCl2(dppf)•CH2Cl2 (5 mol%) as the catalyst, and DMF as the solvent. The coupling conditions in Scheme 3.20 are identical to those reported by Taylor and co-workers.218
Scheme 3.20: Suzuki cross-coupling reactions of olefinic aziridines.
We were pleased to find that elevated temperatures were not required for either the hydroboration or coupling step. The coupling could proceed at room temperature overnight to give product yields of 28 to 70%. Along with (2-bromoallyl)trimethylsilane (3.70), vinyl bromide 3.79 and vinyl iodide 3.80 served as viable coupling partners to give substituted aziridines 3.78a and 3.78b in 47% and 51% yield respectively. Similar yields were obtained when an aryl halide was used as the electrophilic coupling partner (i.e. 3.81 – 3.85). The only exception being 4-nitro-bromobenzene (3.83), which afforded aziridine 3.78e in only 28% yield. The reaction not only tolerated the presence of an aziridine ring in the nucleophile partner, but also a number of other functional groups present in the electrophile partner (i.e. esters 3.80 and 3.85, phenol 3.82, ketone 3.84, and nitro group 3.83).

Some of the low yields observed in the cross-coupling reaction can be attributed to difficulties in purification. All of the cross-coupling products (to some extent) co-eluted with 9-BBN by-products from the reaction when EtOAc : hexanes mixtures were used as the mobile phase in silica gel chromatography. Upon further experimentation, it was found that better separation of the undesired by-products from the target aziridines could be achieved when benzene was used as the mobile phase, though no significant difference in yield can be noted. The cross-coupling reaction conditions were not optimized and the yields presented in Scheme 3.20 are of analytically pure material.

One should note that another set of coupling conditions presented later in this dissertation also proved successful in the Suzuki-cross coupling reaction of olefinic aziridines, though no significant improvement in product yield was observed. The conditions involve the use
of Cs$_2$CO$_3$ (300 mol%) as the base, PdCl$_2$(dppf)$\cdot$CH$_2$Cl$_2$ (9 mol%) as the catalyst, and a THF / H$_2$O solvent system. These conditions have been reported by Molander and co-workers.\textsuperscript{227} The practical advantages offered by these conditions lie the use of Cs$_2$CO$_3$ as a solid and the avoidance of DMF as a solvent.

The advantages of the Suzuki cross-coupling reaction of olefinic aziridines are multifold. One should note that for many of examples of this reaction the organolithium or Grignard reagent that might be required to prepare the target aziridine from $N$-Ts-aziridine methanol \textsuperscript{2.159} would not be readily accessible. Such is the case with aziridines \textsuperscript{3.78a-g} in Scheme 3.20. Thus, this method is an excellent complement to the addition of an organometallic reagent to an aziridine as a route to substituted aziridines. Furthermore, the Suzuki coupling reaction requires the use of only slight excess of one of the coupling partners (i.e. 1.1 eq. of R-X with 1.0 eq. of olefin). In contrast, the allylsilane-organocuprate approach generally requires the generation of at least two equivalents of requisite organolithium or Grignard reagent to be reacted with one equivalent of aziridine \textsuperscript{2.159}. This can become a concern when the molecule you wish to use as an organometallic reagent is not commercially available and thus requires precious time and materials for synthesis of enough material to be reacted. It should be noted that there are a host of aryl and vinyl halides and triflates that are either commercially available or readily accessible to be used in the Suzuki protocol. Such is the case with the commercially available electrophiles seen in Scheme 3.20.

In addition to studying the Lewis acid-promoted intramolecular cyclizations of allylsilanes with aziridines, our group has shown recent interest in developing an olefin nucleophile variant. A
A representative example is shown in Scheme 3.21. The development of the Suzuki cross-coupling route has proven to be extremely valuable in the preparation of reactive substrates for this project.

Scheme 3.21: Intramolecular olefin-aziridine cyclization reaction.

3.2.3. Synthesis of chiral C-2 aziridine-allylsilanes

The beginning of this chapter stressed the desire to examine a series of aziridine-allylsilanes with C-2 connectivity (3.1), which differ only in the length of tether between the reacting moieties. Given the inherent success of the Suzuki strategy in the synthesis of racemic C-2 aziridine-allylsilane 3.1b and the potential to apply our methodology to natural product synthesis, logical progression favored using the Suzuki strategy for the preparation of optically pure aziridine-allylsilanes (R)-3.1a-c (Scheme 3.22).
Scheme 3.22: Retrosynthesis of chiral C-2 aziridine-allylsilanes via the Suzuki strategy.

The retrosynthesis of chiral C-2 aziridine-allylsilanes $\text{(R)}$-3.1a-c via the Suzuki strategy involves the coupling of (2-bromoallyl)trimethylsilane (3.70) with the appropriate chiral aziridine-olefin. For aziridine-allylsilanes $\text{(R)}$-3.1b and $\text{(R)}$-3.1c, the desired aziridine-olefins are 3.89 and 3.90 respectively. These could originate via opening of N-Ts-aziridine methanol 2.159a with either a vinyl- or allylcuprate reagent. The desired aziridine-olefin for aziridine-allylsilane $\text{(R)}$-3.1a would be 3.91. This molecule could arrive via appropriate transformation of aziridine-ester 3.92, which is a known compound derived from (S)-serine (2.161).55,173,229,230
Scheme 3.23: Synthesis of chiral C-2 aziridine-allylsilanes \((R)-3.1b\) and \((R)-3.1c\).

Chiral C-2 aziridine-allylsilanes \((R)-3.1b\) and \((R)-3.1c\) were readily prepared by the Suzuki strategy (Scheme 3.23).\(^{221}\) Serine-derived aziridine \(2.159a\)\(^{173}\) was treated with either vinylmagnesium bromide or allylmagnesium chloride in the presence of CuCN to provide a series of silyl ether homologs \((3.93\) and \(3.94\)) in good yield. The silyl protecting group of the homologs was removed with \(n\)-Bu\(_4\)NF and Mitsunobu ring closure provided olefinic aziridines \(3.89\) and \(3.90\)\(^{231}\) in excellent overall yield. Thus, the desired olefinic aziridines for the Suzuki coupling originated via the organocuprate / \(N\)-Ts-aziridine methanol method. Subsequent Suzuki cross-coupling under standard conditions with bromoallylsilane \(3.70\) provided optically-pure aziridine-allylsilanes \((R)-3.1b\) and \((R)-3.1c\) in 58% and 68% yield respectively.

Unfortunately, the Suzuki strategy towards chiral C-2 aziridine allylsilane \((R)-3.1a\) proved unsuccessful (Scheme 3.24).\(^{222}\) Aziridine ester \(3.92\) was prepared in 92% yield by the
Mitsunobu ring closure of methyl N-(4-methylphenyl)-\((S)\)-serinate (2.162) using Ph₃P (110 mol%) and DEAD (110 mol%) in THF at room temperature for 18 h. The ester was reduced to the aldehyde (3.97) by reaction with DIBAL-H. Wittig reaction of the aldehyde provided known vinyl aziridine 3.91 in 29% yield over two steps. The low yield for these two steps could be due to the instability of aldehyde 3.97 or attack of the Wittig reagent at the aziridine ring.64

Hydroboration of olefin 3.91 followed by Suzuki coupling conditions did not provide any of the desired product \((R)\)-3.1a. Examination of the crude NMR mixture showed no aziridine-containing products and suggests organoborane 3.98 might be unstable.

Scheme 3.24: Attempted synthesis of chiral C-2 aziridine-allylsilane \((R)\)-3.1a via Suzuki reaction.
The instability of organoborane 3.98 could potentially be related to the aza-Payne rearrangement of activated 2-aziridinemethanols under basic conditions (Scheme 3.25). The similarities of alkoxide-aziridine 3.100 to organoborane 3.98 suggest that the organoborane is unstable and could potentially undergo aziridine opening rather than Suzuki coupling.

Scheme 3.25: Comparison of organoborane 3.98 to the aza-Payne rearrangement of alkoxide-aziridines.

Given the lack of success using the Suzuki strategy, the synthesis of chiral C-2 aziridine-allylsilane 3.1a was envisioned using the allylsilane-organocuprate / N-Ts-aziridine methanol strategy. A retrosynthesis depicting this strategy is provided in Scheme 3.26. The strategy is highlighted by the use of organolithium 3.103 as a nucleophile to open aziridine
2.159a. The organocuprate variant\textsuperscript{234} of organolithium 3.103 has been reported via the known allylselenide 3.104.\textsuperscript{235}

\begin{center}
\begin{tikzpicture}
\node (R-3.1a) at (0,0) {\text{\(2.159a\)}};
\node (CuX) at (2.5,0) {\text{\(\text{CuX}\)}};
\node (TBSO) at (5,0) {\text{\(\text{TBSO}\)}};
\node (Me3Si) at (7.5,0) {\text{\(\text{Me}_3\text{Si}\)}};
\node (R-3.1a) at (0.25,1.5) {\text{\((R)-3.1a\)}};
\node (3.104) at (7.5,-1.5) {\text{3.104}};
\node (3.103) at (5,-1.5) {\text{3.103}};
\node (3.106) at (2.5,-3) {\text{3.106}};

\draw[->] (R-3.1a) -- (CuX);
\draw[->] (CuX) -- (TBSO);
\draw[->] (TBSO) -- (Me3Si);
\draw[->] (R-3.1a) -- node[above] {\text{\(\text{Me}_3\text{Si}\)}} (3.104);
\draw[->] (R-3.1a) -- node[above] {\text{\(\text{Me}_3\text{Si}\)}} (3.103);
\draw[->] (3.106) -- node[above] {\text{\(\text{Me}_3\text{Si}\)}} (3.104);
\end{tikzpicture}
\end{center}

Scheme 3.26: Retrosynthesis of chiral C-2 aziridine-allylsilane (\(R\))-3.1a via the allylsilane-organocuprate / N-Ts-aziridine methanol strategy.

Allylselenide 3.104 was prepared according to the reported method (Scheme 3.27).\textsuperscript{235}

2-(Hydroxymethyl)allytrimethylsilane (3.107) was prepared by silylation of 2-methyl-2-propen-1-ol dianion followed by hydrolysis of silyl ether 3.106.\textsuperscript{236} Alcohol 3.107 was mesylated according to the procedure reported by Clive and co-workers.\textsuperscript{237} Allylselenide 3.104 was synthesized in 90% distilled yield via treatment of mesylate 3.108 with MeSeLi (generated \textit{in situ} from MeLi and Se) in THF at 25°C.
The synthesis of chiral $C$-$2$ aziridine-allylsilane $(R)$-$3.1a$ was accomplished via nucleophilic attack of aziridine $2.159a$ (Scheme 3.28).$^{1,2,173}$ Allylselenide $3.104$ was subjected to Li-Se exchange$^{235}$ then transmetallated in the presence of CuCN$^{234}$ to generate higher-order cyanocuprate $3.109$. Reaction of aziridine $2.159a$ with the organometallic allylsilane reagent provided ring-opened product $3.110$ in $64\%$ yield. Deprotection with $n$-Bu$_4$NF followed by a Mitsunobu reaction formed the aziridine ring to give aziridine-allylsilane $(R)$-$3.1a$ in good overall yield.$^{221}$
3.3. Reactivity of C-2 aziridine-allylsilanes

With the desired C-2 aziridine-allylsilanes (3.1) in hand, racemic aziridine-allylsilane 3.1b was used as an initial test substrate to explore the cyclization reaction.

3.3.1. Cyclization of a racemic C-2 aziridine-allylsilane as a test substrate

Given the reactivity displayed by C-3 aziridine-allylsilanes (1.1) and the reaction conditions used to cyclize C-2 allylsilane epoxides (Section 3.1.1), racemic C-2 aziridine-allylsilane 3.1b was treated with 110 mol% of BF$_3$OEt$_2$ at −78°C for 4 hours then warmed to −25°C for an additional 15 hours (Scheme 3.29).
We were pleased to find these conditions provided racemic exocyclic $\gamma$-amino olefin 3.2b as the major product of the reaction in 86% yield\textsuperscript{221}. The cyclization proceeded in an identical manner to the C-3 aziridine-allylsilanes (1.1) with attack of the allylsilane at the internal carbon of the aziridine ring to produce the six-membered carbocycle. The desilylated azabicyclo[3.2.1]-system (3.4b, racemic) was also isolated in low yield (6%). With the gratifying results of this test reaction in hand, we turned to the chiral substrates to explore cyclization conditions to selectively yield exocyclic $\gamma$-amino olefins.

3.3.2. Cyclizations of chiral C-2 aziridine-allylsilanes

3.3.2.1. Synthesis of exocyclic $\gamma$-amino olefins

Treatment of aziridine-allylsilane ($R$)-3.1b with a stoichiometric amount of BF$_3$•OEt$_2$ at $-78^\circ$C followed by warming of the reaction to $-25^\circ$C provided exocyclic olefin ($R$)-3.2b in nearly quantitative yield (97%). Aziridine-allylsilane ($R$)-3.1c was cyclized in a similar manner though additional BF$_3$•OEt$_2$ (200 mol%) and higher temperatures (0°C) were needed for cyclization to the
seven-membered ring. Exocyclic olefin \((\text{R})\)-3.2c was achieved in moderate yield (51%) after purification. The other major product (ca. 35%) of the reaction appears to be the product of protodesilylation of \((\text{R})\)-3.1c and proved difficult to isolate cleanly (Scheme 3.30).221

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{H} & \quad (100 \text{ mol\%}) \\
\text{NTs} & \quad -78 \text{ to } -25^\circ \text{C}, \\
23 \text{ hrs.} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{H} & \quad (200 \text{ mol\%}) \\
\text{NTs} & \quad -78 \text{ to } 0^\circ \text{C}, \\
20 \text{ hrs.} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{Ts} \\
\text{H} & \quad \text{N} \\
\text{H} & \quad \text{proto-} \\
\text{desilylated} & \quad (\text{R})-3.1c, \\
\text{ca. 35\%} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{Ts} \\
\text{H} & \quad \text{NHTs} \\
\text{H} & \quad \text{NHTs} \\
\text{Ts} & \quad \text{proto-} \\
\text{desilylated} & \quad (\text{R})-3.1c, \\
\text{ca. 35\%} & \\
\end{align*}
\]

\[
\begin{align*}
(\text{R})-3.1b & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{H} & \quad (100 \text{ mol\%}) \\
-78 \text{ to } -25^\circ \text{C}, \\
23 \text{ hrs.} & \\
\text{NHTs} & \quad (\text{R})-3.2b \\
97\% & \\
\end{align*}
\]

\[
\begin{align*}
(\text{R})-3.1c & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{H} & \quad (200 \text{ mol\%}) \\
-78 \text{ to } 0^\circ \text{C}, \\
20 \text{ hrs.} & \\
\text{NHTs} & \quad (\text{R})-3.2c, 51\% \\
\end{align*}
\]

\[
\begin{align*}
(\text{R})-3.1c & \quad \text{BF}_3\cdot\text{OEt}_2 \\
\text{H} & \quad \text{proto-} \\
\text{desilylated} & \quad (\text{R})-3.1c, \\
\text{ca. 35\%} & \\
\end{align*}
\]

Scheme 3.30: Synthesis of exocyclic \(\gamma\)-amino olefins via intramolecular cyclization of chiral C-2 aziridine-allylsilanes.

In general, the C-2 aziridine-allylsilanes (3.1) appear to be more reactive when compared to C-3 aziridine-allylsilanes (1.1). As we saw in Chapter 1, typically 300 mol\% of BF\(_3\)·OEt\(_2\) and 0\(^\circ\)C reaction temperature was needed for cyclizations of C-3 aziridine-allylsilanes to their \(\gamma\)-amino olefin counterpart. Chiral C-2 aziridine-allylsilane \((\text{R})\)-3.1b required only stoichiometric amount of BF\(_3\)·OEt\(_2\) and lower reaction temperatures (-78 to -25\(^\circ\)C) for cyclization to exocyclic \(\gamma\)-amino olefin \((\text{R})\)-3.2b to occur in nearly quantitative yield. Furthermore, only two equivalents of Lewis acid
were needed for cyclization of aziridine-allylsilane (\textit{R})-3.1\textbf{c} to its exocyclic $\gamma$-amino olefin counterpart. These conditions are milder when compared to the cyclization conditions of C-3 aziridine-allylsilanes and suggest the C-2-connected substrates are more reactive.

One should note that due to the challenging nature of forming a seven-membered ring additional BF$_3$\textcdot OEt$_2$ (200 mol\%) and higher temperatures (0˚C) were needed for cyclization of aziridine-allylsilane (\textit{R})-3.1\textbf{c} to occur. Furthermore, this notion of ring-size of the target product could also dictate whether a protodesilylation pathway is competing with the cyclization pathway. Generally six-membered rings are easier to form than seven-membered rings. This potentially explains why protodesilylated starting material was seen in the cyclization of aziridine-allylsilane (\textit{R})-3.1\textbf{c} and not in the cyclization of (\textit{R})-3.1\textbf{b}. One should also note that protodesilylation of the starting aziridine-allylsilane was rarely seen in the cyclizations of C-3 substrates. However, this phenomenon was definitely noted in the cyclization of C-2 aziridine-allylsilane (\textit{R})-3.1\textbf{c}.

The formation of exocyclic $\gamma$-amino olefin (\textit{R})-3.2\textbf{b} via cyclization of chiral C-2 aziridine-allylsilane (\textit{R})-3.1\textbf{b} can be explained by the Sakurai reaction mechanism pictured in Scheme 3.31.
Scheme 3.31: Intramolecular Sakurai reaction of chiral C-2 aziridine-allylsilane (R)-3.1b

BF₃•OEt₂ initially coordinates to the aziridine nitrogen thereby activating the ring for nucleophilic attack by the π-bond of the allylsilane in an SN₂ manner. The result of this process is the generation of a stable tertiary β-silyl carbocation 3.113. This tertiary carbocation would be considered more stable than the secondary β-silyl carbocation seen in the intramolecular Sakurai reactions of C-3 aziridine-allylsilanes. The presence of a more stable tertiary β-silyl carbocation 3.113 could explain why the C-2 substrates are more reactive than the C-3 substrates, and why the presence of a small amount of desilylated azabicyclo[3.2.1]-product (3.4b, racemic) was noted in the cyclization of racemic aziridine-allylsilane 3.1b under colder temperatures and 110 mol% BF₃•OEt₂ reaction conditions. This desilylated azabicycle product could arise via trapping...
of the more stable and longer lasting cation with the inherent sulfonamide nucleophile followed by protodesilylation. However, in this reaction cation 3.113 undergoes elimination to give exocyclic olefin \((R)-3.2b\).

### 3.3.2.2. Synthesis of azabicyclo[x.2.1]-systems

Aziridine-allylsilanes \((R)-3.1b\) and \((R)-3.1c\) were cyclized with greater than stoichiometric amounts of BF\(_3\)•OEt\(_2\) (300 mol%) and warmed to room temperature in the hopes of forming azabicyclo[x.2.1]-systems (Scheme 3.32).

![Scheme 3.32: Synthesis of desilylated azabicyclo[x.2.1]-systems via intramolecular cyclization of chiral C-2 aziridine-allylsilanes.](image_url)
After subjecting substrate \((\text{R})\)-3.1b to these conditions, desilylated azabicyclo[3.2.1]octane \((1\text{R}, 5\text{S})\)-3.4b was isolated in good yield (77%) while approximately a 1 : 1 mixture of isomerized amino olefins was obtained in 15% yield. Treatment of aziridine-allylsilane \((\text{R})\)-3.1c in a similar manner gave an approximate 1 : 1 : 1 mixture of isomerized amino olefins as the major product (54% yield) while the desilylated azabicyclo[4.2.1]nonane \((1\text{R}, 6\text{S})\)-3.4c was achieved in only 31% yield. We hoped refluxing conditions could potentially drive the mixture of amino olefins towards bicycle \((1\text{R}, 6\text{S})\)-3.4c formation though minimal changes in yield were observed (51 and 37% for yields of isomerized amino olefins and \((1\text{R}, 6\text{S})\)-3.4c respectively). It remains unclear as to how these desilylated azabicyclo[x.2.1]-systems are being formed.221

3.3.2.2.1. Desilylated azabicycles resulting from intramolecular cyclizations of C-3 aziridine-allylsilanes

In addition to \(\gamma\)-amino olefins 1.2 and silylated azabicycles 1.3, desilylated azabicycles 1.4 can also result from the intramolecular cyclization of C-3 aziridine-allylsilanes 1.1. In general, these products could be seen when aziridine-allylsilanes 1.1 were treated with 300 mol% of BF$_3$•OEt$_2$ at temperatures ranging from 0˚C to room temperature.79 We have suggested two potential mechanisms for the formation of these products (Scheme 3.33). The first route involves the reaction of acid with \(\gamma\)-amino olefin 1.2 to generate intermediate 3.114, which can react with the inherent nitrogen nucleophile to form the ring-closed product 1.4. The second route involves protodesilylation of a silylated azabicycle 1.3 to desilylated azabicycle 1.4. With these thoughts in
mind, Dr. Susan Donaldson performed individual reaction studies to draw conclusions about the mechanisms of desilylated azabicycle formation.\footnote{79}

\begin{align*}
\textbf{1.2} & \quad \text{n} = 1, 2 \\
\textbf{3.114} & \quad \text{n} = 1, 2 \\
\textbf{1.4} & \quad \text{n} = 1, 2 \\
\textbf{1.3} & \quad \text{n} = 1, 2
\end{align*}

Scheme 3.33: Possible reaction mechanisms of desilylated azabicycle formation resulting from the intramolecular cyclizations of C-3 aziridine-allylsilanes.

In order to show that azabicycles could arise from $\gamma$-amino olefins, compound \textbf{1.92b} was treated with 300 mol\% of BF$_3$•OEt$_2$ at 0°C for one hour then warmed to room temperature overnight. The crude reaction mixture was analyzed by GC and showed the presence of desilylated azabicycle \textbf{3.115} and unreacted olefin \textbf{1.92b} in a ratio of 3 : 1 \footnote{79} (Scheme 3.34).

Additionally, desilylated azabicycles can form as the major product directly from C-3 aziridine-allylsilanes given the appropriate reaction conditions. As an example, cyclization of aziridine-allylsilane ($\textit{R}$)-\textbf{1.80b} using 300 mol\% BF$_3$•OEt$_2$ at refluxing conditions provided desilylated azabicycle \textbf{3.116} as the major product in good yield (79\%) \footnote{79} (Scheme 3.35).
Scheme 3.34: Conversion of a \( \gamma \)-amino olefin into a desilylated azabicycle using \( BF_3 \cdot OEt_2 \).

Finally, desilylated azabicycles could potentially arise via protodesilylation of a silylated azabicycle. In order to confirm this reaction mechanism, silylated bicycle 3.117 was treated with 300 mol% of \( BF_3 \cdot OEt_2 \) at 0°C for 1 hour then warmed to room temperature overnight (Scheme
3.36. GC and NMR analysis of the crude reaction mixture showed the presence of olefin 1.92c and desilylated azabicycle 3.118, thus confirming the protodesilylation pathway.79

Scheme 3.36: Protodesilylation of a silylated azabicycle to a desilylated azabicycle.

3.3.2.2.2. Potential reaction mechanisms for the formation of desilylated azabicyclo[3.2.1]-systems

Considering the results of the reactions Dr. Donaldson performed regarding potential mechanisms of desilylated azabicycle formation, three possible mechanisms (A – C) can be suggested for the formation of desilylated azabicyclo[3.2.1]-systems (3.4) (Scheme 3.37).
Scheme 3.37: Possible pathways for the formation of desilylated azabicyclo[x.2.1]- systems.

Pathway A is highlighted by cyclization of aziridine-allylsilane 3.1 to silylated azabicycle 3.3 followed by protodesilylation to desilylated azabicyclo[x.2.1]-system 3.4. Pathway B illustrates initial protodesilylation of aziridine-allylsilane 3.1 to the corresponding aziridine-olefin followed by cyclization to desilylated azabicyclo[x.2.1]-system 3.4. This pathway could support the formation of isomerized γ-amino olefins 3.2 seen under the requisite cyclization conditions since there is no longer any –SiMe₃ group present to direct the elimination step. We have shown pathway B to be a viable pathway in the formation of desilylated azabicycles because...
protodesilylated \((R)-3.1b\) (i.e. olefin \((R)-3.1b\)) can be cyclized to azabicyclo[3.2.1]octane \(1R, 5S\)-3.4b (71% yield) using 300 mol\% of BF\(_3\)-OEt\(_2\) at room temperature.\(^{228}\) Finally, pathway C shows initial cyclization of the aziridine-allylsilane to \(\gamma\)-amino olefin 3.2 (either exocyclic or isomerized) followed by cyclization to desilylated azabicyclo[x.2.1]-system 3.4. Considering the apparent ease with which the trimethylsilyl group tends to undergo protodesilylation in C-2 substrates, we suggest pathways B or C are the most likely contributing pathways to desilylated azabicyclo[x.2.1]-system formation.

### 3.3.2.3. The notable behavior of chiral C-2 aziridine-allylsilane 3.1a

Cyclizations of aziridine-allylsilanes \((R)-3.1b\) and \((R)-3.1c\) proceeded with attack of the allylsilane at the internal carbon of the aziridine ring, which is consistent with the intramolecular cyclizations of C-3 aziridine-allylsilanes. However, chiral C-2 aziridine-allylsilane \((R)-3.1a\) provided an alternative cyclization behavior (Scheme 3.38).\(^{221}\)

![Scheme 3.38: The notable behavior of chiral C-2 aziridine-allylsilane \((R)-3.1a\).](image-url)
Treatment of chiral C-2 aziridine-allylsilane \((R)-3.1a\) with 200 mol% of BF\(_3\)·OEt\(_2\) and warming to 0°C gave six-membered ring 3.119 as the major product (50% yield). Products resulting from the attack of the internal carbon of the aziridine (i.e. \((R)-3.2a\)) were not observed, only those resulting from attack of the terminal position. Therefore, aziridine-allylsilane \((R)-3.1a\) displays comparable reactivity to allylsilane-epoxides possessing identical tether length and C-2 connectivity (see Section 3.1.2). Additionally, protodesilylation of \((R)-3.1a\) was detected by \(^1\)H NMR though purification of this product (ca. 37%) again proved troublesome.

3.3.2.4. Application of intramolecular chiral C-2 aziridine-allylsilane methodology to the synthesis of an azabicyclo[3.3.1]nonane

In an effort to extend the synthesis of azabicyclo[x.y.1]-systems, exocyclic \(\gamma\)-amino-olefin \((R)-3.2b\) was subjected to a hydroboration-oxidation sequence to provide a mixture of cis \((3.120a)\) and trans \((3.120b)\) amino alcohols.\(^{221}\) The mixture of alcohols was then cyclized under Mitsunobu conditions to provide azabicyclo-[3.3.1]nonane 3.24 resulting from closure of the cis amino alcohol 3.120a. When olefin \((R)-3.2b\) was hydroborated with 9-BBN, \(^1\)H NMR of the crude reaction mixture showed a 1 : 1 mixture of cis and trans amino alcohols. Subsequent Mitsunobu ring closure provided azabicycle 3.24 in 51% yield from olefin \((R)-3.2b\). However, when BH\(_3\)·THF was used in the hydroboration a 1 : 2 mixture of cis and trans amino alcohols was observed, thus providing only 30% yield of 3.24 after the Mitsunobu reaction. Therefore, chiral C-2 aziridine-
allylsilane \((R)-3.1b\) proved to be a valuable intermediate towards azabicyclo[3.2.1] and [3.3.1]-systems (Scheme 3.39).

![Scheme 3.39: Synthesis of an azabicyclo[3.3.1]nonane from \(\gamma\)-amino olefin \((R)-3.2b\).]

3.4. Chapter summary

This chapter describes the synthesis and intramolecular cyclizations of \(C\)-2 aziridine-allylsilanes. Due to an initial failure in the allylsilane-organocuprate / \(N\)Ts-aziridine methanol approach, a new converse strategy for the synthesis of \(C\)-2 aziridine-allylsilanes was developed. The coupling of a nucleophilic aziridine with an electrophilic allylsilane highlights the converse strategy of \(C\)-2 aziridine-allylsilane synthesis. The Suzuki cross-coupling reaction of olefinic aziridines is not only an effective route for the synthesis of \(C\)-2 aziridine-allylsilanes, but for other
substituted aziridines as well. This represents the first example of a palladium coupling reaction applied to an aziridine-containing molecule and proves complementary to other methods of aziridine synthesis utilizing organocuprate reagents.

The chapter also shows that connection of C-2 of an allylsilane to a tethered aziridine ring yields exocyclic $\gamma$-amino olefins and desilylated azabicyclo[x.2.1]-systems upon cyclization with BF$_3$•OEt$_2$. Furthermore, manipulation of a specific exocyclic $\gamma$-amino olefin provided access to an azabicyclo[3.3.1]nonane. This methodology should be useful for the preparation of natural products and pharmacologically active agents containing these bicyclic heterocyclic systems.
CHAPTER 4

SYNTHESIS AND REACTIVITY OF A TETHER-SUBSTITUTED C-3 AZIRIDINE-ALLYLSILANE: STUDIES TOWARD THE SYNTHESIS OF (+)-α-SKYTANTHINE

4.1. Introduction

We saw in Chapter 1 that treatment of racemic C-3 aziridine-allylsilane 1.80a with 300 mol% of BF₃•OEt₂ at 0°C for 4 hours gave a mixture of cis 1.81a and trans 1.81b γ-amino olefins in good yield (84%) (Scheme 4.1). While the yield for this reaction would be considered desirable, the diastereoselectivity would be considered moderate at best with formation of the cis isomer 1.81a slightly favored over the trans isomer 1.81b in a ratio of 2.6 : 1. As a result, one of the goals of our lab has always been to improve the diastereoselectivity of intramolecular C-3 aziridine-allylsilane cyclizations.

We hypothesized in Chapter 1 that C-3 aziridine-allylsilanes react intramolecularly via chair-like conformations to produce the stereochemistry observed in the products. We also suggested that biasing the population of reactive conformations could potentially reflect a change in the diastereoselectivity of the cyclization. Since the populations of reactive conformations of C-3 aziridine-allylsilanes are mainly governed by steric considerations, manipulation of variables that can affect the steric of the reaction system could potentially reflect a change in the formation of one diastereomer over another. To this end, we previously examined a series of C-3 aziridine-
allylsilanes containing different nitrogen activating groups on the aziridine ring (see Section 1.4.1.4). Unfortunately, none of the derivatives examined produced better diastereoselectivity when compared to the tosylated aziridine substrate. However, there are other variables of the reaction system one could change to potentially reflect an improvement in diastereoselectivity.

Although changing the substitution pattern of the aziridine nitrogen did not improve the diastereoselectivity of the reaction, perhaps substituting the tether connecting the two reactive moieties could inflect a positive change in diastereoselectivity. A generalized example of this strategy is shown in Scheme 4.1. Substituting the tether with an R group could bias the population distribution of reactive conformations of substrate 4.1, the result of which could be a potential change in the diastereoselectivity of products 4.2 formed upon cyclization.

Scheme 4.1: The notion of a tether-substituted aziridine-allylsilane.
4.1.1. The search for a target aziridine-allylsilane

Given our desire to study a tether-substituted C-3 aziridine-allylsilane (i.e. 4.1), the next questions become what type of group to do we want to place on the tether and where do we want the substitution to occur. Considering these questions at hand, the possibilities of a target aziridine-allylsilane to study the tether-substituted problem seem endless. However, given the tandem goal of trying to apply intramolecular aziridine-allylsilane methodology to the total synthesis of natural products, the search for a target aziridine-allylsilane can be greatly reduced.

The 3-azabicyclo[4.3.0]nonane framework is inherent to a number of alkaloids. Representative examples can be found in Scheme 4.2. Previous reports indicate that extracts of the common Latin American bush *Tecoma stans* have been employed as hypoglycemics in folk medicine.\(^{238-241}\) This activity was accredited to the alkaloid tecomanine (4.7).\(^{242}\) Corresponding saturated terpene alkaloids 4.3 – 4.6 have also been reported from plants of the genus *Skytanthus* and other *Tecoma* species.\(^{243-249}\) These alkaloids are reported to have varied biological activity.\(^{250,251}\) Furthermore, altemicydin (4.8) has been isolated and reported to have acaricidal and antitumor activities,\(^{252}\) while delavayine A (4.9) is an antinociceptive substance stemming from the extracts of *Incarvillea delavayi*.\(^{253}\)
Scheme 4.2: Natural products containing a 3-azabicyclo[4.3.0]nonane framework.

A few of these compounds have been synthesized as homochiral entities. Tsunoda and co-workers reported the dehydrocyclization of an amino alcohol as a key step in their stereoselective synthesis of (+)-α-skytanthine (\((+)-4.3\))<sup>254</sup> while a common intermediate derived via a ketene aza-Claisen rearrangement was used by Pombo-Villar et al. to synthesize (-)-α-skytanthine (\((-)-4.3\)) and (-)-N-demethyl-δ-skytanthine (\((-)-4.6\) containing a –NH rather than a –NMe).<sup>255</sup> Marini-Betolo and collaborators established the absolute configurations of (+)-α-skytanthine (\((+)-4.3\)) and (+)-δ-skytanthine (\((+)-4.6\)) via preparation from iridomyrmecin, nepetalic acid, and nepetalinic acid,<sup>256,257</sup> while Oppolzer and Jacobsen reported the enantioselective syntheses of these alkaloids by an intramolecular magnesium-ene reaction.<sup>258</sup> Finally,
Kametani et al. have reported a facile synthesis of (+)-tecomanine ((+)-4.7) using a chiral cyclopentane derivative.259

Skytanthoids 4.3 – 4.6 appear to be the simplest examples provided in Scheme 4.2. A 3-azabicyclo[4.3.0]nonane framework with methyl groups at positions three, five, and nine highlights the key structural features of these alkaloids. Given the goals of applying our methodology to the synthesis of natural products and studying the cyclization of a tether-substituted C-3 aziridine-allylsilane (i.e. 4.1), (+)-α-skytanthine ((+)-4.3) appears to be a justifiable target given an appropriate retrosynthesis. Such a synthesis is proposed in Scheme 4.3.

\[\text{NMe} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{4.1} \]
\[\text{OH} \quad \text{NHTs} \quad \text{H} \quad \text{H} \quad \text{4.10} \]
\[\text{SiMe}^3 \quad \text{NTsH} \quad \text{5} \quad \text{5} \quad \text{9} \quad \text{9} \quad \text{4.11a} \]

Scheme 4.3: Retrosynthesis of (+)-α-skytanthine via a tether-substituted C-3 aziridine-allylsilane.

(+)-α-Skytanthine ((+)-4.3) could potentially be made by Mitsunobu ring closure of amino alcohol 4.10 followed by tosyl removal and methylation of the nitrogen. Alcohol 4.10 could stem via a hydroboration-oxidation sequence of olefin 4.11a. However, one should note that an appropriate hydroboration protocol would be needed to set the stereochemistry of the methyl group at position five. Finally, γ-amino olefin 4.11a could originate via an intramolecular Sakurai
reaction of tether-substituted C-3 aziridine-allylsilane 4.12a. The cyclization of this aziridine-allylsilane could proceed through the reactive chair-like conformations pictured in Scheme 4.4.

Scheme 4.4: Reactive conformations of tether-substituted C-3 aziridine-allylsilane 4.12a.

Cyclization of aziridine-allylsilane 4.12a in conformation A or B could proceed to give carbocycle 4.11a with protons Hₐ and Hₕ oriented cis to each other, while cyclization of conformation C or D could proceed to give carbocycle 4.11b with protons Hₐ and Hₕ oriented trans. Upon closer examination of these suggested reactive conformations, conformation A
appears to be the most energetically favorable. This conformation depicts the allylsilane, aziridine, and C-9 methyl group all oriented equatorially. Recall that synclinal transition states (allylsilane equatorial) are preferred over antiperiplanar transition states (allylsilane axial) in the intramolecular reactions of allylsilanes. A possible explanation for this preference could be the unfavorable $A^{(1,3)}$ interaction between the allylic protons of the allylsilane and the axial hydrogen of the forming ring when the allylsilane is in an axial orientation. Conformation B precludes any product formation due to the steric interactions present when the allylsilane, aziridine, and C-9 methyl group are all oriented axially. Conformations C and D have either the allylsilane or aziridine oriented equatorially. However, the steric interactions present in these conformations make them less favorable when compared to conformation A.

One should note the methyl group in position nine and its preferred orientation. The A value for a methyl group on a cyclohexane ring is 1.74 kcal/mole higher when compared to a hydrogen. Therefore, there is slight preference for the C-9 methyl group to be oriented equatorially. To conclude, considering the reactive chair-like conformations and steric issues presented, conformation A could potentially dominate the population of reactive conformations of aziridine-allylsilane 4.12a and consequently favor formation of cis olefin 4.11a upon cyclization. With these thoughts in mind, approaches to the synthesis of tether-substituted C-3 aziridine-allylsilane 4.12a were initiated.
4.2. Synthesis of a tether-substituted C-3 aziridine-allylsilane with potential application to (+)-α-skytanthine synthesis

4.2.1. Attempted synthesis of target aziridine-allylsilane 4.12a via the allylsilane-organocuprate / N-Ts-aziridine methanol approach

The chiral variant of C-3 aziridine-allylsilane 1.80a (i.e. (R)-1.80a) has been prepared via the allylsilane-organocuprate / N-Ts-aziridine methanol strategy described in Section 2.4.3 (Scheme 4.5). Aziridine-allylsilane 4.12a differs from chiral substrate (R)-1.80a only in the substitution of methyl groups at positions five and nine. Given the inherent success of the allylsilane-organocuprate / N-Ts-aziridine-methanol strategy in the synthesis of (R)-1.80a, a retrosynthesis of tether-substituted aziridine-allylsilane 4.12a can be suggested based on this strategy with only slight modifications to both the aziridine and allylsilane partners (Scheme 4.5).
Scheme 4.5: Retrosynthesis of tether-substituted aziridine-allylsilane 4.12a via the allylsilane-organocuprate / N-Ts-aziridine methanol strategy.

The appropriate coupling partners for the synthesis of tether-substituted C-3 aziridine-allylsilane 4.12a via the allylsilane-organocuprate / N-Ts-aziridine methanol strategy would be organocuprate 4.13 and aziridine 4.14. The synthesis of allylsilane-organocuprate reagent 2.160a (R = Me) stemmed from lithium-halogen exchange of the corresponding allylsilane-iodide followed by transmetalation in the presence of copper. The iodide in turn originated via appropriate transformation of the allylsilane-alcohol, which was the product of a nickel-catalyzed \( \text{Me}_3\text{SiCH}_2\text{MgCl} \)-opening of dihydrofuran. In order to synthesize cuprate 4.13 via this protocol, the key pieces needed would be iodide 4.16, alcohol 4.17, and dihydrofuran 4.18. We also saw that
commercially available amino acids serve as common precursors to aziridines such as the case of aziridine 2.159a stemming from (S)-serine. The appropriate amino acid for the synthesis of aziridine 4.14 would be D-allo-threonine (4.15) and it should be noted that the transformation of this amino acid into aziridine 4.14 has been previously reported.\textsuperscript{261} However, there are no examples in the literature of aziridine 4.14 being opened by an organocuprate reagent. Therefore, in order to determine whether the allylsilane-organocuprate / N-Ts-aziridine methanol strategy could be applied to the synthesis of aziridine-allylsilane 4.12a, an initial series of ring-opening reactions were performed using an aziridine related to 4.14 and simple organocuprate reagents.

4.2.1.1. Attempted ring opening of a threonine-derived aziridine with simple organocuprates

D-allo-threonine (4.15) is a commercially available substance, but is rather expensive. In order to alleviate this problem, an aziridine related to 4.14 (i.e. 4.23) was prepared in a manner similar to the reported\textsuperscript{261} method of Fujii et al. starting from commercially available and inexpensive DL-threonine (DL-4.19) (Scheme 4.6).
Amino acid DL-4.19 was esterified and tosylated to provide diprotected amino acid 4.20 in 65% yield over two steps. LiBH₄ reduction of the methyl ester followed by protection of the primary hydroxyl group as the tert-butyldimethylsilyl ether provided amino alcohol 4.22 in good overall yield. A final Mitsunobu reaction provided aziridine 4.23 in 89% yield. With this aziridine in hand, its behavior in the presence of simple organocuprate reagents was examined (Scheme 4.7).
Scheme 4.7: Attempted opening of threonine-derived aziridine 4.23 with simple organocuprates.

Treatment of aziridine 4.23 using either copper-catalyzed Grignard or Lewis acid organocuprate reaction conditions resulted only in the recovery of starting aziridine. No ring-opened products were noted in these reactions. However, ring opening was achieved with the use of Gillman cuprates derived from commercially available n-butyllithium. Treatment of aziridine 4.23 with one equivalent of n-Bu$_2$LiCu gave ring-opened product 4.24 in 24% yield while the use of five equivalents of this reagent showed slight improvement (50% yield). However, given the results presented in Scheme 4.7, one can conclude that aziridine 4.23 proves difficult to open even with readily available organocuprate reagents. The only semi-successful reaction...
involved the use of five equivalents of Gillman cuprate reagent. This would mean that at least ten equivalents of allylsilane-iodide 4.16 would be needed to generate five equivalents organocuprate reagent 4.13, and provide only 50% yield of aziridine-opened product upon reaction. This seems highly inadequate since allylsilane-iodide 4.16 is not readily available and must be synthesized. Therefore, the results of these test reactions suggest that the allylsilane-organocuprate / N-Ts-aziridine methanol strategy would not be an efficient method for the synthesis of tether-substituted C-3 aziridine-allylsilane 4.12a. As a result, we turned our attention towards the synthesis of a C-3 tether-substituted aziridine-allylsilane via the Suzuki cross-coupling approach discussed previously in Chapter 3.

4.2.2. The Suzuki cross-coupling approach to a tether-substituted C-3 aziridine-allylsilane

We noted in Chapter 3 that the Suzuki cross-coupling route to substituted aziridines is an excellent complement to other methods of aziridine synthesis utilizing organocuprate reagents. With this thought in mind, a new retrosynthesis of a tether-substituted C-3 aziridine-allylsilane was envisioned via the Suzuki strategy (Scheme 4.8).
Scheme 4.8: Retrosynthesis of a tether-substituted C-3 aziridine-allylsilane via the Suzuki cross-coupling strategy.

Tether-substituted C-3 aziridine-allylsilane 4.12b could potentially be made via Suzuki cross-coupling of organoborane 4.25 with vinyl iodide 4.26. It should be noted that Negishi and co-workers have previously reported the preparation of iodide 4.26. Organoborane 4.25 could stem from hydroboration of aziridine-olefin 4.27, which could arrive via appropriate transformation of known amino acid derivative 4.28.

One should note that Scheme 4.8 highlights the potential retrosynthesis of aziridine-allylsilane 4.12b, which contains a trans allylsilane rather than the cis allylsilane seen in substrate 4.12a. However, both of these aziridine-allylsilanes (i.e. 4.12a or 4.12b) could potentially give γ-amino 4.11a upon cyclization in the Sakurai reaction mode. With this thought in mind and the availability of iodide 4.26 via reported methods, a retrosynthesis for aziridine-allylsilane 4.12b via
the Suzuki cross-coupling strategy has been suggested rather than a retrosynthesis for 4.12a via
the same strategy.

Given that aziridine-allylsilane 4.12b contains a new reaction variable (i.e. *trans*
allylsilane orientation) that our group has yet to encounter, new reactive conformations can be
drawn and examined (Scheme 4.9).

![Diagram showing reactive conformations of tether-substituted C-3 aziridine-allylsilane 4.12b.]

Scheme 4.9: Reactive conformations of tether-substituted C-3 aziridine-allylsilane 4.12b.
The reactive chair-like conformations drawn in Scheme 4.9 differ from those in Scheme 4.4 in that these conformations show a \textit{trans}-substituted allylsilane rather a \textit{cis}-substituted substrate. However, similar predictions can be made to those previously discussed because the arrangement of the key moieties (i.e. the allylsilane, the aziridine ring, and the C-9 methyl group) is comparable amongst the schemes. Cyclization of aziridine-allylsilane 4.12b in conformation A or B could proceed to give carbocycle 4.11a with protons H\textsubscript{a} and H\textsubscript{b} oriented on the same side (i.e. \textit{cis}), while cyclization of conformation C or D could proceed to give carbocycle 4.11b with protons H\textsubscript{a} and H\textsubscript{b} oriented \textit{trans} to each other. Once again, conformation A appears to be the most favorable due to arrangement of the allylsilane, aziridine, and C-9 all oriented equatorially.

With these thoughts in mind, the synthesis of tether-substituted C-3 aziridine-allylsilane 4.12b was initiated via the Suzuki strategy.

4.2.2.1. Synthesis of tether-substituted C-3 aziridine-allylsilane 4.12b via the Suzuki strategy

Initial synthetic efforts went towards the synthesis of known amino acid 4.28 (Scheme 4.10).\textsuperscript{262,263} The amino group of glycine (4.29) was protected as the trifluoroacetamide using ethyl trifluoroacetate according to the procedure reported by Curphey.\textsuperscript{264} Subsequent coupling of commercially available crotly alcohol to the free acid using DCC gave ester 4.30 in 82\% yield from glycine. Since the crotly alcohol that is commercially available from Aldrich Chemical Co. comes as a mixture of isomers, it was determined via \textsuperscript{1}H NMR that the \textit{E} : \textit{Z} ratio for ester 4.30 was approximately 20 : 1. Crotly ester 4.30 was then subjected to an asymmetric chelate-Claisen
rearrangement in the presence of the chinchona alkaloid quinine to give rise to the γ,δ-
unsaturated amino acid 4.28 in a highly diastereoselective fashion.263

\[ \text{H}_2\text{N} \text{CO}_2\text{H} \]

\[ \text{C}_2\text{H}_5\text{CO}_2\text{Et} \]

\[ \text{crotyl alcohol,} \]

\[ \text{DCC} \]

\[ \text{TfaHN CO}_2\text{H} \]

\[ \text{4.29} \]

\[ \text{82\% (two steps),} \]

\[ \text{ca. 20 : 1 (E : Z)} \]

\[ \text{TfaHN CO}_2\text{H} \]

\[ \text{4.30} \]

\[ \text{LHMDS} \]

\[ \text{Mg(OEt)}_2 \]

\[ \text{quinine} \]

\[ \text{TfaHN CO}_2\text{H} \]

\[ \text{4.31} \]

\[ \text{TfaHN CO}_2\text{H} \]

\[ \text{4.32} \]

\[ \text{TfaHN CO}_2\text{H} \]

\[ \text{4.28} \]

\[ \text{81\% crude} \]

\[ \text{crystallize with} \]

\[ \text{(S)-phenethylamine (PEA)} \]

\[ \text{4.32} \]

\[ \text{34\%,} \]

\[ >99\% \text{ ee} \]

Scheme 4.10: Synthesis of amino acid 4.28 via an asymmetric chelate-Claisen

rearrangement.

The formation of the \textit{syn}-product 4.28 stems from the \textit{E}-configured ester due to preferential rearrangement in a chair-like transition state\textsuperscript{265} while the corresponding \textit{anti}-product can arise via the \textit{Z}-isomer.\textsuperscript{266} The use of the chiral ligand quinine has been shown to improve the diastereomeric purity of the reaction.\textsuperscript{267,268} The enantiomeric purity of amino acid derivative 4.28 was increased by crystallization of diastereomeric salt 4.32 using (S)-
phenethylamine. One should note that the yield for this step was rather poor (34%) when compared previous literature reports.\textsuperscript{262,263}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {TfaHN CO\textsubscript{2}H-PEA \textbf{4.32}};
  \node (B) at (2,0) {TfaHN CO\textsubscript{2}H \textbf{4.28}};
  \node (C) at (2,0.5) {1) K\textsubscript{2}CO\textsubscript{3}, MeOH, H\textsubscript{2}O \rightarrow \textbf{4.28}};
  \node (D) at (4,0) {MeOH, HCl \rightarrow TshN CO\textsubscript{2}Me \textbf{4.33}, 82\% from \textbf{4.28}};
  \node (E) at (4,0.5) {3) TsCl \rightarrow \textbf{4.33}};
  \node (F) at (6,0) {MeOH, HCl \rightarrow \textbf{4.28}};
  \node (G) at (6,0.5) {2) MeOH, HCl \rightarrow \textbf{4.33}};
  \node (H) at (8,0) {LiAlH\textsubscript{4}};
  \node (I) at (8,0.5) {\textbf{4.27}, 86\% \rightarrow Ph\textsubscript{3}P DIAD \rightarrow \textbf{4.34}, 92\%};
  \node (J) at (6,1) {\textbf{4.34}};
  \node (K) at (4,1) {TsN HNTs}.
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.11}: Synthesis of aziridine-olefin \textbf{4.27}.

Amino acid \textbf{4.28} was subsequently transformed into the desired aziridine-olefin \textbf{4.27} (Scheme 4.11). Initial removal of the trifluoroacetamide group from \textbf{4.28} under basic hydrolysis conditions followed by esterification and tosylation provided diprotected amino acid \textbf{4.33} in 82\% yield over three steps. The ester was reduced to the alcohol in good yield (92\%) using LiAlH\textsubscript{4}. Subsequent Mitsunobu ring closure provided the aziridine \textbf{4.27} in 86\% yield.
With the olefin partner in hand, we turned our attention towards the synthesis of the allylsilane coupling partner 4.26 (Scheme 4.12). Vinyl iodide 4.26 was prepared according to the procedure reported by Negishi and co-workers. Zirconium-catalyzed carboalumination of propargyltrimethylsilane (2.79) followed by iodinolysis gave (E)-1-ido-2-methyl-3-trimethylsilylpropene (4.26) in 40% yield.


With both coupling partners in hand, the Suzuki cross-coupling reaction was initiated (Scheme 4.13). The hydroboration of aziridine-olefin 4.27 was allowed to proceed for 3.5 hours at room temperature using 110 mol% of 9-BBN. Subsequent Suzuki coupling of the organoborane in the presence of Cs2CO3 (300 mol%), PdCl2(dppf)-CH2Cl2 (9 mol%), and iodide 4.26 (110 mol%) in a THF / H2O solvent system provided target aziridine-allylsilane 4.12b in 48% yield after chromatography.
4.2.2.1.1. Determination of optical purity of synthetic intermediates via chiral HPLC

In order to determine the optical purity of ester 4.33, alcohol 4.34, and aziridine-olefin 4.27, the corresponding enantiomers of these compounds were synthesized and chiral HPLC analysis was performed. The enantiomers (4.36 – 4.38) were synthesized in an analogous way to the reactions presented in Schemes 4.10 and 4.11. However, a subtle change in the Claisen rearrangement must be noted (Scheme 4.14).
Amino acid 4.35 is also a known compound that stems from the asymmetric chelate-Claisen rearrangement of crotyl ester 4.30. This time the rearrangement was performed in the presence of $\text{Al(Oi-Pr}_3\text{)}$ as the metal chelate and quinidine as the chiral additive to give the $S$-configured amino acid 4.35 in 54% crude yield. One should note that this amino acid was not subjected to crystallization and was taken on crude to the subsequent steps of the synthesis.

Removal of the trifluoroacetamide group from crude amino acid 4.35 followed by esterification and tosylation provided diprotected amino acid 4.36 in 62% yield over three steps. The ester was reduced to the alcohol in good yield (89%) using $\text{LiAlH}_4$. Subsequent Mitsunobu ring closure provided aziridine 4.38 in 94% yield.
With both enantiomers in hand, chiral HPLC analysis was initiated. Chiral HPLC was performed using a \( (R, R) \)-WHELK-O1 5/100 HPLC column (250 mm X 4.6 mm, particle size 5 \( \mu \)m) purchased from Regis Technologies. HPLC runs were performed using %10 EtOH in hexanes at a flow rate of 1.5 mL / minute. Three HPLC runs were performed for each set of enantiomers (i.e. enantiomeric esters 4.33 and 4.36, enantiomeric alcohols 4.34 and 4.37, and enantiomeric aziridines 4.27 and 4.38). The first HPLC run involved analysis of a prepared racemic mixture (i.e. ca. 1 : 1 mixture of each enantiomer) to confirm separation conditions. The second HPLC run involved analysis of the enantiomer derived from the quinidine / non-crystallized series (i.e. compounds 4.36 – 4.38). Finally, the third HPLC run involved analysis of the enantiomer derived from the quinine / crystallized series (i.e. ester 4.33, alcohol 4.34, and aziridine-olefin 4.27). We were pleased to find that the optical purity of each of the compounds derived from the quinine / crystallized series was >98% ee. All HPLC traces discussed in this section may be found at the end of the experimental section (Chapter 5).

4.2.2.2. Synthesis of a control C-3 aziridine-allylsilane containing no tether-substitution

In order to study the effect of the methyl substituent on the tether in the cyclization reaction, a control C-3 aziridine-allylsilane containing no tether-substitution and the same allylsilane moiety seen in 4.12b was synthesized (Scheme 4.15).
Scheme 4.15: Synthesis of a control C-3 aziridine-allylsilane containing no tether-substitution.

The hydroboration of aziridine-olefin 3.89 was allowed to proceed for 3 hours at room temperature using 110 mol% of 9-BBN. Subsequent Suzuki coupling of the organoborane in the presence of Cs₂CO₃ (300 mol%), PdCl₂(dppf)•CH₂Cl₂ (9 mol%), and iodide 4.26 (110 mol%) in a THF / H₂O solvent system provided control aziridine-allylsilane 4.39 in 66% yield after chromatography.

4.3. Cyclizations of a tether-substituted C-3 aziridine-allylsilane with potential application to (+)-α-skytanthine synthesis

With control C-3 aziridine-allylsilane 4.39 and tether-substituted C-3 aziridine-allylsilane 4.12b in hand, intramolecular cyclization studies in the presence of BF₃•OEt₂ were initiated. The control substrate 4.39 was initially examined to determine whether this trans-allylsilane C-5-substituted substrate would behave in a similar manner to cis aziridine-allylsilane 1.80 (Scheme 4.16).
Scheme 4.16: Cyclization of control C-3 aziridine-allylsilane 4.39 with 100 mol% of BF$_3$•OEt$_2$.

Aziridine-allylsilane 4.39 was treated with 100 mol% of BF$_3$•OEt$_2$ at –78°C then warmed to 0°C for an additional 17.5 hours. After work-up and chromatography, two products were isolated. The major product of the reaction was the formation of an inseparable mixture of cis and trans γ-amino olefins 4.40 in 59% yield. The apparent ratio of diastereomers was 1.5 : 1 (cis : trans) based on $^1$H NMR integration values for the sulfonamide protons. The other product of the reaction that was isolated was cis-fused silylated azabicycle 4.41 in 19% yield. It should be noted that silylated azabicycle 4.41 can be converted to γ-amino olefin 4.40 using fluoride ion.$^{25}$ Therefore, the true diastereomeric ratio for the cyclization of aziridine-allylsilane 4.39 is 2.3 : 1 (cis : trans), which proves comparable to the cyclization results for substrate 1.80a (i.e. 2.6 : 1 cis : trans). However, we were happy to see that the cyclization of 4.39 proceeds in an identical manner to 1.80a with attack of the allylsilane at the internal carbon of the aziridine ring to give the corresponding five-membered carbocycle in good yield. The sulfonamide protons in olefin 4.40
can be seen as two distinct triplets when C\textsubscript{6}D\textsubscript{6} is used as the NMR solvent. It should be noted that the use of CDCl\textsubscript{3} as a NMR solvent for determining the ratio of cyclization products is not recommended due to the inability of peaks to distinctly separate. However, the use C\textsubscript{6}D\textsubscript{6} can help alleviate this problem somewhat. Furthermore, attempting to discern diastereomeric ratios of cis to trans \(\gamma\)-amino olefin cyclization products by HPLC has been\textsuperscript{171} and continues to be, problematic due to the lack of good separation. Potential reaction mechanisms for the formation of these products are shown in Scheme 4.17.

Initial coordination of BF\textsubscript{3}•OEt\textsubscript{2} to the aziridine nitrogen activates the ring for attack by the \(\pi\)-bond of the allylsilane in an S\textsubscript{N}2 manner. The result of this process is the formation of a stable tertiary \(\beta\)-silyl carbocation 4.43. This intermediate can undergo elimination in the presence of a nucleophile to give \(\gamma\)-amino olefin 4.40. The suggested conformation of intermediate 4.43 would produce the cis carbocycle 4.40 with protons H\textsubscript{a} and H\textsubscript{b} on the same side. Furthermore, intermediate cation 4.43 could be trapped by the inherent sulfonamide nucleophile to produce cis-fused silylated azabicycle 4.41. The second ring closure could proceed in a highly stereoselective manner due to the fact \(\beta\)-silyl carbocations do not rotate around the single bond between C-1 and C-2.\textsuperscript{3-8,30-34} Also, nucleophile approach must take place \textit{anti} to the silicon. Therefore, the \textit{trans} olefin geometry of the allylsilane could be retained and suggests the stereochemistry depicted in cyclization product 4.41a (i.e. protons H\textsubscript{b} and the methyl group on opposite sides). However, it should be noted that the stereochemistry of product 4.41 was not confirmed.
Scheme 4.17: Mechanisms and stereochemical rationale for the cyclization of control C-3 aziridine-allylsilane 4.39.

Scheme 4.18: Cyclization of tether-substituted C-3 aziridine-allylsilane 4.12b.
Satisfied with the results of the cyclization of control C-3 aziridine-allylsilane 4.39, we turned our attention towards the cyclization of tether-substituted C-3 aziridine-allylsilane 4.12b (Scheme 4.18).

It is evident by the results in Scheme 4.18 that substitution of a methyl group on the tether connecting the two reactive moieties clearly has an effect on the products seen upon cyclization. Tether-substituted C-3 aziridine-allylsilane 4.12b was cyclized under the same reaction conditions as the control aziridine-allylsilane 4.39 (i.e. 100 mol% of BF$_3$•OEt$_2$, –78°C to 0°C, 20 hours). After work-up and chromatography, two products were isolated. The major product of the reaction was the formation of six-membered carbocycle 4.44 in 33% yield. This product results from attack of the allylsilane at the terminal carbon of the aziridine ring and not the internal carbon as we have traditionally seen with C-3 aziridine-allylsilanes. Clearly the substitution of a methyl group on the tether has produced an alternative mode of cyclization. The structure of compound 4.44 can be confirmed by the appearance of the sulfonamide proton as a D$_2$O-exchangeable distinct doublet in the $^1$H NMR. Traditionally the sulfonamide protons in the five-membered carbocycles appear as distinct triplets due to splitting by the aminomethyl protons. Olefin 4.44 appears as a single diastereomer by $^1$H and $^{13}$C NMR and its stereochemistry was assigned based on formation of a corresponding azabicycle (see Section 4.3.1).

The other isolated product from the cyclization of 4.12b under stoichiometric BF$_3$•OEt$_2$ conditions was an inseparable mixture of cis and trans five-membered carbocycles 4.11. However, this mixture of $\gamma$-amino olefins was only isolated in 12% yield. It should be noted that separation of isomeric olefins 4.11 and 4.44 by silica gel column chromatography proves to be
difficult. No separation of these olefins could be achieved using EtOAc : hexanes mixtures as the mobile phase. Separation of these compounds was only achieved using 100% benzene as the mobile phase. The yields for olefins 4.11 and 4.44 in Scheme 4.18 are of analytically pure material. The apparent ratio of olefin 4.11 diastereomers was 2.2 : 1 (cis : trans) based on \(^1\)H NMR integration values for the sulfonamide protons and proton Hb. When the NMR solvent is C\(_6\)D\(_6\), the sulfonamide protons show up as two distinct triplets while proton H\(_b\) shows up as two distinct multiplets.

In an effort to potentially improve the yield of \(\gamma\)-amino olefins 4.11, tether-substituted C-3 aziridine-allylsilane 4.12b was cyclized under another set of reaction conditions (Scheme 4.19). Following the reaction conditions and protocol of Dr. Punit Seth for the cyclization of \(\text{cis}\) C-3 aziridine-allylsilane 1.80a\(^{26}\) \(\text{trans}\) tether-substituted C-3 aziridine-allylsilane 4.12b was treated with 300 mol% of BF\(_3\)•OEt\(_2\) at 0°C for 14.5 hours.

\[
\begin{align*}
4.12b & \xrightarrow{\text{BF}_3\text{•OEt}_2 (300 \text{ mol\%})} 4.11 \text{ contaminated with } 4.44 \\
& \text{CH}_2\text{Cl}_2, 0^\circ \text{C, 14.5 h} \quad 32\% \quad 4.45 \quad 16\%, \text{ ca. } 1:1 \quad 4.46
\end{align*}
\]

Scheme 4.19: Cyclization of 4.12b under reported conditions and protocol of Seth.\(^{26}\)
Unfortunately, these reaction conditions offered no advantage in terms of improved olefin formation. In fact, a mixture of isomeric olefins 4.11 and 4.44 was achieved in 32% yield and no separation of isomers could be achieved under benzene chromatography conditions. Furthermore, a 1:1 mixture of what is believed to be desilylated azabicycles 4.45 and 4.46 was obtained in 16% yield. Perhaps the presence of excess Lewis acid catalyzed the formation of these products by the mechanisms previously discussed in Section 3.3.2.2.1. Desilylated azabicycle formation was not observed in the cyclizations of aziridine-allylsilanes 4.39 and 4.12b when stoichiometric amount of BF₃•OEt₂ was used.

It is evident from the previous experiments that the substitution of a methyl group on the tether at C-9 has not improved the diastereoselectivity of the cyclization reaction as we had hoped. No improvement in diastereoselectivity can be observed upon comparing cyclization results of cis C-3 aziridine-allylsilane 1.80a with either trans control C-3 aziridine-allylsilane 4.39 or trans tether-substituted C-3 aziridine-allylsilane 4.12b. The only conclusion that can be drawn about the tether-substituted methyl group at C-9 is that it somehow contributes to an alternative mode of cyclization behavior that we have not traditionally seen with C-3 aziridine-allylsilanes. A possible explanation for this behavior could be the reactive conformations depicted in Scheme 4.20.
Upon closer examination of conformation A in Scheme 4.20, we hypothesize that there could be an unfavorable steric interaction between the equatorial C-9 methyl group and the bulky tosyl group of the equatorially-oriented aziridine. As a result, a slightly more favorable conformation (i.e. conformation E) could potentially be adopted in which the aziridine ring is no longer oriented equatorially, but rather lies as part of a future cyclohexane ring. Subsequent attack at the terminal carbon of the aziridine (i.e. b) through conformation E would result in the formation of the six-membered ring 4.44. Perhaps a smaller activating group on the nitrogen
could limit the noted steric interaction in conformation A and generate more five-membered ring product upon cyclization. To test this hypothesis, a mesylated analog of tether-substituted C-3 aziridine-allylsilane 4.12b was synthesized and cyclized. It should be noted that the A value for a methyl group is 1.74 kcal / mole while a phenyl group has an A value of 2.8 kcal / mole.81,82

Scheme 4.21: Synthesis of a mesylated tether-substituted C-3 aziridine-allylsilane.

Amino acid 4.28 was subsequently transformed into desired mesylated aziridine-olefin 4.49 (Scheme 4.21). Initial removal of the trifluoroacetamide group from 4.28 followed by esterification and mesylation provided diprotected amino acid 4.47 in 66% yield over three steps. The ester was reduced to the alcohol in good yield (92%) using LiAlH₄ and subsequent Mitsunobu ring closure provided aziridine 4.49 in 91% yield. The hydroboration of aziridine-olefin 4.49 was
allowed to proceed for 5 hours at room temperature using 110 mol% of 9-BBN. Subsequent Suzuki coupling of the organoborane in the presence of Cs₂CO₃ (300 mol%), PdCl₂(dppf)-CH₂Cl₂ (9 mol%), and iodide 4.26 (110 mol%) in a THF / H₂O solvent system provided mesylated aziridine-allylsilane 4.50 in 34% yield after chromatography.

![Scheme 4.22: Cyclization of mesylated tether-substituted C-3 aziridine-allylsilane 4.50.](image)

Mesylated aziridine-allylsilane 4.50 was treated under the same cyclization conditions as tosylated aziridine-allylsilane 4.12b in Scheme 4.18 (i.e. 100 mol% BF₃•OEt₂, -78 to 0°C, 18 h.).

The major product of the reaction was an inseparable mixture of five-membered carbocycle 4.51 and six-membered carbocycle 4.52 in 54% yield. The ratio of carbocycles was determined to be 1 : 1 by ¹H NMR integration values for the sulfonamide protons (two distinct triplets for cis and trans 4.51 and one distinct doublet for 4.52). Therefore, the use of the smaller mesyl group showed slight improvement in terms of desired five-membered carbocycle formation when compared to its tosyl counterpart (recall that cyclization of tosylated aziridine-allylsilane 4.12b gave a 45% yield of 1 : 3 five-membered : six-membered carbocycles).
4.3.1. Formation of azabicycles via a hydroboration-oxidation / Mitsunobu reaction sequence of γ-amino olefins. Synthesis of the 3-azabicyclo[4.3.0]nonane skeleton of (+)-α-skytanthine

The cyclizations in the previous section are by no means optimal and would require significant improvement in order to justify the use of the methodology for an efficient natural products synthesis. However, in an effort to extend the synthesis of azabicyclic systems, select γ-amino olefin products from the previous section were subjected to a hydroboration-oxidation / Mitsunobu reaction sequence.

As we saw in Chapter 3 with the synthesis of azabicyclo[3.3.1]nonane 3.24, the choice of borane can have a significant effect on the stereochemistry of the hydroboration reaction. With respect to the reported syntheses of (+)-α-skytanthine (+(+)-4.3), two groups have used a hydroboration-oxidation / ring-closure strategy to form the 3-azabicyclo[4.3.0]nonane framework inherent to the alkaloid.254,258
In their reported synthesis of (+)-α-skytanthine, Tsunoda and co-workers hydroborated olefin 4.53 using catecholborane (Scheme 4.23). The hydroboration-oxidation sequence provided an inseparable mixture of amino alcohols 4.54, which was subjected to Mitsunobu ring closure to afford a 92 : 8 mixture (via GC) of piperidines 4.55a and 4.55b in 81% yield from the olefin. The piperidines were separated by silica gel chromatography and diastereomer 4.55a was converted to (+)-α-skytanthine (4.3) in two additional steps.

Oppolzer and Jacobsen also reported a hydroboration-oxidation / ring-closure approach to (+)-α-skytanthine (Scheme 4.24). Hydroboration of olefin 4.56 using 400 mol% of BH₃•THF followed by oxidation gave a 4.2 : 1 C-5 epimeric mixture from which (+)-α-iridodiol 4.58 was
separated by chromatography. Conversion of \(4.58\) to (+)-\(\alpha\)-skytanthine (4.3) was accomplished in two additional steps. However, hydroboration of olefin 4.57 with 500 mol\% of 9-BBN proceeded with reverse selectivity to give alcohol 4.59 as a 6 : 1 C-5 epimeric mixture. Crude 4.59 was subsequently converted to (+)-\(\delta\)-skytanthine (4.6) in three additional steps. The selectivity displayed by BH\(_3\)-THF on substrate 4.56 was related to the influence of the internal hydroxyl group to direct the \(\pi\)-faciality of the olefin hydroboration.\(^{269}\)

![Scheme 4.24: Oppolzer and Johnson approach to skytanthoids.](image)

The five-membered \(\gamma\)-amino olefin product 4.11 shows similar functionality when compared to compound 4.56. They both contain the same type of olefin unit, the C-9 methyl
group, and a potential directing group of hydroboration is present. Given these similarities and our desire to construct the azabicycle framework of (+)-α-skytanthine (4.3), select γ-amino olefins from Section 4.3 were hydroborated using BH$_3$•THF as the hydroborating regent.

To test the hydroboration-oxidation / Mitsunobu sequence as a strategy to form 3-azabicyclo[4.3.0]nonanes, γ-amino olefin 4.40 was initially examined (Scheme 4.25).


A 2 : 1 cis to trans mixture of γ-amino olefins 4.40 was hydroborated with 400 mol% of BH$_3$•THF at room temperature for 15 hours. Subsequent oxidation provided a crude mixture of amino alcohols 4.60 in 95% crude yield. The crude amino alcohol mixture was subjected to a Mitsunobu reaction to give an inseparable mixture of 3-azabicyclo[4.3.0]nonanes 4.61 in 77% yield from olefin 4.40. Examination of the $^1$H NMR of bicycle 4.61 in CDCl$_3$ shows two distinct doublets with integration values in a ratio of 4.2 : 1 suggesting a corresponding ratio of C-5 methyl epimers that is comparable to the experiments of Oppolzer and Johnson.$^{258}$ However, there is the possibility of forming either the cis or trans ring junction of 3-azabicyclo[4.3.0]nonane
4.61 due to the flexible nature of the 6-5 system. Examination of the 1H NMR of bicycle 4.61 in either CDCl₃ or C₆D₆ does not suggest the formation of a single cis or trans 6-5 ring system, but more than likely a mixture. Given the 2 : 1 cis to trans mixture of starting olefin 4.40, we suggest the cis 6-5 system predominates in the bicycle 4.61 mixture. The result of this reaction sequence justifies the use of a hydroboration-oxidation / Mitsunobu succession to form additional azabicycle systems.

The hydroboration-oxidation / Mitsunobu protocol was subsequently applied to six-membered carbocycle 4.44, which also contains γ-amino olefin unit (Scheme 4.26).

γ-Amino olefin 4.44 as a single diastereomer was hydroborated with 400 mol% of BH₃•THF at room temperature for 15 hours. Subsequent oxidation provided a crude mixture of

Scheme 4.26: Hydroboration-oxidation / Mitsunobu sequence of olefin 4.44.
amino alcohols 4.62 in 96% crude yield. The crude amino alcohol mixture was subjected to a Mitsunobu reaction to give 2-azabicyclo[3.3.1]nonane 4.63 in 50% yield from olefin 4.44. The result of this reaction sequence confirms the stereochemistry of C-3 in single diastereomer 4.44. When the 1,3-substituents are in a cis relationship to one another, ring closure during the Mitsunobu reaction is possible. The same can not be said for a trans 1,3-substitution pattern. Examination of the ^1H and ^13C NMR of bicycle 4.63 shows the presence of a single diastereomer. Azabicycle 4.63 was subjected to crystallization and sent for X-ray analysis in an attempt to confirm structure and to assign the stereochemistry of C-4. At the time of this dissertation, no crystallographic data is available.

Finally, the hydroboration-oxidation / Mitsunobu protocol was applied to γ-amino olefin 4.11 in an attempt to construct the 3-azabicyclo[4.3.0]nonane framework of (+)-α-skytanthine ((+)-4.3) (Scheme 4.27).
A 2:1 cis to trans mixture of γ-amino olefins 4.11 was hydroborated with 400 mol% of BH$_3$•THF at room temperature for 20.5 hours. Subsequent oxidation provided a crude mixture of amino alcohols 4.64 in 94% crude yield. The crude amino alcohol mixture was subjected to a Mitsunobu reaction to give an inseparable mixture of 3-azabicyclo[4.3.0]nonanes 4.65 in 62% yield from olefin 4.11. Upon examination of the $^1$H NMR of azabicycle 4.65 in CDCl$_3$ and C$_6$D$_6$, it is difficult to discern a confident diastereomeric ratio due to peak overlap. Fortunately, the diastereomeric mixture was subjected to crystallization in ether and x-ray analysis confirmed the structure of 4.65a (Figure 4.1). Azabicycle 4.65a is the tosylated analog of nor-α-skytanthine (4.66), which has been previously transformed into (+)-α-skytanthine (4.3).$^{254,255}$
4.4. Chapter summary

With intentions of applying our methodology to synthesis of natural products and studying the effect of a substituted-tether on the diastereoselectivity of intramolecular C-3 aziridine-allylsilane cyclizations, a C-3 aziridine-allylsilane containing a methyl substituent on the tether was envisioned based on a proposed retrosynthesis of (+)-α-skytanthine. The targeted aziridine-allylsilane differs from our traditional cis C-3 aziridine-allylsilanes not only in tether substitution, but also in substitution at C-2 of the allylsilane and trans orientation of the olefin. Upon initial failure of the allylsilane-organocuprate / N-Ts-aziridine methanol strategy, the target aziridine-allylsilane was synthesized via Suzuki cross-coupling of a known allylsilane-vinyl iodide with a
chiral aziridine-olefin containing the key methyl substituent. The chiral aziridine-olefin stemmed from transformation of a known amino acid in good yield and high optical purity.

Unfortunately, the diastereoselectivity of products resulting from the cyclization of the tether-substituted C-3 aziridine-allylsilane did not improve when compared to the cyclization of a control C-3 aziridine-allylsilane. In fact, the tether-substituted aziridine-allylsilane offered an additional mode of cyclization when compared to the control aziridine-allylsilane. Along with products resulting from traditional attack of the allylsilane at the internal carbon of the aziridine ring, tether-substituted C-3 aziridine-allylsilane also gave products resulting from attack of the allylsilane at the terminal aziridine carbon. This type of behavior was not seen in our previous cyclizations of C-3 aziridine-allylsilanes. Due to the potential presence of unfavorable steric interactions between the tosyl group of the aziridine ring and the methyl substituent of the tether, the alternative cyclization behavior was hypothesized to arrive via a change in the reactive conformation of the tether-substituted aziridine-allylsilane.

Finally, a hydroboration-oxidation / Mitsunobu reaction sequence was performed on select γ-amino olefin cyclization products to form 3-azabicyclo[4.3.0]nonane and 2-azabicyclo[3.3.1]nonane frameworks. One of the 3-azabicyclo[4.3.0]nonanes synthesized represents the tosylated analog of a known compound, nor-α-skytanthine.
CHAPTER 5

EXPERIMENTAL

General. $^1$H spectra were recorded on a Bruker AG 250 MHz spectrometer. $^{13}$C spectra were recorded on a Varian VX 400 MHz spectrometer. Chemical shifts are reported in ppm relative to CDCl$_3$ (7.27 for $^1$H, 77.23 for $^{13}$C) or C$_6$D$_6$ (7.16 for $^1$H, 128.39 for $^{13}$C). Coupling constants ($J$) are reported in Hz. Thin layer chromatography (TLC) was performed on EM Science pre-coated silica gel 60 F$_{254}$ aluminum foils. Purification of the reaction products was carried out by flash chromatography using a glass column dry-packed with silica gel (ICN SiliTech 32-63D 60Å) according to the method of Still.\textsuperscript{270} Visualization was accomplished with UV light, I$_2$, and / or phosphomolybdic acid solution followed by heating. HRMS measurements were determined at The Ohio State University Chemical Instrument Center with a Kratos MS-30 mass spectrometer in the electron impact (EI) mode. Optical activity was measured on an Autopol IV automatic polarimeter. Chiral HPLC was performed using a (R, R)-WHELK-O 1 5/100 HPLC column (250 mm X 4.6 mm, particle size 5 um) purchased from Regis Technologies. HPLC runs were performed using %10 EtOH in hexanes at a flow rate of 1.5 mL / minute. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were distilled from sodium and benzophenone prior to use. Dimethylformamide (DMF), dichloromethane (CH$_2$Cl$_2$), and boron trifluoride diethyl etherate
(BF$_3$·OEt$_2$) were distilled from CaH$_2$ before use. Triethylamine (Et$_3$N) was distilled from CaH$_2$ and stored over KOH pellets. Methanol (MeOH) was distilled from Mg and I$_2$ and stored over molecular sieves. All reactions were carried out in flame-dried glassware under an Ar atmosphere unless otherwise specified.

Methyl $N$-[(4-methylphenyl)sulfonyl]-2-aminopent-4-enoate (3.74). Distilled MeOH (20 mL) was cooled to 0˚C and treated dropwise with freshly distilled acetyl chloride (7.1 mL, 100 mmol). After the addition, the mixture was stirred for 1 hour at 0˚C. DL-2-Amino-4-pentenoic acid (2.30 g, 20 mmol) was added portionwise over 5 minutes and the mixture was refluxed for 24 hours. The reaction was cooled to room temperature and diluted with MeOH. The crude mixture was concentrated to dryness to provide the methyl ester hydrochloride salt, which was used without purification. The crude salt was suspended in CH$_2$Cl$_2$ (20 mL) and cooled to 0˚C for careful addition of Et$_3$N (7.0 mL, 50 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional hour. The reaction was recooled to 0˚C and p-toluenesulfonyl chloride (4.19 g, 22 mmol) was added portionwise over 5 minutes. After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 24 hours. The reaction was diluted with CHCl$_3$ and washed with 1M HCl. The layers were separated and the aqueous layer was extracted with CHCl$_3$. The combined
organic layers were washed with sat. aq. NaHCO$_3$ solution, brine, dried (MgSO$_4$), filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to give 4.54 g of ester 3.74 (80% from the acid). $R_f$ 0.23 (25% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.72 (d, 2H, $J=8.78$ Hz), 7.28 (d, 2H, $J=7.80$ Hz), 5.70–5.53 (m, 1H), 5.30 (d, 1H, $J=8.78$ Hz), 5.10–5.03 (m, 2H), 4.02 (m, 1H), 3.51 (s, 3H), 2.44 (t, 2H, $J=6.85$ Hz), 2.41 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 171.2, 143.5, 136.7, 131.3, 129.5, 127.1, 119.4, 55.2, 52.2, 37.3, 21.3. HRMS for C$_{13}$H$_{17}$NO$_4$S•Na$^+$ calcd 306.0770, found 306.0772.

![Chemical Structure](image)

N-[(4-methylphenyl)sulfonyl]-2-amino-4-pentenol (3.75). Dry LiCl (0.99 g, 23.4 mmol) was added to a stirred solution of ester 3.74 (2.21 g, 7.81 mmol) in THF (10.9 mL) and EtOH (21.8 mL). The mixture was cooled to 0℃ and NaBH$_4$ (0.89 g, 23.4 mmol) was added over 5 minutes. After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 14 hours. The reaction was quenched with acetone and concentrated to a white residue, which was carefully dissolved in 1 M HCl : EtOAc (ca. 1 : 1). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO$_4$), filtered, concentrated, and chromatographed (40% EtOAc in hexanes) to give 1.60 g of alcohol 3.75 (80%). $R_f$ 0.27 (40% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.77 (d, 2H, $J=8.78$ Hz), 7.29 (d, 2H, $J=8.78$ Hz).
Hz), 5.55–5.38 (m, 1H), 5.37 (d, 1H, $J=7.83$ Hz), 4.99-4.93 (m, 2H), 3.62-3.48 (m, 2H), 3.29 (m, 1H), 2.69 (br s, 1H), 2.41 (s, 3H), 2.16 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 143.4, 137.4, 133.3, 129.5, 127.0, 118.3, 63.9, 54.9, 35.8, 21.4. HRMS for C$_{12}$H$_{17}$NO$_3$S•Na$^+$ calcd 278.0821, found 278.0823.

![Structure of NTs](image)

2-[2-Propanoyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.72). Ph$_3$P (1.81 g, 6.90 mmol) was added to a stirred solution of alcohol 3.75 (1.60 g, 6.27 mmol) in THF (24.7 mL). The mixture was cooled to 0°C and diethyl azodicarboxylate (1.1 mL, 6.90 mmol) was added dropwise. After the addition, the ice bath was removed and the reaction was warmed to room temperature and stirred for an additional 16 hours. The mixture was concentrated and chromatographed (8 to 15% EtOAc in hexanes) to give 1.23 g of aziridine 3.72 (82%). $R_f$ 0.21 (15% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.82 (d, 2H, $J=7.80$ Hz), 7.33 (d, 2H, $J=8.80$ Hz), 5.68–5.52 (m, 1H), 5.10-4.95 (m, 2H), 2.80 (m,1H), 2.63 (d, 1H, $J=6.85$ Hz), 2.44 (s, 3H), 2.31-2.14 (m, 2H), 2.10 (d, 1H, $J=3.90$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 144.4, 134.9, 132.7, 129.5, 127.8, 117.5, 39.1, 35.0, 33.0, 21.5. HRMS for C$_{12}$H$_{17}$NO$_3$S•Na$^+$ calcd 260.0716, found 260.0710.
2-[4-[(Trimethylsilyl)methyl]-4-pentenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.1b). A stirred solution of olefin 3.72 (0.42 g, 1.77 mmol) in THF (6.1 mL) was cooled to 0°C and treated with 9-BBN (4.3 mL, 0.5 M in THF, 2.13 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 3 hours. DMF (3.1 mL) and K₂PO₄ (1.2 mL, 3 M in H₂O, 3.72 mmol) were added followed quickly by the addition of (2-bromoallyl)trimethylsilane 3.70²¹⁹ (0.3 mL, 1.95 mmol). PdCl₂(dppf)·CH₂Cl₂ (0.07 g, 0.09 mmol) was added and the mixture was stirred at room temperature for 18.5 hours then concentrated to the DMF layer. The residue was taken up in Et₂O and washed with H₂O. The layers were separated and the aqueous layer was extracted with Et₂O (X2). The combined organic layers were washed with sat. aq. NaHCO₃ solution, dried (MgSO₄), filtered, concentrated, and chromatographed (100% benzene) to give 0.36 g of racemic aziridine-allylsilane 3.1b (58%). R, 0.31 (10% EtOAc in hexanes). ¹H NMR (C₆D₆, 250 MHz) δ 7.89 (d, 2H, J=8.78 Hz), 6.73 (d, 2H, J=7.83 Hz), 4.59 (app s, 2H), 2.71-2.62 (m, 1H), 2.44 (d, 1H, J=6.85 Hz), 1.86 (s, 3H), 1.80 (t, 2H, J=6.85 Hz), 1.52 (d, 1H, J=4.88 Hz), 1.41 (s, 2H), 1.35-0.96 (m, 4H), 0.01 (s, 9H). ¹³C NMR (C₆D₆, 100 MHz) δ 146.9, 143.8, 136.8, 129.6, 128.3, 107.7, 40.0, 37.8, 33.5, 31.1, 26.6, 25.2, 21.1, -1.3. HRMS for C₁₈H₂₆NO₂SSi•Na⁺ calcd 378.1530, found 378.1538.
2-[4-Methyl-4-pentenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78a). Olefin 3.72 (0.25 g, 1.06 mmol) was dissolved in THF (3.7 mL), cooled to 0˚C, and treated with 9-BBN (2.5 mL, 0.5 M in THF, 1.27 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 3 hours. DMF (1.8 mL) and K₃PO₄ (0.7 mL, 3 M in H₂O, 2.22 mmol) were added followed quickly by the addition of 2-bromopropene (0.1 mL, 1.16 mmol). Finally, PdCl₂(dppf)•CH₂Cl₂ (43.1 mg, 0.0528 mmol) was added and the mixture was stirred at room temperature for 21 hours. The mixture was concentrated to the DMF layer and taken up in Et₂O and sat. aq. NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with Et₂O (X2). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (10% EtOAc in hexanes) to give 0.14 g of aziridine 3.78a (47%). Rₖ 0.36 (20% EtOAc in hexanes). ¹H NMR (CDCl₃, 250 MHz) δ 7.84 (d, 2H, J=7.80 Hz), 7.34 (d, 2H, J=8.78 Hz), 4.67 (app s, 1H), 4.56 (app s, 1H), 2.71 (m, 1H), 2.66 (d, 1H, J=6.83 Hz), 2.45 (s, 3H), 2.08 (d, 1H, J=3.93 Hz), 1.94 (t, 2H, J=7.80 Hz), 1.64 (s, 3H), 1.64-1.51 (m, 1H), 1.41-1.23 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 144.9, 144.3, 135.0, 129.5, 127.9, 110.0, 40.2, 36.8, 33.6, 30.7, 24.5, 22.0, 21.5. HRMS for C₁₅H₂₁NO₂S•Na⁺ calcd 302.1185, found 302.1169.
2-[Ethyl cis-hex-4-enate]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78b). Olefin 3.72 (0.22 g, 0.926 mmol) was dissolved in THF (3.2 mL), cooled to 0°C, and treated with 9-BBN (3.7 mL, 0.5 M in THF, 1.85 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 3 hours. DMF (1.6 mL) and K$_3$PO$_4$ (0.7 mL, 3 M in H$_2$O, 1.94 mmol) were added followed quickly by addition of ethyl cis-3-iodoacrylate (0.1 mL, 1.02 mmol). Finally, PdCl$_2$(dpff) (36.7 mg, 0.05 eq.) was added and the mixture was stirred at room temperature for 18 hours. The reaction was concentrated to the DMF layer then taken up in Et$_2$O and sat. aq. NaHCO$_3$ solution. The layers were separated and the aqueous layer was extracted with Et$_2$O (X2). The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (15% EtOAc in hexanes) to give 0.16 g of ester 3.78b (51%). $R_f$ 0.36 (25% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.82 (d, 2H, $J=8.78$ Hz), 7.34 (d, 2H, $J=7.80$ Hz), 6.13-6.02 (m, 1H), 5.78-5.72 (m, 1H), 4.155 (q, 2H, $J=7.80$ Hz), 2.75 (m, 1H), 2.63 (d, 1H, $J=4.88$ Hz), 2.65-2.56 (m, 2H), 2.44 (s, 3H), 2.07 (d, 1H, $J=3.90$ Hz), 1.67-1.55 (m, 1H), 1.48-1.35 (m, 3H), 1.28 (t, 3H, $J=6.83$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 166.1, 149.0, 144.3, 134.9, 129.5, 127.9, 120.2, 59.7, 39.8, 33.7, 30.7, 28.0, 25.9, 21.5, 14.1. HRMS for C$_{17}$H$_{23}$NO$_4$S•Na$^+$ calcd 360.1240, found 360.1230.
2-[3-Phenylpropyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78c). Olefin 3.72 (0.23 g, 0.96 mmol) was dissolved in THF (3.3 mL), cooled to 0°C, and treated with 9-BBN (2.3 mL, 0.5 M in THF, 1.15 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 3 hours. DMF (1.7 mL) and K3PO4 (0.7 mL, 3 M in H₂O, 2.01 mmol) were added followed quickly by addition of bromobenzene (0.1 mL, 1.05 mmol). Finally, PdCl2(dppf)•CH2Cl2 (39.1 mg, 0.0479 mmol) was added and the mixture was stirred at room temperature for 17 hours. The reaction was concentrated to the DMF layer and taken up in Et₂O and sat. aq. NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with Et₂O (X2). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (100% CH₂Cl₂) to give 0.14 g of aziridine 3.78c (47%). Rf 0.32 (20% EtOAc in hexanes). 1H NMR (CDCl₃, 250 MHz) δ 7.84 (d, 2H, J=7.80 Hz), 7.34-7.18 (m, 5H), 7.08 (d, 2H, J=8.78 Hz), 2.75 (m, 1H), 2.65 (d, 1H, J=6.85 Hz), 2.56 (t, 2H, J=6.85 Hz), 2.42 (s, 3H), 2.06 (d, 1H, J=3.90 Hz), 1.70-1.51 (m, 3H), 1.41-1.30 (m, 1H). 13C NMR (CDCl₃, 100 MHz) δ 144.4, 141.5, 135.0, 129.5, 128.2, 127.9, 125.7, 40.0, 34.9, 33.7, 30.6, 28.2, 21.5. HRMS for C₁₈H₂₁NO₂S•Na⁺ calcd 338.1185, found 338.1173.
2-[3-(4-Hydroxyphenyl)propyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78d). Olefin 3.72
(0.23 g, 0.97 mmol) was dissolved in THF (3.4 mL), cooled to 0˚C, and treated with 9-BBN (2.3
mL, 0.5 M in THF, 1.16 mmol). After the addition, the ice bath was removed and the mixture was
warmed to room temperature and stirred for an additional 4 hours. DMF (1.7 mL) and K3PO4 (0.7
mL, 3 M in H2O, 2.03 mmol) were added followed quickly by the addition of 4-iodophenol (0.23 g,
1.06 mmol). Finally, PdCl2(dppf)•CH2Cl2 (39.5 mg, 0.048 mmol) was added and the mixture was
stirred at room temperature for 15 hours. The reaction was concentrated to the DMF layer and
taken up in Et2O and sat. aq. NaHCO3 solution. The layers were separated and the aqueous
layer was extracted with Et2O (X2). The combined organic layers were dried (MgSO4), filtered,
concentrated, and chromatographed (25% EtOAc in pet ether) to give 0.19 g of phenol 3.78d
(60%). Rf 0.26 (25% EtOAc in pet ether). 1H NMR (CDCl3, 250 MHz) δ 7.83 (d, 2H, J=8.78 Hz),
7.33 (d, 2H, J=7.83 Hz), 6.93 (d, 2H, J=7.83 Hz), 6.74 (d, 2H, J=8.78 Hz), 5.15 (s, 1H) 2.75 (m,
1H), 2.63 (d, 1H, J=6.85 Hz), 2.48 (t, 2H, J=6.85 Hz), 2.42 (s, 3H), 2.06 (d, 1H, J=3.90 Hz), 1.67-
1.46 (m, 3H), 1.39-1.28 (m, 1H). 13C NMR (CDCl3, 100 MHz) δ 153.7, 144.5, 134.8, 133.5, 129.6,
129.2, 127.9, 115.0, 40.2, 34.0, 33.7, 30.5, 28.4, 21.5. HRMS for C18H21N2O2S•Na+ calcd
354.1134, found 354.1116.
2-[3-(4-Nitrophenyl)propyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78e). Olefin 3.72 (0.23 g, 0.97 mmol) was dissolved in THF (3.4 mL), cooled to 0°C, and treated with 9-BBN (2.3 mL, 0.5 M in THF, 1.16 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 3 hours. DMF (1.7 mL) and K3PO4 (0.7 mL, 3 M in H2O, 2.04 mmol) were added followed quickly by addition of 1-bromo-4-nitrobenzene (0.22 g, 1.07 mmol). Finally, PdCl2(dppf)•CH2Cl2 (39.6 mg, 0.0485 mmol) was added and the mixture was stirred at room temperature for 17 hours. The reaction was concentrated to the DMF layer and taken up in Et2O and sat. aq. NaHCO3 solution. The layers were separated and the aqueous layer was extracted with Et2O (X2). The combined organic layers were dried (MgSO4), filtered, concentrated, and chromatographed (20% EtOAc in pet ether) to give 97.6 mg of aziridine 3.78e (28%). Rf 0.25 (30% EtOAc in hexanes). 1H NMR (CDCl3, 250 MHz) δ 8.14 (d, 2H, J=8.78 Hz), 7.84 (d, 2H, J=8.78 Hz), 7.34 (d, 2H, J=7.80 Hz), 7.27 (d, 2H, J=8.78 Hz), 2.84-2.71 (m, 1H), 2.71 (t, 2H, J=7.83 Hz), 2.635 (d, 1H, J=6.85 Hz), 2.43 (s, 3H), 2.06 (d, 1H, J=4.88 Hz), 1.79-1.55 (m, 3H), 1.38-1.27 (m, 1H). 13C NMR (CDCl3, 100 MHz) δ 149.5, 146.3, 144.5, 134.9, 129.6, 129.0, 127.9, 123.5, 39.4, 34.7, 33.8, 30.5, 28.0, 21.5. HRMS for C18H20N2O4S•Na+ calcd 383.1036, found 383.1016.
2-[3-(4-acetylphenyl)propyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78f). Olefin 3.72 (0.24 g, 1.02 mmol) was dissolved in THF (3.5 mL), cooled to 0°C, and treated with 9-BBN (2.4 mL, 0.5 M in THF, 1.22 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 4 hours. DMF (1.8 mL) and K3PO4 (0.7 mL, 3 M in H2O, 2.14 mmol) were added followed quickly by the addition of 4'-bromoacetophenone (0.22 g, 1.12 mmol). Finally, PdCl2(dppf)•CH2Cl2 (41.5 mg, 0.051 mmol) was added and the mixture was stirred at room temperature for 15 hours. The reaction was concentrated to the DMF layer and taken up in Et2O and sat. aq. NaHCO3 solution. The layers were separated and the aqueous layer was extracted with Et2O (X2). The combined organic layers were dried (MgSO4), filtered, concentrated, and chromatographed (25% EtOAc in pet ether) to give 0.26 g of ketone 3.78f (70%). Rf 0.24 (30% EtOAc in hexanes). 1H NMR (CDCl3, 250 MHz) δ 7.84 (app t, 4H, J=8.78 Hz), 7.32 (d, 2H, J=7.83 Hz), 7.18 (d, 2H, J=7.80 Hz), 2.75 (m, 1H), 2.63 (t, 2H, J=6.83 Hz), 2.63 (d, 1H, J=6.83 Hz), 2.58 (s, 3H), 2.41 (s, 3H), 2.05 (d, 1H, J=4.88 Hz), 1.71-1.54 (m, 3H), 1.38-1.26 (m, 1H). 13C NMR (CDCl3, 100 MHz) δ 197.6, 147.4, 144.4, 135.0, 134.9, 129.5, 128.4, 128.4, 127.8, 39.7, 34.9, 33.7, 30.5, 27.9, 26.4, 21.5. HRMS for C20H23NO3S•Na+ calcd 380.1291, found 380.1291.
2-[3-(Methyl 4-benzoate)propyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.78g). Olefin 3.72 (0.25 g, 1.06 mmol) was dissolved in THF (3.7 mL), cooled to 0˚C, and treated with 9-BBN (2.5 mL, 0.5 M in THF, 1.27 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 4 hours. DMF (1.8 mL) and K3PO4 (0.7 mL, 3 M in H2O, 2.22 mmol) were added followed quickly by the addition of methyl 4-bromobenzoate (0.25 g, 1.16 mmol). Finally, PdCl2(dppf)•CH2Cl2 (43.1 mg, 0.053 mmol) was added and the mixture was stirred at room temperature for 15 hours. The reaction was concentrated to the DMF layer and taken up in Et2O and sat. aq. NaHCO3 solution. The layers were separated and the aqueous layer was extracted with Et2O (X2). The combined organic layers were dried (MgSO4), filtered, concentrated, and chromatographed (20% EtOAc in pet ether) to give 0.26 g of ester 3.78g (65%). Rf 0.31 (30% EtOAc in hexanes). 1H NMR (CDCl3, 250 MHz) δ 7.93 (d, 2H, J=7.80 Hz), 7.82 (d, 2H, J=8.78 Hz), 7.31 (d, 2H, J=7.83 Hz), 7.14 (d, 2H, J=7.83 Hz), 3.90 (s, 3H), 2.73 (m, 1H), 2.63 (d, 1H, J=6.83 Hz), 2.60 (t, 2H, J=6.83 Hz), 2.40 (s, 3H), 2.05 (d, 1H, J=4.48 Hz), 1.71-1.51 (m, 3H), 1.36-1.26 (m, 1H). 13C NMR (CDCl3, 100 MHz) δ 166.9, 147.1, 144.4, 134.9, 129.5, 128.2, 127.9, 127.8, 51.9, 39.8, 34.9, 33.7, 30.5, 27.9, 21.5. HRMS for C20H23NO4S•Na+ calcd 396.1240, found 396.1246.
(2R)-1-(tert-Butyldimethylsilyl)oxo-N-[(4-methylphenyl)sulfonyl]-2-amino-4-pentene (3.93).

Vinylmagnesium bromide (30.6 mL, 1 M in THF, 30.60 mmol) was added to a −78°C slurry of CuCN (0.50 g, 5.64 mmol) in Et₂O (34 mL). After stirring for 20 minutes, a solution of aziridine 2.159a (3.44 g, 10.07 mmol) in THF (51 mL) was added via cannula. After the addition, the mixture was maintained at 0°C for 4 days then quenched with a solution composed of 10% conc. NH₄OH / 90% sat. aq. NH₄Cl solution. The mixture was diluted with Et₂O and stirred at room temperature until all solids were dissolved (ca. 4 hrs.). The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (10% EtOAc in hexanes) to give 3.31 g of silyl ether 3.93 (89%). Rᵣ 0.32 (15% EtOAc in hexanes), [α]²⁴D = +17.9° (c 1.1, EtOAc).

¹H NMR (CDCl₃, 250 MHz) δ 7.75 (d, 2H, J=7.80 Hz), 7.30 (d, 2H, J=8.80 Hz), 5.68–5.51 (m, 1H), 5.04-4.98 (m, 2H), 4.75 (d, 1H, J=7.80 Hz), 3.53-3.48 (m, 1H), 3.39-3.33 (m, 1H), 3.28 (m, 1H), 2.43 (s, 3H), 2.25 (t, 2H, J=6.83 Hz), 0.85 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 143.2, 137.8, 133.6, 129.5, 127.0, 118.2, 63.4, 54.2, 36.2, 25.7, 21.4, 18.1, -5.7.

HRMS for C₁₉H₂₅NO₃SSi•Na⁺ calcd 392.1686, found 392.1706.
(2R)-1-(tert-Butyldimethylsilyl)oxo-N-[(4-methylphenyl)sulfonyl]-2-amino-5-hexene (3.94).

Allylmagnesium chloride (30.5 mL, 2 M in THF, 60.94 mmol) was added to a −78˚C slurry of CuCN (1.01 g, 11.23 mmol) in Et₂O (67.7 mL). After stirring for 20 minutes, a solution of aziridine 2.159a¹⁷³ (6.85 g, 20.05 mmol) in THF (101.6 mL) was added via cannula. After the addition, the reaction was maintained at 0˚C for 45 hours then quenched with a solution composed of 10% conc. NH₄OH / 90% sat. aq. NH₄Cl solution. The mixture was diluted with Et₂O and stirred at room temperature until all solids were dissolved (ca. 6 hrs.). The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (10% EtOAc in hexanes) to give 5.80 g of silyl ether 3.94 (75%). Rᵣ 0.24 (10% EtOAc in hexanes), [α]²⁵ₒ = +25.4˚ (c 2.7, EtOAc).

¹H NMR (CDCl₃, 250 MHz) δ 7.75 (d, 2H, J=8.78 Hz), 7.29 (d, 2H, J=8.78 Hz), 5.79–5.63 (m, 1H), 4.98-4.90 (m, 2H), 4.81 (d, 1H, J=7.80 Hz), 3.44-3.29 (m, 2H), 3.24 (m, 1H), 2.42 (s, 3H), 2.07-1.96 (m, 2H), 1.61-1.52 (m, 2H), 0.84 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 143.2, 138.3, 137.7, 129.6, 127.0, 115.0, 64.0, 54.4, 31.4, 29.7, 25.8, 21.4, 18.2, -5.6.

HRMS for C₁₉H₃₃NO₃SSi•Na⁺ calcd 406.1843, found 406.1855.
(2R)-N-[(4-methylphenyl)sulfonyl]-2-amino-4-pentenol (3.95). A stirred solution of silyl ether 3.93 (4.70 g, 12.71 mmol) in THF (30.1 mL) was cooled to 0°C and treated with n-Bu₄NF (14.0 mL, 1 M in THF, 13.98 mmol). After 2 hours at 0°C, the reaction was partitioned between H₂O and Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (40% EtOAc in hexanes) to give 2.49 g of alcohol 3.95 (77%). Analytical data was the same as that reported for 3.75 except [α]₂⁴D = -3.5° (c 2.4, EtOAc).

(2R)-N-[(4-methylphenyl)sulfonyl]-2-amino-5-hexenol (3.96). A stirred solution of silyl ether 3.94 (5.80 g, 15.12 mmol) in THF (30.2 mL) was cooled to 0°C and treated with n-Bu₄NF (16.6 mL, 1 M in THF, 16.63 mmol). After 1 hour at 0°C, the reaction was partitioned between H₂O and Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (40% EtOAc in hexanes) to give 3.59 g of alcohol 3.96 (88%). Rf 0.33 (50% EtOAc in hexanes), [α]₂⁴D = +3.5° (c 2.8, EtOAc). ¹H NMR (CDCl₃, 250 MHz) δ 7.79 (d, 2H,
$J=8.80 \text{ Hz}$, 7.31 (d, 2H, $J=7.83 \text{ Hz}$), 5.68–5.51 (m, 1H), 5.37 (d, 1H, $J=8.80 \text{ Hz}$), 4.90-4.81 (m, 2H), 3.61-3.45 (m, 2H), 3.26 (m, 1H), 2.48 (br s, 1H), 2.42 (s, 3H), 2.03-1.78 (m, 2H), 1.61-1.38 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 143.5, 137.7, 137.3, 129.7, 127.1, 115.2, 64.5, 55.0, 30.8, 29.6, 21.5. HRMS for C$_{13}$H$_{19}$NO$_3$S•Na$^+$ calcd 292.0978, found 292.097.

![](3.89, n = 1)

(2R)-2-[2-Propenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.89). Ph$_3$P (1.27 g, 4.83 mmol) was added to a stirred solution of alcohol 3.95 (1.12 g, 4.39 mmol) in THF (22.0 mL). The mixture was cooled to 0°C and diethyl azodicarboxylate (0.8 mL, 4.83 mmol) was added dropwise. After the addition, the ice bath was removed and reaction was warmed to room temperature and stirred for an additional 4 hours. The mixture was concentrated and chromatographed (8% to 15% EtOAc in hexanes) to give 0.94 g of aziridine 3.89 (90%). Analytical data was the same as that reported for 3.72 except $[\alpha]_{D}^{24} = +18.9^\circ$ (c 4.3, EtOAc).

![](3.90, n = 2)

(2R)-2-[3-Butenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (3.90). Ph$_3$P (0.78 g, 2.96 mmol) was added to a stirred solution of alcohol 3.96 (0.72 g, 2.69 mmol) in THF (13.5 mL). The
mixture was cooled to 0°C and diethyl azodicarboxylate (0.5 mL, 2.96 mmol) was added dropwise. After the addition, the ice bath was removed and reaction was warmed to room temperature and stirred for an additional 4 hours. The mixture was concentrated and chromatographed (15% EtOAc in hexanes) to give 0.63 g of aziridine 3.90 (93%). Rf 0.32 (15% EtOAc in hexanes), [α]$_D^{25}$ = -7.0˚ (c 3.6, EtOAc). $^1$H NMR (CDCl$_3$, 250 MHz) δ 7.83 (d, 2H, $J$=7.80 Hz), 7.34 (d, 2H, $J$=8.78 Hz), 5.81–5.65 (m, 1H), 5.01-4.93 (m, 2H), 2.75 (m, 1H), 2.63 (d, 1H, $J$=6.83 Hz), 2.44 (s, 3H), 2.08 (d, 1H, $J$=4.90 Hz), 2.09-1.99 (m, 2H), 1.72-1.58 (m, 1H), 1.52-1.37 (m, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 144.4, 136.9, 135.1, 129.6, 127.9, 115.5, 39.7, 33.8, 30.7, 30.6, 21.6. HRMS for C$_{13}$H$_{17}$NO$_2$S$\cdot$Na$^+$ calcd 274.0872, found 274.0860.

\[
\begin{align*}
\text{(R)-3.1b, \ n = 1}
\end{align*}
\]

\((2R)-2\{4\{-[\text{Trimethylsilyl}]\text{methyl}\}-4\text{-pentenyl}\}-N\{-[\text{4-methylphenyl}]\text{sulfonyl}\}\text{aziridine ((R)-3.1b)}\). Aziridine-allylsilane (R)-3.1b was prepared using aziridine 3.89 (0.42 g, 1.77 mmol) following the same procedure as reported for racemic 3.1b. This reaction provided 0.36 g of (R)-3.1b (58%). Analytical data was the same as that reported for racemic 3.1b except [α]$_{22}^{225}$ = +14.5˚ (c 0.9, EtOAc).
(2R)-2-[[Trimethylsilyl)methyl]-5-hexenyl]-N-[(4-methylphenyl)sulfonyl]aziridine ((R)-3.1c). A stirred solution of olefin 3.90 (0.98 g, 3.90 mmol) in THF (13.4 mL) was cooled to 0˚C and treated with 9-BBN (8.6 mL, 0.5 M in THF, 4.29 mmol). After the addition, the ice bath was removed and the mixture was warmed to room temperature and stirred for an additional 7 hours.

(2-Bromoallyl)trimethylsilane 3.70 \(2^{19}\) (0.84 g, 4.34 mmol), DMF (5.0 mL), K_3PO_4 (2.7 mL, 3 M in H_2O, 8.18 mmol), and PdCl_2(dppf)-CH_2Cl_2 (0.16 g, 0.19 mmol) were added to a separate flask and the organoborane solution was added via cannula with an additional DMF (1.7 mL) rinsing. After the addition, the reaction was stirred at room temperature for 25 hours then poured into Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O (X3). The combined organic layers were dried (MgSO_4), filtered, concentrated, and chromatographed (50% hexanes in benzene then 100% benzene) to give 0.96 g of aziridine-allylsilane \((R)-3.1c\) (68%). \(R_f\) 0.34 (Benzene), \([\alpha]^{24}_{D65} = +16.2^\circ\) (c 7.5, EtOAc). \(^1^H\) NMR (CDCl_3, 250 MHz) \(\delta\) 7.81 (d, 2H, \(J=7.80\) Hz), 7.32 (d, 2H, \(J=8.80\) Hz), 4.51 (app s, 1H), 4.48 (app s, 1H), 2.71 (m, 1H), 2.62 (d, 1H, \(J=4.88\) Hz), 2.43 (s, 3H), 2.05 (d, 1H, \(J=4.88\) Hz), 1.85 (t, 2H, \(J=7.80\) Hz), 1.47 (s, 2H), 1.59-1.16 (m, 6H), 0.00 (s, 9H). \(^{13}C\) NMR (CDCl_3, 100 MHz) \(\delta\) 147.1, 144.3, 135.1, 129.6, 127.9, 107.0, 40.3, 37.9, 33.7, 31.2, 27.1, 26.6, 26.4, 21.6, -1.4. HRMS for C_{19}H_{31}NO_2SSi•Na calcd 388.1737, found 388.1735.
(2R)-2-Ethene-N-[(4-methylphenyl)sulfonyl]aziridine (3.91). A solution of ester 3.92\(^{173}\) (0.95 g, 3.71 mmol) in CH\(_2\)Cl\(_2\) (70 mL) was cooled to –78°C and treated with DIBAL-H (4.1 mL, 1 M in hexanes, 4.08 mmol). The mixture was stirred at –78°C for 2 hours then an additional 0.5 eq. of DIBAL-H (1.9 mL) was added. The reaction was stirred at –78°C for 1 hour then quenched by the addition of NaF (2.58 g) and H\(_2\)O (1.8 mL). The mixture was warmed to room temperature and stirred for 30 minutes. The crude mixture was filtered through Celite eluting exhaustively with CH\(_2\)Cl\(_2\) then concentrated to yield the crude aldehyde, which was used immediately without further purification. A suspension of Ph\(_3\)PMel (3.74 g, 9.26 mmol) in THF (85.7 mL) was cooled to –20°C and treated with KHMDS (18.5 mL, 0.5 M in toluene, 9.26 mmol) dropwise. The resulting yellow ylid suspension was stirred at –20°C for 2 hours before a solution of the crude aldehyde (assume 3.71 mmol) in THF (8.6 mL) was added via cannula. After 1 hour at –20°C, the reaction was poured into H\(_2\)O and Et\(_2\)O. The layers were separated and the aqueous layer was extracted with Et\(_2\)O (X2). The combined organic layers were dried (MgSO\(_4\)), filtered, concentrated, and chromatographed (15% EtOAc in hexanes) to give 0.24 g of olefin 3.91 (29% from ester 3.92). \(R_f\) 0.45 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.82 (d, 2H, \(J=8.78\) Hz), 7.33 (d, 2H, \(J=8.80\) Hz), 5.58–5.37 (m, 2H), 5.25–5.20 (m, 1H), 3.27 (m, 1H), 2.77 (d, 1H, \(J=4.88\) Hz), 2.43 (s, 3H), 2.21 (d, 1H, \(J=4.88\) Hz). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 144.7, 135.2,
Additional analytical data has been previously reported.\textsuperscript{232}

(2R)-1-(tert-Butyldimethylsilyl)oxo-\textit{N}-(4-methylphenyl)sulfonyl]-2-amino-5-(trimethylsilyl)methyl-5-hexene (3.110). A solution of allyl selenide 3.104\textsuperscript{235} (1.44 g, 6.51 mmol) in THF (4.3 mL) was added dropwise to a –78°C stirred solution of \textit{n}-BuLi (3.3 mL, 1.96 M in hexanes, 6.51 mmol). After 40 minutes, the allyllithium solution was transferred via cannula into a flask containing a –78°C slurry of CuCN (0.29 g, 3.25 mmol) in THF (3.8 mL). After 8 minutes, the mixture was warmed to 0°C and stirred for 1 hour. The reaction was recooled to –78°C and a solution of aziridine 2.159a\textsuperscript{173} (0.74 g, 2.17 mmol) in THF (2.3 mL) was added via cannula. After the addition, the reaction was maintained at 0°C for 22.5 hours then quenched with a solution composed of 10% conc. NH\textsubscript{4}OH / 90% sat. aq. NH\textsubscript{4}Cl solution. The mixture was diluted with Et\textsubscript{2}O then stirred at room temperature to allow the solids to dissolve. The layers were separated and the aqueous layer was extracted with Et\textsubscript{2}O (X3). The combined organic layers were washed with H\textsubscript{2}O, brine, dried (MgSO\textsubscript{4}), filtered, concentrated, and chromatographed (100% hexanes then 100% benzene) to give 0.66 g of allylsilane-silyl ether 3.110 (64%). \( R_f \) 0.29
(Benzene), $[\alpha]_{D}^{24} = +16.5^\circ$ (c 4.3, EtOAc). $^1$H NMR (C$_6$D$_6$, 250 MHz) $\delta$ 7.85 (d, 2H, $J$=7.83 Hz), 6.81 (d, 2H, $J$=7.83 Hz), 4.99 (d, 1H, $J$=7.80 Hz), 4.65 (s, 1H), 4.61 (s, 1H), 3.51-3.32 (m, 3H), 2.03-1.72 (m, 3H), 1.93 (s, 3H), 1.63-1.51 (m, 1H), 1.45 (s, 2H), 0.88 (s, 9H), 0.02 (s, 6H), -0.03 (s, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 146.6, 143.1, 138.2, 129.6, 127.0, 107.3, 30.2, 26.6, 25.8, 21.4, 18.2, -1.4, -5.6. HRMS for C$_{23}$H$_{43}$NO$_3$SSi$_2$•Na$^+$ calcd 492.2394, found 492.2403.

(2$R$)-N-[(4-methylphenyl)sulfonyl]-2-amino-5-(trimethylsilyl)methyl-5-hexenol (3.111). A stirred solution of silyl ether 3.110 (1.87 g, 3.97 mmol) in THF (4.1 mL) was cooled to 0°C and treated with $n$-Bu$_4$NF (4.4 mL, 1 M in THF, 4.37 mmol). The reaction was stirred for 30 minutes at 0°C then partitioned between H$_2$O and Et$_2$O. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried (MgSO$_4$), filtered, concentrated, and chromatographed (60% Et$_2$O in hexanes) to give 1.39 g of alcohol 3.111 (98%). $R$, 0.24 (30% EtOAc in hexanes), $[\alpha]_{D}^{24} = -4.9^\circ$ (c 7.4, EtOAc). $^1$H NMR (C$_6$D$_6$, 250 MHz) $\delta$ 7.94 (d, 2H, $J$=7.83 Hz), 6.89 (d, 2H, $J$=8.78 Hz), 5.94 (d, 1H, $J$=7.80 Hz), 4.57 (s, 1H), 4.55 (s, 1H), 3.72-3.64 (m, 1H), 3.56-3.48 (m, 1H), 3.37-3.35 (m, 1H), 3.20 (t, 1H, $J$=5.88 Hz), 1.95 (s, 3H), 1.92-1.51 (m, 4H), 1.35 (s, 2H), -0.02 (s, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 146.2,
143.3, 137.8, 129.7, 127.1, 107.4, 64.5, 55.4, 34.1, 29.6, 26.5, 21.5, -1.5. HRMS for C_{13}H_{19}NO_{3}SSi•Na⁺ calcd 378.1530, found 378.1513.

(2R)-2-[(3-[Trimethylsilyl)methyl]-3-butenyl]-N-[(4-methylphenyl)sulfonyl]aziridine ((R)-3.1a). Ph₃P (0.98 g, 3.72 mmol) was added to a stirred solution of alcohol 3.111 (1.20 g, 3.38 mmol) in THF (13.3 mL). The mixture was cooled to 0°C and diethyl azodicarboxylate (0.6 mL, 3.72 mmol) was added dropwise. After the addition, the ice bath was removed and the reaction was warmed to room temperature and stirred for an additional 2.5 hours. The mixture was concentrated and chromatographed (2% to 15% EtOAc in hexanes) to give 0.82 g of aziridine (R)-3.1a (72%). Rₐ 0.37 (15% EtOAc in hexanes), [α]_{D}^{24} = -10.2° (c 5.8, EtOAc). ¹H NMR (C₆D₆, 250 MHz) δ 7.88 (d, 2H, J=8.78 Hz), 6.74 (d, 2H, J=8.80 Hz), 4.57 (s, 2H), 2.74-2.64 (m, 1H), 2.44 (d, 1H, J=6.85 Hz), 1.86 (s, 3H), 1.83 (t, 2H, J=7.80 Hz), 1.54 (d, 1H, J=4.88 Hz), 1.53-1.38 (m, 1H), 1.35 (s, 2H), 1.33-1.09 (m, 1H), -0.04 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz) δ 145.9, 144.4, 135.1, 129.6, 128.0, 107.4, 40.1, 35.1, 33.7, 29.6, 26.8, 21.6, -1.5. HRMS for C_{15}H_{17}NO_{3}SSi•Na⁺ calcd 360.1424, found 360.1411.
3-((N-[4-methylphenyl)sulfonyl]aminomethyl)-1-methylenecyclohexane (3.2b, racemic). A stirred solution of racemic aziridine 3.1b (0.94 g, 2.68 mmol) in CH₂Cl₂ (26.8 mL) was cooled to −78˚C and treated with freshly distilled BF₃•OEt₂ (0.2 mL, 1.34 mmol). After 1 hour at −78˚C, another 0.6 eq. (0.2 mL, 1.61 mmol) of BF₃•OEt₂ was added. The reaction was stirred at −78˚C for 3 hours then maintained at −25˚C for 15 hours. The reaction was quenched with sat. aq. NaHCO₃ solution then warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (25% Et₂O in hexanes) to first provide 44.7 mg of racemic desilylated bicycle 3.4b (6%), followed by 0.64 g of racemic exocyclic olefin 3.2b (86%).

Rᵣ 0.49 for racemic desilylated bicycle 3.4b, 0.41 for racemic exocyclic olefin 3.2b (25% EtOAc in hexanes). ¹H NMR (C₆D₆, 250 MHz) δ 7.90 (d, 2H, J=8.78 Hz), 6.84 (d, 2H, J=7.83 Hz), 5.26 (t, 1H, J=6.85 Hz), 4.62 (d, 2H, J=4.88 Hz), 2.67 (t, 2H, J=5.85 Hz), 2.19-2.01 (m, 2H), 1.92 (s, 3H), 1.79-1.66 (m, 1H), 1.54-1.32 (m, 4H), 1.17-1.03 (m, 1H), 0.87-0.72 (m, 1H). ¹³C NMR (C₆D₆, 100 MHz) δ 147.7, 142.9, 138.4, 129.7, 127.5, 108.3, 48.8, 39.1, 38.9, 35.0, 29.8, 26.6, 21.1. HRMS for C₁₈H₂₁NO₂S•Na⁺ 302.1185, found 302.1169.
A stirred solution of aziridine (R)-3.1b (0.53 g, 1.52 mmol) in CH$_2$Cl$_2$ (15.2 mL) was cooled to –78˚C and treated with freshly distilled BF$_3$•OEt$_2$ (0.2 mL, 1.52 mmol). The reaction was stirred for 1 hour at –78˚C then maintained at -25˚C for 22 hours. The reaction was quenched with sat. aq. NaHCO$_3$ solution then warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (25% Et$_2$O in hexanes) to give 0.41 g of exocyclic olefin (R)-3.2b (97%). Analytical data was the same as that reported for racemic 3.2b except $[\alpha]_{D}^{23} = -21.5^\circ$ (c 1.8, EtOAc).

(3R)-3-(N-[(4-methylphenyl)sulfonyl]aminomethyl)-1-methylenebicyclohexane ((R)-3.2b). A stirred solution of aziridine (R)-3.1b (0.37 g, 1.0 mmol) in CH$_2$Cl$_2$ (10.0 mL) was cooled to –78˚C and treated with freshly distilled BF$_3$•OEt$_2$ (0.3 mL, 2.0 mmol). The reaction was stirred for 1 hour at –78˚C then maintained at 0˚C for 19 hours. The reaction was quenched with sat. aq. NaHCO$_3$.
solution then warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (25% Et₂O in hexanes) to give 0.15 g of exocyclic olefin (R)-3.2c (51%). Rf 0.40 (25% EtOAc in hexanes), [α]D²⁴ = +7.5° (c 2.2, EtOAc). ¹H NMR (CDCl₃, 250 MHz) δ 7.75 (d, 2H, J=8.78 Hz), 7.30 (d, 2H, J=8.80 Hz), 4.88 (t, 1H, J=5.85 Hz), 4.69 (app s, 1H), 4.64 (app s, 1H), 2.79 (t, 2H, J=6.83 Hz), 2.42 (s, 3H), 2.38-2.24 (m, 1H), 2.18-1.85 (m, 2H), 1.72-1.57 (m, 5H), 1.42-1.07 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 148.9, 143.2, 137.0, 129.6, 127.0, 112.0, 49.0, 39.3, 39.2, 36.1, 32.7, 28.2, 26.8, 21.5. ¹H and ¹³C NMR also contained signals representing a small amount (ca. <5%) of isomerized amino olefin. HRMS for C₁₆H₂₃NO₂S•Na⁺ calcd 316.1342, found 316.1338.

(1R, 5S)-3.4b

(1R, 5S)-5-Methyl-6-[(4-methylphenyl)sulfonyl]-6-azabicyclo[3.2.1]octane ((1R, 5S)-3.4b). A stirred solution of allylsilane (R)-3.1b (0.38 g, 1.07 mmol) in CH₂Cl₂ (10.8 mL) was cooled to –78°C and treated with freshly distilled BF₃·OEt₂ (0.4 mL, 3.22 mmol). After the addition, the ice bath was removed and the reaction was stirred at room temperature for 16 hours then quenched with sat. aq. NaHCO₃ solution and diluted with CH₂Cl₂. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (X2). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (15% EtOAc in hexanes) to give 0.23 g of
\((1R, 5S)-3.4b\) (77%).  \(R_f\) 0.49 (25% EtOAc in hexanes), \([\alpha]^{24}_D = -6.4^\circ\) (c 2.2, EtOAc).  \(^1\)H NMR (C\(_6\)D\(_6\), 250 MHz) \(\delta\) 7.82 (d, 2H, \(J=8.78\) Hz), 6.83 (d, 2H, \(J=8.80\) Hz), 3.52 (d, 1H, \(J=9.76\) Hz), 3.24-3.18 (m, 1H), 2.19-2.12 (m, 1H), 1.94 (s, 3H), 1.88-1.66 (m, 2H), 1.45 (s, 3H), 1.36-1.25 (m, 3H), 1.11-0.99 (m, 3H).  \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 142.3, 139.9, 129.3, 126.5, 66.4, 54.4, 47.2, 37.8, 32.4, 29.9, 24.9, 21.4, 19.3. HRMS for C\(_{15}\)H\(_{21}\)NO\(_2\)S•Na\(^+\) calcd 302.1185, found 302.1189.

\((1R, 6S)-3.4c\)

\((1R, 6S)-6\)-(Methyl-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[4.2.1]nonane ((1\(R\), 6\(S\))-3.4c). A stirred solution of aziridine \((R)-3.1c\) (0.38 g, 1.04 mmol) in CH\(_2\)Cl\(_2\) (10.4 mL) was cooled to –78°C and treated with freshly distilled BF\(_3\)•OEt\(_2\) (0.4 mL, 3.11 mmol). After the addition, the ice bath was removed and the reaction was stirred at room temperature for 23 hours then refluxed for 23 hours. The reaction was diluted with CH\(_2\)Cl\(_2\) and quenched with sat. aq. NaHCO\(_3\) solution. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (X2). The combined organic layers were dried (MgSO\(_4\)), filtered, concentrated, and chromatographed (15% EtOAc in hexanes) to give 0.11 g of \((1R, 6S)-3.4c\) (37%). \(R_f\) 0.46 (25% EtOAc in hexanes), \([\alpha]^{24}_D = -7.9^\circ\) (c 3.5, EtOAc). \(^1\)H NMR (C\(_6\)D\(_6\), 250 MHz) \(\delta\) 7.82 (d, 2H, \(J=7.80\) Hz), 6.85 (d, 2H, \(J=8.78\) Hz), 3.29 (d, 1H, \(J=9.78\) Hz), 3.19-3.12 (m, 1H), 2.69-2.58 (m, 1H), 1.95 (s, 3H), 1.86-1.71 (m, 1H), 1.69-1.12 (m, 9H), 1.43 (s, 3H). \(^13\)C NMR (C\(_6\)D\(_6\), 100 MHz) \(\delta\) 142.1, 139.9, 129.4, 127.5, 68.6, 56.4,
43.7, 40.8, 34.9, 33.5, 28.8, 25.5, 23.9, 21.1. HRMS for C_{16}H_{23}NO_2S•Na^+ calcd 316.1342, found 316.1330.

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\text{NHTs}
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3.119
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4-(\text{N-[(4-methylphenyl)sulfonyl]amino})-1-methylene cyclohexane (3.119). A stirred solution of aziridine (\textbf{R})-3.1a (0.18 g, 0.54 mmol) in CH\_2Cl\_2 (5.4 mL) was cooled to -78°C and treated with freshly distilled BF\_3•OEt\_2 (0.1 mL, 1.09 mmol). The reaction was stirred at -78°C for 1 hour then maintained at 0°C for 16.5 hours. The mixture was quenched with sat. aq. NaHCO\_3 solution then warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH\_2Cl\_2 (X2). The combined organic layers were dried (MgSO\_4), filtered, concentrated, and chromatographed (25% Et\_2O in hexanes) to give 71.6 mg of olefin 3.119 (50%). \( R_f \) 0.37 (25% EtOAc in hexanes). \(^1\text{H NMR (CDCl}_3\text{, 250 MHz) } \delta\) 7.79 (d, 2H, \( J=7.83 \) Hz), 7.30 (d, 2H, \( J=8.80 \) Hz), 4.84 (d, 1H, \( J=6.83 \) Hz), 4.60 (app s, 2H), 3.35-3.21 (m, 1H), 2.43 (s, 3H), 2.26-2.17 (m, 2H), 2.05-1.93 (m, 2H), 1.86-1.68 (m, 2H), 1.38-1.23 (m, 2H). \(^{13}\text{C NMR (CDCl}_3\text{, 100 MHz) } \delta\) 146.5, 143.2, 138.2, 129.6, 126.9, 108.3, 51.8, 34.4, 32.4, 21.5. HRMS for C\_14\text{H}_{19}\text{NO}_2\text{S•Na}^+ calcd 288.1029, found 288.1032.
(1\textit{R}, 5\textit{S})-3-[(4-methylphenyl)sulfonyl]-3-azabicyclo[3.3.1]nonane (3.24). 

Using 9-BBN. A solution of olefin (\textit{R})-3.2b (0.55 g, 1.98 mmol) in THF (4.1 mL) was treated with 9-BBN (15.8 mL, 0.5 M in THF, 7.91 mmol) at room temperature and stirred for 6.5 hours. The reaction was cooled to 0°C and treated with EtOH (4.65 mL) dropwise followed by stirring for 5 minutes to quench the excess 9-BBN. 6 N aq. NaOH (1.6 mL) was added dropwise followed by 30% H₂O₂ (2.9 mL). After the addition, the mixture was refluxed for 1 hour, cooled to room temperature, and diluted with H₂O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (X2). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. ¹H NMR of the crude reaction mixture indicated a 1 : 1 mixture of cis and trans amino alcohols 3.120. The crude mixture was chromatographed (50% EtOAc in hexanes) to give 0.59 g of a mixture of alcohols 3.120 (100%), which was immediately used in the Mitsunobu reaction. Ph₃P (0.57 g, 2.18 mmol) was added to a stirred solution of the alcohol mixture 3.120 (0.59 g, 1.98 mmol) in THF (7.8 mL). The mixture was cooled to 0°C and diethyl azodicarboxylate (0.3 mL, 2.18 mmol) was added dropwise. After the addition, the ice bath was removed and the reaction was warmed to room temperature and stirred for an additional 17 hours. The mixture was concentrated and chromatographed (4% to 10% EtOAc in hexanes) to give 0.28 g of bicycle 3.24 (51% from (\textit{R})-3.2b). 

Using BH₃•THF. A stirred solution of olefin (\textit{R})-3.2b (0.52 g, 1.85 mmol) in THF (3.8 mL) was treated with BH₃•THF (7.4 mL, 1 M in THF, 7.41
mmol) at 0°C then warmed to room temperature and stirred for an additional 6.5 hours. The above oxidation protocol was followed using EtOH (4.7 mL), 6 N aq. NaOH (1.5 mL), and 30% H₂O₂ (2.7 mL). Standard work up gave 0.54 g of a 1 : 2 mixture (via crude ¹H NMR) of cis and trans amino alcohols 3.120 (99%), which was immediately used in the Mitsunobu reaction. Ph₃P (0.53 g, 2.02 mmol) was added to a stirred solution of the alcohol mixture 3.120 (0.54 g, 1.83 mmol) in THF (7.2 mL). The mixture was cooled to 0°C and treated with diethyl azodicarboxylate (0.3 mL, 2.02 mmol) dropwise. After the addition, the ice bath was removed and the reaction was warmed to room temperature and stirred for an additional 15 hours. The mixture was concentrated and chromatographed (4% to 10% EtOAc in hexanes) to give 0.15 g of bicycle 3.24 (30% from (R)-3.2b). Rᵣ 0.43 (25% EtOAc in hexanes). ¹H NMR (CDCl₃, 250 MHz) δ 7.61 (d, 2H, J=7.50 Hz), 7.31 (d, 2H, J=7.50 Hz), 3.75 (d, 2H, J=11.73 Hz), 2.51-2.42 (m, 3H), 2.42 (s, 3H), 1.89-1.85 (m, 4H), 1.73-1.44 (m, 4H), 1.36-1.30 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 143.1, 132.5, 129.4, 127.6, 51.1, 32.4, 30.6, 28.0, 21.4, 20.8. HRMS for C₁₅H₂₁NO₂S•Na⁺ calcd 302.1185, found 302.1169.

Crotyl N-Trifluoroacetylglutamate (4.30). Et₃N (13.9 mL, 100 mmol) and freshly distilled ethyl trifluoroacetate (14.9 mL, 125 mmol) were added to a suspension of glycine (4.29) (7.51 g, 100 mmol) in dry MeOH (50 mL). The mixture was stirred at room temperature for 26 hours, diluted
with dry MeOH (50 mL), cooled to 5˚C, and treated with previously activated Dowex 50 wx8-100 resin (40 g). After stirring for 10 minutes, the resin was filtered off with MeOH and the mixture was concentrated to provide the crude trifluoroacetamide, which was used without purification.

Crotyl alcohol (4.3 mL, 50 mmol) was added to a 0˚C suspension of the crude acid (8.55 g, 50 mmol) in Et₂O (100 mL). A solution of DMAP (0.61 g, 5 mmol) and DCC (10.32 g, 50 mmol) in CH₂Cl₂ (75 mL) was added via cannula. After the addition, the ice bath was removed and the reaction was warmed to room temperature and stirred for an additional 23 hours. The urea was filtered off with CH₂Cl₂ and the organic layer was concentrated. The residue was taken up in CH₂Cl₂ and washed with 1 M HCl and sat. aq. NaHCO₃ solution. The aqueous layers were then extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (30% Et₂O in hexanes) to give 9.27 g of crotyl ester 4.30 (ca. 20:1 E : Z via ¹H NMR) (82% from glycine). Rᵣ 0.26 (15% EtOAc in hexanes). ¹H NMR (CDCl₃, 250 MHz) δ 7.01 (br s, 1H), 5.83 (m, 1H), 5.57 (m, 1H), 4.75* (d, 0.1H, J=6.83 Hz, *signal from minor Z olefin), 4.61 (d, 2H, J=6.83 Hz), 4.11 (d, 2H, J=4.88 Hz), 1.72 (d, 3H, J=6.83 Hz). HRMS for C₇O₃NF₃H₁₀•Na⁺ calcd 248.0505, found 248.0501. Additional analytical data has been previously reported.263
(2R,3S)-3-Methyl-N-(Trifluoroacetyl)-2-aminopent-4-enoic acid (S)-phenethylammonium salt (4.32). A suspension of ester 4.30 (5.00 g, 22.22 mmol), quinine (14.42 g, 44.44 mmol), and Mg(OEt)$_2$ (3.05 g, 26.67 mmol) in THF (225.4 mL) was stirred for 20 minutes at room temperature. The mixture was cooled to –78˚C and treated dropwise with LHMDS (100 mL, 1 M in THF, 100 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 16 hours. The mixture was cooled to 0˚C and quenched dropwise with sat. aq. KHSO$_4$ solution (250 mL). After the addition, the ice bath was removed and the mixture was warmed to room temperature. The white precipitate was filtered off with EtOAc (2 X 100 mL) and the layers were separated. The organic layer was washed with sat. aq. KHSO$_4$ solution (100 mL) then extracted with sat. aq. NaHCO$_3$ solution (3 X 100 mL). The combined basic extracts were acidified to pH 1 with solid KHSO$_4$ then extracted with EtOAc (3 X 100 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated to give 4.08 g of crude acid 4.28 (81%). (S)-(−)-α-methylbenzylamine (3.8 mL, 29.13 mmol) was added to a solution of crude acid 4.28 (7.29 g, 32.37 mmol) in Et$_2$O (323.7 mL). Crystallization at room temperature over days provided 3.82 g of the diastereomeric salt 4.32 (34%). [α]$^2_3$D = −34.4˚ (c = 1.0, CHCl$_3$). $^1$H NMR (CDCl$_3$, 250 MHz) δ 0.86 (d, 3H, J=6.85 Hz), 1.52 (d, 3H, J=6.85 Hz), 1.52 (d, 3H, J=6.85 Hz), 2.51 (m, 1H), 4.01 (br s, 1H), 4.19 (q, 1H, J=6.83 Hz), 4.96 (m, 2H), 5.60 (m, 1H), 6.92 (br s, 1H), 7.34 (s, 5H), 8.47 (br s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 14.8, 21.1, 39.8, 51.2, 58.4, 114.5, 115.3, 126.2, 128.9, 129.1, 205
HRMS for C_{16}O_{3}N_{2}F_{3}H_{22} calcd 347.1577, found 347.1587.

Additional analytical data has been previously reported.\textsuperscript{263}

(2R,3S)-3-Methyl N-[(4-methylphenyl)sulfonyl]-2-aminopent-4-enoate (4.33). The PEA salt 4.32 was dissolved in sat. aq. KHSO\textsubscript{4} solution and extracted with EtOAc (X3). The combined organic layers were dried (MgSO\textsubscript{4}), filtered, and concentrated to give free acid 4.28, which was used without further purification. A solution of free acid 4.28 (0.76 g, 3.39 mmol) in MeOH (128.8 mL) was treated with H\textsubscript{2}O (7.7 mL) and K\textsubscript{2}CO\textsubscript{3} (2.44 g, 17.65 mmol) then refluxed for 16.5 hours. The mixture was cooled to room temperature, acidified to pH 7 using concentrated HCl, and concentrated to provide the crude amino acid salt, which was used without further purification. A suspension of the crude salt (assume 3.39 mmol) in dry MeOH (6.8 mL) was cooled to 0°C and treated carefully with freshly distilled AcCl (1.2 mL, 16.94 mmol). After the addition, the reaction was refluxed for 14.5 hours, cooled to room temperature, and concentrated to provide the crude methyl ester hydrochloride salt, which was used without further purification. A suspension of the crude ester salt (assume 3.39 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (6.8 mL) was cooled to 0°C and treated with Et\textsubscript{3}N (1.2 mL, 8.47 mmol) and TsCl (0.71 g, 3.73 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 13 hours. The mixture was diluted with CHCl\textsubscript{3} and washed with 1 M HCl. The aqueous layer was extracted with CHCl\textsubscript{3}. The combined organic
layers were washed with sat. aq. NaHCO₃ solution, brine, dried (MgSO₄), filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to give 0.83 g of diprotected amino acid 4.33 (82% from acid 4.28). Rf 0.23 (25% EtOAc in hexanes), [α]D²⁵ = -9.0° (c = 5.2, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 7.67 (d, 2H, J=8.80 Hz), 7.24 (d, 2H, J=8.78 Hz), 5.59 (m, 1H), 5.32 (d, 1H, J=10.76 Hz), 5.01 (m, 2H), 3.81 (m, 1H), 3.39 (s, 3H), 2.47 (m, 1H), 2.38 (s, 3H), 0.99 (d, 3H, J=6.83 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 171.0, 143.5, 137.9, 136.7, 129.5, 127.2, 116.7, 59.9, 51.9, 41.4, 21.4, 15.8. HRMS for C₁₄H₁₉NO₄S•Na⁺ calcd 320.0927, found 320.0922. Anal. Calcd for C₁₄NO₄SH₁₉: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.83; H, 6.37; N, 4.64. Chiral HPLC tR = 9.609 min. (>98% ee) (The HPLC trace for ester 4.33 may be found at the end of this chapter).

![Formula](https://example.com/formula.png)

**4.34**

(2R,3S)-3-Methyl-N-[[(4-methylphenyl)sulfonyl]-2-amino-4-pentenol (4.34). A solution of ester 4.33 (1.00 g, 3.35 mmol) in THF (8.4 mL) was cannulated into a 0°C suspension of LiAlH₄ (0.64 g, 16.74 mmol) in THF (6.7 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 20 hours. The reaction was successively quenched dropwise with H₂O (0.64 mL), 15% aq. NaOH (0.64 mL), and H₂O (1.91 mL), stirring for 15 minutes after each addition. The precipitate was filtered off with EtOAc and the mixture was concentrated. Chromatography (40% EtOAc in hexanes) provided 0.83 g of alcohol 4.34 (92%). Rf 0.36 (50% EtOAc in hexanes), [α]D²⁵ = -7.1° (c = 5.2, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 7.76 (d, 2H,
J = 8.80 Hz), 7.28 (d, 2H, J = 8.78 Hz), 5.54 (m, 1H), 5.38 (d, 1H, J = 7.80 Hz), 4.97 (m, 2H), 3.55 (m, 2H), 3.12 (m, 1H), 2.60 (br s, 1H), 2.41 (s, 3H), 2.28 (m, 1H), 0.89 (d, 3H, J = 6.83 Hz). 13C NMR (CDCl3, 100 MHz) δ 143.4, 139.6, 137.8, 129.6, 127.1, 116.0, 62.4, 59.4, 39.6, 21.5, 16.4. HRMS for C13H19SO3N•Na+ calcd 292.0978, found 292.0978. Anal. Calcd for C13SO3NH19: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.03; H, 7.09; N, 5.12. Chiral HPLC tR = 8.977 min. (>98% ee) (The HPLC trace for alcohol 4.34 may be found at the end of this chapter).

Diisopropyl azodicarboxylate (0.2 mL, 1.19 mmol) was added dropwise to a 0°C solution of alcohol 4.34 (0.29 g, 1.09 mmol) and PPh3 (0.31 g, 1.19 mmol) in THF (5.4 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 16 hours. The mixture was concentrated and chromatographed (5 to 15% EtOAc in hexanes) to give 0.23 g of aziridine 4.27 (86%). Rf 0.26 (15% EtOAc in hexanes), [α]25D = -20.5° (c = 5.5, CHCl3). 1H NMR (CDCl3, 250 MHz) δ 7.81 (d, 2H, J = 8.78 Hz), 7.32 (d, 2H, J = 7.83 Hz), 5.67 (m, 1H), 5.02 (m, 2H), 2.63 (d, 1H, J = 6.85 Hz), 2.59 (m, 1H), 2.43 (s, 3H), 2.11 (d, 1H, J = 4.88 Hz), 1.91 (m, 1H), 0.89 (d, 3H, J = 6.83 Hz). 13C NMR (CDCl3, 100 MHz) δ 144.5, 138.6, 134.9, 129.6, 128.0, 115.2, 44.3, 39.3, 32.8, 21.6, 17.1. HRMS for C13H17SO2N•Na+ calcd 274.0872, found 274.0867. Anal. Calcd for C13NSO2H17: C,
62.12; H, 6.82; N 5.57. Found: C, 62.36; H, 6.83; N, 5.48. Chiral HPLC t_R = 6.007 min. (>98% ee) (The HPLC trace for aziridine 4.27 may be found at the end of this chapter).

(2R)-2-[(1S)-1-Methyl-5-[(Trimethylsilyl)methyl]-4-hexenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (4.12b). 9-BBN (9.3 mL, 0.5 M in THF, 4.66 mmol) was added to a 0˚C solution of olefin 4.27 (1.06 g, 4.23 mmol) in THF (20 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 4 hours. H_2O (4.2 mL) and a solution of iodide 4.26^92 (1.19 g, 4.68 mmol) in THF (10 mL) were added to a flask containing Cs_2CO_3 (4.14 g, 12.70 mmol) and PdCl_2(dppf)-CH_2Cl_2 (0.31 g, 0.38 mmol). The organoborane solution was then added via cannula to the iodide flask with an additional THF (3 mL) rinsing. The reaction was stirred in the dark for 17 hours then poured into H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (X2). The combined organic layers were washed with H_2O, brine, dried (MgSO_4), filtered, concentrated, and chromatographed (100% benzene) to give 0.69 g of aziridine-allylsilane 4.12b (43%). R_t 0.36 (15% EtOAc in hexanes), [α]^29_D = -11.3° (c =1.6, CHCl_3). ¹H NMR (CDCl_3, 250 MHz) δ 7.83 (d, 2H, J=7.80 Hz), 7.33 (d, 2H, J=7.80 Hz), 4.84 (t, 1H, J=6.83 Hz), 2.66 (d, 1H, J=6.83 Hz), 2.51 (m, 1H), 2.45 (s, 3H), 2.12 (d, 1H, J=4.88 Hz), 1.96 (q, 2H, J=7.83 Hz), 1.56 (s, 3 H), 1.44 (s, 2H), 1.38-1.21 (m, 3H), 0.77 (d,
$3H, J=6.85$ Hz), -0.01 (s, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 144.3, 135.1, 133.3, 129.5, 128.1, 121.7, 45.6, 34.9, 34.6, 33.4, 29.8, 25.4, 21.6, 18.5, 17.5, -1.3. HRMS for $C_{20}SiNSO_2H_{33}\cdot Na^+$ calcd 402.1893, found 402.1897.

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**4.36** CO$_2$Me

**4.36**

(2S,3R)-3-Methyl $N$-[(4-methylphenyl)sulfonyl]-2-aminopent-4-enoate (4.36). A suspension of ester **4.30** (3.38 g, 15 mmol), quinidine (12.17 g, 37.5 mmol), and Al(Oi-Pr)$_3$ (3.68 g, 18 mmol) in THF (181.7 mL) was stirred for 20 minutes at room temperature. The mixture was cooled to -78°C and treated dropwise with LHMDS (76.5 mL, 1 M in THF, 76.5 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 14 hours. The mixture was cooled to 0°C and quenched dropwise with sat. aq. KHSO$_4$ solution. After the addition, the ice bath was removed and the mixture was warmed to room temperature. The white precipitate was filtered off with EtOAc and the layers were separated. The organic layer was washed with sat. aq. KHSO$_4$ solution then extracted with sat. aq. NaHCO$_3$ solution (X3). The combined basic extracts were acidified to pH 1 with solid KHSO$_4$ then extracted with EtOAc (X3). The combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated to provide 1.82 g of crude acid **4.35** (54%) which was used without further purification. A solution of crude acid **4.35** (1.62 g, 7.19 mmol) in MeOH (273.4 mL) was treated with H$_2$O (16.4 mL) and K$_2$CO$_3$ (5.18 g, 37.47 mmol) then refluxed for 14 hours. The mixture was cooled to room temperature, acidified to pH 7 using...
concentrated HCl, then concentrated to provide a crude amino acid salt, which was used without further purification. A suspension of the crude salt (assume 7.19 mmol) in dry MeOH (14.4 mL) was cooled to 0°C and treated with freshly distilled AcCl (2.6 mL, 35.96 mmol). After the addition, the reaction was refluxed for 17 hours, cooled to room temperature, then concentrated to provide the crude methyl ester hydrochloride salt, which was used without further purification. A suspension of the crude amino ester salt (assume 7.19 mmol) in CH₂Cl₂ (14.4 mL) was cooled to 0°C and treated with Et₃N (2.5 mL, 17.98 mmol) and TsCl (1.51 g, 7.91 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 4 days. The mixture was diluted with CHCl₃ and washed with 1 M HCl. The aqueous layer was extracted with CHCl₃. The combined organic layers were washed with sat. aq. NaHCO₃ solution, brine, dried (MgSO₄), filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to give 1.33 g of ester 4.36 (62% from acid 4.35). Analytical data was the same as that reported for enantiomer 4.33 except [α]²⁷D = +7.0° (c = 4.8, CHCl₃) and chiral HPLC tᵣ = 8.193 min. (ca. 54% ee) (The HPLC trace for ester 4.36 may be found at the end of this chapter).

![Structure of compound 4.37](image)

**(2S,3R)-3-Methyl-N-[(4-methylphenyl)sulfonyl]-2-amino-4-pentenol (4.37).** A solution of ester 4.36 (1.22 g, 4.10 mmol) in THF (10.3 mL) was added via cannula to a 0°C suspension of LiAlH₄ (0.78 g, 20.52 mmol) in THF (8.2 mL). After the addition, the ice bath was removed and the
reaction was stirred for an additional 19 hours. The reaction was successively quenched dropwise with \( \text{H}_2\text{O} \) (0.78 mL), 15% aq. \( \text{NaOH} \) (0.78 mL), and \( \text{H}_2\text{O} \) (2.34 mL), stirring for 15 minutes after each addition. The precipitate was filtered off with \( \text{EtOAc} \) and the mixture was concentrated. Chromatography (40% EtOAc in hexanes) gave 0.98 g of alcohol 4.37 (89%). Analytical data was the same as that reported for enantiomer 4.34 except \([\alpha]^{25}_D = +5.0^\circ \) (c = 6.8, \( \text{CHCl}_3 \)) and chiral HPLC \( t_R = 9.554 \text{ min.} \) (ca. 71% ee) (The HPLC trace for alcohol 4.37 may be found at the end of this chapter).

\[
\text{H}_3\ldots
\]
\[
\text{TsN}
\]

(2S)-2-[(1R)-1-Methyl-2-propenyl]-\( \text{N} \)-[(4-methylphenyl)sulfonyl]aziridine (4.38). Diisopropyl azodicarboxylate (0.7 mL, 3.43 mmol) was added dropwise to a 0°C solution of alcohol 4.37 (0.84 g, 3.12 mmol) and \( \text{PPh}_3 \) (0.90 g, 3.43 mmol) in \( \text{THF} \) (15.6 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 13 hours. The mixture was concentrated and chromatographed (4 to 15% EtOAc in hexanes) to give 0.74 g of aziridine 4.38 (94%). Analytical data was the same as that reported for enantiomer 4.27 except \([\alpha]^{25}_D = +16.1^\circ \) (c = 9.7, \( \text{CHCl}_3 \)) and chiral HPLC \( t_R = 6.539 \text{ min.} \) (ca. 75% ee) (The HPLC trace for aziridine 4.38 may be found at the end of this chapter).
(2R)-2-[5-[(trimethylsilyl)methyl]-4-hexenyl]-N-[(4-methylphenyl)sulfonyl]aziridine (4.39).  9-BBN (7.1 mL, 0.5 M in THF, 3.55 mmol) was added to a 0˚C solution of olefin 3.89 (0.77 g, 3.23 mmol) in THF (20 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 3 hours. H2O (3.2 mL) and a solution of iodide 4.26 (0.90 g, 3.55 mmol) in THF (5.2 mL) were added to a flask containing Cs2CO3 (3.16 g, 9.68 mmol) and PdCl2(dppf)•CH2Cl2 (0.24 g, 0.29 mmol). The organoborane solution was added to the iodide flask via cannula. The reaction was stirred in the dark for 14.5 hours then poured into H2O and Et2O. The layers were separated and the aqueous layer was extracted with Et2O (X2). The combined organic layers were washed with H2O, brine, dried (MgSO4), filtered, concentrated, and chromatographed (100% benzene) to give 0.78 g of aziridine-allylsilane 4.39 (66%). Rf 0.35 (15% EtOAc in hexanes), [α]26 D = -6.1˚ (c = 0.52, CHCl3). 1H NMR (CDCl3, 250 MHz) δ 7.82 (d, 2H, J=7.80 Hz), 7.33 (d, 2H, J=7.80 Hz), 4.82 (t, 1H, J=7.80 Hz), 2.72 (m, 1H), 2.63 (d, 1H, J=6.85 Hz), 2.45 (s, 3H), 2.05 (d, 1H, J=4.88 Hz), 1.92 (q, 2H, J=6.83 Hz), 1.55 (s, 3H), 1.44 (s, 2H), 1.60-1.25 (m, 4H), -0.01 (s, 9H). 13C NMR (CDCl3, 100 MHz) δ 144.3, 135.2, 133.3, 129.6, 121.6, 40.4, 33.7, 30.8, 29.8, 27.4, 27.1, 21.6, 18.6, -1.3. HRMS for C19SiNSO2H31•Na+ calcd 388.1737, found 388.1747.
cis and trans-(1R)-2-(2-Propenyl)-1-[(4-methylphenyl)sulfonyl]aminomethyl-cyclopentane (4.40) and (3aR, 6aS)-N-[(4-Methylphenyl)sulfonyl]-1-methyl-1-
[(trimethylsilyl)methyl]hexahydrocyclopent[a]pyrrole (4.41). A solution of aziridine-
allylsilane 4.39 (0.30 g, 0.83 mmol) in CH₂Cl₂ (8.3 mL) was cooled to −78°C and treated with
freshly distilled BF₃•OEt₂ (0.1 mL, 0.83 mmol). After the addition, the reaction was warmed to 0°C
and maintained at this temperature for 17.5 hours. The mixture was quenched with sat. aq.
NaHCO₃ and warmed to room temperature. The mixture was diluted with CH₂Cl₂ and H₂O and
the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic
layers were washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed
(100% benzene) to first give 57.3 mg of bicycle 4.41 (19%) followed by an inseparable mixture of
142.7 mg of olefins 4.40 (59%, ca. 1.5 : 1 cis : trans). Data for bicycle 4.41: Rf 0.40 (15% EtOAc
in hexanes). ¹H NMR (CDCl₃, 250 MHz) δ 7.71 (d, 2H, J=7.80 Hz), 7.26 (d, 2H, J=7.80 Hz), 3.62
(t, 1H, J=9.76 Hz), 2.92 (dd, 1H, J=15.63, 5.85 Hz), 2.67-2.50 (m, 1H), 2.41 (s, 3H), 2.32-2.22 (m,
1H), 1.91-1.80 (m, 1H), 1.74-1.12 (m, 5H), 1.49 (s, 3H), 1.45 (s, 2H), 0.04 (s, 9H). ¹³C NMR
(CDCl₃, 100 MHz) δ 142.5, 138.6, 129.2, 127.1, 70.7, 56.8, 54.1, 38.8, 31.9, 31.3, 28.2, 26.0,
25.0, 21.4, 0.4. Data for olefins 4.40: Rf 0.27 (15% EtOAc in hexanes), [α]²⁶D = -8.8° (c = 7.3,
CHCl₃). (* denotes signal from minor isomer) ¹H NMR (C₆D₆, 250 MHz) δ 7.95-7.91 (two
overlapping d, 4.15H), 6.87-6.82 (two overlapping d, 4.20H), 5.63 (t, 1H, J=5.88 Hz), 5.55* (t, 0.68H, J=6.83 Hz), 4.70-4.68 (two overlapping app s, 3.24H), 4.60* (app s, 0.82H), 3.08-3.06 (m, 1.26H), 2.91-2.82* (m, 0.90H), 2.78-2.65 (m, 1.04H), 2.62-2.54* (m, 0.53H), 2.13-2.08 (m, 2.14H), 1.92 (s, 3H), 1.90* (s, 3H), 1.86-1.68 (m, 2.03H), 1.57* (s, 3H), 1.50 (s, 3H), 1.57-1.14 (m, 12.79H). 13C NMR (CDCl3, 100 MHz) δ 147.3, 145.5*, 143.2, 143.1*, 137.1*, 137.0, 129.6, 129.6*, 127.0, 127.0*, 111.0, 110.9*, 52.1*, 49.3, 47.5, 44.1*, 42.4, 40.8*, 31.7, 30.1*, 29.0, 27.6*, 23.8, 23.3, 23.3*, 22.6*, 21.4, 19.1*. HRMS for C16NSO2H23•Na+ calcd 316.1342, found 316.1344.

\[ \text{cis and trans-(1R, 5S)-2-(2-Propenyl)-5-methyl-1-[4-methylphenyl)sulfonyl]aminomethyl-cyclopentane (4.11) and (1S, 3S, 6S)-3-(2-Propenyl)-6-methyl-1-[4-methylphenyl)sulfonyl]amino-cyclohexane (4.44).} \]

A solution of aziridine-allylsilane 4.12b (0.60 g, 1.59 mmol) in CH2Cl2 (15.9 mL) was cooled to −78°C and treated with freshly distilled BF3•OEt2 (0.2 mL, 1.59 mmol). After the addition, the reaction was warmed to 0°C and maintained at this temperature for 20 hours. The mixture was quenched with sat. aq. NaHCO3 and warmed to room temperature. The mixture was diluted with CH2Cl2 and H2O and the layers were separated. The aqueous layer was extracted with CH2Cl2. The combined organic layers were washed with brine, dried (MgSO4), filtered, concentrated, and chromatographed (100%
benzene) to first give an inseparable mixture of 57.4 mg of cyclopentanes **4.11** (12%, ca. 2.2:1 *cis*: *trans*) followed 162.5 mg of cyclohexane **4.44** (33%). Data for cyclopentanes **4.11**: $R_f$ 0.42 (100% benzene), $[\alpha]_{D}^{24} = +41.0^\circ$ (c = 3.1, CHCl$_3$). († denotes signal from minor isomer) $^1$H NMR (C$_6$D$_6$, 250 MHz) $\delta$ 7.88 (two overlapping d, 3.61H), 6.85-6.80 (two overlapping d, 3.62H), 5.29 (t, 1H, $J$=6.83 Hz), 5.16† (t, 0.46H, $J$=5.88 Hz), 4.74-4.68 (three overlapping app s, 2.93H), 4.62 (app s, 0.58H), 3.06-2.87 (m, 1.88H), 2.92-2.73 (m, 1.77H), 2.73-2.62 (m, 0.51H), 2.32† (q, 0.54H, $J$=6.83 Hz), 2.11 (q, 1.16H, $J$=6.83 Hz), 1.91 (s, 3H), 1.88† (s, 3H), 1.83-1.63 (m, 0.75H), 1.55† (s, 3H), 1.52 (s, 3H), 1.60-1.48 (m, 1.66H), 1.44-1.22 (m, 2.86H), 1.12-0.96 (m, 0.66H), 0.92-0.88 (two overlapping d, 5.76H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 148.3, 146.1†, 143.2, 143.2†, 137.0†, 136.9, 129.6, 129.6†, 127.1, 127.0†, 111.4†, 111.2, 53.0, 49.4†, 48.3, 48.1†, 46.2, 44.4, 37.7, 37.2†, 33.1, 33.1†, 29.6, 28.6†, 23.1†, 23.1, 21.5†, 21.5, 19.4, 18.8†. HRMS for C$_{17}$NSO$_2$H$_{25}$•Na$^+$ calcd 330.1498, found 330.1505. Data for cyclohexane **4.44**: $R_f$ 0.30 (100% benzene), $[\alpha]_{D}^{24} = +81.0^\circ$ (c = 8.3, CHCl$_3$). $^1$H NMR (C$_6$D$_6$, 250 MHz) $\delta$ 7.96 (d, 2H, $J$=7.80 Hz), 6.84 (d, 2H, $J$=7.83), 5.54 (d, D$_2$O-exchangeable, 1H, $J$=8.78 Hz), 4.66 (app s, 1H), 4.63 (app s, 1H), 2.92 (m, 1H), 2.00-1.90 (m, 1H), 1.90 (s, 3H), 1.73-1.63 (m, 1H), 1.49-1.34 (m, 2H), 1.49 (s, 3H), 1.15-0.75 (m, 4H), 0.91 (d, 3H, $J$=6.83 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 148.8, 143.0, 138.6, 129.5, 126.9, 108.6, 59.2, 44.3, 39.8, 38.2, 34.1, 30.7, 21.4, 20.8, 18.8. HRMS for C$_{17}$NSO$_2$H$_{25}$•Na$^+$ calcd 330.1498, found 330.1508.
(2R,3S)-3-Methyl N-[methylsulfonyl]-2-aminopent-4-enoate (4.47). The PEA salt 4.32 was dissolved in sat. aq. KHSO₄ solution and extracted with EtOAc (X3). The combined organic layers were dried (MgSO₄), filtered, and concentrated to give the free acid 4.28, which was used without further purification. A solution of free acid 4.28 (1.71 g, 7.61 mmol) in MeOH (289.2 mL) was treated with H₂O (17.4 mL) and K₂CO₃ (5.48 g, 39.64 mmol) then refluxed for 18 hours. The mixture was cooled to room temperature, acidified to pH 7 using concentrated HCl, then concentrated to provide the crude amino acid salt, which was used without further purification. A suspension of the crude salt (assume 7.61 mmol) in dry MeOH (15.2 mL) was cooled to 0°C and treated with freshly distilled AcCl (2.7 mL, 38.04 mmol). After the addition, the reaction was refluxed for 19 hours, cooled to room temperature, then concentrated to provide the crude methyl ester hydrochloride salt, which was used without further purification. A suspension of the crude amino ester salt (assume 7.61 mmol) in CH₂Cl₂ (15.2 mL) was cooled to 0°C and treated with Et₃N (2.7 mL, 19.02 mmol) and freshly distilled MsCl (0.7 mL, 8.37 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 16.5 hours. The mixture was diluted with CHCl₃ and washed with 1M HCl. The aqueous layer was extracted with CHCl₃. The combined organic layers were washed with sat. aq. NaHCO₃ solution, brine, dried (MgSO₄), filtered, concentrated, and chromatographed (35% EtOAc in hexanes) to give 1.11 g of the N-mesylated methyl ester 4.47 (66% from acid 4.28). Rᵢ 0.34 (40% EtOAc in hexanes), [α]D = -
5.4˚ (c = 3.2, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 5.74 (m, 1H), 5.14 (m, 3H), 4.07 (m, 1H), 3.76 (s, 3H), 2.93 (s, 3H), 2.66 (m, 1H), 1.04 (d, 3H, J=6.85 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 171.7, 138.1, 116.8, 59.9, 52.4, 41.3, 40.9, 15.1.  HRMS for C₈H₁₅NO₄S•Na⁺ calcd 244.0614, found 244.0607.

(2R, 3S)-3-Methyl-N-[methylsulfonyl]-2-amino-4-pentenol (4.48). A solution of ester 4.47 (1.04 g, 4.69 mmol) in THF (11.7 mL) was added via cannula to a 0˚C suspension of LiAlH₄ (0.89 g, 23.43 mmol) in THF (9.4 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 16 hours. The reaction was successively quenched dropwise with H₂O (0.89 mL), 15% aq. NaOH (0.89 mL), and H₂O (2.67 mL), stirring for 15 minutes after each addition. The precipitate was filtered off with EtOAc and the mixture was concentrated. Chromatography (65% EtOAc in hexanes) provided 0.83 g of alcohol 4.48 (92%). Rf 0.18 (65% EtOAc in hexanes), [α]²⁷D = -9.7˚ (c = 2.6, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 5.73 (m, 1H), 5.11 (m, 3H), 3.73 (dd, 1H, J=3.93, 2.93 Hz), 3.59 (dd, 1H, J=5.85, 5.88 Hz), 3.33 (m, 1H), 3.03 (s, 3H), 2.64 (br s, 1H), 2.41 (m, 1H), 1.09 (d, 3H, J=6.83 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 139.8, 116.2, 63.2, 59.9, 41.8, 40.2, 16.5.  HRMS for C₇H₁₅SO₃N•Na⁺ calcd 216.0665, found 216.0653.
(2R)-2-[(1S)-1-Methyl-2-propenyl]-N-[methylsulfonyl]aziridine (4.49). Diisopropyl azodicarboxylate (0.9 mL, 4.43 mmol) was added dropwise to a 0 °C solution of alcohol 4.48 (0.78 g, 4.03 mmol) and PPh₃ (1.16 g, 4.43 mmol) in THF (20.1 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 65 hours. The mixture was concentrated and chromatographed (4 to 30% EtOAc in hexanes) to give 0.64 g of aziridine 4.49 (91%). Rᵣ 0.48 (40% EtOAc in hexanes), [α]₂⁵^D = -74.4° (c = 5.0, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 5.76 (m, 1H), 5.09 (m, 2H), 3.03 (s, 3H), 2.61 (m, 1H), 2.55 (d, 1H, J = 6.85 Hz), 2.14 (d, 1H, J = 3.90 Hz), 2.06 (m, 1H), 1.13 (d, 3H, J = 6.85 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 138.5, 115.4, 43.5, 39.4, 38.9, 32.3, 17.0. HRMS for C₇H₁₅SO₂N⁺Na⁺ calcd 198.0559, found 198.0560.

(2R)-2-[(1S)-1-Methyl-5-[(trimethylsilyl)methyl]-4-hexenyl]-N-[methylsulfonyl]aziridine (4.50). 9-BBN (3.3 mL, 0.5 M in THF, 1.64 mmol) was added to a 0 °C solution of olefin 4.49 (0.26 g, 1.49 mmol) in THF (11.6 mL). After the addition, the ice bath was removed and the reaction
was stirred for an additional 5 hours. H₂O (1.5 mL) and a solution of iodide 4.26 (0.42 g, 1.64 mmol) in THF (5 mL) were added to a flask containing Cs₂CO₃ (1.46 g, 4.48 mmol) and PdCl₂(dppe)•CH₂Cl₂ (0.11 g, 0.13 mmol). The organoborane solution was added via cannula to the iodide flask with an additional THF (1.6 mL) rinsing. The reaction was stirred in the dark for 19 hours then poured into H₂O and Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O (X2). The combined organic layers were washed with H₂O, brine, dried (MgSO₄), filtered, concentrated, and chromatographed (100% benzene) to give 155.1 mg of aziridine-allylsilane 4.50 (34%). \( R \delta 0.41 \) (25% EtOAc in hexanes). \( ^1H \) NMR (CDCl₃, 250 MHz) \( \delta 4.89 \) (t, 1H, \( J=6.83 \) Hz), 3.07 (s, 3H), 2.61 (d, 1H, \( J=6.83 \) Hz), 2.54 (m, 1H), 2.1 (d, 1H, \( J=4.90 \) Hz), 2.04 (q, 2H, \( J=6.83 \) Hz), 1.57 (s, 3H), 1.46 (s, 2H), 1.45-1.27 (m, 3H), 1.06 (d, 3H, \( J=5.85 \) Hz), 0.00 (s, 9H). \( ^13C \) NMR (CDCl₃, 100 MHz) \( \delta 133.5, 121.6, 45.0, 39.4, 34.8, 34.6, 33.0, 29.8, 25.4, 18.6, 17.7, -1.3. \)

(1R)-5-Methyl-N-[(4-methylphenyl)sulfonyl]-3-azabicyclo[4.3.0]nonane (4.61). BH₃•THF (2.8 mL, 1 M in THF, 2.82 mmol) was added to solution of olefin 4.40 (0.21 g, ca. 2 : 1 cis : trans, 0.71 mmol) in THF (1.45 mL). After the addition, the reaction was stirred at room temperature for 15 hours then cooled to 0°C. EtOH (1.7 mL) was added dropwise and the mixture was stirred for 5
minutes. 6 N NaOH (0.6 mL) was added dropwise followed by 30% H₂O₂ (1.0 mL). After the addition, the mixture was heated to reflux for 1 hour then cooled to room temperature. The reaction was poured into EtOAc and H₂O and the layers were separated. The aqueous layer was extracted with EtOAc (x2). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated to provide 209.6 mg (95%) of a mixture of amino alcohols 4.60, which was used without purification. The crude mixture of amino alcohols 4.60 (assume 0.71 mmol) was dissolved in THF (3.5 mL) and treated with Ph₃P (0.20 g, 0.78 mmol). The mixture was cooled to 0˚C and treated with diisopropyl azodicarboxylate (0.2 mL, 0.78 mmol). After the addition, the ice bath was removed and the reaction was stirred for an additional 18.5 hours. The mixture was concentrated and chromatographed (100% benzene) to provide 158.7 mg of an inseparable mixture of azabicycle 4.61 diastereomers (77% from 4.40, ca. 4.2 : 1 C-5 epimers). Rᵣ 0.34 (15% EtOAc in hexanes), [α]²⁴ₑ = +29.9° (c = 1.6, CHCl₃). ¹H NMR (CDCl₃, 250 MHz) δ 7.65-7.62 (overlapping d, 2.43 H), 7.33-7.27 (overlapping d, 2.69H), 4.03-3.97 (m, 0.36H), 3.80-3.78 (m, 0.06H), 3.76-3.73 (m, 0.06H), 3.68 (m, 0.11H), 3.64-3.63 (m, 0.12H), 3.51-3.41 (m, 1.72H), 2.64 (d, 0.34H, J= 3.93 Hz), 2.59 (d, 0.32H, J=3.90 Hz), 2.43 (s, 3.69H), 2.35 (d, 0.13H, J=2.93 Hz), 2.30 (d, 0.12H, J=2.93 Hz), 2.05-1.91 (m, 2.06H), 1.87-1.80 (m, 0.24H), 1.78-1.44 (m, 7.25H), 1.44-1.17 (m, 1.16H), 1.17-1.04 (m, 0.26H), 0.99 (d, 0.71H, J=6.83 Hz), 0.86 (d, 3H, J=5.88 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 143.1, 143.0, 133.6, 129.6, 129.5, 129.4, 127.5, 127.5, 127.5, 127.5, 127.4, 52.9, 52.5, 51.8, 51.7, 51.4, 48.0, 47.2, 47.1, 46.3, 44.4, 43.9, 43.0, 38.7, 38.6, 36.8, 36.1, 30.9, 30.7, 30.1, 29.0, 28.2, 28.2, 27.8, 27.6, 26.6, 26.5, 22.0, 21.6, 21.4, 21.4, 21.0, 17.5, 17.1, 17.0, 11.2. HRMS for C₁₆NSO₂H₂₃•Na⁺ calcd 316.1342, found 316.1342.
(1S, 5S, 8S)-4,8-Dimethyl-N-[(4-methylphenyl)sulfonyl]-2-azabicyclo[3.3.1]nonane (4.63).

BH₃•THF (2.1 mL, 1 M in THF, 2.11 mmol) was added to a solution of olefin 4.44 (0.16 g, 0.53 mmol) in THF (1.1 mL). After the addition, the reaction was stirred for 15 hours then cooled to 0°C. EtOH (1.2 mL) was added dropwise and the mixture was stirred for 5 minutes before adding 6 N NaOH (0.4 mL) and 30% H₂O₂ (0.8 mL). The mixture was refluxed for 1 hour then cooled to room temperature and diluted with H₂O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (X2). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated to give 165.7 mg of amino alcohol 4.62 (96%), which was used without further purification. Diisopropyl azodicarboxylate (0.1 mL, 0.58 mmol) was added dropwise to a 0°C solution of alcohol 4.62 (0.17 g, 0.53 mmol) and PPh₃ (0.15 g, 0.58 mmol) in THF (2.6 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 23.5 hours. The mixture was concentrated and chromatographed (100% benzene) to give 80.9 mg of bicycle 4.63 (50% from olefin 4.44) as a single diastereomer. Rᵣ 0.41 (15% EtOAc in hexanes), [α]²³_D = -15.9° (c = 1.1, CHCl₃). ¹H NMR (C₆D₆, 250 MHz) δ 7.77 (d, 2H, J=7.83 Hz), 6.83 (d, 2H, J=7.83 Hz), 3.67-3.60 (m, 2H), 2.49-2.41 (m, 2H), 2.09-1.92 (m, 2H), 1.92 (s, 3H), 1.67-1.61 (m, 1H), 1.39-1.22 (m, 1H), 1.19-0.78 (m, 4H), 0.86 (d, 3H, J=7.80 Hz), 0.59 (d, 3H, J=6.83 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 142.9, 135.3, 129.5, 127.3, 54.7, 47.5.
33.3, 32.5, 32.3, 26.5, 22.6, 21.6, 21.4, 20.3, 16.7. HRMS for C_{17}NSO_{2}H_{25} Na\(^{+}\) calcd 330.1498, found 330.1497.

(1\(R\), 9\(S\))-5,9-Dimethyl-N-[(4-methylphenyl)sulfonyl]-3-azabicyclo[4.3.0]nonane (4.65).

BH\(_{3}\)•THF (0.9 mL, 1 M in THF, 0.93 mmol) was added to a 0˚C solution of olefin 4.11 (71.3 mg, 0.23 mmol, ca. 2 : 1 cis : trans) in THF (1.4 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 20.5 hours. The mixture was diluted with 1 mL of THF then cooled to 0˚C. EtOH (0.6 mL) was added dropwise and the mixture was stirred for 5 minutes before adding 6 N NaOH (0.2 mL) and 30% H\(_{2}\)O\(_{2}\) (0.3 mL). The mixture was refluxed for 1 hour then cooled to room temperature and diluted with H\(_{2}\)O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (X2). The combined organic layers were washed with brine, dried (MgSO\(_{4}\)), filtered, and concentrated to give 71.1 mg of amino alcohol 4.64 (94%), which was used without further purification. Diisopropyl azodicarboxylate (0.05 mL, 0.26 mmol) was added dropwise to a 0˚C solution of alcohol 4.64 (75.8 mg, 0.23 mmol) and PPh\(_{3}\) (67.2 mg, 0.26 mmol) in THF (1.2 mL). After the addition, the ice bath was removed and the reaction was stirred for an additional 19.5 hours. The mixture was concentrated and chromatographed (2 to 15% EtOAc in hexanes) to give 43.9 mg of bicycle 4.65 (62% from olefin
4.11) as an inseparable mixture of diastereomers. \( R_f \) 0.41 (15% EtOAc in hexanes). \(^1\mathrm{H}\) NMR (C\(_6\)D\(_6\), 250 MHz) \( \delta \) 7.77-7.68 (overlapping d, 2H), 6.88-6.85 (overlapping d, 2.05H), 4.22-4.16 (m, 0.68H), 3.72-3.67 (overlapping app s, 1.28H), 2.31 (d, 0.16H, \( J=3.90 \) Hz), 2.27 (d, 0.16H, \( J=3.90 \) Hz), 2.06 (d, 0.27H, \( J=2.95 \) Hz), 2.02 (d, 0.27H, \( J=3.90 \) Hz), 1.94 (s, 3H), 1.80-1.41 (m, 1.01H), 1.43-0.98 (m, 1.93H), 0.98-0.90 (overlapping d, 3.02H), 0.85-0.61 (m with overlapping d, 2.75H), 0.61-0.52 (overlapping d, 1.72H). \(^{13}\mathrm{C}\) NMR (CDCl\(_3\), 100 MHz) \( \delta \) 143.1, 143.1, 133.8, 133.5, 129.6, 129.5, 129.5, 127.6, 127.5, 127.5, 53.0, 52.2, 51.7, 51.6, 48.0, 47.0, 45.6, 44.9, 43.6, 36.6, 33.0, 32.2, 31.7, 31.6, 30.2, 27.6, 25.3, 21.5, 19.2, 18.7, 17.3, 11.2. HRMS for C\(_{17}\)NSO\(_2\)H\(_2\)\textsuperscript{•}Na\(^+\) calcd 330.1498, found 330.1510. Crystallization in Et\(_2\)O at room temperature over days followed by X-ray analysis confirmed the structure of bicycle 4.65a ((1\(R\), 5\(R\), 6\(R\), 9\(S\))-5,9-Dimethyl-N-[(4-methylphenyl)sulfonyl]-3-azabicyclo[4.3.0]nonane) (Figure 4.1).
Figure 5.1: Chiral HPLC trace of racemic ester mixture.
Figure 5.2: Chiral HPLC trace of ester from non-PEA / quinidine series.
Figure 5.3: Chiral HPLC trace of ester from PEA / quinine series.

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168
Figure 5.4: Chiral HPLC trace of racemic alcohol mixture.
Figure 5.5: Chiral HPLC trace of alcohol from non-PEA / quinidine series.
Figure 5.6: Chiral HPLC trace of alcohol from PEA / quinine series.
Figure 5.7: Chiral HPLC trace of racemic aziridine mixture.
Figure 5.8: Chiral HPLC trace of aziridine from non-PEA / quinidine series.
Figure 5.9: Chiral HPLC trace of aziridine from PEA / quinine series.
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