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ABSTRACT

Iminoacetonitriles participate as reactive dienophiles in intermolecular and intramolecular Diels-Alder cycloadditions leading to quinolizidines, indolizidines, and piperidines. The resultant α-amino nitrile cycloadducts are versatile synthetic intermediates which can be further elaborated by stereoselective alkylation, reduction, reductive cyclization, and Bruylants reactions. The first part of this thesis describes the full details of our studies on the synthesis of iminoacetonitriles, the scope of their Diels-Alder reactions, and the synthetic elaboration of the α-amino nitrile cycloadducts to provide access to a variety of substituted quinolizidine and indolizidine derivatives. The second part of this thesis reports on the total synthesis of quinolizidine (−)-217A and our efforts directed toward the total synthesis of indolizidine (−)-235B'.

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Acknowledgments

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Part I

Introduction and Background
Chapter 1 – Introduction

Cyclization and Annulation Strategies

The vast number of natural products and pharmaceutical agents that contain a ring system has motivated our research group’s interest in developing practical, reliable, and efficient methods for the preparation of cyclic and polycyclic molecules. Cyclizations and annulations\(^1\) represent the two general strategies for constructing cyclic systems (Scheme 1). A cyclization strategy involves the intramolecular formation of one new bond whereas an annulation strategy involves the formation of two new bonds in either an intramolecular or intermolecular fashion to form the cyclic structure. With the formation of two new bonds, annulations provide a more convergent and powerful strategy than cyclizations for the synthesis of cyclic compounds. Annulation strategies also provide the possibility of creating multiple stereocenters in a single step, and intramolecular versions allow for the efficient and rapid assembly of polycyclic systems.

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Cycloadditions of Conjugated Enynes

Cycloaddition reactions comprise the most common type of annulation and rank among the most powerful transformations available to synthetic chemists. The Diels-Alder cycloaddition, first reported in 1928 by Otto Diels and Kurt Alder, is perhaps the most important of all six-membered ring-forming reactions and has been widely employed as the pivotal step in numerous natural product syntheses. The [4+2] cycloaddition reaction of dienes and "dienophiles," each of which can incorporate a wide range of functionality, allows access to a diverse range of carbocyclic and heterocyclic molecules. In recent years, our laboratory has explored the possibility of reacting an enyne with an enynophile, in a process akin to the Diels-Alder cycloaddition, to form new aromatic and dihydroaromatic systems (Scheme 2).

Scheme 2

Despite a few scattered reports in the literature describing intramolecular [4+2] cycloadditions of conjugated enynes, the generality and scope of this fascinating reaction remained undefined until our laboratory began to investigate this transformation as an efficient route to highly substituted aromatic and heteroaromatic compounds. In 1994, our laboratory was the first to report studies that established the feasibility of these cycloadditions as a practical

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method for organic synthesis and discussed possible mechanisms for these reactions.\(^5\) Subsequent work in our group has demonstrated that enyne cycloadditions can be conducted under thermal conditions, as well in the presence of protic and Lewis acids, with a variety of substituents on the enyne, enynophile, and connecting tether.\(^6\)

Our laboratory has also investigated the possibility of incorporating a heteroatom into the enyne or enynophile in variants of the cycloaddition leading to heterocyclic molecules. Initially, we explored the feasibility of replacing a carbon atom in the enyne with an oxygen atom as shown in eq 1. Melanie Wills discovered that the \([4+2]\) cycloaddition of conjugated alkynyl carbonyl compounds provides access to dihydroisobenzofurans with a variety of functionality (eq 1).\(^7\)

\[
\begin{array}{c}
\text{R}_1 \\
\text{X} \\
\text{Z} \\
\text{Z} \\
\hline \\
\end{array}
\quad \rightarrow 
\begin{array}{c}
\text{R}_1 \\
\text{X} \\
\text{Z} \\
\end{array}
\]

Next, we became interested in the development of new types of activated imine derivatives with the ability to function as reactive \(2\pi\) components. For example, the ability to use an imine as a reactive \(2\pi\) component would allow access to substituted nitrogen heterocycles and would provide a powerful extension of the scope of the enyne cycloaddition.

Examination of the literature on activated imines that participate in related cycloadditions revealed that none of the conventional imine derivatives were ideal for the enyne cycloadditions we envisioned.\(^8\) We consequently turned our attention to \textit{iminoacetonitriles}, a class of electron-deficient imines whose cycloaddition chemistry had not previously been examined. Our interest


\(^7\) For a discussion regarding the scope and mechanism of this cycloaddition, see Wills, M. S. B.; Danheiser, R. L. \textit{J. Am. Chem. Soc.} \textbf{1998}, \textit{120}, 9378.

\(^8\) For a discussion of \([4+2]\) cycloadditions of imines, see Chapter 2.
in this class of imines derived from the expectation that they should function as reactive partners in a variety of cycloaddition and annulation processes, providing access to cyclic α-amino nitriles of diverse ring size (Scheme 3). α-Amino nitriles are exceptionally versatile intermediates for the synthesis of nitrogen heterocycles. Metalation provides opportunities for alkylation and other carbon-carbon bond-forming processes, while exposure to Lewis acids furnishes iminium ions which can be intercepted with Grignard reagents (Bruylants reaction) and organosilanes, or engaged in Mannich reactions and other useful "cation-π"-type cyclization processes.  

Scheme 3

In fact, it appeared to us that iminoacetonitriles would be a valuable 2π component in a variety of different annulation and cycloaddition processes including, in particular, the hetero Diels-Alder reaction. To place our work in perspective, the next chapter provides a brief

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overview on the *state of the art* with regard to imino dienophiles in intramolecular and intermolecular aza Diels-Alder cycloadditions.
Chapter 2 – Diels-Alder Reactions of Imino Dienophiles

The development of imine derivatives as $2\pi$ components in aza Diels-Alder reactions has greatly facilitated the ease with which nitrogen heterocycles can be synthesized in an efficient manner. This chapter provides a brief overview of the most commonly used imino dienophiles in intermolecular and intramolecular Diels-Alder cycloadditions. This discussion will emphasize the reactions of “activated” imines, since these imines tend to be the most reactive in hetero $[4+2]$ cycloadditions. Although simple unactivated imines can participate as $2\pi$ components in Diels-Alder cycloadditions, these reactions often require harsh conditions and tend to be limited in substrate scope. The two general approaches employed to activate imine derivatives involve (a) attaching an electron-withdrawing group to the carbon and/or nitrogen of the imine, and (b) the use of the iminium ions as dienophiles.

Intermolecular Diels-Alder Reaction of Imino Dienophiles

The use of activated imines as dienophiles in the intermolecular Diels-Alder reaction has attracted considerable attention. Among the most important classes of activated imino dienophiles are $N$-sulfonylimines (e.g., 1), $N$-acylimines (e.g., 2 and 3), $C$-acylimines

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(e.g., 4), oximino ester derivatives (e.g., 5\textsuperscript{15} and 6\textsuperscript{16}), and iminium ions (e.g., 7).\textsuperscript{17,18} Although several types of imino dienophiles exist for the aza Diels-Alder reaction, the most useful are the C-acylimines developed by Bailey and coworkers and these imines will be the focus of this section.

![Chemical Structures]

Bailey and coworkers have shown that the C-acylimine 9 represents the state of the art for imino dienophiles in terms of ease of synthesis, substrate scope, stereocontrol, and synthetic utility of the resulting Diels-Alder cycloadducts.\textsuperscript{19} Imine 9 was synthesized in 94% yield as a stable white solid by simply stirring ethyl glyoxylate hydrate with benzhydrylamine (eq 2). Reaction of imine 9 with a variety of dienes in the presence of 1 equiv of TFA in trifluoroethanol delivers the desired cycloadducts 10-14 in 42-95% yield. In the case of acyclic dienes, the \textit{endo}


cycloadduct is formed exclusively with complete regiocontrol. However, in the case of cyclic dienes (e.g., cyclopentadiene and cyclohexadiene), the exo cycloadduct is formed predominantly (>97:3). Also, reaction of imine 14 with trans-2,4-hexadiene occurs with suprafacial addition to give the cis-substituted cycloadduct 14 consistent with the Woodward-Hoffmann rules.20

Bailey and coworkers have extended this chemistry to include asymmetric reactions by using imines such as 15 with a 1-phenylethyl auxiliary on nitrogen; both enantiomeric forms of this imine are readily available. Cycloadditions of chiral imine 15 with cyclic dienes provide products with good asymmetric induction (84-100% de), but reactions with acyclic dienes produce products with varying levels of selectivity (26-68% de).21 However, Bailey has shown that excellent asymmetric induction for acyclic dienes can be achieved if a second matched chiral auxiliary is introduced into the ester functionality (e.g., 16).22 Finally, Bailey and coworkers have demonstrated the synthetic utility of the cycloadducts of these reactions by applications to the efficient total synthesis of pinidine23 and the asymmetric synthesis of pipecolic acid.

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derivatives. However, it is important to note that Bailey’s methodology only provides access to cis-2,6-disubstituted piperidines. Several important natural products possess a trans-2,6-disubstituted piperidine, and thus a method that would allow access to both diastereomers would be a valuable addition to synthetic methodology.

![Structures 15, 16, and Pinidine]

**Intramolecular Diels-Alder Reactions of Imino Dienophiles**

The most extensive investigations of the intramolecular imino Diels-Alder reaction have been carried out by Weinreb and Grieco using N-acylimines and iminium ions, respectively. Weinreb’s strategy employs the thermolysis of N-acetoxymethyl amides 17 to generate N-acylimines 18 as reactive dienophiles which then undergo cycloaddition in situ (eq 3). By varying the length of the tether, Weinreb and coworkers have synthesized both indolizidines \( n = 1 \) and quinolizidines \( n = 2 \) 19 using this approach.

$$\begin{align*}
\text{OAc} & \quad \text{n} = 1,2 \\
\text{17} & \quad 180-370 \degree \text{C} \\
\text{-AcOH} & \\
\text{18} & \quad \text{19} \\
\end{align*}$$

---


In some cases, Weinreb obtained cycloadducts with excellent stereoselectivity as illustrated with the example shown in eq 4. This cycloaddition apparently proceeds via a transition state where the carbonyl group adopts an \textit{endo} orientation and the benzyloxyethyl group is pseudoequatorial on the developing six-membered ring.\textsuperscript{26} However, in cycloadditions leading to indolizidines, the level of stereoselectivity drops significantly with respect to the allylic substituent.\textsuperscript{27}

\begin{equation}
\text{OR} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{OAc}
\end{array} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{OR}
\end{array}
\end{equation}

180 °C, 2 h
dichlorobenzene

Weinreb and coworkers extended their method to include imine dienophiles bearing acyl groups on both carbon and nitrogen.\textsuperscript{28} For example, thermolysis of 20 affords imine 21 which then undergoes Diels-Alder cycloaddition to afford the bicyclic carbamate 22 as a single diastereomer in 83% yield. It was suggested that the \textit{N}-acyl group, rather than the \textit{C}-acyl group, occupies an \textit{endo} orientation with the alkyl substituent in a pseudoequatorial position in the transition state. Weinreb and coworkers have applied this elegant methodology to the total of synthesis of several natural products including \textit{epi}-lupinine,\textsuperscript{26} slaframime,\textsuperscript{27} and anhydrocannabiniasativene.\textsuperscript{29}

Grieco and coworkers have shown that simple iminium ions generated in situ undergo smooth Diels-Alder cycloadditions to give nitrogen heterocycles.\textsuperscript{30} For example, addition of dienyl amines 23 to aqueous HCl and formaldehyde leads to the expected indolizidine 25 or quinolizidine 26 in good to excellent yield via cycloaddition of the corresponding iminium ions 24. Unfortunately, Grieco reports that utilizing other aldehydes in place of formaldehyde (such as acetaldehyde) lead to low yields and a complex mixture of products. Consequently, this method does not provide access to C-4 substituted quinolizidines or indolizidines. Although Wang and coworkers have shown that lanthanide triflates catalyze intermolecular cycloadditions of simple iminium ions,\textsuperscript{18} the use of lanthanide triflates for related intramolecular cycloadditions has not been reported.

Unlike Weinreb’s N-acylimines, iminium ions do not react with good stereocontrol in Diels-Alder reactions. For example, treatment of dienyl aldehyde 27 with aqueous ammonium chloride delivers cycloadducts 28a and 28b as a 69:31 mixture of diastereomers in 55\% yield (eq 7).\textsuperscript{31} It is also important to note that by using a dienyl aldehyde such as 27 instead of a dienyl


amine, Grieco has extended the methodology to the synthesis of nitrogen heterocycles in which the nitrogen atom is not located at the ring juncture of the new bicyclic system.

\[
\begin{align*}
\text{NH}_4\text{Cl, EtOH/H}_2\text{O} & \quad 75^\circ\text{C, 48 h} \\
\text{H}_3\text{C} & \quad \text{Pr} \\
\text{CHO} & \\
27 & \quad 55\% \\
\text{H}_3\text{C} & \quad \text{H} \\
\text{H} & \quad \text{Pr} \\
\text{N} & \\
\text{Pr} & \quad \text{H} \\
\text{H} & \quad \text{Pr} \\
\text{H} & \\
\text{28a} & \quad 69:31 \\
\text{H} & \quad \text{Pr} \\
\text{H} & \quad \text{Pr} \\
\text{28b}
\end{align*}
\]

Summary

Although elegant methodology exists for the intermolecular and intramolecular Diels-Alder cycloaddition of imino dienophiles, we believed that iminoacetonitriles would have several advantages as 2π components in [4+2] cycloadditions and would provide access to substituted nitrogen heterocycles not easily obtained via previous methodology.\(^{32}\) This thesis describes the full details of our studies on the synthesis of iminoacetonitriles, the scope of their Diels-Alder reactions, and the synthetic elaboration of the \(\alpha\)-amino nitrile cycloadducts to provide access to a variety of substituted quinolizidine and indolizidine derivatives. Part III also reports on the total synthesis of quinolizidine \((-\text{-})-217\text{A}\) and our efforts directed toward the total synthesis of indolizidine \((-\text{-})-235\text{B}\).

\[\text{NC} \quad \text{R} \quad \text{R}^1\]

Part II

Diels-Alder Cycloadditions of Iminoacetonitriles
Chapter 3 – Preparation of Iminoacetonitriles

The limitations associated with the Diels-Alder reactions of known imine derivatives motivated us to explore the cycloadditions and annulations of a new class of activated imines: iminoacetonitriles. Initial studies by Adam Renslo focused on the application of iminoacetonitriles in intramolecular enyne cycloadditions (eq 8); however, subsequently we decided to undertake the systematic investigation of a wide range of cycloadditions involving these species, beginning with the Diels-Alder reaction. In order for iminoacetonitriles to serve as useful building blocks, however, it was first necessary to develop effective procedures for the synthesis of this novel class of activated imines. This chapter describes the development and implementation of a Mitsunobu reaction as a key step in the synthesis of iminoacetonitriles, and it also reviews the literature procedures that existed for the preparation of this class of imines prior to our work.

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{N} \\
\text{CN}
\end{array}
\quad\rightarrow\quad
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{N} \\
\text{CN}
\end{array}
\]  \hspace{1cm} (8)

Previous Approaches to the Preparation of Iminoacetonitriles

At the outset of the investigations in our laboratory, iminoacetonitriles were relatively unknown compounds. In 1970, Boyer and Dabek had reported the first synthesis of an iminoacetonitrile, demonstrating that chlorination of \(N\)-\(t\)-butylaminoacetonitrile (prepared via the Strecker reaction) with \(t\)-butyl hypochlorite followed by elimination of HCl with triethylamine afforded 33 in 46\% yield.\(^{33}\) In a subsequent report, Boyer and Dabek found that using calcium

hypochlorite and calcium hydroxide led to increased yields and improved substrate scope (eq 9).\(^{34}\)

\[
\begin{align*}
\text{R}^-\text{N}^-\text{CN} & \xrightarrow{\text{1) Ca(OCI)}_2} \text{R}^-\text{N}^-\text{CN} \\
& \xrightarrow{\text{2) Ca(OH)}_2} \text{R}^-\text{N}^-\text{CN}
\end{align*}
\]

\[\text{(9)}\]

\[\begin{array}{c}
30 \text{ R} = \text{Me} \quad 25\% \\
31 \text{ R} = \text{Et} \quad 50\% \\
32 \text{ R} = \text{i-Pr} \quad 72\% \\
33 \text{ R} = \text{t-Bu} \quad 76\%
\end{array}\]

After we began our investigations on the synthesis of iminoacetonitriles, a modification of Boyer’s protocol, involving a one-pot procedure, was reported by Selva and coworkers.\(^{35}\) Selva discovered that treatment of several \(\alpha\)-amino nitriles with 1.5 equiv of aqueous \(\text{NaOCl}\) at 10 °C afforded the expected iminoacetonitriles in good yield (67-90%) with preference for the \(E\) isomer (eq 10).

\[
\begin{align*}
\text{R}^1\text{N}^-\text{CN} & \xrightarrow{\text{NaOCl}} \text{R}^1\text{N}^-\text{CN} \\
67-90\% \\
\text{E/Z 90:10}
\end{align*}
\]

\[\text{(10)}\]

\[\begin{array}{c}
\text{R}^1, \text{R}^2 = \text{H, alkyl, or aryl}
\end{array}\]

Initially, we focused on extending this approach to the synthesis of iminoacetonitrile Diels-Alder substrates such as \(38\). Since we were concerned about the stability of the dienyl portion of \(38\) to hypochlorite reagents, we decided to employ the mild chlorinating reagent \(N\)-chlorosuccinimide in our studies. As shown in Scheme 4, Adam Renslo developed a “one-flask” procedure for conversion of \(\alpha\)-amino nitriles (e.g., \(37\)) to the desired iminoacetonitriles. Treatment of \(37\) with 1 equiv of NCS followed by addition of 1 equiv of sodium methoxide delivered iminoacetonitrile \(38\) as a mixture of \(E\) and \(Z\) isomers in 66% yield.\(^{36}\)

\[\text{34} \text{ Boyer, J. H.; Kooi, J. J. Am. Chem. Soc. 1976, 98, 1099.} \]
\[\text{36} \text{ Amos, D. T.; Renslo, A. R.; Danheiser, R. L. J. Am. Chem. Soc. 2003, 125, 4970.} \]
Recently, we discovered that a slightly modified procedure leads to improved yields of iminoacetonitriles (Scheme 5). For example, alkylation of phenethylamine 39 with 1 equiv of bromoacetonitrile delivered α-amino nitrile 40 in 96% yield. Reaction of 40 with NCS followed by elimination by treatment with 1 equiv of potassium ethoxide at 0 °C for 2 h then afforded iminoacetonitrile 41 in 77% yield. This modified procedure is superior to our previous procedure in that the elimination is extremely clean (by tlc analysis), which allows for a simple purification by column chromatography.

**Mitsunobu Approach to the Preparation of Iminoacetonitriles**

Although the method described above reliably furnished access to the desired iminoacetonitriles, for the preparation of our cycloaddition substrates we were not satisfied with employing amines such as 36 as starting materials. Even though amines are fairly simple to synthesize, all of the synthetic sequences we envisioned for the preparation of our cycloaddition substrates would involve the preparation of the amine from an alcohol derivative via substitution with azide or cyanide, followed by reduction. Consequently, a more expeditious route was
developed by David Amos that begins with readily available alcohols and utilizes the previously unknown sulfonamide 43. Sulfonamide 43 is easily prepared by treating the commercially available hydrochloride salt of aminoacetonitrile 42 with one equiv of triflic anhydride in the presence of Hünig's base (eq 11). This simple procedure provides multi-gram quantities of 43 in high purity as a low-melting solid that is stable for months when stored under argon at ca. 4 °C.

\[
\begin{align*}
\text{CN} & \quad \xrightarrow{1.0 \text{ equiv } \text{Tf}_2\text{O}} \quad \text{CN} \\
\text{NH}_2\text{SO}_2\text{CF}_3 & \quad \xrightarrow{2.2 \text{ equiv } i-\text{Pr}_2\text{NEt}} \quad \text{NH}_2\text{SO}_2\text{CF}_3
\end{align*}
\]

A typical example of the application of this approach developed by David Amos is shown in Scheme 6. Mitsunobu coupling reaction of alcohol 44 with sulfonamide 43, followed by elimination of trifluoromethanesulfinic acid, provides the desired iminoacetonitrile via a simple two-step protocol in excellent yield.

**Scheme 6**

Preparation of Iminoacetonitriles

As discussed previously, the method outlined in Scheme 6 was applied by David Amos to the synthesis of a variety of iminoacetonitrile cycloaddition substrates. This section details the preparation of several new cycloaddition substrates that were required in my further studies on the scope of the iminoacetonitrile cycloaddition reaction. The first target molecules I examined were the indolizidine (n = 1) and quinolizidine (n = 2) precursors 58, 60, and 62 shown in Table
1. The requisite alcohols 51 and 52 were prepared utilizing a Suzuki cross-coupling reaction between 1-iodocyclohexene and the vinyl boronic acids 48. To prepare the requisite boronic acids (48), commercially available alkynols 46 were protected as the corresponding pivalate esters and then hydroborated with dibromoborane and converted to the boronic acid via the method of Brown. The coupling of vinyl iodide 49 and boronic acids 48 (used without purification) under standard Suzuki cross-coupling conditions afforded the desired dienes 50 in 80-88% yield. DIBAL reduction then cleaved the pivalate group to provide alcohols 51 and 52 in 85-88% yield.

Next, we turned our attention to synthesizing an alcohol substrate of type 56 with a C-6 methyl substituent. Compound 55 was prepared according to the method of Noyori. Thus, allylation of dihydropyran 53 via in situ generation of 2-methoxytetrahydropyran (54) afforded tetrahydropyran 55 in 71% yield. Exposing 55 to Schlosser's base then provided dienyl

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37 1-Iodocyclohexene was prepared by treating the hydrazone derivative of cyclohexanone with iodine according to Pross, A.; Sternhell, S. Aust. J. Chem. 1970, 23, 989.
39 For reviews on the Suzuki cross-coupling, see: (a) Bellina, F.; Carpita, A.; Rossi, R. Synthesis 2004, 15, 2419. (b) Miyaura, N. In Metal-Catalyzed Cross-Coupling Reactions, 2nd ed; Diederich, F., de Meijere, A.; Wiley-VCH: New York, 2004; Chapter 2.
alcohol 44 as a single isomer (Scheme 8). The large coupling constant \( (J = 17.5 \text{ Hz}) \) observed between the protons on C-5 and C-6 indicated the presence of an \( E \)-olefin. Swern oxidation of 44 followed by addition of methylmagnesium bromide afforded the desired secondary alcohol 56 in 80% yield.

Scheme 8

As summarized in Table 1, our Mitsunobu-elimination protocol allowed for the efficient conversion of the alcohols described above to the desired iminoacetonitriles in excellent yield. In each case, the iminoacetonitriles were produced as a mixture of \( E \) and \( Z \) isomers. Thus, subjecting alcohols 51 and 52 to our standard Mitsunobu reaction conditions afforded triflamides 57 and 59 in 83-90% yield. The subsequent elimination reactions proceeded uneventfully on exposure of these intermediates to \( \text{Cs}_2\text{CO}_3 \) to give iminoacetonitriles 58 and 60, each in 86% yield.

42 The stereochemical assignment of the imine isomers was obtained from the four-bond coupling observed between the imino hydrogen and the \( \alpha \)-methylene hydrogen atoms. For example,

43 The stereochemistry of the iminoacetonitrile (e.g., 38) is not crucial, as we will demonstrate in chapter 4 that iminoacetonitrile isomers interconvert under the conditions of the \([4+2]\) cycloaddition.
yield. Under our standard conditions, however, the Mitsunobu reaction of secondary alcohol 56 was extremely sluggish at room temperature and delivered a low yield of the desired triflamide 61. Fortunately, we found that by switching the solvent to benzene and heating at 55 °C for 4 h, triflamide 61 could be obtained in 78% yield. The slow rate of this reaction was not unexpected as Mitsunobu reactions proceed via a $S_N2$ mechanism and therefore are greatly affected by the steric environment of the reacting carbon.

**Table 1. Synthesis of Iminoacetonitriles**

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>triflamide</th>
<th>yield (%)$^c$</th>
<th>iminoacetonitrile</th>
<th>yield (%)$^c$ ($E/Z$ ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="52.png" alt="" /></td>
<td><img src="57.png" alt="" /></td>
<td>83-85</td>
<td><img src="61.png" alt="" /></td>
<td>86 (78:22)</td>
</tr>
<tr>
<td>2</td>
<td><img src="51.png" alt="" /></td>
<td><img src="59.png" alt="" /></td>
<td>90</td>
<td><img src="62.png" alt="" /></td>
<td>86 (70:30)</td>
</tr>
<tr>
<td>3</td>
<td><img src="56.png" alt="" /></td>
<td><img src="61.png" alt="" /></td>
<td>78</td>
<td><img src="62.png" alt="" /></td>
<td>90-95 (79:21)</td>
</tr>
</tbody>
</table>

$^a$ 1.05 equiv $\text{TfNHCH}_2\text{CN}$, 1.2 equiv $\text{Ph}_3\text{P}$, 1.2 equiv DEAD, THF-toluene, rt, 0.5-4 h (entry 3: benzene, rt, 12 h then 55 °C, 4 h). $^b$ 3-4 equiv Cs$_2$CO$_3$, THF, 45-55 °C, 2-4 h. $^c$ Isolated yield of products purified by column chromatography.

Optimization studies on the trifluoromethanesulfinate elimination step showed that cesium carbonate and potassium carbonate both furnish the desired product. However, by using
cesium carbonate the reaction proceeds faster and leads to fewer side products and higher yields (by ca. 20\%) of the desired imine. Although 4 equiv of cesium carbonate were used in every case, the reaction does proceed with 1 equiv although at a slower reaction rate. Also, the optimal temperature for the elimination proved to be 55 °C; however, the reaction does proceed fairly efficiently at room temperature if carried out over ca. 24 h.

In general, iminoacetonitriles are susceptible to hydrolysis under slightly acidic conditions and tend to slowly decompose at room temperature (ca. 30\% decomposition after two weeks). Therefore, we do not usually store iminoacetonitriles for extended periods of time. However, iminoacetonitriles are easily purified by column chromatography as long as the silica gel is pretreated with one percent triethylamine to avoid acidic hydrolysis.
Chapter 4 – Intramolecular \([4+2]\) Cycloadditions of Iminoacetonitriles

Although the Diels-Alder cycloaddition of a number of iminoacetonitriles had previously been studied by David Amos\(^{36}\) we felt there were several aspects of this chemistry that required further investigation. This chapter describes the details of our studies aimed at examining the mechanism of the iminoacetonitrile cycloaddition, expanding the scope of the cycloaddition to include the synthesis of tricyclic systems, and our investigation of the feasibility of promoting the cycloaddition under mild conditions with either Lewis or Brønsted acids.

**Thermal Iminoacetonitrile Cycloadditions**

In our original study, David Amos had discovered that simply heating the appropriate iminoacetonitriles in toluene leads to the formation of the desired Diels-Alder cycloadducts, usually as a single diastereomer. For example, heating a toluene solution of 38 (80:20 mixture of \(E\) and \(Z\) imine isomers) at 120 °C in the presence of 3 equiv of BHT in a sealed tube affords cycloadduct 63 in 67-70% yield after purification by column chromatography (eq 12). Interestingly, in this and other cases the cycloadduct with an exo-oriented axial cyano group is obtained as the exclusive product of the reaction.\(^{36}\) Experiments carried out by David Amos\(^{44}\) suggest that the initially formed epimeric cycloadducts equilibrate through an iminium ion to afford the axial cyano isomer which is favored as a consequence of the “\(\alpha\)-amino nitrile anomeric effect.”\(^{45}\)


In order to better understand the mechanism of the iminoacetonitrile cycloaddition, I carried experiments to carefully monitor the cycloaddition of iminoacetonitrile 38 by $^1$H NMR. These experiments were conducted in sealed NMR tubes by dissolving iminoacetonitrile 38, 3 equiv of BHT, and a known amount of anisole (as internal standard) in 1 mL of benzene-$d_6$ (ca. concentration of 0.05 M). A $^1$H NMR spectrum was taken at time zero and then the tube was heated at 120 °C for 21-25 h. At several points during the cycloaddition, the reaction tube was removed from the heating bath, and a $^1$H NMR spectrum was recorded. With the assumption that the amount of internal standard did not change during the course of the experiment, the amount of iminoacetonitrile 38 and cycloadduct 63 was calculated.

As can be seen in Figure 1, the cycloaddition follows first order kinetics with respect to iminoacetonitrile 38. As expected, the rate of disappearance of iminoacetonitrile 38 was unaffected by the addition of BHT; however, BHT did significantly increase the yield of the reaction by ca. 40%. In an attempt to reduce the amount of BHT used in the cycloaddition, we screened the reaction using various concentrations of this additive. Unfortunately, we discovered that 3 or more equiv of BHT gave the best results. Based on the result that BHT does not affect the rate of disappearance of iminoacetonitrile 38, we hypothesized that BHT is in fact inhibiting decomposition of the cycloadduct, presumably through radical pathways. This is not unreasonable, as one might envision the possibility of loss of a hydrogen atom generating a captodatively stabilized radical at C-4. In order to confirm this hypothesis, we subjected cycloadduct 63 to our standard cycloaddition conditions (toluene, 120 °C) with and without
BHT. After 12 h, the cycloadduct in the absence of BHT had decomposed by 20% relative to the cycloadduct with BHT (3 equiv).

![Reaction Scheme]

**Figure 1.** Effect of BHT on the Rate of the Iminoacetonitrile Diels-Alder Cycloaddition

In addition to studying the effect that BHT has on the rate of the cycloaddition, we were also interested in monitoring the relative reactivity of the $E$ and $Z$ iminoacetonitrile isomers in the cycloaddition. Interestingly, we discovered that the initial ratio (80:20) of $E$ and $Z$ isomers of iminoacetonitrile 38 equilibrates to a thermodynamic ratio (60:40) of $E$ and $Z$ isomers before any cycloadduct is formed, and this ratio then remains constant throughout the course of the cycloaddition. This observation suggests that either the imine isomers undergo cycloaddition at the same rate, or one isomer is reacting faster but interconversion occurs rapidly and maintains the thermodynamic ratio. Unfortunately, this provides little insight into the reactivity of each imine isomer, and further studies are required.
Acid-Promoted Iminoacetonitrile Cycloadditions

In an effort to expand the scope of the iminoacetonitrile cycloaddition, particularly to substrates that react sluggishly or are completely unreactive under thermal conditions, we next shifted our focus to the development of an acid-promoted cycloaddition. Examples have been reported in the literature of acid-promoted Diels-Alder cycloadditions of related imino dienophiles, and it therefore appeared possible that our reactions might be accelerated by acid.\(^\text{10}\)

At first, we investigated the use of Lewis acids with a known affinity for cyano groups, such as copper, silver, and zinc salts. In this case we hypothesized that ionization of cyanide might produce a nitrilium ion that could undergo an accelerated Diels-Alder reaction. We also explored Lewis acids known to catalyze related imine cycloadditions,\(^\text{10}\) such as Yb(OTf)\(_3\), Sc(OTf)\(_3\), and BF\(_3\)-OEt\(_2\). Surprisingly, under completely anhydrous conditions, attempted cycloaddition of imine 38 in the presence of these additives led to recovery of unreacted starting material (38) in 95% yield. It is important to recall that iminoacetonitriles are extremely susceptible to hydrolysis under slightly acid conditions and therefore it is crucial to run acid-catalyzed reactions under completely anhydrous conditions. Interestingly, in one experiment we noticed that cycloaddition of 38 with Cu(OTf)\(_2\) in the presence of a trace of H\(_2\)O delivered a 1:1 mixture of 63 and the hydrolysis byproduct 64 in 40% yield (eq 11).

![Chemical structure and reaction](image)

Encouraged by the possibility that the reaction in the above experiment was actually being promoted by trifluoromethanesulfonic acid generated \textit{in situ}, we investigated the use of several Brønsted acids, such as TsOH, CSA, TFA, AcOH, and H\(_3\)PO\(_4\). We discovered that acids
with pKa values less than -1 are effective promoters of the cycloaddition, whereas reaction in the presence of weaker acids such as TFA and AcOH afford the cycloadduct in low yields (less than 15%) accompanied by extensive decomposition. Presumably, decomposition is initiated by acid-catalyzed hydrolysis or nucleophilic addition to the iminoacetonitrile moiety.

Optimization studies revealed that methanesulfonic acid in CH₂Cl₂ (0.1 M) is the most effective promoter of the iminoacetonitrile cycloaddition. For example, treatment of iminoacetonitrile 38 with 1 equiv of MsOH in CH₂Cl₂ under anhydrous conditions delivers the desired α-amino nitriles 63a and 63b in 80% yield as a 55:45 mixture of epimers (Scheme 9). The mixture of epimers at C-4 is inconsequential due to the fact that further transformations at the C-4 carbon are controlled by stereoelectronic effects independent of the C-4 cyano group stereochemistry (for a discussion, see Part III). If desired, heating the mixture in CH₃CN equilibrates the isomers to afford exclusively the thermodynamically favored axial oriented nitrile (Scheme 9). It is important to note that the addition of 4Å molecular sieves (ca. 10 mg of 4 Å molecular sieves per 1 mL CH₂Cl₂) is crucial to the success of the cycloaddition. Sieves presumably serve to completely inhibit hydrolysis of the iminoacetonitrile which otherwise significantly reduces the yield of the cycloaddition. Also, 1 equiv of MsOH is required for complete consumption of the starting material; this is not unexpected as the nitrogen atom in the cycloadduct is more basic than the nitrogen atom in the imine.
Mechanism of the Acid-Promoted Cycloaddition of Iminoacetonitriles

Analysis of the mechanism and stereochemical course of the iminoacetonitrile cycloaddition is challenging due to the possibility for isomerization of the isomeric imine substrates as well as the α-amino nitrile cycloadducts under the conditions of the reaction. As mentioned above, axial nitriles are the major or exclusive products of the reaction, and several observations suggest that this is the result of thermodynamic control. In the case of acid-promoted cycloadditions, treatment of iminoacetonitrile 65 with 1 equiv of MsOH at -78 °C for 1 h followed by quenching with aqueous sodium bicarbonate at -78 °C furnishes 66b (equatorial nitrile) as a single diastereomer. However, all attempts to purify this compound by column chromatography led to a mixture (ca. 55:45) of 66a and 66b. This experiment demonstrates that the kinetic product of the cycloaddition is the equatorial nitrile and the cycloadducts equilibrate through an iminium ion to afford the thermodynamic product (axial nitrile). Also, α-amino nitrile cycloadducts (e.g., 81 in Scheme 14) with electron-withdrawing groups in the connecting
tether have been found to equilibrate more slowly due to inductive destabilization of the intermediate iminium ion.

\[
\text{1 equiv MsOH} \\
4\text{Å MS, CH}_2\text{Cl}_2 \\
-78 ^\circ\text{C 1 h} \\
\text{OSiR}_3 \\
\text{H} \\
\text{SiR}_3 = \text{Sit-BuMe}_2 \\
\text{(14)}
\]

\[65 \rightarrow 66a \quad R^1 = \text{CN}, \quad R^2 = \text{H} \\
66b \quad R^1 = \text{H}, \quad R^2 = \text{CN}
\]

The facility of the acid-promoted cycloaddition of iminoacetonitriles is remarkable and of great synthetic importance. With regard to mechanism, in iminoacetonitriles such as 38 there are two possible sites of protonation. Protonation of the cyano group could lead to ionization to form nitrilium ion 67 which could then undergo [4+2] cycloaddition. Alternatively, protonation of the imine could generate the iminium ion 69 which might then be the intermediate undergoing Diels-Alder cycloaddition (Scheme 10).
It will be recalled that the intramolecular Diels-Alder reaction investigated by Grieco and coworkers involved the in situ generation of a reactive iminium ion as a dienophile (see p 18). Cycloadditions involving iminium 69 (Scheme 10) should be more facile than the iminium ions studied by Grieco because the cyano group should destabilize the adjacent carbocation thereby increasing the reactivity of the dienophile. In order to test this hypothesis, we examined the reactivity of imine 71 lacking the cyano group. As shown in eq 15, treatment of imine 71 (E isomer by $^1$H NMR analysis) with 1 equiv of MsOH led to recovered starting material with no sign of the desired cycloadduct. Although this experiment seems to support the hypothesis that the increased reactivity of 69 is a result of destabilization of the adjacent carbocation by the cyano group, the increased reactivity of imine 38 versus imine 71 could also be the result of steric hindrance in the transition state (cyano versus ethyl) or increased reactivity of the Z-imine isomer versus the E-isomer. As previously discussed, the E and Z isomers of iminoacetonitriles such as 38 equilibrate under the Diels-Alder reaction conditions whereas the E and Z isomers of imines such as 71 do not equilibrate. Therefore, if the Z isomer is the reactive imine isomer in the cycloaddition, then this could account for the difference in Diels-Alder reactivity between imines 38 and 71.

![Chemical Structures](image)

**Scope of the Intramolecular [4+2] Cycloadditions of Iminoacetonitriles**

Having developed conditions for acid-promoted cycloadditions of iminoacetonitriles, we turned our attention to investigating the scope of this process. This section begins with the
results of an examination of the acid-promoted cycloaddition of several iminoacetonitriles previously prepared by David Amos.\textsuperscript{36} Of particular interest were iminoacetonitriles that Amos discovered were either sluggish or unreactive under the original thermal cycloaddition conditions. The second part of this section explores the application of the iminoacetonitrile cycloaddition to the synthesis of tricyclic systems which had not previously been investigated.

Initially, we decided to investigate the acid-promoted Diels-Alder cycloaddition of iminoacetonitrile 65 (Scheme 11). In the event, cycloaddition of imine 65 with 1 equiv of MsOH afforded 66a in 88-89\% yield as a single diastereomer after heating the crude product in CH\textsubscript{3}CN at 45 °C for 1.5 h.

\textbf{Scheme 11}

\[
\begin{align*}
\text{65} & \xrightarrow{1 \text{ equiv MsOH, 4Å MS}} \text{66a} \\
& \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt, 15 min;}} \text{CH}_3\text{CN, 45 °C, 1.5 h} \\
& \xrightarrow{88-89\%} \\
& \text{or} \\
& \xrightarrow{3.0 \text{ equiv BHT, toluene, 120 °C, 15 h}} 79-87\% \\
\text{73} & \xrightarrow{1 \text{ equiv MsOH, 4Å MS}} \text{74a, 74b} \\
& \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt, 90 min;}} \text{CH}_3\text{CN, 45 °C, 1.5 h} \\
& \xrightarrow{83\% \text{ for 81:19, 58\% \text{ for 73:29}}} \\
& \xrightarrow{3.0 \text{ equiv BHT, toluene, 130 °C, 48 h}} \\
\end{align*}
\]
Next, we explored the preparation of indolizidine 74 via the acid-promoted cycloaddition of iminoacetonitrile 73. As shown in Scheme 11, cycloaddition of imine 73 in the presence of MsOH furnishes indolizidines 74a and 74b as a 30:70 mixture of C-5 isomers. In this case, heating the mixture of cycloadducts (74) in CH$_3$CN at 45 °C for 1.5 h affords an 81:19 mixture of 74a and 74b which represents the thermodynamic ratio. Interestingly, the rate of the cycloaddition of imine 73 (3-carbon tether) is significantly slower than imine 50 (4-carbon tether) under thermal conditions. However, the acid-promoted cycloadditions of imines 65 and 73 are extremely facile at room temperature and produce the desired cycloadducts in consistently higher yields as compared to the thermal reactions.

Our attention was next focused on the feasibility of using silyl enol ethers as part of the diene component. These experiments were aimed at laying the groundwork for applications of the cycloaddition in the total synthesis of certain alkaloid natural products. As shown in eq 16, thermal cycloaddition of imine 75 affords 76 in 71-78% yield as a single diastereomer. Initial investigations of the acid-promoted cycloaddition of imine 75 were completely unsuccessful due to decomposition of the silyl enol ether under the acidic reaction conditions. However, by conducting the reaction at -78 °C with dropwise addition of MsOH, we were able to obtain cycloadduct 76 in 60% yield with only a trace of decomposition. It should be emphasized that for the cases shown in Scheme 11 and eq 16 exactly 1 equiv of MsOH was used to avoid competing desilylation reactions.

\[
\begin{align*}
1 \text{ equiv MsOH, } 4\AA \text{ MS} \\
\text{CH}_2\text{Cl}_2, -78 \degree \text{C, 1 h;} \\
\text{CH}_3\text{CN, 45 \degree \text{C, 1.5 h}} \quad 60\%
\end{align*}
\]

\[
\begin{align*}
\text{or} \\
3.0 \text{ equiv BHT,} \\
\text{toluene, 120 \degree \text{C, 24 h}} \\
71-78\%
\end{align*}
\]
The next stage of our investigation of the scope of the iminoacetonitrile cycloaddition involved the synthesis of the tricyclic systems 77, 78, and 80 (Scheme 12 and eq 17). The first two cases we examined involved vinylcyclohexenes as diene components. Subjecting imines 58 and 60 to thermal and acid-promoted cycloadditions afforded cycloadducts 77 and 78, in each case as a single diastereomer. To assign the stereochemistry of the cyano group at C-4, we first calculated the dihedral angles for both epimers and then used the Karplus curve to predict coupling constants for the proton at C-4. For an axial cyano group (calculated dihedral angle of 80°), the coupling constant would be expected to fall between 0 and 1 Hz. On the other hand, for an equatorial cyano group (calculated dihedral angle of 45°), the coupling constant would be expected to fall between 4 and 8 Hz.46,47 The proton at C-4 of cycloadduct 77 appeared as a singlet in the 1H NMR spectrum and thus is consistent with an axially disposed cyano group cis to the C-3 proton (Scheme 12).48

46 Dihedral angles calculated with Chem3D, version 7.0.1; CambridgeSoft; Cambridge, MA, 2002.
48 The stereochemistry of indolizidine 78 was established by comparing its NMR spectra to that of quinolizidine 77.
Once again, the acid-promoted cycloadditions proceeded in consistently higher yield as compared to thermal reactions. As expected, suprafacial cycloaddition leads to a single product in which the two ring junction hydrogens are cis. As expected from previous results, the rate of the thermal cycloaddition leading to 78 was considerably slower than the homologous case leading to 77. An important trend to point out is that thermal cycloadditions of imines such as 60 and 73 leading to indolizidines are relatively sluggish and generally proceed in modest yield.

The final tricyclic case we studied involved the preparation of benzoquinolizidine 80 (Scheme 13). As previously reported by Amos, cycloaddition of imine 79 under thermal conditions afforded cycloadducts 80a and 80b in 44-45% yield as a 79:21 mixture of epimers. However, acid-promoted cycloaddition of this imine produced cycloadducts 80a and 80b in improved yield (60%). It should be mentioned that at elevated temperatures, especially in polar
solvents such as CH$_3$CN, cycloadducts 80a and 80b suffered from instability, which most likely contributed to the relatively low yield observed in this case.$^{49}$

Our next goal was to investigate the acid-promoted cycloaddition of iminoacetonitrile 81. We were particularly interested in the reactivity of imine 81 due to the presence of the electron-withdrawing sulfonamide nitrogen in the connecting tether. As previously reported by Amos, thermal cycloaddition of 81 in toluene afforded 82a and 82b in 90-95% yield as a 37:63 mixture of C-4 isomers. Interestingly, Amos had found that conducting the reaction in a more polar solvent such as CH$_3$CN afforded cycloadduct 82a in 61-64% yield as a single diastereomer, albeit in lower yield. The relatively slow equilibration rate of cyano isomers 82a and 82b compared to other quinolizidine cycloadducts is a result of inductive destabilization of the intermediate iminium ion by the electron-withdrawing sulfonamide group. As expected from these results, the acid-promoted cycloaddition of imine 81 at room temperature affords cycloadduct 82b (kinetic product) in 71% yield as a single diastereomer. Once again, heating

$^{49}$ For the stereochemical assignment of 80a and 80b, see reference 44 (pp 103-104).
82b in CH$_3$CN equilibrates the C-4 cyano group to afford exclusively the thermodynamically favored axial oriented nitrile. It should be mentioned that cycloadducts 82a and 82b both possess a cis-relationship between the methyl group and ring junction hydrogen atom consistent with suprafacial cycloaddition to the diene.

![Scheme 14](image)

**Scheme 14**

- **81** → **82a** + **82b**
  - 3.0 equiv BHT, toluene, 120 °C, 36 h
    - 90-95% (37:63)
  - 3.0 equiv BHT, CH$_3$CN, reflux, 24 h
    - 61-64% (100:0)
  - 1 equiv MsOH, 4Å MS
    - CH$_2$Cl$_2$, rt, 1 h
      - 71% (0:100)
    - CH$_2$Cl$_2$, rt, 1 h;
      CH$_3$CN, 45 °C, 18 h
      - 71% (100:0)

At this stage, we decided to examine the feasibility of preparing cycloadducts with substituents at the C-6 position such as 83. These cycloadducts are of particular importance due to the abundance of biologically active 4,6-disubstituted quinolizidine natural products. Amos had found in our previous studies that iminoacetonitriles with substituents alpha to the imine such as 62 are completely unreactive under thermal conditions. Unfortunately, the acid-

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50 For a recent review of the chemistry and biology of quinolizidine alkaloids, see: Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1-161.
promoted cycloaddition of iminoacetonitrile 62 (1 equiv MsOH, CH₂Cl₂, rt) also failed to produce the desired cycloadduct 83 (unreacted 62 was recovered in ca. 90% yield). However, we discovered that reaction in a more polar solvent (CH₃CN instead of CH₂Cl₂) affords cycloadducts 83a and 83b in 70% yield as a 67:33 mixture. One possible explanation for this solvent effect is that protonation of 62 to form either the key iminium ion of type 69 (see Scheme 10) or nitrilium ion of type 67b is much more favorable in acetonitrile. Alternatively, perhaps the nitrilium ion of type 67b is the species undergoing cycloaddition and its formation is much faster in the more polar solvent. Finally, it is possible that the rate of cycloaddition of the intermediate carbocation (either of type 67b or 69) is faster in the more polar solvent, perhaps due to the formation of a more reactive solvent-separated ion pair.

\[ \text{62} \xrightarrow{1 \text{ equiv MsOH, } 4\text{A MS}} \ \text{CH₃CN, -30 °C to rt, 4 h; CH₃CN, 45 °C, 1.5 h} \quad (70\% \quad (67:33)} \quad \text{83a} + \quad \text{83b} \quad (17) \]

The stereochemistry of cycloadducts 83a and 83b was established by NMR analysis. The protons at C-4 of 83a and 83b appeared as doublets and therefore were assigned as equatorial. The carbon of the methyl group in 83a is shifted downfield (19.3 ppm vs 11.6 ppm) relative to the carbon of the methyl group in 83b. The equatorial methyl group lies in the deshielding cone of a C-C bond of the ring skeleton and therefore is expected to appear further downfield than the axial methyl group.⁵¹

---

Next, we were interested in exploring the acid-promoted cycloaddition of iminoacetonitrile 84 (Scheme 15). Previous work by David Amos showed that under thermal conditions cycloadducts 85a and 85b are obtained in 73% yield as a 55:45 mixture of isomers at C-9.\textsuperscript{36,52} Acid-promoted cycloaddition of imine 84 under standard conditions (1 equiv MsOH, CH\textsubscript{2}Cl\textsubscript{2}, rt) also furnishes 85a and 85b as a 55:45 mixture, albeit in slightly improved yield. However, we discovered that conducting the reaction at -78 °C afforded cycloadduct 85a in 81% yield as a single diastereomer after heating the crude product in CH\textsubscript{3}CN at 45 °C for 1.5 h. This is an exciting result as it provides the opportunity to use a C-9 stereogenic center as a directing group in a diastereoselective cycloaddition.

\textsuperscript{52} For the stereochemical assignment of 85a and 85b, see reference 36 (pp 106-107).
Enantioselective Intramolecular [4+2] Cycloadditions of Iminoacetonitriles

Having investigated the scope of the acid-promoted iminoacetonitrile cycloaddition, we turned our attention to the possibility of using chiral Brønsted acids for an enantioselective version. Recently, several laboratories have shown that chiral phosphoric acids (e.g., 88) function as powerful organocatalysts for activation of imine functional groups which then participate in a number of useful asymmetric reactions.\(^\text{53}\) Of particular relevance to our work, the laboratories of Akiyama\(^\text{54}\) and Gong\(^\text{55}\) have developed enantioselective aza Diels-Alder reactions catalyzed by chiral phosphoric acids.

As shown in Scheme 16, Akiyama and coworkers discovered that chiral phosphoric acid 88, derived from (R)-BINOL, catalyzes the Diels-Alder cycloaddition of aryl imines (e.g., 86) with Danishefsky's diene to give piperidinone derivatives 89 in 72-100% yield and 78-91% ee. Akiyama and coworkers attribute the good levels of enantioselectivity to a nine-membered transition state in which one face of the imine is blocked by the acid catalyst. Akiyama and coworkers have also shown that the steric bulk of the aryl groups at the 3 and 3' positions are crucial for high levels of enantioselectivity.\textsuperscript{54}

Scheme 16

\[
\begin{align*}
\text{HO} & \quad 5 \text{ mol} \% \ 88 \\
\text{OMe} & \quad 1.2 \text{ equiv AcOH} \\
\text{Ar} & \quad \text{toluene, } -78 ^\circ \text{C, 12 h} \\
\text{N} & \quad 72-100\% \ 
\text{ArOSiMe}_3 & \quad 78-91\% \text{ ee}
\end{align*}
\]

Gong and coworkers developed a direct asymmetric aza Diels-Alder reaction catalyzed by chiral phosphoric acid 92, which involves the in situ generation of the diene (Scheme 14). Gong reasoned that under the acidic reaction conditions cyclohexenone (91) would enolize and the resulting dienol would behave as a 4\pi component in the cycloaddition. In the event, treatment of aldimine 90 with cyclohexenone and 92 afforded cycloadduct 93 with good enantioselectivity. Although substitution at the 3 and 3' positions of the catalyst is important
for high levels of enantioselectivity, Gong noticed that sterically congested aryl groups, such as 4-t-BuC₆H₆, actually had a deleterious effect on enantioselectivity. Gong and coworkers also found that H₈-BINOL-derived phosphoric acids (e.g., 92) lead to higher selectivity than the corresponding BINOL-derived acids.⁵⁵

Encouraged by this work, our efforts were directed toward the development of an enantioselective Diels-Alder cycloaddition of iminoacetonitriles. Our initial efforts focused on the cycloaddition of imine 65 with commercially available phosphoric acid 95 (Scheme 18). Treatment of imine 65 with 1 equiv of 95 in CH₂Cl₂ for 24 h afforded the desired cycloadduct, which upon reductive decyanation afforded 94 as racemic mixture. Although this reaction was not enantioselective, we were glad to see that phosphoric acids of type 95 do promote the iminoacetonitrile cycloaddition. Therefore, we decided to try the bulkier phosphoric acid 96,
which is readily accessible from commercially available (R)-BINOL.\textsuperscript{56} In this case, quinolizidine 94 was obtained in ca. 25\% ee, albeit in low yield (ca. 10\%). It should be mentioned that the cycloaddition step in both cases is extremely sluggish and affords several by-products. In order to increase the rate and success of the cycloaddition, the acidity of the phosphoric acid needs to be increased as discussed in the section on acid-promoted cycloadditions.\textsuperscript{57} Although the overall yield (ca. 10\%) and enantiomeric excess are low, we are confident that manipulation of the steric bulk and electronic properties of the 3 and 3’ aryl groups will lead to an effective chiral phosphoric acid for our iminoacetonitrile cycloaddition.

**Scheme 18**

\[
\begin{align*}
1) & \quad 1 \text{ equiv } 95 \text{ or } 96 \\
& \quad 4 \text{ Å MS, CH}_2\text{Cl}_2 \\
& \quad \text{rt, 24 h} \\
2) & \quad \text{Na, NH}_3, \text{THF} \\
& \quad -78 \degree \text{C, 1 h} \\
\end{align*}
\]

Summary

In conclusion, iminoacetonitriles participate in acid-promoted intramolecular [4+2] cycloadditions affording quinolizidine and indolizidine ring systems. In comparison to thermal cycloadditions, acid-promoted cycloadditions of iminoacetonitriles generally afford cycloadducts in higher yields, with better selectivity, with faster reaction rates, and under milder reaction conditions.


\textsuperscript{57} Acids 79 and 80 have pka values of ca. -1 to 0.
Chapter 5 – Intermolecular [4+2] Cycloadditions of Iminoacetonitriles

Introduction

The piperidine substructure is one of the most common motifs found in natural products and pharmaceutical compounds. According to Watson and coworkers, the piperidine substructure was mentioned in over 12,000 compounds in clinical or pre-clinical studies from July 1988 through December 1998.58 The important biological activities of piperidines have thus stimulated the development of new methods, and considerable synthetic effort has been invested in this area.59

One of the most important methods for the synthesis of six-membered rings is the Diels-Alder reaction. Therefore, the development of imine derivatives as 2π components in aza Diels-Alder reactions has greatly facilitated the ease with which piperidines can be synthesized in an efficient manner. Although several types of imino dienophiles exist for the aza Diels-Alder reaction, the most useful are the C-acylimines developed by Bailey and coworkers. As discussed in chapter 2, Bailey and coworkers have demonstrated that imine 9 represents the state of the art for imino dienophiles. As shown in eq 18, cycloadditions of imine 9 with a variety of dienes afford piperidine cycloadducts (10-14) in good yield with excellent diastereoselectivity. It is important to note that Bailey’s methodology only provides access to cis-2,6-disubstituted piperidines. Since a number of important natural products possess a trans-2,6-disubstituted piperidine structure, a method that would allow access to both diastereomers would be a valuable addition to synthetic methodology.

2,6-Disubstituted piperidines represent a subclass of naturally occurring piperidines that have stimulated considerable synthetic interest due to their wide range of pharmacological activities. Two prominent examples are (−)-solenopsin A, a constituent of the venom of the *Solenopsis* species, and (+)-himbacine, a piperidine alkaloid isolated from the bark of *Galbulimina baccata* of the magnolia family. These two natural products have appeared as novel drug candidates for the treatment of Alzheimer’s disease.

The importance of piperidines, specifically 2,6-disubstituted piperidines, encouraged us to explore the feasibility of intermolecular [4+2] cycloadditions of iminoacetonitriles. As shown in eq 19, the ability to use an iminoacetonitrile as a reactive $2\pi$ component in intermolecular
hetero Diels-Alder cycloadditions would provide access to substituted piperidines in a highly convergent fashion. The synthetically versatile α-amino nitrile moiety of the resulting cycloadduct would then allow for the synthesis of a variety of both cis- and trans-2,6-disubstituted piperidines in contrast to Bailey’s methodology.

![Diagram of cycloaddition reaction](image)

(19)

**Synthesis of Benzyliminoacetonitrile**

For our initial studies, we decided to focus on iminoacetonitrile 98 with the expectation that a benzyl group would be readily removable from the cycloadducts. Iminoacetonitrile 98 was previously synthesized by Selva and coworkers as shown in eq 20. Selva discovered that treatment of amino nitrile 97 with aqueous NaOCl at 10 °C affords imines 98 and 99 as a 90:10 mixture in 90% yield. Unfortunately, we found that separation of the desired iminoacetonitrile 98 from 99 was extremely difficult and not practical for large scale applications. Therefore, we decided to explore alternative methods for the synthesis of iminoacetonitrile 98.

![Equation for synthesis of benzyliminoacetonitrile](image)

(20)

We next investigated the synthesis of 98 via elimination of trifluoromethanesulfinate from triflamide 100 which was synthesized from the corresponding alcohol via our Mitsunobu strategy. Disappointingly, under standard elimination conditions (Cs$_2$CO$_3$) the regioisomeric imine 99 was isolated in 85% yield with no sign of the desired iminoacetonitrile 98. After
screening a variety of bases, however, NaH was found to provide the best ratio of imines 98 and 99, but still as a mixture (65:35 ratio) (eq 21).

\[ \text{Ph} \text{N} \text{CN} \xrightarrow{1 \text{ equiv NaH}} \text{Ph} \xrightarrow{\text{THF, 0 }^\circ\text{C, 2 h}} \text{Ph} \frac{\text{65:35}}{\text{98} + \text{99}} \] (21)

Discouraged by these results, we next examined the use of our original elimination protocol (NCS, base). Treating amine 97 with NCS followed by KOEt afforded the desired iminoacetonitrile 98 in 70-75% yield (eq 22). The crude \(^1\text{H}\) NMR spectrum indicated less than 1% of the conjugated imine 99 had formed under these conditions. However, immediate purification on acetone-deactivated silica gel was crucial to avoid isomerization to the alternative imine. Also, benzyliminoacetonitrile 98 is fairly unstable at room temperature and can only be stored for a few weeks in CH\(_2\)Cl\(_2\) solution at 4 °C before isomerization takes place.

\[ \text{Ph} \text{N} \text{CN} \xrightarrow{1.0 \text{ equiv NCS}} \text{Ph} \xrightarrow{\text{THF, rt, 30 min; 1.0 equiv KOEt}} \frac{\text{70-75\%}}{\text{97} \rightarrow \text{98} \ E/Z \ 70:30} \] (22)

**Scope of the Intermolecular Iminoacetonitrile Cycloaddition**

With an effective method for preparation of benzyliminoacetonitrile 98 in hand, our efforts were next directed at exploring the reactivity of 98 as a 2\(\pi\) component in hetero Diels-Alder cycloadditions. Heating imine 98 with isoprene and 3 equiv of BHT in toluene at 120 °C led to recovered imine with no sign of the desired cycloadduct. Notably, however, none of the isomerized imine was formed under these conditions. Undeterred by these results, we shifted our focus to acid-promoted cycloadditions. As shown in Scheme 19, reaction of imine 98 with 3
equiv of isoprene and 1 equiv of MsOH in CH$_2$Cl$_2$ at -78 °C for 1 h followed by a basic workup afforded the known cycloadduct 102$^{64}$ in 91% yield as a single regioisomer. Comparison of the coupling constants for the indicated proton at C-6 to literature values confirmed the presence of an axial oriented nitrile.$^{65}$ Optimization studies demonstrated that the number of equiv of isoprene could be reduced to 1.5 equiv without a decrease in the yield. As expected from our intramolecular cycloaddition studies, 1 equiv of MsOH was required for complete consumption of iminoacetonitrile 98.

In order to rationalize the observed regiochemistry of the intermolecular iminoacetonitrile cycloaddition, one must invoke frontier molecular orbital theory. As is the case with more conventional Diels-Alder reactions, the HOMO$_{diene}$ and LUMO$_{dienophile}$ frontier molecular orbitals (FMOs) control the regiochemistry of aza Diels-Alder reactions.$^{66}$ As shown below, in the case of imino dienophiles, a larger atomic coefficient on the carbon atom of the C=N bond (A) leads to a preference for product I, while a larger coefficient on the nitrogen atom (B) favors the

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$^{65}$ Husson and coworkers assigned the nitrile as axial due to the lack of a large coupling constant (axial-axial) for the proton at C-2.

regioisomeric product II. The majority of imino dienophiles react to provide products with the substitution pattern of I. However, imines with two electron-withdrawing groups on the carbon atom tend to afford products with substitution pattern II. The observation that iminoacetonitrile 98 affords cycloadduct 102, consistent with substitution pattern I, suggests that the largest atomic coefficient in the LUMO is located on the carbon atom of the C=N bond as is the case with simple imines baring only alkyl and aryl substituents.

With conditions for the intermolecular cycloaddition of iminoacetonitriles in hand, efforts were directed toward exploring the scope of the cycloaddition. As shown in Scheme 20, the cycloaddition of imine 98 with 2-methyl-1,3-pentadiene afforded cycloadduct 104 in 87% yield as a single diastereomer with an axial oriented cyano group. As shown below, the structure and stereochemical assignment of cycloadduct 104 were confirmed by comparison to the known piperidine 105.
Next, cycloaddition of imine 98 and 2,4-hexadiene was examined and was found to produce cycloadduct 107 as a single diastereomer in 79% yield (Scheme 21). The cis-relationship between the C-3 and C-6 methyl groups is consistent with suprafacial addition of the diene to the imine. Comparison of the chemical shifts and coupling constants in 107 to the known piperidine 105 established the stereochemistry at C-2, C-3, and C-6. The absence of an equatorial-equatorial J-coupling of ca. 2.0 Hz for the C-2 proton in compound 107 indicated that the C-3 methyl group occupies an equatorial orientation. Based on the observed difference in chemical shift between the C-6 protons of 107 and 105, we concluded that the C-6 proton of 107 was equatorial.
The last case we explored involved the cycloaddition of imine 98 and silyl enol ether 108\(^{67}\) to provide cycloadduct 109 in 51% yield as a single diastereomer (Scheme 22). As shown in Scheme 22, comparison of the chemical shift and coupling constant values for cycloadduct 109 and the known piperidine 105\(^{64}\) elucidated the stereochemistry of the key stereocenters, at C-6 and C-2. The lower yield in this case is most likely a result of competing decomposition of silyl enol ether 108 under the acidic conditions of the reaction. In contrast to 104 and 107, cycloadduct 109 was initially isolated as a mixture of nitrile isomers. However, simply heating the mixture at 45 °C in CH\(_3\)CN for 1.5 h affords the thermodynamically favored product with an axial cyano group. Cycloadduct 109 should be a useful intermediate as it should be possible to selectively install substituents at C-2, C-5, and C-6 utilizing the α-amino nitrile moiety and the masked carbonyl at C-4.

\(^{67}\) For the synthesis of silyl enol ether 91, see: Jacobi, P. A.; Cai, G. Heterocycles 1993, 35, 1103.
Scheme 22

Ph
N
CN
98

+ CH₂CH₂CN, 45 °C, 1.5 h

CH₂Cl₂, -78 °C, 1 h;

1 equiv MsOH

1H NMR 3.70 ppm

dd, J = 5.7, 1.8 Hz

13C NMR 21.0 ppm

1H NMR 1.27 ppm, d, J = 6.3 Hz

1H NMR 3.25-3.30 ppm, m

Summary

In conclusion, benzyliminoacetonitrile participates in acid-promoted intermolecular [4+2] cycloadditions with a variety of dienes affording piperidine ring systems. The cycloadducts are obtained as single regioisomers and diastereomers with axial oriented cyano groups in good yield.
Part III

Synthetic Utility of

α-Amino Nitrile Cycloadducts
Chapter 6 – Transformations of α-Amino Nitrile Cycloadducts

As discussed in Chapter 1, one of our primary reasons for exploring iminoacetonitriles as 2π components in aza Diels-Alder cycloadditions was our expectation that the α-amino nitrile cycloadducts would serve as versatile synthetic intermediates amenable to further elaboration. This chapter begins with a brief overview of previous studies on α-amino nitrile transformations and then provides details of our work involving the synthetic elaboration of α-amino nitrile cycloadducts to give substituted quinolizidines and indolizidines.

Introduction and Background

As shown in Scheme 23, α-amino nitriles are exceptionally versatile intermediates for the synthesis of nitrogen heterocycles. The simplest and most well-known reaction of α-amino nitriles is hydrolysis to produce amino acids, as demonstrated by Strecker in 1850. Several other useful transformations such as reduction and nucleophilic addition are possible based on the nitrile moiety, but the focus of this chapter will be on the application of α-amino nitriles as latent iminium ions.

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The ability of α-amino nitriles to function as stable precursors to iminium ions and the ease with which ionization of the cyano group occurs provides for a wide range of further reactions, such as Mannich condensations, cation-π type cyclizations, and Bruylants reactions. A complementary mode of reactivity involves metallation of the nitrile to afford stabilized lithium derivatives that can then undergo a variety of carbon-carbon bond-forming reactions. Thus, by proper choice of reaction conditions, the carbon atom of the α-amino nitrile can function as either a nucleophilic or electrophilic species.

The simplest transformation in which α-amino nitriles function as latent iminium ion precursors is reductive decyanation (Scheme 23). This type of reduction is usually carried with NaBH₄ in EtOH, with either heat or a large excess of reducing agent (10 equiv). However, a variety of other reagents have been reported for the reductive decyanation of α-amino nitriles.

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69 For a review on reductive decyanations, see Mattalia, J. M.; Marchi-Delapierra, C.; Hazimeh, H.; Chanon, M. *Arkivoc* 2006, 4, 90.
including LiAlH₄, BH₃, Zn(BH)₄, NaBH₃CN, KBH₄, and alkali metals in liquid NH₃. Although several methods are well known for this transformation, David Amos found that consistently superior yields (ca. 10% higher) are obtained using NaBH₃CN in AcOH. For example, Amos found that treatment of 66a with NaBH₃CN and AcOH in CH₃CN delivered quinolizidine 110 in 91-92% yield (eq 23), while with NaBH₄ in refluxing EtOH 110 was obtained in 83% yield.

![Chemical reaction](image)

A unique mode of reactivity of α-amino nitriles that deserves special mention is the Bruylants reaction. Typically, organometallic species such as alkyl lithium compounds react with nitriles via a 1,2-addition pathway. However, reaction of an α-amino nitrile with a Grignard reagent usually leads to ionization of the cyano group to generate an iminium ion due to the Lewis acidic nature of the magnesium species present in the Grignard reagent. The iminium ion is then trapped by organomagnesium compounds to give the substitution product rather than the “normal” addition product (eq 24). Several types of Grignard reagents have been utilized in the Bruylants reaction including alkyl, vinyl, aryl, and alkynyl magnesium halides. A modification of the Bruylants reaction involves reaction with Grignard reagents in the

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77 For examples of the Bruylants reaction, see: (a) Albrecht, H.; Dollinger, H. Synthesis 1985, 743. (b) Agami, C.; Couty, F.; Evano, G. Org. Lett. 2000, 2, 2085.
presence of a Lewis acid which enables the reaction to be conducted at low temperatures (-78 °C). In addition to Grignard reagents, silyl enol ethers, ketones, malonates, indoles, and organozinc compounds also react with these latent iminium ions to afford substitution products analogous to those formed in the Bruylants reaction.

\[ \text{R}^1\text{MgX} \rightarrow [\text{R}^1\text{N}^+\text{R}] \rightarrow \text{R}^1\text{R}^2 \text{N} \] (24)

The chemistry discussed above has been elegantly utilized in the laboratories of Husson and Polniaszek, among others. Husson and coworkers have exploited the reactivity of the \( \alpha \)-amino nitrile moiety of non-racemic \( N \)-(cyanomethyl)oxazolidines (e.g., 111) for the synthesis of several natural products. As shown in Scheme 24, metallation of 111 with LDA followed by alkylation with propyl bromide afforded 112 in 98% yield. Reduction of 112 with \( \text{NaBH}_4 \) followed by removal of the chiral auxiliary afforded \( \text{S} \)-(+)\-coniine in good yield and excellent enantiomeric purity. To access \( \text{R} \)-(--)\-coniine, Husson and coworkers used the electrophilic nature of the \( \alpha \)-amino nitrile moiety. Ionization of the cyano group upon treatment of 111 with silver tetrafluoroborate afforded an intermediate iminium ion, which upon addition of propylmagnesium bromide provided the overall substitution product 113. Subsequent removal of the chiral auxiliary afforded \( \text{R} \)-(--)\-coniine in good yield with excellent stereochemical purity.

Polniaszek and Belmont utilized α-amino nitrile 114 in the total synthesis of several indolizidine alkaloids. As shown in Scheme 25, alkylation of the metalated nitrile with alkyl bromides followed by reductive decyanation furnished indolizidine 115 in good yield as a single diastereomer. Alternately, Bruylants reaction of α-amino nitrile 114 with Grignard reagents delivered the stereocomplementary product 116, again as a single diastereomer.

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In summary, α-amino nitriles are extremely versatile intermediates for the synthesis of nitrogen heterocycles. Our iminoacetonitrile cycloaddition methodology provides a general and efficient route to polycyclic α-amino nitriles, and we were excited to investigate the elaboration of these cycloadducts to demonstrate their utility as synthetic intermediates.

**Transformations of α-Amino Nitrile Cycloadducts**

Our early studies on the transformations of α-amino nitrile cycloadducts focused on reactions involving quinolizidine 66a and indolizidine 74 as prototype systems. These cycloadducts are readily accessible on a multigram scale, stable to long term storage, and easy to handle. The first part of this chapter discusses the reductive decyanation, alkylation, and Bruylants reaction of α-amino nitriles 66a and 74. The second part of this chapter then describes our efforts toward the synthesis of quinolizidines and indolizidines incorporating quaternary centers, including spiroquinolizidines.

**Alkylation/Reductive Decyanation**

Previous studies by David Amos had established conditions for the tandem alkylation-reductive decyanation of our α-amino nitrile cycloadducts. For example, as illustrated in Scheme 26, treatment of 66a with 2.1 equiv of LDA\(^8\) at \(-78\) °C followed by quenching with ethyl iodide afforded the tertiary α-amino nitrile 117 in quantitative yield, though with only 90% purity. Further purification was not attempted as tertiary α-amino nitriles such as 117 decompose upon purification by silica gel chromatography. Therefore, treatment of 117 without prior purification with NaBH\(_3\)CN under our standard reductive decyanation conditions delivered

\(^8\) Employing less LDA led to the recovery of starting material.
quinolizidine 119 in 87% yield (overall from 66a) as a single diastereomer.\textsuperscript{36} As expected, the reductive decyanation of the tertiary $\alpha$-amino nitrile 117 was considerably faster than the reduction of the secondary $\alpha$-amino nitrile 66a due to the increased stability of the tetrasubstituted iminium ion intermediate. Using similar conditions, I extended the tandem alkylation-reductive decyanation protocol developed by Amos to the synthesis of 120. Thus, alkylation of 66a with allyl bromide followed by reductive decyanation afforded quinolizidine 120 in 86% overall yield as a single diastereomer. The allyl group of 120 was assigned as equatorial (\textit{endo}) based on NMR analysis and comparison with the spectra previously reported by Amos\textsuperscript{36} for the related compounds 119 and 121 as shown below.

\begin{center}
\textbf{Scheme 26}
\end{center}

\[
\begin{align*}
\text{66a} & \xrightarrow{2.1 \text{ equiv LDA, THF, } -78 \degree \text{C}} \text{then R-Br, } 0 \degree \text{C, 1 h}} \\
\text{117 } R = \text{Et} & \quad \text{118 } R = \text{CH}_2\text{CH=CH}_2
\end{align*}
\]

\[
\begin{align*}
4 \text{ equiv NaBH}_3\text{CN} & \quad 8 \text{ equiv AcOH} \\
\text{MeCN, rt, 1 h} & \quad 86-87\% \text{ overall}
\end{align*}
\]

\[
\begin{align*}
\text{119 } R = \text{Et} & \quad \text{120 } R = \text{CH}_2\text{CH=CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{3.21 ppm} & \quad \text{119} & \quad \text{2.77 ppm} & \quad \text{121} & \quad \text{3.24 ppm} & \quad \text{120}
\end{align*}
\]
The stereochemical control observed in the reductive decyanation step is of particular significance. As shown in eq 25, the stereochemistry of the tertiary α-amino nitrile 117 is irrelevant as the first step in the reductive decyanation involves ionization of the cyano group to generate iminium ion 122. This carbocation is then trapped via exo (axial) addition of a nucleophile (hydride in this case) which is predicted by stereoelectronic considerations to occur such that approach of the nucleophile maintains maximum orbital overlap with the developing lone pair on nitrogen.85

As mentioned previously, several biologically active indolizidine alkaloids are substituted at the C-5 carbon. Therefore, our efforts were next directed at applying the tandem alkylation-reductive decyanation to the synthesis of indolizidine 123 (Scheme 27). In the event, treatment of α-amino nitrile 74 with 2.1 equiv of LDA followed by quenching the metalated nitrile with 4-bromobutene afforded the tertiary α-amino nitrile in quantitative yield (85% purity) as a single diastereomer. Subjecting the unpurified tertiary α-amino nitrile to our standard reductive decyanation conditions then delivered indolizidine 123 in 49% yield as a 65:35 mixture of isomers. As discussed below, spectroscopic studies (vide infra) confirmed that both isomers possess an equatorial butenyl substituent, trans to the ring junction hydrogen, and that the two isomers in fact differ as conformational isomers, with trans and cis azaindane systems, respectively.

In order to confirm the structure of indolizidine 123, we hydrogenated the mixture to afford indolizidines 124 and 125 in quantitative yield as a 77:23 mixture of isomers which were shown to differ only by the configuration at the new C-7 center determined in the hydrogenation. This finding indicates that the original indolizidine isomers 123 must both have the same configuration at C-5, and thus must be conformational isomers differing with regard to having a cis or trans azabicyclic skeleton. The assignment of the C-7 stereocenter was established by comparison of the chemical shifts of the protons at C-10 of 124 and 125 to related compounds.\(^8\)

As shown below, the butenyl group (R') in 124 was assigned as equatorial (endo) based on NMR analysis and comparison of the H\textsubscript{3a} chemical shift in each compound with the spectra previously reported by Polniaszek and coworkers\(^{83a}\) for the related compounds 126 and 127.

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\(^{86}\) Wyman and coworkers found that the C-10 protons of \(\text{N} \quad \text{OR} \quad \text{10}\) are deshielded by ca. 0.15 ppm relative to the equatorial (CH\textsubscript{2}OR) isomer, see Wyman, P. A.; Gaster, L. M.; King, F. D.; Sutton, J. M.; Ellis, E. S.; Wardle, K. A.; Young, T. J. *Bioorg. Med. Chem.* 1996, 4, 255.
In order to obtain further support for our assignment for 123, we investigated the energy difference between cis- and trans-fused indolizidines I and II using ab initio methods. As can be seen in Figure 2, the trans-fused saturated indolizidine (Ia) was calculated to be 2.5 kcal/mol more stable than the cis-fused saturated indolizidine (Ib), consistent with literature values. In contrast, calculation of the energy difference between the trans- and cis-fused unsaturated indolizidines II revealed that trans-fused form IIa is only 0.1 kcal/mol more stable than the cis-fused form IIb. This is in accordance with our observation that the related unsaturated indolizidine 123 exists as a mixture of trans- and cis-fused indolizidines whereas the hydrogenation products are observed to be only trans-fused systems.

87 The trans-fused indolizidine is 2.4 kcal/mol more stable than the cis-fused indolizidine, see Aaron, H. S.; Ferguson, C. P. Tetrahedron Lett. 1968, 9, 6191.
Figure 2. Relative energies for saturated and unsaturated indolizidines calculated using MacSpartan '04 (ab initio HF-6-311+G**) (Wavefunctions, Irvine, CA).

Bruylants Reaction

We next turned our attention to the Bruylants reaction of α-amino nitrile 66a. Some of the earlier results obtained by David Amos are shown in Scheme 27. Thus, Amos had found that treatment of 66a with 3 equiv of ethylmagnesium bromide in Et₂O affords quinolizidine 121 in 85% yield as an 88:12 mixture of β and α ethyl stereoisomers. As predicted by stereoelectronic principles (vida supra), the intermediate iminium ion is trapped via axial addition of the Grignard reagent to give the major diastereomer 121. Interested in exploring the scope of this process with respect to different types of Grignard reagents, Amos found that aryl and alkynyl Grignard reagents deliver the expected quinolizidines 128 and 129 in excellent yield as a single diastereomer in each case (Scheme 27). Of particular importance is the stereocomplementary nature of transformations 66a→119 (Scheme 26) and 66a→121, in which the C-4 stereocenter can be controlled to provide either diastereomer depending on the protocol employed.
It should be noted that the ability of our strategy to provide efficient access to substituted quinolizidines and indolizidines such as 119 and 121 is of particular importance, since nitrogen heterocycles of this type are not available via the intramolecular Diels-Alder reactions of iminium ions described by Grieco. As discussed in Chapter 2, Grieco reported that iminium ions derived from formaldehyde readily undergo the desired cycloaddition, but in the case of iminium ions derived from acetaldehyde “the reaction rate was substantially retarded and the number of byproducts was significantly increased.” To obtain more specific data on the scope of the Grieco iminium ion Diels-Alder reaction, David Amos investigated the reactions shown in eq 26. As expected, the formiminium ion derived from 130 and HCHO afforded the expected cycloadduct 131 in good yield; however, the analogous reaction of 130 with propionaldehyde failed to deliver the expected cycloadduct 132 and instead resulted in the formation of a complex mixture of products. In contrast, as discussed above, our iminoacetonitrile cycloaddition strategy...
not only provides access to substituted quinolizidines and indolizidines such as 132, but also allows us to selectively generate either of the two stereoisomers.

\[
\text{NH}_2 \quad \text{O} \quad \text{Sit-BuMe}_2 \quad \text{4 equiv } R^1\text{CHO} \quad \text{HCl, H}_2\text{O} \quad 65 \degree \text{C} \quad 24 \text{h} \quad \text{H} \quad \text{OH} \quad (26)
\]

130

131 \( R^1=\text{H} \quad 60-66\% \)

132 \( R^1=\text{Et} \quad 0\% \)

**Synthesis of Quinolizidines and Indolizidines with Quaternary Centers**

Next, we turned our attention to the application of this chemistry for the synthesis of quinolizidines and indolizidines incorporating quaternary centers. The diastereoselective installation of quaternary centers has always been a challenging problem in organic synthesis. We envisioned that by using a combination of alkylation reactions and stereocontrolled additions to iminium ions, stereoisomeric quinolizidines and indolizidines with quaternary centers would be available with a high degree of stereocontrol. As illustrated in Scheme 28, this has indeed turned out to be the case. Thus, alkylation of 66a with ethyl iodide followed by Bruylants reaction with methylmagnesium bromide affords quinolizidine 133 as a single diastereomer. The diastereomeric quinolizidine 134 was prepared by reaction of the metalated nitrile with methyl iodide and subsequent reaction with ethylmagnesium bromide. It is crucial to the success of the Bruylants reaction that upon scaling up the reaction (>100 mg) the Grignard reagent is pre-cooled to 0 °C before addition to the alkylated α-amino nitrile. If the Grignard reagent is not pre-cooled to 0 °C, the yield of the reaction is decreased (ca. 30-40%) because the alkylated α-

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amino nitrile (obtained from the first step) rapidly decomposes upon addition of the Grignard reagent.

Scheme 28

The stereochemical assignments of the quaternary centers in 133 and 134 are based on the observed resonances for the C-11 methyl groups in the $^1$H NMR spectrum. The protons of the C-11 methyl group in quinolizidine 134 are shifted downfield (1.10 ppm vs 0.88 ppm) relative to the protons in the C-11 methyl group of 133. The equatorial methyl group lies in the deshielding cone of a C-C bond of the ring skeleton and therefore is expected to appear further downfield than the axial methyl group. This assignment is consistent with axial delivery of the Grignard nucleophile to the iminium ion as previously discussed.

A second strategy for installing quaternary centers exploits the nucleophilic character of a metalated α-amino nitrile and the electrophilic character of the nitrile group itself. Alkylation of 74 with ethyl iodide followed by addition of methyllithium provided the expected imine, which upon hydrolysis by added silica gel afforded 136 in 73% yield (overall from 74) as a single
diastereomer (Scheme 29). The cyano group of the alkylated α-amino nitrile 135 was anticipated to be axially disposed due to the anomeric effect, and thus ketone 136 is predicted to have the stereochemistry shown.

Scheme 29

![Scheme 29 diagram](image)

The stereochemistry of the quaternary center in 136 was established using NOE difference experiments. Irradiation of the ring junction hydrogen produced an NOE enhancement at the acetyl methyl group confirming the equatorial disposition of the ethyl group. Interestingly, irradiation of H₃a₈⁹ produced an NOE enhancement at the C-6 axial hydrogen (H₆a) and not at the ring junction hydrogen leading to the conclusion that 136 exists as the cis-azaindane conformational isomer as shown below.

89 The chemical shifts of the C-3 protons are well resolved in the ¹H NMR spectrum of 136. The more deshielded proton (2.98 ppm vs 2.55 ppm) was assigned as the equatorial proton (H₃e) due to the fact that it lies in the deshielding cone of a C-C bond of the ring skeleton.
Next, indolizidine 138 was prepared in 67% yield by reacting the metalated α-amino nitrile with ethyl iodide to give tertiary α-amino nitrile 137 which was immediately treated with ethynylmagnesium bromide. Again, as predicted on the basis of stereoelectronic considerations, diastereomer 138 was obtained as the exclusive product of the reaction (Scheme 30). However, in this case, we isolated a 65:35 mixture of trans- and cis-fused indolizidine conformational isomers which could be separated by column chromatography.

Unambiguous assignment of the trans- and cis-fused indolizidine ring systems was accomplished by employing difference NOE experiments. First, identification of H₃e and H₃a in
the spectra of the major and minor isomers was made by NMR analysis. The chemical shifts of
the C-3 protons are well resolved in the $^1$H NMR spectra of both isomers. The more deshielded
proton (for major-138 2.91 ppm vs 2.39 ppm and for minor-138 3.14 ppm vs 2.82 ppm) was
assigned as ($\text{H}_3\text{e}$) due to the fact that it lies in the deshielding cone of a C-C bond of the ring
skeleton.\textsuperscript{51} Irradiation of the ring junction hydrogen in the major ring system produced NOE
enhancements at $\text{H}_{3a}$ and the acetylene hydrogen. These results rule out the possibility of the
structure of the major isomer being $trans$-139. However, irradiation of the $\text{H}_{6a}$ proton did not
produce an NOE enhancement at $\text{H}_{3a}$. Therefore, we concluded that the major isomer is $trans$-
138. Next, irradiation of $\text{H}_{3a}$ of the minor product produced NOE enhancements at the C-6 axial
hydrogen ($\text{H}_{6a}$) and the ethyl group which supports the assignment of the minor isomer as $cis$-
138 instead of $cis$-139.
The preceding reaction sequences for the installation of quaternary centers take advantage of all three reactive characteristics of the α-amino nitrile moiety. The alkylation employs the nucleophilic character of metalated nitriles, while the formation of the ketone demonstrates the electrophilic nature of the cyano group, and the Bruylants reaction exploits the latent iminium ion character present in this functional group. Therefore, implementing the appropriate tactics allows the incorporation of different functional groups with complementary stereochemistry.

*Synthesis of Spiroquinolizidines*

Our attention was next focused on utilizing α-amino nitrile cycloadducts for the synthesis of spiro-fused azatricyclic systems. Besides being structurally intriguing molecules, these systems are also found in biologically active natural products such as halichlorine. Halichlorine, a marine alkaloid isolated from the sponge *Halichondria okadai* Kadota, inhibits the expression of VCAM-1 (Vascular Cell Adhesion Molecule-1) and therefore has been identified as a lead compound for the development of antiinflammatory drugs.\(^90,91\) Initially, we envisioned using ring closing metathesis as shown in Scheme 31 to form the spirocyclic system of molecules such as 141.\(^92\)

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\(^{92}\) For a review on metathesis reactions in organic synthesis, see Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Germany, 2003; vol. 2.
Unfortunately, attempts to synthesize the RCM quinolizidine substrate 140 were unsuccessful (Scheme 32). Alkylation of cycloadduct 66a proceeded normally, but the resulting tertiary α-amino nitrile 142 decomposed upon addition of the alkyl Grignard reagent (precooled to 0 °C) to give a mixture of several products, two of which we have been tentatively assigned as 144 and 145. The Grignard reagent appears to deprotonate the iminium ion 143 at C-3 or C-11 to give the dienamine byproducts. It also appears that the rate of deprotonation of 143, probably at the activated allylic C-11 position, occurs at a much faster rate than nucleophilic addition to the iminium ion in this case. Unfortunately, we did not try any other Grignard reagents in the Bruylants reaction of 142 and therefore we cannot say with certainly that it is the substrate structure that is solely responsible for the failure of the Bruylants reaction.
Scheme 32

A second approach we explored is shown in Scheme 33 and involves an enyne ring closing metathesis strategy to deliver the spiroquinolizidine.\(^{93}\) Thus, alkylation of the metalated nitrile with 4-bromobutene followed by addition of ethynylmagnesium bromide afforded quinolizidine 146 in 65% yield as a single diastereomer.\(^{94}\) The success of the Bruylants reaction in this case is attributable to two factors which we believe suppress the rate of deprotonation. First, ethynylmagnesium bromide is less basic than allylmagnesium bromide. Second, the side chain does not have a double-bond located so as to allow formation of a conjugated dienamine similar to 144. With 146 in hand, we investigated the enyne ring closing metathesis reaction and found that treatment of 146 with 5 mol % of 147 in toluene at 85 °C for 2 h affords spiroquinolizidine 148 in 82% yield. Efforts to employ less catalyst led to incomplete conversion and low yields.


\(^{94}\) The assignment of the quaternary center in 146 was confirmed by a NOE enhancement produced at the acetylenic proton upon irradiation of the ring junction hydrogen.
Finally, we explored the feasibility of using a reductive cyclization to form the spirocyclic system. Our interest in reductive cyclization of nitriles originated from consideration of the elegant work of Rychnovsky and coworkers. As shown in Scheme 34, Rychnovsky has shown that exposure of cyanohydrin 149 to 4,4'-di-t-butylbiphenylide (LiDBB) affords spirocycle 153 in excellent yield as a single diastereomer.\textsuperscript{95} Mechanistic studies of the reductive lithiation of cyanohydrins showed that the stereochemistry of the organolithium intermediate is controlled by the preference of the unpaired electron in 150 to occupy an orbital with axial orientation due to anomeric stabilization. Following a second electron transfer, the lithium compound 152 cyclizes to deliver spirocycle 153.\textsuperscript{96}


Scheme 34

Rychnovsky and coworkers have also extended this methodology to α-amino nitriles with pendant phosphate leaving groups (e.g., eq 27). Reductive lithiation of 154 with LiDBB and subsequent cyclization affords spirocycle 155 in 85% yield. Consistent with previous cyanohydrin reductive cyclization studies, this reductive spiroannulation is highly stereoselective and produces a 92:8 mixture of trans- and cis-155.97

Inspired by this work, we decided to explore the reductive spiroannulation of α-amino nitrile cycloadducts. As shown in Scheme 35, alkylation of the metalated nitrile with 1-chloro-5-iodopentane afforded tertiary α-amino nitrile 156, which without purification underwent reductive cyclization with LiDBB to deliver spiroquinolizidine 157 in 51% overall yield from 66a. Although this is a fairly simple example, it does demonstrate that the reductive cyclization of α-amino nitrile cycloadducts is a powerful method for the stereocontrolled synthesis of spirocyclic systems.

Summary

In conclusion, our \(\alpha\)-amino nitrile cycloadducts undergo a variety of useful synthetic transformations leading to a variety of substituted quinolizidines and indolizidines. These transformations take advantage of the latent iminium ion character of \(\alpha\)-amino nitriles, along with the reactivity of the cyano group. These studies provided a better understanding of the reactivity of our \(\alpha\)-amino nitrile cycloadducts, enabling us to apply this methodology to the total synthesis of quinolizidine and indolizidine natural products as described in the following two chapters.
Chapter 7 – Total Synthesis of Quinolizidine (−)-217A

As discussed in the previous chapter, the intramolecular [4+2] cycloaddition of iminoacetonitriles provides access to α-amino nitrile cycloaducts that are versatile synthetic intermediates for the synthesis of quinolizidines and other nitrogen heterocyclic systems. This chapter describes the total synthesis of the natural product quinolizidine (−)-217A utilizing an iminoacetonitrile cycloaddition as the key step.

Introduction

The importance of substituted quinolizidines and indolizidines as synthetic targets is well established. The skeletons of a number of bioactive natural products incorporate these structures, and many of these compounds are available in very limited amounts from their natural source. Highly toxic quinolizidine and indolizidine alkaloids isolated from the skin of poisonous amphibians have attracted much interest as research tools for neurophysiological investigations, and recently quinolizidine alkaloids obtained from marine sources have been identified as lead compounds for the development of anticancer, anti-inflammatory, and cardiovascular drugs. A number of ingenious methods have been developed in response to the synthetic challenge posed by these molecules, and these alkaloids have served as a popular testing ground for methods for the construction of pyrrolidines, piperidines, and various azabicyclic systems. 99

98 For a recent review of the chemistry and biology of indolizidine and quinolizidine alkaloids, see Daly, J. W.; Garaffo, H. M.; Spande, T. F. In Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1-161.
A majority of these "izidine" type alkaloids can be classified as either 1,4-disubstituted quinolizidines or 5,8-disubstituted indolizidines. As shown in Scheme 36, there are four possible diastereomers for each class and currently there are known examples of each type of alkaloid except 159, 164, and 165. Even though elegant methods exist for the synthesis of these types of alkaloids, we felt that our iminoacetonitrile cycloaddition chemistry would be a valuable addition to the synthetic methodology because we should be able to access all possible stereoisomers from a few common α-amino nitrile cycloadducts. As discussed in Chapter 6, the stereochemistry at C-4 of quinolizidines (and C-5 of indolizidines) can be controlled by employing the proper choice of reagents in the synthetic elaboration of α-amino nitriles. For example, the tandem alkylation-reductive decyanation affords the equatorial oriented side chain \((R^2)\), whereas the Bruylants reaction produces the axial oriented side chain. On the other hand, the stereochemistry at C-1 of quinolizidines and C-8 of indolizidines can be manipulated by the proper application of thermodynamic or kinetic control. For example, thermodynamic control can provide routes to systems such as 158, 160, 162, and 164 where \(R^1\) is an equatorial side chain. Alternatively, hydrogenation of a C1-C2 (quinolizidine) or C7-C8 (indolizidine) alkene double bond is expected to occur from the less hindered \(exo\) face of the azabicyclic system to afford the axial \(R^1\) side chain.

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100 For a review of quinolizidines and indolizidines isolated from nature, see Daly, J. W.; Spande, T. F.; Garraffo, H. M. J. Nat. Prod. 2005, 68, 1556.

In order to further test and refine our iminoacetonitrile cycloaddition methodology, we have undertaken the synthesis of several bioactive quinolizidine and indolizidine alkaloids such as 217A,\textsuperscript{102} 207I,\textsuperscript{102b} and 235B'.\textsuperscript{103} By employing an intramolecular Diels-Alder cycloaddition of iminoacetonitriles, we expected to be able to efficiently access the bicyclic core of these quinolizidine and indolizidine alkaloids in only 5-6 steps. With an $\alpha$-amino nitrile handle, we would then be able to elaborate the aforementioned cycloadducts into the fully adorned natural products.

This chapter describes the application of the iminoacetonitrile cycloaddition as a key step in the total synthesis of quinolizidine (-)-217A, an amphibian alkaloid isolated in minute quantities by Daly in 1993 from skin extracts of the Madagascan frog *Mantella baroni*. Alkaloid (-)-217A, along with several other 1,4-disubstituted quinolizidines and 5,8-disubstituted indolizidines, is believed to be dietary in origin based on the fact that many of the “izidine” type alkaloids have also been detected in ants, which the Mantelline and Dendrobates frogs are known to eat.\(^{104}\) Our goal was the development of an efficient approach to the synthesis of quinolizidine 217A capable of supporting the preparation of significant quantities of the target alkaloid.

**Previous Total Syntheses of 217A**

Pearson and coworkers published the first total synthesis of 217A in 1998, producing racemic 217A in 20 steps.\(^{105}\) As shown in Scheme 37, Pearson’s synthesis commences with the preparation of lactone 167. Addition of allyltrimethylsilane to aldehyde 166\(^{106}\) followed by cyclization of the resultant hydroxy ester gave lactone 167 in 73% yield. Methylation of 167 followed by oxidation and protection afforded lactone 168 as a 1:1 mixture of diastereomers.

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\(^{106}\) Aldehyde 166 was prepared in 2 steps from commercially available valerolactone, see Huckstep, M.; Taylor, R. *J. K. Synthesis* 1982, 130.
which were separated later in the synthesis. Reduction of lactone 168 and subsequent olefination afforded 169 in 52% yield.

The next stage of Pearson’s synthesis utilized an azide cycloaddition and subsequent stereoselective imine reduction to form the trisubstituted piperidine subunit 173 (Scheme 38). Thus, installation of the azide group via standard displacement chemistry afforded 170 in 84% yield with inversion of the C-4 stereocenter. Next, dipolar cycloaddition of azide 170 afforded an intermediate triazoline which decomposed via elimination of N₂ to give imine 171. Stereoselective reduction of imine 171 with NaBH₄ then produced piperidine 172 as a 57:43
mixture of epimers at C-1. Finally, saponification of 172 and separation of the diastereomers afforded 173 in 34% yield (overall from 170).

**Scheme 38**

With the stereocenters at C-4 and C-10 set, piperidine 173 was converted into alkaloid 217A in a straightforward fashion (Scheme 39). Reduction of the carboxylic acid and cyclization of the resulting alcohol afforded quinolizidine 174 in 65% yield. Liberation of the aldehyde and subsequent olefination using Yamamoto’s method provided the enyne 175 in 42% yield as a single isomer. Finally, desilylation of 175 afforded racemic quinolizidine 217A (176) in 90% yield. Although the synthesis provided racemic material and was fairly lengthy, it did confirm the relative stereochemistry proposed by Daly and coworkers.  

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In 2003, Panek and coworkers reported the first enantioselective synthesis of quinolizidine (−)-217A via an approach requiring 20 steps. The key step in Panek’s route is an intramolecular imine crotylation using a chiral organosilane to give a highly enantioenriched tetrahydropyridine. As shown in Scheme 40, enantiopure vinylsilane 177, prepared via resolution, was converted into 178 via a DCC-mediated esterification. Silyl enol ether formation and subsequent heating afforded the Ireland ester Claisen rearrangement product 179 in 70% yield as a single diastereomer. Esterification of 179 followed by reduction of the azide provided amine 180 in 74% yield.

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109 Vinylsilane 177 was prepared in 5 steps from trans-crotonaldehyde, see Panek, J. S.; Sparks, M. A. Tetrahedron: Asymmetry 1990, 1, 801.
With the synthesis of chiral silane 180 complete, the stage was set for the key [4+2] tetrahydropyridine annulation (Scheme 41). In the event, condensation of amine 181 with aldehyde 182 afforded imine 183. Subsequent cyclization via an intramolecular crotylsilane addition and Cbz-protection afforded tetrahydropyridine 184 in 60% yield as a single diastereomer. Hydrogenation and deacetylation of 184 provided piperidine 185 in 90% yield.
As depicted in Scheme 42, cyclization of alcohol 186 afforded quinolizidine 187 in 93% yield. Homologation of the ester via reduction to the aldehyde and Wittig olefination provided enol ether 188 in 67% yield as an $E/Z$ mixture of isomers. Hydrolysis of enol ether 188 and subsequent Yamamoto olefination installed the enyne side chain which upon desilylation afforded alkaloid (−)-217A (176) in 57% yield (overall from 188).
Total Synthesis of Quinolizidine (-)-217A

Retrosynthetic Analysis

Our goal was the development of an approach to the synthesis of quinolizidine 217A considerably more efficient than these earlier syntheses and capable of supporting the preparation of significant quantities of the target alkaloid. Scheme 43 outlines our retrosynthetic strategy, which features the intramolecular iminoacetonitrile cycloaddition $191 \rightarrow 190$ as a pivotal step. Alkylation of $190$ would then be employed to install the enynylmethyl side chain, and stereoelectronic control in the subsequent reductive decyanation step was expected to deliver the desired stereochemistry at C-4. Control of the stereochemistry at C-1 would be established by epimerization of the ketone intermediate $189$ derived from the silyl enol ether cycloadduct. In this first generation synthesis, we elected to employ resolution to provide access to the natural
(-)-isomer as well as the unnatural isomer, deferring for future study the possibility of employing chiral Brønsted acids to catalyze an asymmetric version of the cycloaddition.

\[ \text{Scheme 43} \]

\[
\begin{align*}
\text{176} & \quad \text{\rightarrow} \quad \text{189} \quad \text{\rightarrow} \quad \text{191} \\
\text{190} & \quad \text{\leftarrow} \quad \text{191}
\end{align*}
\]

**Preparation of \( \alpha \)-Amino Nitrile Cycloadduct 190**

Our first synthetic subgoal was the development of an efficient route to cycloaddition substrate 191. Based on our previous studies, we anticipated that 191 would be available from sulfonamide 196 by elimination of trifluoromethanesulfinate on exposure to a weak base such as carbonate. Scheme 44 outlines our efficient four-step route to 196. Mitsunobu coupling of commercially available 5-hexenol with \( \text{CF}_3\text{SO}_2\text{NHCH}_2\text{CN} \) provided the expected sulfonamide, and ozonolysis then furnished aldehyde 193 in excellent yield. Wittig olefination of 193 using the acylphosphorane 194\textsuperscript{110} produced the desired \((E)-\alpha,\beta\)-unsaturated ketone 195 in 85-87% yield.

yield after purification by column chromatography. Finally, conversion to the desired enol ether was achieved using the general procedure of Dunogues et al. to afford 196 in excellent yield after purification by column chromatography on acetone-deactivated silica gel. Attempts to use stronger bases, such as NaH and LDA, for formation of the silyl enol ether were unsuccessful due to decomposition of the base-sensitive triflamide moiety.

Inspired by the recent advances made in olefin metathesis, we envisioned a more direct route for the synthesis of 195 employing a cross-metathesis strategy (eq 28). However, all attempts to synthesize 195 via the cross-metathesis reaction of triflamide 192 and 3-methyl-3-

---

111 The crude product of the Wittig reaction consisted of a 90:10 mixture of E and Z enones.
113 For reviews on cross metathesis, see: (a) reference 92 (b) Connan, S. J.; Blechert, S. Angew. Chem., Int. Ed. 2003, 42, 1900. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. J. Am. Chem. Soc. 2003, 125, 11360.
buten-2-one were frustrated by the homodimerization of 192. Also, efforts to isolate and re-subject the homodimer of 192 to the cross-metathesis reaction were completely unsuccessful leading to the conclusion that the dimer is unreactive in secondary metathesis. Interestingly, the cross-metathesis reaction of triflamide 192 with methyl vinyl ketone afforded the expected enone 198 in 90% yield as a single isomer.

\[
\begin{align*}
\text{[Image]} & \quad \text{3 equiv } \ce{H3C} \ce{O} \\
& \quad \text{5 mol % 197, CH2Cl2, rt, 2 h} \\
\rightarrow & \quad \text{[Image]}
\end{align*}
\]

As shown in Scheme 45, exposure of 196 to the action of cesium carbonate led to the elimination of trifluoromethanesulfinate and formation of iminoacetonitrile 191 as the expected mixture of E and Z imine isomers. The stereochemistry of this intermediate is not crucial, since iminoacetonitrile isomers interconvert under the conditions of the [4+2] cycloaddition. Heating iminoacetonitrile 191 at 130 °C for 36 h then produced the desired α-amino nitrile cycloadduct 190a in good yield. As discussed in Chapter 4, addition of BHT was found to be beneficial in suppressing decomposition of the desired product. As expected, the isomer with an \textit{exo}-oriented (axial) cyano group was isolated as the exclusive product of the reaction as a consequence of the “α-amino nitrile anomeric effect.”\textsuperscript{45}
Next, we explored the acid-promoted cycloaddition of iminoacetonitrile 196. Initial attempts were frustrated by decomposition of 196 presumably via competing reaction of the silyl enol ether moiety with MsOH. However, conducting the reaction at -78 °C with dropwise addition of MsOH afforded cycloadducts 190a and 190b in 68% yield as a mixture of epimers at C-4. As previously discussed, simply heating the mixture in CH₃CN at 45 °C for 1.5 h delivers 190a as a single diastereomer (axial nitrile). It should be emphasized that the α/β mixture of nitriles is inconsequential due to the fact that further transformations at the C-4 carbon are controlled by stereoelectronic principles independent of the C-4 cyano group stereochemistry (see Chapter 6).

*Alkylation/Reductive Decyanation of α-Amino Cycloadduct 190*

For the next stage of the synthesis, alkylation of α-amino nitrile 190, we initially focused our attention on the enynylmethyl compounds 203-206. As shown in Scheme 46, alcohol 202
was prepared from ethyl propiolate in good yield utilizing a previously published method.\textsuperscript{114} Alkylating agents 203-206 were then prepared from alcohol 202 as previously described in good yield.\textsuperscript{115}

**Scheme 46**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 equiv LiBr</td>
<td>1.2 equiv AcOH</td>
</tr>
<tr>
<td>CH\textsubscript{3}CN, reflux, 24 h</td>
<td>Br\textsubscript{-} CO\textsubscript{2}Et</td>
</tr>
<tr>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>58% (overall from 199)</td>
<td></td>
</tr>
<tr>
<td>2.2 equiv DIBAL-H</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 1 h</td>
</tr>
<tr>
<td>84%</td>
<td></td>
</tr>
</tbody>
</table>

Surprisingly, the desired enyne 170 was obtained at best in only 30% overall yield after alkylation of 190a with any of these enynes followed by reductive decyanation (Scheme 47). It is important to recall that purification of the intermediate alkylation product is best avoided due to decomposition of the tertiary α-amino nitrile on silica gel. Although alkylation with model alkylating agents such as allyl bromide proceeded smoothly (quantitative yield), complex


mixtures resulted from the reaction of 190 with enynylmethyl derivatives 203-206. Interestingly, the addition of additives known to improve alkylation reactions, such as DMPU, HMPA, DMSO, and LiCl, had no effect on the reaction.

![Scheme 47](image-url)

Although we have been unable to characterize any of the byproducts of this reaction, we speculate that electron transfer to the enynylmethyl halide from the metalated nitrile (thus generating a captodative stabilized amino nitrile radical) may be complicating this alkylation.\(^\text{116}\) Other conceivable side reactions include the deprotonation of the enynylmethyl halide\(^\text{117}\) and addition of the lithiated nitrile to the enyne moiety.\(^\text{118}\) We therefore turned our attention to a less unsaturated allylic halide, (Z)-3-bromo-1-chloro-propene, with the idea of later elaborating the full enyne moiety via a Sonogashira coupling reaction.

In the event, we were pleased to find that alkylation of 190 with (Z)-3-bromo-1-chloro-propene proceeded cleanly, and reductive decyanation of the unpurified alkylation product with


\(^\text{117}\) For examples of the metatation of allylic halides, see Julia, M.; Verpeaux, J.-N.; Zahneisen, T. *Synlett* 1990, 769.

\(^\text{118}\) For addition of organolithium compounds to conjugated enynes, see Brandsma, L. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: Oxford, 2004; p 74.
sodium cyanoborohydride then afforded the desired quinolizidine 207 in 74-77% overall yield (eq 29).

![Chemical reaction](image)

As discussed in chapter 6, axial delivery of hydride to the intermediate iminium ion leads to formation of the desired diastereomer as the exclusive product of the reaction. The allyl group of 207 was assigned as equatorial (endo) based on NMR analysis and comparison with the spectra previously reported by Amos for the related compounds 119 and 121 as shown below.

![NMR spectra](image)

**Preparation and Reductive Deoxygenation of Ketone 207**

With the synthesis of quinolizidine 207 complete, we were poised to unmask the C-2 carbonyl. Treatment of silyl enol ether 207 with 1.1 equiv of n-Bu$_4$NF in THF generated ketone 208 as a single diastereomer with the C-1 methyl group in the desired equatorial orientation (Scheme 48). The stereochemical assignment of the C-1 methyl group was based on the comparison of its chemical shift to that of an equatorial and axial oriented methyl group in the...
related compounds 209 and 210.\textsuperscript{119} Comparison of the C-6 equatorial proton of 208 to that of 119 confirmed the assignment of the C-4 stereocenter as shown below. As expected, reactions employing less than 1 equiv of \(n\text{-Bu}_4\)NF afforded a mixture of epimers at C-1 confirming that excess \(n\text{-Bu}_4\)NF was in fact equilibrating the C-1 methyl group to the thermodynamically favored equatorial orientation.

At this stage of the synthesis, we decided to investigate the resolution of quinolizidine (±)-208. We chose (\(R\))-(\(-\))-1,1′-binaphthyl-2,2′-diylphosphoric acid (211)\textsuperscript{120} as our resolving agent based on the fact that several examples exist in the literature of 211 being used to resolve related quinolizidines.\textsuperscript{121} Thus, treatment of (±)-208 with 1.0 equiv of 211 afforded a white solid which was recrystallized twice from MeOH and then treated with 10% ammonium hydroxide solution to give enantiomerically pure (\(-\))-208 in 44% overall yield from the racemate. The

\textsuperscript{119} Quéguiner, G.; Ribereau, P.; Godard, A. *Tetrahedron* 1995, 51, 3247.
\textsuperscript{120} Jacques, J.; Fouquey, C. *Tetrahedron Lett.* 1971, 12, 4617.
The enantiomeric purity of the product was determined by $^1$H NMR analysis of the salt formed by reaction with $(R)$-$(−)$-1,1'-binaphthyl-2,2'-diylphosphoric acid: the phosphoric acid (1.0 equiv) was added to a solution of 208 in ca. 0.7 mL of CDCl$_3$. The C-1 methyl group appeared as a doublet ($J = 6.5$ Hz) at 1.01 ppm; no doublet at 1.19 ppm could be detected. Similar analysis of racemic 208 showed two doublets (1:1 ratio) at 1.19 and 1.01 ppm.

The next stage of the synthesis, involving reductive excision of the carbonyl group, proved unexpectedly difficult. Initial attempts to effect deoxygenation of ketone 208 (as well as derivatives of the corresponding alcohol) were complicated by the formation of a byproduct tentatively identified as the tricyclic amine 215. As shown in Scheme 49, treatment of tosylhydrazone 213 with NaBH$_3$CN in acidic DMF/sulfolane afforded a 30:70 mixture of the desired deoxygenated product 214 and tricyclic amine 215. Similarly, Barton-McCombie reduction of 216 with $n$-Bu$_3$SnH and AIBN delivered a 50:50 mixture of 214 and 215.

---

123 The structure of 215 was tentatively assigned based on its molecular formula, C$_{13}$H$_{22}$NCI (MW = 227 found by mass spectrometry), and $^1$H NMR spectrum. The absence of vinyl protons and the presence of a primary alkyl chloride with the C-13 methylene protons coupled to the C-12 methine proton suggest a tricyclic structure. In addition, the presence of Bohlmann bands in the FT-IR indicate a trans-fused quinolizidine.
126 Ratio of products (214:215) determined by gas chromatography.
Although two seemingly unrelated methods afforded the same byproduct, this was not totally unexpected in view of the fact that both reactions proceed through radical intermediate 218 (Scheme 50). For example, hydride reduction of tosylhydrazone 213 is expected to afford the intermediate diazene 217 which then fragments to give radical intermediate 218. Cyclization onto the vinyl chloride furnishes 215 whereas intermolecular hydrogen abstraction delivers 214. Consistent with this mechanistic explanation, we found that the ratio of the two products was influenced by the concentration of the reaction mixture with lower concentrations favoring the cyclization product.
Since this byproduct appeared to arise from cyclization of a C-2 radical intermediate onto the vinyl chloride appendage, we focused our attention on strategies in which the reduction step could be carried out in the presence of efficient hydrogen atom transfer agents so as to more effectively intercept the intermediate radical prior to cyclization. Success was achieved by means of the one-pot protocol outlined in Scheme 51. Thus, reduction of the tosylhydrazone of \((-\)-208 with \(\text{NaBH}_3\text{CN}\) in the presence of \textit{tert}-butyl mercaptan completely suppressed the undesired radical cyclization and furnished vinyl chloride 214 in 63-66\% overall yield.

Scheme 51

\[
\begin{align*}
\text{CH}_3 & \quad \text{H} = 1.2 \text{ equiv } \text{TsNHNNH}_2, \text{ cat } \text{TsOH} \\
\text{DMF, sulfolane, } 110 \ ^\circ\text{C, } 2 \text{ h} & \\
\text{CH}_3 & \quad \text{H} \\
\text{NHTs} & \\
\text{208} & \rightarrow \\
\text{213} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{CH}_3 \\
\text{214} & \rightarrow \\
\text{4.0 equiv } \text{NaBH}_3\text{CN} & \\
\text{15 eq } \text{t-BuSH} & \\
\text{110 }^\circ\text{C, } 5 \text{ h} & \\
\text{63-66}\% & \\
\end{align*}
\]

**Endgame**

Having effectively removed the C-2 carbonyl group, we were poised to conquer the total synthesis of quinolizidine 217A. As shown in eq 31, Sonogashira coupling with trimethylsilylacetylene proceeded smoothly, provided that the acetylene was added slowly to suppress competing alkyne dimerization. Finally, desilylation with \(\text{K}_2\text{CO}_3\) in methanol afforded
quinolizidine $(-)-217A$ ([α]$^D_2$ -14 (c 0.8, CHCl$_3$), lit.$^{108}$ [α]$^D_0$ -13.75 (c 0.4, CHCl$_3$)) with spectral characteristics identical with those reported for synthetic 217A by Pearson and Panek (Tables 6 and 7).$^{105,108}$ The only structural information that exists in the literature for natural 217A is the $^1$H NMR of 217A·DCl.$^{104}$ Therefore, Pearson and coworkers converted their synthetic material to its DCl salt, and then compared their $^1$H NMR spectrum with that of an authentic sample of the alkaloid. This experiment showed that their synthetic 217A had spectral characteristics identical with those reported for the natural product. Since the spectral data for our synthetic 217A matches that of Pearson’s synthetic material, we are confident that our material is in fact the natural product 217A.

\[
\begin{align*}
1) & \text{cat. PdCl}_2(\text{PhCN})_2 \\
& \text{cat. Cul} \\
& 2.0 \text{ eq } \text{Me}_3\text{Si} \\
& \text{piperidine, rt, 24 h} \\
2) & \text{1.0 eq } \text{K}_2\text{CO}_3, \text{MeOH,} \\
& \text{rt, 2 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{80-82\%} \\
\text{Quinolizidine } (-)-217A
\end{align*}
\]

Summary

In conclusion, the intramolecular iminoacetonitrile [4+2] cycloaddition functions as a key step in an efficient assembly of the quinolizidine core of the amphibian alkaloid $(-)-217A$, enabling the total synthesis of this natural product in only 12 steps. The application of iminoacetonitrile cycloadditions in the synthesis of other bioactive alkaloids is currently under investigation.
### Table 6. \(^1\text{H}\) NMR (CDCl\(_3\)) Spectral Data for Quinolizidine 217A\(^{68,71}\)

<table>
<thead>
<tr>
<th>Atom #</th>
<th>(m)</th>
<th>(\delta)</th>
<th>(J) (Hz)</th>
<th>(\delta)</th>
<th>(J) (Hz)</th>
<th>(\delta)</th>
<th>(J) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(14)</td>
<td>dt (1H)</td>
<td>6.1</td>
<td>11</td>
<td>6.09</td>
<td>10.8, 7.25</td>
<td>6.1</td>
<td>10.9, 7.1</td>
</tr>
<tr>
<td>H(13)</td>
<td>ddt (1H)</td>
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<td>5.49</td>
<td>10.8, 1.3</td>
<td>5.48</td>
<td>10.9, 2.0, 1.6</td>
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<tr>
<td>H(6)</td>
<td>br d (1H)</td>
<td>3.27</td>
<td>11</td>
<td>3.25</td>
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<tr>
<td>H(16)</td>
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<tr>
<td>H(12,10)</td>
<td>m (2H)</td>
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<td>2.47-2.62</td>
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<tr>
<td>H(12)</td>
<td>m (1H)</td>
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<td>2.03</td>
<td>2.05-2.10</td>
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<tr>
<td>H(6)</td>
<td>m (1H)</td>
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<td>1.93</td>
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<td>H(1-4, 7-9)</td>
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<tr>
<td>H(11)</td>
<td>d (3H)</td>
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<td>0.83</td>
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### Table 7. \(^{13}\text{C}\) NMR (CDCl\(_3\)) Data for Quinolizidine 217A\(^{68,71}\)

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<tr>
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<th>Pearson (100 MHz)</th>
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<th>Maloney (75 MHz)</th>
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<tr>
<td>(\delta)</td>
<td>(\delta)</td>
<td>(\delta)</td>
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</tr>
<tr>
<td>143.5</td>
<td>143.4</td>
<td>143.9</td>
<td></td>
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<tr>
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<td>82</td>
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<tr>
<td>69.8</td>
<td>69.5</td>
<td>69.9</td>
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<td>34.9</td>
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<tr>
<td>34</td>
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<tr>
<td>30.3</td>
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<td>30.5</td>
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<tr>
<td>26.3</td>
<td>26.2</td>
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<tr>
<td>24.8</td>
<td>24.6</td>
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<td></td>
</tr>
<tr>
<td>19.4</td>
<td>19.2</td>
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Chapter 8 – Studies Directed Toward the Total Synthesis of Indolizidine (−)-235B′

As demonstrated in the previous chapters, intramolecular [4+2] cycloaddition of iminoacetonitriles provide access to α-amino nitrile cycloadducts, which have proved to be versatile synthetic intermediates for the synthesis of nitrogen heterocycles. This chapter discusses our efforts toward the total synthesis of indolizidine 235B′ utilizing an iminoacetonitrile cycloaddition as the key step.

Introduction

The isolation, biological evaluation, and total synthesis of naturally occurring alkaloids isolated from the skin extracts of the Dendrobatidae family of neotropical arrow poison frogs has been an active area of research.\cite{128} In particular, a small sub-group of 5,8-disubstituted indolizidines have been identified as inhibitors of nicotinic acetylcholine receptors.\cite{127} These receptors act as key components in the physiological processes of reward, cognition, learning, and memory, and are widely expressed in the mammalian brain. Thus, nicotinic acetylcholine receptors are implicated in several neurological disorders such as Alzheimer's disease, schizophrenia, and bipolar disorder.

One 5,8-disubstituted indolizidine that has generated considerable interest in the past few years is alkaloid (−)-235B′. Indolizidine (−)-235B′ was isolated in minute quantities by Daly and coworkers in 1988 from skin extracts of the Panamanian poison frog *Dendrobates speciosus*.\cite{128}

\begin{footnotesize}
\begin{enumerate}
\end{enumerate}
\end{footnotesize}
Recently, Toyooka and coworkers discovered that alkaloid (-)-235B' is a potent noncompetitive inhibitor of α2β2-neuronal acetylcholine receptors in a highly subtype-selective manner. These results suggest that alkaloid (-)-235B' is a promising lead compound for the development of drugs to treat cholinergic disorders such as autosomal dominant nocturnal frontal lobe epilepsy.\(^{129}\)

![Indolizidine (-)-235B'](image)

This chapter describes the application of the iminoacetonitrile cycloaddition as a key step in the total synthesis of indolizidine (-)-235B'. Our goal is the development of an efficient approach to the synthesis of this alkaloid capable of supporting the preparation of significant quantities of material.

**Previous Syntheses of 235B'**

Holmes and coworkers published the first total synthesis of 235B' in 1991, producing racemic 235B' in 14 steps.\(^{130}\) Their approach employed an intramolecular nitrone dipolar cycloaddition as a key step to control the relative stereochemistry of the substituents of the piperidine subunit. As shown in Scheme 52, the first stage of the synthesis involved the


preparation of cycloaddition substrate 222. The synthesis began with the formation of hydrazone 220 from commercially available hex-5-en-2-one in 67% yield. Regioselective alkylation of hydrazone 220 with 6-bromohexene followed by treatment with hydroxylamine hydrochloride delivered oxime 221 in 69% yield. Oxime 221 was then reduced with sodium cyanoborohydride and the resulting hydroxylamine was condensed with 4-acetoxybutanal to give nitrone 222 in 60% yield.

With the synthesis of nitrone 222 complete, the stage was set for the key intramolecular dipolar cycloaddition (Scheme 53). In the event, heating a toluene solution of 222 afforded cycloadduct 223 which upon hydrolysis delivered alcohol 224 in excellent yield as a single diastereomer. Mesylation of alcohol 224 led to spontaneous cyclization to give the quaternary ammonium salt, and subsequent reductive cleavage of the N-O bond with zinc in acetic acid furnished indolizidine 225 in excellent yield.
As depicted in Scheme 54, indolizidine 225 was converted into the target alkaloid in a straightforward fashion. Inversion of the C-8 stereochemistry of 225 was achieved by Swern oxidation to give aldehyde 226, followed by epimerization on basic alumina to give predominantly the equatorial isomer (ca. 13:1). Subsequent reduction and purification of the resulting equatorial alcohol afforded 227 in 46% yield. Lastly, mesylation of alcohol 227 and reduction with LiBEt₃H gave racemic indolizidine 235B' in 58% yield.
In 1997, Toyooka and coworkers reported the first enantioselective synthesis of indolizidine (−)-235B' via a 29 step route. Although the length of this synthesis precludes it from providing useful quantities of material, the synthesis does display a high level of selectivity in generating the three stereocenters. Toyooka controlled the stereochemistry at C-5 by employing a 9-azabicyclo[3.3.1]nonene derivative in a cyclic template strategy, cleaving an internal olefin to afford the piperidine subunit of 235B' with the desired C-5 stereochemistry. A subsequent stereoselective cuprate addition afforded the piperidine subunit with all three stereocenters set.

As shown in Scheme 55, the synthesis commenced with meso diacetate 228, prepared in 9 steps from 1,5-cyclooctadiene. Lipase-catalyzed hydrolysis of diacetate 228 followed by oxidation afforded ketone 229 in 65% yield as a single enantiomer. Enol ether formation

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followed by ozonolysis, reduction, and silylation provided piperidine 230 in 79% yield as a single diastereomer. Sodium hydride elimination of acetic acid from 230 afforded the cuprate addition precursor 231 in 92% yield.

With the synthesis of 231 complete, the stage was set for the key stereoselective cuprate addition to set the final two stereocenters. As depicted in Scheme 56, addition of methyl cuprate to 231 followed by hydride reduction of the ester group afforded piperidine 232 in 86% yield as a single diastereomer. The stereochemistry of the methyl cuprate addition is a result of preferred axial attack of the cuprate reagent, leading to a chair-like intermediate where the C-5 side chain occupies a pseudo-axial orientation owing to A\textsuperscript{1,3} strain. Subjecting 232 to a series of functional group manipulations afforded piperidine 233. This series of steps elongated the C-9 side chain
by two carbons. Protection of the free hydroxyl group of 233 and subsequent desilylation delivered alcohol 234 in 88% yield.

With the C-5, C-8, and C-9 stereocenters set, alcohol 234 was converted into alkaloid 235B’ in a straightforward manner (Scheme 57). The carbon chain homologation of 234 at the C-5 position to give 236 was performed via a sequence involving mesylation of the hydroxyl group, substitution of the resulting mesylate group with NaI to give 235, and subsequent cross coupling. Finally, cyclization of the amino alcohol resulting from liberation of the amino and hydroxyl groups delivered indolizidine (−)-235B’ in 65% yield.
Efforts Toward the Total Synthesis of Indolizidine (-)-235B’

Retrosynthetic Analysis

Our goal was the development of an approach to the synthesis of indolizidine (-)-235B’ that would be considerably more efficient than these earlier syntheses and capable of supporting the preparation of significant quantities of the target alkaloid. Our retrosynthetic strategy closely resembles that of quinolizidine 217A with the only major difference being that it involves the synthesis and elaboration of an indolizidine cycloadduct instead of a quinolizidine cycloadduct.

Scheme 51 outlines our retrosynthetic strategy, which features the intramolecular iminoacetonitrile cycloaddition 239→238 as a pivotal step. Alkylation of 238 would then be employed to install the heptenyl side chain, and stereoelectronic control in the subsequent reductive decyanation step was expected to deliver the desired stereochemistry at C-5. Control of the stereochemistry at C-8 would be established by epimerization of the ketone intermediate.
237 derived from the enol ether cycloadduct. In this first generation synthesis, we elected to employ resolution to provide access to the natural (−)-isomer as well as the unnatural isomer, deferring for future study the possibility of employing chiral Brønsted acids to catalyze an asymmetric version of the cycloaddition.

**Scheme 58**

Indolizidine (−)-235B' → 237

Preparation of α-Amino Nitrile Cycloadduct

Our first synthetic subgoal was the development of an efficient route to cycloaddition substrate 239. Based on our previous studies on the total synthesis of 217A, we anticipated that 239 would be available from sulfonamide 243. Scheme 59 outlines our efficient four-step route to 243 which closely resembles the analogous sequence in our synthesis of 217A. Mitsunobu coupling of commercially available 4-pentenol (240) with TfNHCH₂CN provided the expected sulfonamide 241 in 92% yield. Ozonolysis of triflamide 241 and subsequent Wittig olefination
of the resulting aldehyde using the acylphosphorane $^{194}$ produced the desired (E)-α,β-
unsaturated ketone 242 in 81% overall yield after purification by column chromatography.
Unexpectedly, the intermediate aldehyde was unstable to silica gel and therefore was used in the
Wittig olefination without further purification. We also discovered that switching from toluene
at 70 °C (conditions used in our 217A route) to refluxing THF led to consistently higher yields
(ca. 10%) in the Wittig reaction. Finally, conversion to the desired silyl enol ether 243 was
achieved using the general procedure of Dunogues et al. $^{112}$ to afford 243 in 91% yield after
purification on acetone-deactivated silica gel.

As shown in Scheme 60, exposure of 243 to the action of cesium carbonate led to the
elimination of trifluoromethanesulfinate and formation of iminoacetonitrile 239 as the expected
mixture of $E$ and $Z$ imine isomers. Heating iminoacetonitrile 239 at 120 °C for 36 h then produced the desired $\alpha$-amino nitrile cycloadducts 238a and 238b in 10-15% yield as a 60:40 mixture of epimers (Scheme 60). Discouraged by this result, we shifted our focus to the acid-promoted cycloaddition of 239. Unfortunately, cycloaddition of 239 at -78 °C failed to deliver cycloadduct 238 and led to recovered iminoacetonitrile. This was not unexpected as previous results have shown that cycloadditions affording indolizidines are extremely sluggish at -78 °C. However, efforts to conduct the cycloaddition at higher temperatures (-40 to 0 °C) were complicated by competing decomposition of the iminoacetonitrile presumably via reaction of the silyl enol ether with acid. We also explored the possibility of increasing the reaction rate of the cycloaddition by increasing the polarity of the solvent. However, switching the solvent from dichloromethane to propionitrile afforded a complex mixture of several products with no sign of the desired cycloadduct.
Next, we explored the possibility of increasing the stability of iminoacetonitrile 239 by increasing the acid stability of the silyl enol ether portion. We felt that by switching from a t-butyldimethylsilyl group to a more acid stable group such as t-butyldiphenylsilyl or triisopropylsilyl would allow the reaction temperature to be increased to promote the cycloaddition while avoiding the competing decomposition pathway. As shown in Scheme 61, imines 246 and 247 were synthesized in excellent yield from enone 242. Disappointingly, the acid-promoted cycloadditions of 246 and 247 were completely unsuccessful. At -78 °C with 1 equiv of MsOH in dichloromethane, both imines were completely unreactive. However, upon warming to -30 °C, cycloadducts 206 and 207 were obtained in ca. 5% yield with extensive decomposition of the iminoacetonitriles.

**Scheme 61**

![Chemical diagram showing the synthesis of iminoacetonitriles and cycloadducts](image-url)

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>244 SiR₃ = Si(t-Bu)Ph₂</td>
<td>50%</td>
</tr>
<tr>
<td>245 SiR₃ = Si(i-Pr)₃</td>
<td>79%</td>
</tr>
<tr>
<td>248 SiR₃ = Si(t-Bu)Ph₂</td>
<td>82%</td>
</tr>
<tr>
<td>249 SiR₃ = Si(i-Pr)₃</td>
<td>89%</td>
</tr>
</tbody>
</table>
Discouraged by these results, we shifted our focus to enol acetate derivatives (e.g., 251). We felt that the less electron-donating acetate group would reduce the susceptibility of the dienyl enol acetate towards protonation and subsequent decomposition in acid-promoted cycloadditions. Although an enol acetate should be fairly stable under acidic conditions, we were concerned about basic hydrolysis under our elimination conditions. Therefore, we decided to use an enol pivalate which would be expected to be stable under both acidic and basic conditions.

As shown in Scheme 62, iminoacetonitrile 251 was synthesized in two steps from enone 242. Initially, the synthesis of enol pivalate 250 proved unexpectedly difficult. Attempts to install the enol pivalate using pivaloyl chloride or trimethylacetic anhydride with a variety of bases, such as pyridine and DMAP, were unsuccessful leading to recovered starting material. However, we found that activation of the pivaloyl chloride with NaI in the presence of triethylamine afforded 250 in 91% yield. Finally, elimination of trifluoromethanesulfinate furnished iminoacetonitrile 251 in 86% yield as a 75:25 mixture of E and Z isomers.
With imine 251 in hand, the stage was set for the key iminoacetonitrile cycloaddition. In the event, the acid-promoted cycloaddition of iminoacetonitrile 251 afforded cycloadducts 252a and 252b in 79% yield as a 50:50 mixture of epimers at C-5 (eq 32). As predicted, the enol pivalate 251 was significantly more stable than the silyl enol ethers 246 and 247 under the acidic reaction conditions allowing the cycloaddition to occur smoothly at 0 °C without significant decomposition. It is important to emphasize that the mixture of epimers at C-5 is inconsequential due to the fact that further transformations at the C-5 carbon are controlled by stereoelectronic principles independent of the C-5 cyano group stereochemistry (see Chapter 6).

**Alkylation/Reductive Decyanation of α-Amino Cycloadduct 252**

Having completed the synthesis of cycloadduct 252, we focused our attention on installing the C-5 side chain of the target alkaloid. As depicted in Scheme 63, we were pleased to find that alkylation of 252 with 7-bromoheptene proceeded cleanly; however, reductive decyanation of the unpurified alkylation product with several hydride reagents (NaBH₄, ZnBH₄, NaBH₃CN) afforded a complex mixture of several products. Presumably, the intermediate iminium ion 253 is decomposing via dienamine 255. It should be mentioned that similar problems were encountered in the attempted alkylation-reductive decyanation of cycloadduct 238 (silyl enol ether case). Interestingly, as seen in our 217A synthesis, the tandem alkylation-reductive decyanation of the related quinolizidine 190 works beautifully. One possible explanation is that the accelerated rate of formation of the dienamine byproduct (255) in the...
indolizidine case versus the quinolizidine case is a result of the increased angle strain in the intermediate iminium ion (253).

![Scheme 63](image)

We therefore next shifted our focus to a radical-based reductive decyanation procedure that would avoid the formation of an iminium ion. As shown in Scheme 64, alkylation of 252 with 7-bromoheptene followed by reductive decyanation with sodium in liquid ammonia afforded quinolizidine 254 in 25% yield (ca. 90% purity) as a single diastereomer.\textsuperscript{133} As expected, sodium in liquid ammonia not only removed the cyano group but also cleaved the enol pivalate revealing the C-2 carbonyl. Unfortunately, the overall yield of the two-step reaction sequence was fairly low, and difficulties were encountered in purifying ketone 254.

\textsuperscript{133} NMR analysis and comparison to quinolizidine 208 (p 95) confirmed the stereochemistry at C-5 and C-8.
However, with ketone 254 in hand we were poised to complete the total synthesis of alkaloid (−)-235B'. Unexpectedly, deoxygenation of 254 via the tosyl hydrazone derivative afforded a 95:5 mixture of indolizidine 237D and indolizidine 235B'. Based on the hypothesis that reduction of the alkene was presumably occurring via the in situ generation of diimide, we decided to employ a sacrificial olefin to inhibit the undesired reduction. Adding excess 1-hexene or cyclopentene to the reaction mixture afforded a much improved 20:80 mixture of indolizidine 237D and the desired indolizidine 235B'. Unfortunately, attempts to completely suppress the reduction through the addition of dicyclopentadiene and 1-hexyne, as well as the use of different reaction solvents (dioxane, THF, EtOH, AcOH, and DMF), were fruitless. Therefore, we decided to explore other deoxygenation methods.134

Interested in the possibility of using a Barton-McCombie deoxygenation reaction,\textsuperscript{135} we shifted our focus to the synthesis of alcohol 255 (Scheme 66). Surprisingly, we found that simply adding ethanol to the sodium/liquid ammonia reduction flask delivered the desired alcohol 255 in 65\% yield as a single diastereomer. As shown below, the assignment of the C-7 stereocenter of 255 was based on the chemical shift of the C-7 proton which is consistent with an axial orientation.\textsuperscript{136} The C-5 side chain of 255 was assigned as equatorial based on NMR analysis and comparison with the spectra reported by Polniaszek\textsuperscript{83} for related indolizidine compounds (see 126 and 127 on pp 66). Unfortunately, initial efforts using the classical Barton-McCombie deoxygenation to remove the C-7 hydroxyl group have been unsuccessful due to problems synthesizing the thiocarbonyl derivatives.


\textsuperscript{136} For \textsuperscript{1}H NMR data of 256 and 257, see Rader, C. P.; Young, R. L.; Aaron, H. S. \textit{J. Org. Chem.} 1965, \textit{30}, 1536.
Summary

In conclusion, this chapter describes our efforts toward the total synthesis of indolizidine (−)-235B' utilizing the intramolecular Diels-Alder cycloaddition of iminoacetonitriles as a key step. These studies are by no means complete, and further efforts are currently underway in the Danheiser laboratory to complete the total synthesis of indolizidine (−)-235B'.
Part IV

Experimental Procedures
**General Procedures.** All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

**Materials.** Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. N,N-Diisopropylamine, triethylamine, and diisopropylethylamine were distilled under argon from calcium hydride. Methanesulfonic acid and trifluoromethanesulfonic anhydride were distilled under argon from phosphorus pentoxide. NaI was dried under vacuum (0.1 mmHg) at 70 °C for 24 h. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. n-Butyllithium was titrated in tetrahydrofuran with diphenylacetic acid.137

**Instrumentation.** Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR

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spectrophotometer. Ozonolysis was performed using a Welsbach Ozone machine with an ozone flow rate of ca. 2.75 mmol/3 min. $^1$H NMR and $^{13}$C NMR spectra were measured with an Inova 500, Inova 300, and Bruker 400 spectrometers. $^1$H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl$_3$ peak at 7.27 ppm used as a standard). $^{13}$C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl$_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.
Experimental Procedures for Synthesis of Alcohol Substrates
2,2-Dimethylpropionic acid 4-pentynyl ester (47a). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with DMAP (0.066 g, 0.54 mmol) and 10 mL of CH₂Cl₂. 4-Pentyn-1-ol (0.50 mL, 0.45 g, 5.4 mmol) and pyridine (1.30 mL, 1.30 g, 16.1 mmol) were added via syringe. Pivaloyl chloride (0.79 mL, 0.78 g, 6.4 mmol) was then added dropwise over 2 min via syringe, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of ether and washed with two 20-mL portions of 1.0 N aq HCl solution and 20 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.938 g of colorless oil. Column chromatography on 20 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.820 g (91%) of 47a as a colorless oil: IR (film): 2974, 2874, 2121, 1730, 1482, 1463, 1399, 1366, 1285, 1230 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.16 (t, J = 6.3 Hz, 2 H), 2.30 (dt, J = 7.1, 2.6 Hz, 2 H), 1.97 (t, J = 2.6 Hz, 1 H), 1.87 (app quint, J = 6.7 Hz, 2 H), 1.20 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.4, 83.2, 69.1, 63.0, 39.0, 27.9, 27.4, 15.5; HRMS (m/z) [M+Na]⁺ calcd for C₁₀H₁₆O₂Na, 191.1043; found, 191.1047.
5-Trimethylacetoxy-(E)-1-pentenyl boronic acid (48a). A 25-mL, two-necked, pear-shaped flask equipped with a rubber septum and argon inlet adapter was charged with 47a (0.334 g, 1.99 mmol) and 3 mL of CH₂Cl₂. Dibromoborane-dimethylsulfide solution (2.6 mL, 1.0 M in CH₂Cl₂, 2.6 mmol) was added dropwise via syringe over 3 min. The pale yellow solution was stirred at rt for 17 h, then cooled at 0 °C, and transferred via cannula to a 25-mL round-bottomed flask containing 6 mL of ether and 2 mL of water cooled at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and was then diluted with 40 mL of ether. The organic layer was washed with two 25-mL portions of ice-cold water, and the combined aqueous layers were extracted with 20 ml of ether. The combined organic layers were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.420 g (99% crude yield) of 48a as a pale yellow solid, which was used in the next step without further purification.
5-(1-Cyclohexenyl)-1-trimethylacetoxy-(E)-4-pentene (50a). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude boronic acid 48a (1.863 g, 8.70 mmol), 40 mL of THF, 1-iodocyclohexene (1.533 g, 7.37 mmol), and PdCl₂(dppf)•CH₂Cl₂ (0.054 g, 0.07 mmol). Sodium hydroxide solution (3.0 M in water, 7.37 mL, 22.11 mmol) was then added, and the reaction mixture was stirred at rt for 1.5 h. The resulting orange solution was then diluted with 50 mL of water, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to give 2.011 g of an orange oil. Column chromatography on 20 g of silica gel (elution with 5% EtOAc-hexanes) provided 1.474 g (80%) of 50a a colorless oil: IR (film): 3024, 2931, 2838, 1731, 1480, 1284 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.05 (d, J = 15.9 Hz, 1 H), 5.65 (br s, 1 H), 5.53 (dt, J = 15.6, 7.3 Hz, 1 H), 4.07 (t, J = 6.4 Hz, 2 H), 2.17 (q, J = 7.3 Hz, 2 H), 2.11 (m, 4 H), 1.73 (quint, J = 6.4 Hz, 2 H), 1.63-1.70 (m, 2 H), 1.56-1.62 (m, 2 H), 1.21 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 135.6, 134.5, 127.9, 125.1, 64.1, 39.1, 30.0, 29.0, 27.6, 26.4, 25.0, 23.0, 22.9; HRMS (m/z) [M+Na]⁺ calcd for C₁₆H₂₆O₂Na, 273.1825; found, 273.1816.
5-(1-Cyclohexenyl)-(E)-4-penten-1-ol (51). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with pivalate ester 50a (0.505 g, 1.91 mmol) and 5 mL of CH₂Cl₂. The flask was cooled at -78 °C while DIBAL solution (1.0 M in toluene, 2.4 mL, 2.42 mmol) was added dropwise over 3 min via syringe. The solution was stirred at -78 °C for 1 h and then diluted with 10 mL of 10% aq Rochelle salt solution. The cooling bath was removed, and the reaction mixture was stirred at rt for 2 h. The biphasic mixture was then diluted with 20 mL of water, the aqueous layer was separated and extracted with three 20-mL portions of CH₂Cl₂, and the combined organic layers were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.215 g of a colorless oil. Column chromatography on 10 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.142 g (85%) of 51 as a colorless oil: IR (film): 3328, 3022, 2985, 2928, 2858, 2836, 1651, 1625, 1447, 1436 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.07 (d, J = 15.6 Hz, 1 H), 5.65 (br s, 1 H), 5.55 (dt, J = 15.6, 7.0 Hz, 1 H), 3.67 (t, J = 6.5 Hz, 1 H), 2.10-2.22 (m, 6 H), 1.56-1.73 (m, 6 H), 1.36 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 135.5, 134.1, 127.6, 125.7, 62.6, 32.8, 29.4, 26.0, 24.9, 22.9, 22.8; HRMS (m/z) [M+Na]⁺ calcd for C₁₁H₁₈ONa, 189.1250; found, 189.1254.
2,2-Dimethylpropionic acid 5-hexynyl ester (47b). A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with DMAP (0.443 g, 3.63 mmol), 75 mL of CH₂Cl₂, 5-hexyn-1-ol (4.0 mL, 3.6 g, 36 mmol), and pyridine (8.8 mL, 8.6 g, 109 mmol). Pivaloyl chloride (5.4 mL, 5.3 g, 44 mmol) was then added dropwise over 5 min via syringe, and the resulting solution was stirred at rt for 2 h. The reaction mixture was diluted with 120 mL of ether and 60 mL of satd aq NaHCO₃ solution. The organic layer was separated and washed with two 50-mL portions of aq 1.0 M HCl solution, 60 mL of brine, dried over MgSO₄, filtered, and concentrated to give 6.62 g of colorless oil. Column chromatography on 80 g of silica gel (elution with 2% EtOAc-hexanes) provided 6.34 g (96%) of the 47b as a colorless oil: IR (film): 2959, 2872, 2118, 1728, 1481, 1459, 1398, 1366, 1284 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.05 (t, J = 6.3 Hz, 2 H), 2.21 (dt, J = 7.0, 2.8 Hz, 2 H), 1.94 (t, J = 2.6 Hz, 1 H), 1.71-1.76 (m, 2 H), 1.54-1.61 (m, 2 H) 1.17 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 84.0, 68.9, 63.9, 38.9, 27.8, 27.3, 25.1, 18.2; HRMS (m/z) [M+Na]⁺ calcd for C₁₁H₁₈O₂Na, 205.1204; found, 205.1209.
6-Trimethylacetoxy-(E)-1-hexenylboronic acid (48b). A 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and a 60-mL pressure-equalizing addition funnel with a claisen head fitted with a rubber septum and argon inlet adapter was charged with 47b (6.34 g, 34.8 mmol) and 18 mL of CH₂Cl₂. The addition funnel was charged with dibromoborane-dimethylsulfide solution (1.0 M in CH₂Cl₂, 45.2 mL, 45.2 mmol), which was added dropwise over 20 min. The pale yellow solution was stirred at rt for 8 h, was then cooled to 0 °C and transferred via cannula to a 250-mL round-bottomed flask containing 60 mL of ether and 20 mL of water cooled to 0 °C under argon. The biphasic mixture was stirred at 0 °C for 10 min and was then diluted with 120 mL of ether, and the organic layer was washed with two 50-mL portions of cold water. The combined aqueous layers were extracted with 30 mL of ether, and the combined organic layers were washed with 80 mL of brine, dried over MgSO₄, filtered, and concentrated to give 7.96 g (100 % crude yield) of 48b as a tan solid, which was used in the next step without further purification.
6-(1-Cyclohexenyl)-1-trimethylacetoxy-(E)-5-hexene (50b). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with crude boronic acid 48b (0.843 g, 3.69 mmol), 25 mL of THF, 1-iodocyclohexene (0.500 g, 2.40 mmol), and PdCl$_2$dpdf-CH$_2$Cl$_2$ (0.020 g, 0.02 mmol). Sodium hydroxide solution (3.0 M in water, 2.6 mL, 7.20 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 1 h. The resulting orange solution was then diluted with 50 mL of water, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 50 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 1.017 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.558 g (88%) of 50b a colorless oil: IR (film): 3023, 2932, 2838, 1730, 1480, 1459, 1285, 1157 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.04 (d, $J$ = 15.6 Hz, 1 H), 5.65 (br s, 1 H), 5.53 (dt, $J$ = 15.6, 6.7 Hz, 1 H), 4.06 (t, $J$ = 6.7 Hz, 2 H), 2.12 (m, 6 H), 1.58–1.69 (m, 6 H), 1.46 (q, $J$ = 7.9 Hz, 2 H), 1.20 (s, 9 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 178.9, 135.8, 134.1, 127.7, 126.2, 64.5, 39.0, 32.6, 28.4, 27.5, 26.2, 26.0, 24.9, 22.9, 22.8; HRMS (m/z) [M+Na]$^+$ calcd for C$_{17}$H$_{28}$O$_2$, 287.1982; found, 287.1977.
6-(1-Cyclohexenyl)-(E)-5-hexen-1-ol (52). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with pivalate ester 50b (0.505 g, 1.91 mmol) and 10 mL of CH₂Cl₂. The flask was cooled at -78 °C while Dibal solution (1.0 M in toluene, 4.2 mL, 4.20 mmol) was added dropwise over 6 min via syringe. The solution was stirred at -78 °C for 1 h and then diluted with 20 mL of 10% aq Rochelle salt solution. The cooling bath was removed, and the reaction mixture was stirred at rt for 2 h. The biphasic mixture was then diluted with 35 mL of water, the aqueous layer was separated and extracted with three 20-mL portions of CH₂Cl₂, and the combined organic layers were washed with 35 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.463 g of a colorless oil. Column chromatography on 20 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.303 g (88%) of 52 as a colorless oil: IR (film): 3335, 3022, 2927, 2858, 2837, 1650, 1625, 1448, 1436 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.04 (d, J = 15.6 Hz, 1 H), 5.64 (br s, 1 H), 5.54 (dt, J = 15.6, 6.7 Hz, 1 H), 3.66 (q, J = 6.4 Hz, 2 H), 2.13 (m, 6 H), 1.57-1.69 (m, 6 H), 1.47 (m, 2 H), 1.28 (s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 135.8, 134.1, 127.6, 126.4, 63.2, 32.8, 32.5, 26.0, 25.9, 24.8, 22.9, 22.8; HRMS (m/z) [M+Na]+ calcd for C₁₂H₂₀ONa, 203.1412; found, 203.1403.
1-Methyl-(E)-5,7-octadien-1-ol (56). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with 8 mL of CH₂Cl₂ and oxayl chloride (0.138 mL, 0.205 g, 1.61 mmol). The solution was cooled at -78 °C while DMSO (0.249 mL, 0.252 g, 3.22 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 10 min and then a solution of alcohol 44 (0.156 g, 1.24 mmol) in 4 mL of CH₂Cl₂ was added dropwise over 2 min. After the reaction mixture was stirred at -78 °C for 20 min, Et₃N (0.691 mL, 0.502 g, 4.96 mmol) was added over 2 min, and the solution was stirred at -78 °C for 10 min and rt for 45 min. The cloudy, yellow solution was diluted with 10 mL of CH₂Cl₂ and 10 mL of satd aq NaHCO₃ solution, and the aqueous layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.154 g of a yellow oil, which was used in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a septum and argon inlet adapter was charged with the crude aldehyde from the previous step (0.154 g, 1.24 mmol) and 8 mL of Et₂O. The reaction mixture was cooled at 0 °C while methylmagnesium bromide solution (3.0 M in ether, 0.496 mL, 1.49 mmol) was added via syringe over 1 min, and the reaction mixture was stirred at 0 °C for 2 h, and then diluted with 10 mL of satd aq NH₄Cl solution and 15 mL of Et₂O. The aqueous layer was separated and extracted with three 12-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.235 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 20-35% EtOAc-hexanes) afforded
0.139 g (80%) of 56 as a colorless oil: IR (film): 3353, 3086, 298, 2932, 2860, 1652, 1603, 1458, 1415, 1374 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.33 (ddd, \(J = 17.0, 10.3, 10.3\) Hz, 1H), 6.07 (dd, \(J = 15.2, 10.3\) Hz, 1H), 5.71 (dt, \(J = 15.2, 6.9\) Hz, 1H), 5.11 (d, \(J = 17.0\) Hz, 1H), 4.98 (d, \(J = 10.3\) Hz, 1H), 3.82 (m, 1H), 2.13 (app q, \(J = 7.1\) Hz, 2H), 1.43-1.59 (m, 4H), 1.30 (d, \(J = 4.8\) Hz, 1H), 1.21 (d, \(J = 6.3\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.4, 135.2, 131.5, 115.2, 68.2, 39.0, 32.7, 25.5, 23.8; HRMS (m/z) [M+H]\(^+\) calcld for C\(_9\)H\(_{17}\)O, 141.1280; found, 141.1279.
Experimental Procedures for

Synthesis of Triflamides
N-(Cyanomethyl)-N-(5-(1-cyclohexenyl)-(E)-4-pentenyl)trifluoromethanesulfonamide (59). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.519 g, 1.98 mmol), a solution of HN(Tf)CH₂CN (0.341 g, 1.82 mmol) in 10 mL of THF, and a solution of alcohol 51 (0.275 g, 1.65 mmol) in 10 mL of toluene. DEAD (0.31 mL, 0.345 g, 1.98 mmol) was added dropwise via syringe over 2 min, and the resulting reaction mixture was stirred at rt for 2 h and then concentrated to give 1.243 g of a yellow semi-solid. A solution of this material in CH₂Cl₂ was concentrated onto 2.5 g of silica gel and transferred to the top of a column of 40 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.498 g (90%) of 59 as a colorless oil: IR (film): 3025, 2989, 2932, 2860, 2839, 1651, 1625, 1398, 1230 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.09 (d, J = 15.6 Hz, 1 H), 5.69 (br s, 1 H), 5.48 (dt, J = 15.6, 6.7 Hz, 1 H), 4.33 (br s, 2 H), 3.55 (br s, 2 H), 2.18 (q, J = 6.7 Hz, 2 H), 2.10-2.12 (m, 4 H), 1.82 (quint, J = 7.3 Hz, 2 H), 1.58-1.70 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.7, 128.9, 128.6, 123.3, 119.0 (q, J = 322 Hz), 113.3, 49.2, 36.0, 29.5, 27.6, 26.0, 24.8, 22.8, 22.7; HRMS (m/z) [M+Na]+ calcd for C₁₄H₁₉F₃N₃O₃SNa, 359.1012; found, 359.1017.
**N-(Cyanomethyl)-N-(6-(1-cyclohexenyl)-(E)-5-hexenyl)trifluoromethanesulfonamide** (57). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.312 g, 1.19 mmol), a solution of HN(Tf)CH$_2$CN (0.224 g, 1.19 mmol) in 8 mL of THF, and a solution of alcohol 52 (0.178 g, 0.99 mmol) in 8 mL of toluene. DEAD (0.19 mL, 0.207 g, 1.19 mmol) was added dropwise via syringe over 2 min, and the resulting reaction mixture was stirred at rt for 2 h and then concentrated to give 1.213 g of a yellow semi-solid. A solution of this material in CH$_2$Cl$_2$ was concentrated onto 2.5 g of silica gel and transferred to the top of a column of 30 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.293 g (85%) of 57 as a colorless oil: IR (film): 3024, 2988, 2932, 2860, 2838, 1651, 1625, 1398 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.06 (d, $J$ = 15.7 Hz, 1 H), 5.67 (br s, 1 H), 5.49 (dt, $J$ = 15.6, 6.9 Hz, 1 H), 4.32 (br s, 2 H), 3.55 (br s, 2 H), 2.12-2.18 (m, 6 H), 1.58-1.75 (m, 6 H), 1.47 (quint, $J$ = 7.5 Hz, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.6, 134.9, 128.3, 125.0, 119.9 (q, $J$ = 322 Hz), 113.3, 49.3, 35.8, 32.2, 26.9, 26.1, 26.0, 24.8, 22.8, 22.7; HRMS (m/z) [M+H]$^+$ calcd for C$_{15}$H$_{22}$F$_3$N$_2$O$_2$S, 351.1349; found, 351.1340.
**N-(Cyanomethyl)-N-(1-Methyl-(E)-5,7-octadienyl)trifluoromethanesulfonamide (61).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (1.18 g, 4.49 mmol), a solution of HN(Tf)CH₂CN (0.774 g, 4.11 mmol) in 8 mL of benzene, and a solution of alcohol 56 (0.525 g, 3.74 mmol) in 7 mL of benzene. DIAD (0.868 mL, 0.908 g, 4.49 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 12 h and then at 60 °C for 4 h. The reaction mixture was allowed to cool to rt and then concentrated to give 3.91 g of a red solid. This material was concentrated onto 8 g of silica gel and added to a column of 100 g of silica gel. Gradient elution with 10-35% EtOAc-hexanes provided 0.912 g (78%) of 61 as a colorless oil: IR (film): 3089, 3056, 2989, 2939, 2864, 1653, 1603, 1462, 1422, 1396, 1303, 1266 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.32 (ddd, J = 17.0, 10.4, 10.3 Hz, 1H), 6.08 (dd, J = 15.2, 10.6 Hz, 1H), 5.67 (dt, J = 15.1, 7.1 Hz, 1H), 5.14 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.3 Hz, 1H), 4.12-4.23 (m, 3H), 2.16 (app q, J = 7.1 Hz, 2H), 1.62-1.72 (m, 2H), 1.50 (app quint, J = 7.5 Hz, 2H), 1.40 (d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 137.1, 133.8, 132.2, 117.6 (q, J = 322 Hz), 115.8, 115.0, 57.5, 34.1, 32.1, 30.8, 26.0, 24.6; HRMS [M+H]⁺ Calcd. for C₁₂H₁₈F₃N₂O₂S: 311.1036. Found: 311.1046.
Experimental Procedures for Synthesis of Iminoacetonitriles
5-(1-Cyclohexenyl)-(E)-4-pentenyliminoacetonitrile (60). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs$_2$CO$_3$ (2.131 g, 6.54 mmol) and 4 mL of THF. A solution of triflamide 59 (0.550 g, 1.64 mmol) in 6 mL of THF was added, and the reaction mixture was heated at 55 °C for 2.5 h. The resulting mixture was allowed to cool to rt and then diluted with 20 mL of ether and 40 mL of water. The aqueous layer was separated and extracted with two 25-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 0.371 g of a yellow oil. Column chromatography on 15 g of Et$_3$N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et$_3$N) provided 0.245 g (74%) of 60 (80:20 mixture of E and Z imine isomers by $^1$H NMR analysis) as a pale yellow oil:

IR (film): 2928, 2858, 1624, 1436, 1349 cm$^{-1}$; For E isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (app td, $J = 1.5, 0.3$ Hz, 1 H), 6.04 (d, $J = 15.7$ Hz, 1 H), 5.67 (s, 1 H), 5.44-5.58 (m, 1 H), 3.66 (td, $J = 6.8, 1.4$ Hz, 2 H), 2.12-2.21 (m, 6 H), 1.80-1.86 (m, 2 H), 1.58-1.78 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 136.1, 135.6, 135.0, 128.3, 124.7, 114.7, 62.6, 30.3, 29.8, 26.0, 24.8, 22.8, 22.7: For Z isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 (t, $J = 2.3$ Hz, 1 H), 6.07 (d, $J = 15.5$ Hz, 1 H), 5.67 (s, 1 H), 5.44-5.58 (m, 1 H), 3.85 (td, $J = 6.8, 2.3$ Hz, 2 H), 2.12-2.21 (m, 6 H), 1.80-1.86 (m, 2 H), 1.58-1.78 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.7, 134.9, 131.6, 128.2, 124.8, 114.7, 59.4, 30.5, 30.1, 26.0, 24.8, 22.8, 22.7.
6-(1-Cyclohexenyl)-(E)-5-hexenyliminoacetonitrile (58). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs$_2$CO$_3$ (1.490 g, 4.57 mmol) and 5 mL of THF. A solution of triflamide 57 (0.380 g, 1.08 mmol) in 3 mL of THF was added in one portion, and the reaction mixture was heated at 55 °C for 2.5 h. The resulting mixture was allowed to cool to rt and then diluted with 20 mL of ether and 20 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 0.244 g of a yellow oil. Column chromatography on 20 g of Et$_3$N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et$_3$N) provided 0.174 g (74%) of 58 (77:23 mixture of E and Z imine isomers by $^1$H NMR analysis) as a pale yellow oil: IR (film): 3022, 2928, 2857, 2837, 1623, 1448, 1436, 1349, 1334, 1268 cm$^{-1}$; For E isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (m, 1 H), 6.04 (dt, $J = 15.6$, 5.8 Hz, 1 H), 5.66 (br s, 1 H), 5.51 (dt, $J = 15.6$, 7.0 Hz, 1 H), 3.66 (t, $J = 7.0$ Hz, 1 H), 2.11-2.19 (m, 6 H), 1.57-1.77 (m, 6 H), 1.40-1.52 (m, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.9, 134.5, 128.0, 126.0, 114.9, 63.4, 32.7, 29.7, 27.4, 26.2, 25.0, 23.0, 22.9: For Z isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (m, 1 H), 6.05 (dt, $J = 15.6$, 5.8 Hz, 1 H), 5.66 (br s, 1 H), 5.51 (dt, $J = 15.6$, 7.0 Hz, 1 H), 3.84 (td, $J = 6.7$, 2.1 Hz, 1 H), 2.11-2.19 (m, 6 H), 1.57-1.77 (m, 6 H), 1.40-1.52 (m, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.9, 134.5, 131.7, 128.0, 110.0, 60.1, 32.8, 29.8, 27.5, 26.2, 25.0, 23.0, 22.9.
1-Methyl-(E)-5,7-octadienyliminoacetonitrile (62). A 100-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs$_2$CO$_3$ (2.66 g, 8.16 mmol) and 14 mL of THF. A solution of triflamide 61 (0.634 g, 2.04 mmol) in 6 mL of THF was added, and the reaction mixture was heated at 55 °C for 2 h. The resulting mixture was allowed to cool to room temperature and then diluted with 30 mL of ether and 25 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 0.449 g of a yellow oil. Column chromatography on 20 g of Et$_3$N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et$_3$N) provided 0.331 g (90%) of 62 (as a 92:8 mixture of E and Z imine isomers by $^1$H NMR analysis) as a pale yellow oil: IR (film): 3086, 2973, 2935, 2861, 2361, 1652, 1619, 1603, 1457, 1377, 1319 cm$^{-1}$; For E isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37 (s, 1H), 6.31 (ddd, $J = 17.0$, 10.3, 10.3 Hz, 1 H), 6.06 (dd, $J = 15.2, 10.3$ Hz, 1 H), 5.70 (dt, $J = 15.2, 6.9$ Hz, 1 H), 5.12 (d, $J = 17.2$ Hz, 1 H), 5.12 (d, $J = 17.2$ Hz, 1 H), 4.99 (d, $J = 10.1$ Hz, 1 H), 3.36 (m, 1 H), 2.09 (app q, $J = 7.1$ Hz, 2H), 1.56-1.67 (m, 2 H), 1.26-1.36 (m, 2 H), 1.25 (d, $J = 6.6$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.3, 134.6, 134.7, 131.7, 115.5, 114.7, 68.7, 36.6, 32.4, 26.0, 21.9: For Z isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (s, 1H), 6.31 (ddd, $J = 17.0$, 10.3, 10.3 Hz, 1 H), 6.06 (dd, $J = 15.2, 10.3$ Hz, 1 H), 5.70 (dt, $J = 15.2, 6.9$ Hz, 1 H), 5.12 (d, $J = 17.2$ Hz, 1 H), 4.99 (d, $J = 10.1$ Hz, 1 H), 3.93 (m, 1 H), 2.09 (app q, $J = 7.1$ Hz, 2H), 1.81 (d, $J = 7.3$ Hz, 3 H), 1.56-1.67 (m, 2 H), 1.26-1.36 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.3, 134.7, 134.1, 131.7, 115.4, 114.7, 67.7, 36.7, 32.4, 26.0, 21.8.
Experimental Procedures for Intramolecular Cycloadditions of Iminoacetonitriles
**cis-1,2-Didehydro-4-cyanoquinolizidine (63a) (Acid-Promoted Cycloaddition).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 38 (0.150 g, 0.92 mmol), 4Å molecular sieves (ca. 0.050 g), and 9 mL of CH₂Cl₂. Methanesulfonic acid (0.060 mL, 0.089 g, 0.92 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with 15 mL of satd aq NaHCO₃ and 10 mL of CH₂Cl₂, and the aq layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.181 g of an orange oil. A solution of this material in 10 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) afforded 0.120 g (80%) of 63a as a yellow oil: IR (film): 3035, 2936, 2855, 2807, 2221, 1442, 1396, 1332, 1287, 1237, 1205 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.63-5.67 (m, 1 H), 5.54 (d, J = 10.1 Hz, 1 H), 3.79 (d, J = 6.1 Hz, 1 H), 2.86 (br d, J = 11.6 Hz, 1 H), 2.70-2.77 (m, 2 H), 2.51 (dt, J = 3.1, 11.4 Hz, 1 H), 2.29 (m, 1 H), 1.79-1.85 (m, 1 H), 1.59-1.77 (m, 3 H), 1.26-1.46 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 130.5, 120.4, 116.9, 56.7, 54.0, 51.9, 31.7, 29.5, 25.7, 24.5; Anal. Calcd for C₁₀H₁₄N₂: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.12; H, 8.74; N, 17.29.
2-(tert-Butyldimethylsiloxymethyl)-cis-1,2-didehydro-4-cyanoquinolizidine (66a)

(Acid-Promoted Cycloaddition). A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 65 (0.615 g, 2.01 mmol), 4Å molecular sieves (ca. 100 mg), and 20 mL of CH₂Cl₂. Methanesulfonic acid (0.193 mL, 0.130 g, 2.01 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 15 min. The reaction mixture was diluted with 35 mL of satd aq NaHCO₃ and 30 mL of CH₂Cl₂. The aq layer was separated and extracted with three 25-mL portions of CH₂Cl₂. The combined organic layers were washed with 20 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.738 g of an orange oil. A solution of this material in 10 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.738 g of an orange oil. Purification by column chromatography on 25 g of silica gel (elution with 10% EtOAc-hexanes 1% Et₃N) afforded 0.550 g (89%) of 66a as a pale yellow oil: IR (film): 2934, 2856, 2807, 2767, 2222, 1471, 1462, 1388, 1360, 1326, 1299 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.47 (s, 1 H), 4.06 (s, 2 H), 3.85 (d, J = 6.4 Hz, 1 H), 2.84 (dd, J = 11.6, 1.6 Hz, 1 H), 2.76 (dd, J = 11.0, 2.0 Hz, 1 H), 2.64-2.70 (m, 1 H), 2.51 (dt, J = 3.1, 11.6 Hz, 1 H), 2.24 (d, J = 17.1 Hz, 1 H), 1.70-1.84 (m, 3 H), 1.63 (app tq, J = 4.1, 12.2 Hz, 1 H), 1.42 (app tq, J = 4.0, 12.8 Hz, 1 H), 1.30 (app dq, J = 3.4, 11.6 Hz, 1 H), 0.93 (s, 9 H), 0.09 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 131.9, 124.2, 117.0, 65.9, 56.6, 54.0, 52.3, 32.0, 29.8, 26.0, 25.9, 24.7, 18.5, -5.1; Anal. Calcd for C₁₇H₃₀N₂OSi: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.43; H, 10.05; N, 9.28.
2-(tert-Butyldimethylsiloxy)methyl)-cis-1,2-didehydro-4-cyanoquinolizidine (74a) and 2-(tert-Butyldimethylsiloxy)methyl)-trans-1,2-didehydro-4-cyanoquinolizidine (74b) (Acid-Promoted Cycloaddition). A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 73 (0.592 g, 2.02 mmol), 4Å molecular sieves (ca. 100 mg), and 20 mL of CH₂Cl₂. Methanesulfonic acid (0.131 mL, 0.194 g, 2.02 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with 20 mL of satd aq NaHCO₃ and 20 mL of CH₂Cl₂, and the aq layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.729 g of an orange oil. A solution of this material in 15 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45°C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 10-25% EtOAc-hexanes containing 1% Et₃N) afforded 0.491 g (83%) of 74a and 74b (81:19 mixture by ¹H NMR analysis) as a pale yellow oil: IR (film): 2956, 2930, 2857, 1472, 1463, 1361, 1253 cm⁻¹; For 74a: ¹H NMR (500 MHz, CDCl₃) δ 5.80 (s, 1 H), 4.15 (dd, J = 7.0, 1.5 Hz, 1 H), 4.06 (s, 2 H), 3.01-3.09 (m, 1 H), 2.96 (dt, J = 8.5, 3.4 Hz, 1 H), 2.62-2.68 (m, 1 H), 2.58 (app q, J = 8.5 Hz, 1 H), 2.32 (d, J = 17.4 Hz, 1 H), 1.79-2.05 (m, 3 H), 1.43-1.51 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 132.9, 122.1, 117.1, 66.2, 56.7, 49.9, 48.0, 29.7, 28.9, 26.2, 21.8, 18.7, -4.9: For 74b: ¹H NMR (500 MHz, CDCl₃) δ 5.69 (d, J = 1.5 Hz, 1 H), 4.06 (s, 2 H), 3.90 (dd, J =
8.5, 4.9 Hz, 1 H), 3.43-3.46 (m, 1 H), 2.96 (dt, $J = 8.5, 3.4$ Hz, 1 H), 2.62-2.68 (m, 1 H), 2.58 (app q, $J = 8.5$ Hz, 1 H), 2.44 (dd, $J = 16.8, 8.5$ Hz, 1 H), 1.79-2.05 (m, 3 H), 1.60-1.68 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 133.0, 123.4, 120.0, 66.1, 59.2, 49.3, 48.0, 30.3, 27.2, 26.2, 23.1, 18.6, -4.9; HRMS (m/z) [M]$^+$ calcd for C$_{16}$H$_{28}$N$_2$OSi, 292.1965; found, 292.1954.
2-(tert-Butyldimethylsiloxy)-cis-1,2-didehydro-4-cyanoquinolizidine (76) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 75 (0.178 g, 0.61 mmol), 4Å molecular sieves (ca. 50 mg), and 6 mL of CH2Cl2. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.039 mL, 0.058 g, 0.61 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 1 h, and then diluted with 10 mL of satd aq NaHCO3 and 10 mL of CH2Cl2. The aq layer was separated and extracted with three 12-mL portions of CH2Cl2. The combined organic layers were washed with 10 mL of brine, dried over MgSO4, filtered, and concentrated to give 0.191 g of an orange oil. A solution of this material in 5 mL of CH3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.191 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexanes containing 1% Et3N) afforded 0.092 g (52%) of 76 as a white solid: mp 61-62 °C; IR (CH2Cl2): 2933, 2857, 1678, 1472, 1372, 1287, 1256 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 4.67 (app t, J= 1.8 Hz, 1 H), 3.81 (d, J= 5.5 Hz, 1 H), 2.86 (br d, J= 10.2 Hz, 1 H), 2.73-2.79 (m, 2 H), 2.49 (dt, J= 11.5, 3.1 Hz, 1 H), 2.16 (dt, J= 17.0, 1.8 Hz, 1 H), 1.76-1.79 (m, 1 H), 1.61-1.73 (m, 3 H), 1.38 (tq, J= 12.8, 3.8 Hz, 1 H) 1.25-1.34 (m, 1 H), 0.92 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H); 13C NMR (125 MHz, CDCl3) δ 145.4, 116.8, 107.1, 56.1, 53.7, 53.1, 33.9, 33.0, 25.9, 25.8, 24.3, 18.2, -4.2, -4.4; Anal. Calcd for C16H28N2OSi: C, 65.70; H, 9.65; N, 9.58. Found: C, 65.56; H, 9.63; N, 9.44.
6β-Cyano-1,3,4,6,6aβ,7,8,9,10,11αβ-decahydro-2H-benzo[b]quinolizine (77) Acid-
Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a
rubber septum and argon inlet adapter was charged with imine 58 (0.121 g, 0.56 mmol), 4Å
molecular sieves (ca. 50 mg), and 5 mL of CH₂Cl₂. Methanesulfonic acid (0.040 mL, 0.059 g,
0.62 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt
for 1 h. The reaction mixture was then diluted with 15 mL of saturated NaHCO₃ solution and 10
mL of CH₂Cl₂, and the aqueous layer was separated and extracted with three 8-mL portions of
CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄,
filtered, and concentrated to give 0.125 g of yellow oil. A solution of this material in 4 mL of
CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then
allowed to cool to rt. Concentration gave 0.124 g of a yellow oil which was purified by column
chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) to
give 0.102 g (84%) of 77 as a pale yellow oil: IR (film): 2933, 2856, 2807, 2763, 2222,
1683, 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.15 (s, 1 H), 3.44 (s, 1 H), 2.75 (br d, J = 11.3 Hz, 1
H), 2.67 (dt, J = 11.0, 2.1 Hz, 1 H), 2.45 (td, J = 11.3, 3.1 Hz, 1 H), 2.19 – 2.23 (m, 2 H), 1.96
(m, 1 H), 1.73 – 1.86 (m, 4 H), 1.56 – 1.71 (m, 4 H), 1.22 – 1.53 (m, 4 H); ¹³C NMR (75 MHz,
CDCl₃) δ 136.8, 121.1, 117.5, 58.4, 56.3, 54.0, 43.5, 35.4, 34.1, 32.7, 28.8, 26.6, 26.0, 24.6;

(Thermal Cycloaddition). A threaded Pyrex tube (ca. 50-mL capacity) equipped with a
rubber septum and argon inlet needle was charged with imine 58 (0.174 g, 0.80 mmol), BHT
(0.532 g, 2.41 mmol), and 16 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 13 h, and then allowed to cool to rt and concentrated to afford 0.708 g of a brown oil. A solution of this material in CH₂Cl₂ was concentrated onto 1.5 g of silica gel and transferred to the top of a column of 40 g of silica gel. Gradient elution with 5-10% EtOAc-hexanes containing 1% Et₃N yielded 0.121 g (70%) of 77 as a colorless oil.
5β-Cyano-1,2,3,5,5aβ,6,7,8,9,10aβ-decahydro-benzo[b]indolizine (78) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 34 (0.145 g, 0.72 mmol), 4Å molecular sieves (ca. 50 mg), and 7 mL of CH₂Cl₂. Methanesulfonic acid (0.051 mL, 0.076 g, 0.79 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was then diluted with 15 mL of saturated NaHCO₃ solution and 10 mL of CH₂Cl₂, and the aqueous layer was separated and extracted with three 8-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.187 g of yellow oil. A solution of this material in 4 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt. Concentration gave 0.187 g of a yellow oil which was purified by column chromatography on 8 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) to give 0.101 g (70%) of 78 as a yellow oil (83:17 mixture of trans- and cis-fused indolizidines by ¹H NMR analysis): IR (film): 3049, 2932, 2856, 2769, 2221, 1670, 1459, 1446, 1370, 1320, 1258 cm⁻¹; for trans-fused indolizidine: ¹H NMR (500 MHz, CDCl₃) δ 5.54 (s, 1 H), 3.66 (d, J = 1.4 Hz, 1 H), 2.98 (dt, J = 8.8, 2.7 Hz, 1 H), 2.92 (m, 1 H), 2.56 (app q, J = 9.1 Hz, 1 H), 2.35 (br d, J = 13.1 Hz, 1 H), 2.24 (br d, J = 13.1 Hz, 1 H), 1.97-2.03 (m, 1 H), 1.87-1.97 (m, 2 H), 1.77-1.84 (m, 2 H), 1.39-1.60 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 137.8, 119.5, 117.4, 57.2, 54.8, 50.5, 43.6, 35.4, 34.4, 29.3, 28.2, 26.5, 21.7; for cis-fused indolizidine: ¹H NMR (500 MHz, CDCl₃) δ 5.54 (s, 1 H), 4.12 (br s, 1 H), 3.11 (dt, J = 8.5, 3.2
Hz, 1 H), 2.92 (m, 1 H), 2.66 (app q, \( J = 8.8 \) Hz, 1 H), 2.24 (br d, \( J = 13.1 \) Hz, 1 H), 2.17 (br d, \( J = 13.1 \) Hz, 1 H), 2.07-2.12 (m, 1 H), 1.87-1.97 (m, 2 H), 1.77-1.84 (m, 2 H), 1.39-1.60 (m, 4 H), 1.23-1.32 (m, 2 H); \(^{13} \) C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 137.8, 120.1, 117.4, 55.7, 54.8, 52.5, 40.0, 34.7, 30.7, 30.2, 27.3, 25.9, 21.5; HRMS [M+Na] Calcd. for C\(_{13}\)H\(_{18}\)N\(_2\)Na: 217.1699. Found: 217.1691.

(Thermal Cycloaddition). A threaded Pyrex tube (ca. 100-mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine 60 (0.214 g, 1.06 mmol), BHT (0.701 g, 3.18 mmol), and 21 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 36 h, and then allowed to cool to rt and concentrated to afford 0.921 g of a white solid. A solution of this material in CH\(_2\)Cl\(_2\) was concentrated onto 2 g of silica gel and transferred to the top of a column of 30 g of silica gel. Elution with 7% EtOAc-hexanes containing 1% Et\(_3\)N yielded 0.094 g (44%) of 78 as a yellow oil (83:17 mixture of trans- and cis-fused indolizidines by \(^1\)H NMR analysis).
cis-3,6,7,11b-Tetrahydro-4-cyano-4H-pyrido[2,1-a]isoquinoline (80a) and trans-3,6,7,11b-Tetrahydro-4-cyano-4H-pyrido[2,1-a]isoquinoline (80b) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 79 (0.173 g, 0.82 mmol), 4Å molecular sieves (ca. 50 mg), and 8 mL of CH₂Cl₂. Methanesulfonic acid (0.053 mL, 0.079 g, 0.82 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was then diluted with 15 mL of satd aq NaHCO₃ and 10 mL of CH₂Cl₂, and the aq layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.181 g of an orange oil. A solution of this material in 10 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 25% EtOAc-hexanes containing 1% Et₃N) afforded 0.104 g (60%) of 80a and 80b (79:21 mixture by ¹H NMR analysis) as a white solid: For 80a: IR (CH₂Cl₂): 3054, 2934, 2826, 1741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, J = 7.6 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.12 (dd, J = 7.0, 0.9 Hz, 1 H), 6.30 (d, J = 10.4 Hz, 1 H), 5.82-5.86 (m, 1 H), 4.39 (s, 1 H), 4.06 (dd, J = 6.1, 0.6 Hz, 1 H), 3.18-3.27 (m, 1 H), 2.97-3.02 (m, 2 H), 2.76-2.86 (m, 2 H), 2.36-2.42 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.5, 133.9, 129.4, 127.9, 126.7, 126.2, 124.7, 122.3, 117.0, 56.4, 52.4, 51.0, 29.5, 29.4; Anal. Calcd for C₁₄H₁₄N₂: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.00; H, 7.02; N, 13.52. For 80b: IR (CH₂Cl₂): 3053,
2985, 2933, 2849, 1637, 1496, 1422, 1273 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.12-7.26 (m, 4 H), 7.12 (dd, \(J = 7.0, 0.9\) Hz, 1 H), 5.93 (dt, \(J = 8.2, 2.0\) Hz, 1 H), 5.77-5.82 (m, 1 H), 4.54 (br s, 1 H), 4.12 (dd, \(J = 11.0, 4.9\) Hz, 1 H), 3.18-3.27 (m, 1 H), 2.92-3.05 (m, 4 H), 2.56-2.66 (m, 1 H), 2.30-2.38 (m, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 135.9, 134.5, 129.8, 129.1, 126.9, 126.4, 126.2, 122.7, 119.2, 58.7, 51.1, 43.4, 29.3, 25.7; Anal. Calcd for C\(_{14}\)H\(_{14}\)N\(_2\): C, 79.97; H, 6.71; N, 13.32. Found: C, 79.62; H, 6.55; N, 13.10.
 cis-7-Methyl-2(toluene-4-sulfonyl)-1,3,4,6,7,9a-hexahydro-6-cyano-2H-pyrido[1,2-a]pyrazine (82a) A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 81 (0.151 g, 0.46 mmol), 4Å molecular sieves (ca. 50 mg), and 9 mL of CH₂Cl₂. Methanesulfonic acid (0.030 mL, 0.044 g, 0.46 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 15 min. The reaction mixture was then diluted with 15 mL of satd aq NaHCO₃ and 10 mL of CH₂Cl₂, and the aq layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.185 g of an orange oil. A solution of this material in 15 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at reflux under argon for 18 h, and then allowed to cool to rt and concentrated to give 0.180 g of an orange oil. Purification by column chromatography on 20 g of silica gel (elution with 25% EtOAc-hexanes) provided 0.107 g (71%) of 82a as a white solid: mp = 152-153 °C; IR (CH₂Cl₂): 3054, 2986, 2305, 1598, 1451, 1422, 1345, 1273, 1257 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.72 (ddd, J = 10.0, 5.0, 2.5 Hz, 1 H), 5.43 (d, J = 10.1 Hz, 1 H), 3.74-3.78 (m, 2 H), 3.44 (s, 1 H), 3.14 (dt, J = 11.0, 2.1 Hz, 1 H), 2.80 (dt, J = 11.3, 3.1 Hz, 1 H), 2.63 (dt, J = 11.1, 2.5 Hz, 1 H), 2.53 (dt, J = 11.5, 3.2 Hz, 2 H), 2.44 (s, 3 H), 2.09 (t, J = 11.0 Hz, 1 H), 1.11 (d, J = 6.7 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 144.1, 133.0, 130.0, 129.7, 127.9, 124.3, 116.2, 56.5, 55.5, 51.7, 50.2, 45.8, 35.1, 21.7, 19.9; Anal. Calcd for C₁₇H₂₁N₃O₂S: C, 61.61; H, 6.39; N, 12.68. Found: C, 61.57; H, 6.35; N, 12.47.
cis-6-Methyl-cis-1,2-didehydro-4-cyanoquinolizidine (83a) and cis-6-Methyl-cis-1,2-didehydro-4-cyanoquinolizidine (83b) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 62 (0.141 g, 0.78 mmol), 4Å molecular sieves (ca. 50 mg), and 8 mL of CH$_3$CN. The reaction mixture was cooled at -35 °C while methanesulfonic acid (0.051 mL, 0.075 g, 0.78 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -35 °C for 1 h, 0 °C for 2 h, and then allowed to warm to rt over 1 h. The reaction mixture was then diluted with 15 mL of satd aq NaHCO$_3$ and 10 mL of CH$_2$Cl$_2$, and the aq layer was separated and extracted with three 15-mL portions of CH$_2$Cl$_2$. The combined organic layers were washed with 15 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 0.150 g of an orange oil. A solution of this material in 10 mL of CH$_3$CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.150 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexanes containing 1% Et$_3$N) afforded 0.098 g (70%) of 83a and 83b (67:33 mixture by $^1$H NMR analysis) as a yellow oil: IR (film): 3035, 2969, 2933, 2856, 2797, 2221, 1456, 1439, 1378, 1266 cm$^{-1}$; For 83a: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.64-5.69 (m, 1 H), 5.54 (app dt, $J$ = 10.1, 1.3 Hz, 1 H), 4.26 (d, $J$ = 5.6 Hz, 1 H), 2.98 (br d, $J$ = 9.3 Hz, 1 H), 2.63-2.73 (m, 1 H), 2.43-2.50 (m, 1 H), 2.33 (dm, $J$ = 17.7 Hz, 1 H), 1.68-1.81 (m, 3 H), 1.20-1.65 (m, 3 H), 1.13 (d, $J$ = 6.2 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 131.1, 120.6, 117.0, 56.0, 49.9,
45.9, 35.1, 32.5, 30.0, 24.6, 19.3; For 83b: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.64-5.69 (m, 1 H), 5.59 (app dt, $J = 10.4$, 1.8 Hz, 1 H), 3.74 (d, $J = 5.8$ Hz, 1 H), 3.49 (dm, $J = 12.2$ Hz, 1 H), 3.20 (m, 1 H), 2.63-2.73 (m, 1 H), 2.44 (dm, $J = 17.0$ Hz, 1 H), 1.68-1.81 (m, 3 H), 1.20-1.65 (m, 3 H), 1.27 (d, $J = 6.8$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 132.1, 120.5, 117.0, 57.3, 49.3, 45.9, 33.0, 32.8, 31.6, 20.0, 11.6; HRMS [M+H]$^+$ Calcd. for C$_{11}$H$_{17}$N$_2$: 177.1386. Found: 177.1389.
cis-9-(tert-Butyldimethylsiloxy)-2-methyl-cis-1,2-didehydro-4-cyanoquinolizidine (85a) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 84 (0.150 g, 0.49 mmol), 4Å molecular sieves (ca. 50 mg), and 6 mL of CH₂Cl₂. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.032 mL, 0.047 g, 0.49 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 2 h, and then diluted with 15 mL of satd aq NaHCO₃ and 10 mL of CH₂Cl₂, and the aq layer was separated and extracted with three 12-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.205 g of an orange oil. A solution of this material in 5 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.205 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 2-5% EtOAc-hexanes containing 1% Et₃N) afforded 0.122 g (81%) of 85a as a pale yellow oil: IR (film): 2929, 2856, 2804, 2759, 2222, 1472, 1462, 1388, 1368, 1252 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.19 (s, 1 H), 3.91 (s, 1 H), 3.84 (d, J = 6.1 Hz, 1 H), 2.87 (br s, 1 H), 2.75 (br d, J = 10.7 Hz, 1 H), 2.61-2.68 (m, 1 H), 2.43-2.49 (m, 1 H), 1.98-2.08 (m, 1 H), 2.05 (d, J = 16.5 Hz, 1 H), 1.75-1.83 (m, 1 H), 1.70 (s, 3 H), 1.47-1.58 (m, 2 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 129.4, 123.4, 117.2, 69.2, 61.2, 53.6, 52.7, 33.7, 32.4, 26.0, 22.7, 20.5, 18.4, -4.2, -4.5; HRMS [M+H]+ Calcd for C₁₇H₃₁N₂OSi: 307.2200. Found: 307.2198.
t-BuMe₂SiO

85a
Experimental Procedures for

Intermolecular Cycloadditions of

Iminoisocyanates
**Benzyliminoacetonitrile (98).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NCS (0.311 g, 2.33 mmol) and 8 mL of THF. A solution of amine 97 (0.340 g, 2.33 mmol) in 4 mL of THF was added in one portion, and the reaction mixture was stirred at rt for 40 min. The resulting mixture was cooled at 0 °C while KOEt (1.41 M in ethanol, 1.65 mL, 2.33 mmol) was added dropwise via syringe over 3 min. The reaction mixture was stirred at 0 °C for 2 h, and then diluted with 15 mL of ether and 15 mL of water. The aqueous layer was separated and extracted with two 12-mL portions of ether, and the combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.395 g of an orange oil. Purification by column chromatography on 10 g of acetone-deactivated silica gel (elution with 5% EtOAc-hexanes) provided 0.240 g (72%) of 98 (88:12 mixture of E and Z imine isomers by ¹H NMR analysis) as a yellow oil: IR (film): 3226, 3065, 3033, 2906, 1622, 1496, 1454, 1361 cm⁻¹; For E isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.36 (t, J = 1.6 Hz, 1 H), 7.29-7.35 (m, 3 H), 7.23 (d, J = 6.8 Hz, 2 H), 4.84 (d, J = 1.6 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 136.9, 129.2, 128.7, 128.3, 114.7, 66.1; For Z isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (t, J = 2.2 Hz, 1 H), 7.29-7.35 (m, 3 H), 7.23 (d, J = 6.8 Hz, 2 H), 4.99 (d, J = 2.2 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 135.6, 132.1, 129.1, 128.1, 114.7, 63.6.
1-Benzyl-2-cyano-4-methyl-1,2,3,6-tetrahydopyridine (102). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 98 (0.120 g, 0.83 mmol), 4Å molecular sieves (ca. 0.040 g), isoprene (0.125 mL, 0.085 g, 1.25 mmol), and 5 mL of CH₂Cl₂. The solution was cooled at -78 °C while methanesulfonic acid (0.054 mL, 0.080 g, 0.83 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq NaHCO₃, and the aqueous layer was separated and extracted with three 12-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.170 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 1-10% EtOAc-hexanes containing 1% Et₃N) afforded 0.152 g (91%) of 102 as a colorless oil: IR (CH₂Cl₂): 3027, 2932, 1603, 1496, 1453, 1383 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.35 (m, 5 H), 5.43 (d, J = 2.3 Hz, 1 H), 3.78 (dd, J = 6.5, 1.4 Hz, 1 H), 3.77 (d, J = 13.2 Hz, 1 H), 3.53 (d, J = 13.1 Hz, 1 H), 3.27 (dm, J = 16.5 Hz, 1 H), 3.01 (dm, J = 16.5 Hz, 1 H), 2.52 (dm, J = 17.2 Hz, 1 H), 2.07 (d, J = 17.2 Hz, 1 H), 1.70 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 136.8, 129.3, 129.2, 128.8, 128.0, 119.6, 116.8, 60.1, 49.3, 48.8, 34.0, 22.9; HRMS (m/z) [M+H]+ calcd for C₁₄H₁₆N₂: 213.1386. Found: 213.1389.
1-Benzyl-2-cyano-3,6-dimethyl-1,2,3,6-tetrahydopyridine (107). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 98 (0.090 g, 0.62 mmol), 4Å molecular sieves (ca. 0.030 g), 2,4-hexadiene (0.106 mL, 0.076 g, 0.93 mmol), and 3 mL of CH₂Cl₂. The solution was cooled at -78 °C while methanesulfonic acid (0.041 mL, 0.060 g, 0.62 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq NaHCO₃, and the aqueous layer was separated and extracted with three 10-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.170 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) afforded 0.111 g (79%) of 107 as a yellow oil: IR (CH₂Cl₂): 3030, 2968, 2877, 1722, 1495, 1454, 1379, 1326 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.36 (m, 5 H), 5.73 (dt, J = 10.2, 3.2 Hz, 1 H), 5.48 (dt, J = 10.2, 1.8 Hz, 1 H), 3.99 (d, J = 13.7 Hz, 1 H), 3.86 (d, J = 13.7 Hz, 1 H), 3.56-3.65 (m, 1 H), 3.59 (d, J = 5.9 Hz, 1 H), 2.58-2.62 (m, 1 H), 1.32 (d, J = 7.0 Hz, 3 H), 1.09 (d, J = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.7, 131.4, 128.9, 128.8, 127.8, 126.9, 119.5, 56.3, 53.0, 50.8, 32.4, 17.5, 14.9; HRMS (m/z) [M+H]⁺ calcd for C₁₅H₁₈N₂: 227.1543. Found: 227.1550.
1-Benzyl-2-cyano-4,6-dimethyl-1,2,3,6-tetrahydropyridine (104). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 98 (0.110 g, 0.76 mmol), 4Å molecular sieves (ca. 0.030 g), 2-methyl-1,3-pentadiene (0.130 mL, 0.094 g, 1.14 mmol), and 4 mL of CH₂Cl₂. The solution was cooled at -78 °C while methanesulfonic acid (0.049 mL, 0.073 g, 0.76 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq NaHCO₃, and the aqueous layer was separated and extracted with three 10-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.184 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et₃N) afforded 0.150 g (87%) of 104 as a yellow oil: IR (CH₂Cl₂): 3064, 3029, 2972, 2917, 1495, 1454, 1382, 1345, 1330 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.35 (m, 5 H), 5.31 (d, J = 1.5 Hz, 1 H), 4.19 (d, J = 13.7 Hz, 1 H), 3.69 (dd, J = 5.7, 1.7 Hz, 1 H), 3.26 (d, J = 13.7 Hz, 1 H), 3.18-3.22 (m, 1 H), 2.40 (dm, J = 17.0 Hz, 1 H), 1.99 (d, J = 17.0 Hz, 1 H), 1.70 (s, 3 H), 1.28 (d, J = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 129.1, 128.8, 128.6, 127.8, 126.3, 117.6, 55.9, 53.0, 48.3, 33.7, 22.9, 20.6; HRMS (m/z) [M]+ calcd for C₁₅H₁₈N₂: 227.1543. Found: 227.1545.
1-Benzyl-4-(tert-butyldimethylsiloxy)-2-cyano-6-methyl-1,2,3,6-tetrahydropyridine (109). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 98 (0.250 g, 1.73 mmol), 4Å molecular sieves (ca. 0.100 g), 2-(tert-butyldimethylsiloxy)-1,3-pentadiene (0.515 g, 2.60 mmol), and 18 mL of CH₂Cl₂. The solution was cooled at -78 °C while methanesulfonic acid (0.112 mL, 0.166 g, 1.73 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 20 mL of satd aq NaHCO₃, and the aqueous layer was separated and extracted with three 20-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.184 g of an orange oil. A solution of this material in 10 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.195 g of an orange oil. Purification by column chromatography on 25 g of silica gel (elution with 2% EtOAc-hexanes containing 1% Et₃N) afforded 0.302 g (51%) of 109 as a yellow oil: IR (CH₂Cl₂): 3065, 3032, 2931, 2858, 1682, 1496, 1463, 1373, 1256 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.32 (m, 5 H), 4.74 (t, J = 2.1 Hz, 1 H), 4.18 (d, J = 13.7 Hz, 1 H), 3.70 (dd, J = 5.7, 1.8 Hz, 1 H), 3.25 (d, J = 13.7 Hz, 1 H), 3.24-3.30 (m, 1 H), 2.48 (dm, J = 16.7 Hz, 1 H), 2.03 (dt, J = 16.7, 1.8 Hz, 1 H), 1.27 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.15 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.7, 137.8, 129.0, 128.8, 127.9, 117.2, 108.6, 55.5, 52.3, 48.7, 33.7, 25.8, 21.4, 18.2, -4.2; HRMS (m/z) [M]⁺ calcd for C₂₀H₃₀N₂OSi: 343.2200. Found: 343.2205.
Experimental Procedures for
Transformations of α-Amino Nitriles
2-(tert-Butyldimethylsiloxymethyl)trans-1,2-didehydro-4-(2-propene)quinolizidine (120). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diisopropylamine (0.144 mL, 0.104 g, 1.03 mmol) and 3 mL of THF. The solution was cooled at 0 °C while \( n \)-BuLi (2.54 M in hexanes, 0.406 mL, 1.03 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 66a (0.15 g, 0.49 mmol) in 2 mL of THF was added dropwise via cannula over 1 min. The resulting solution was stirred at -78 °C for 1.5 h, and then allyl bromide (0.089 mL, 0.125 g, 1.03 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 mL of water and 15 mL of ether. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over \( \text{K}_2\text{CO}_3 \), filtered, and concentrated to give 0.201 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with \( \text{NaBH}_3\text{CN} \) (0.123 g, 1.96 mmol) and 3 mL of CH₃CN. Acetic acid (0.225 mL, 0.235 g, 3.92 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at rt for 30 min, and then a solution of the crude nitrile (0.170 g, 0.49 mmol) prepared in the previous step in 2 mL of CH₃CN was added over 1 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 12 mL of CH₂Cl₂. The aqueous layer was separated and extracted with three 10-mL portions of CH₂Cl₂, and the
combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.201 g of an orange oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) afforded 0.136 g (86%) of the quinolizidine 120 as a pale yellow oil: IR (film): 3076, 2930, 2856, 2784, 2739, 1641, 1462, 1442, 1361, 1255 cm⁻¹;¹ H NMR (300 MHz, CDCl₃) δ 5.82 (ddt, J = 17.5, 10.3, 6.9 Hz, 1 H), 5.36 (s, 1 H), 5.05-5.11 (m, 2 H), 4.03 (s, 2 H), 3.24 (br d, J = 11.4 Hz, 1 H), 2.59 (br s, 1 H), 2.46-2.53 (m, 1 H), 2.37-2.41 (m, 1 H), 2.17-2.20 (m, 1 H), 1.89-1.99 (m, 3 H), 1.58-1.74 (m, 4 H), 1.26-1.42 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6H);¹³C NMR (125 MHz, CDCl₃) δ 135.8, 135.5, 124.5, 117.4, 66.5, 62.4, 59.0, 38.0, 33.2, 32.5, 26.7, 26.7, 26.4, 24.8, 18.8, -4.8; HRMS (m/z) [M+H]⁺ calcd for C₁₉H₃₆NOSi, 322.2566; found, 322.2566.
2-(tert-Butyldimethylsiloxymethyl)trans-1,2-didehydro-4-(3-butene)indolizidine (123). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diisopropylamine (0.200 mL, 0.145 g, 1.43 mmol) and 3 mL of THF. The solution was cooled at 0 °C while n-BuLi (2.41 M in hexanes, 0.593 mL, 1.43 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 74 (0.20 g, 0.68 mmol) in 2 mL of THF was added dropwise via cannula over 1 min. The resulting solution was stirred at -78 °C for 1.5 h, and then 4-bromobutene (0.076 mL, 0.101 g, 0.75 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and 10 mL of ether. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over K$_2$CO$_3$, filtered, and concentrated to give 0.236 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with NaBH$_3$CN (0.171 g, 2.72 mmol) and 3 mL of CH$_3$CN. Acetic acid (0.313 mL, 0.327 g, 5.44 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at rt for 30 min, and then a solution of the crude nitrile (0.236 g, 0.68 mmol) prepared in the previous step in 2 mL of CH$_3$CN was added over 1 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 12 mL of CH$_2$Cl$_2$. The aqueous layer was separated and extracted with three 10-mL portions of CH$_2$Cl$_2$, and the
combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.241 g of an orange oil. Column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et₃N) afforded 0.107 g (49%) of the indolizidine 123 (63:37 mixture of trans- and cis-fused indolizidines by ¹H NMR analysis) as a yellow oil: IR (film): 3077, 2956, 2929, 2856, 1641, 1471, 1361 cm⁻¹; For trans-fused indolizidine: ¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddt, J = 17.0, 10.4, 6.6 Hz, 1 H), 5.05 (dd, J = 17.1, 1.6 Hz, 1 H), 4.97 (d, J = 10.3 Hz, 1H), 4.02 (s, 2 H), 3.26 (br s, 1 H), 2.82 (dt, J = 5.9, 2.7 Hz, 1 H), 2.74 (app q, J = 8.8 Hz, 1 H), 2.44 (app q, J = 5.9 Hz, 1 H), 1.95-2.26 (m, 4 H), 1.61-1.89 (m, 4 H), 1.46-1.55 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.9, 135.7, 123.7, 114.8, 66.7, 61.1, 56.1, 45.7, 34.5, 30.6, 29.5, 28.3, 26.2, 22.1, 18.7, -5.0; For cis-fused indolizidine: ¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddt, J = 17.0, 10.4, 6.6 Hz, 1 H), 5.02 (dd, J = 17.2, 1.6 Hz, 1 H), 4.95 (d, J = 10.3 Hz, 1H), 4.00 (s, 2 H), 3.60 (br s, 1 H), 2.86-2.95 (m, 1 H), 2.74 (app q, J = 8.8 Hz, 1 H), 2.44 (app q, J = 5.9 Hz, 1 H), 1.95-2.26 (m, 4 H), 1.61-1.89 (m, 4 H), 1.46-1.55 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 139.1, 133.2, 123.7, 114.6, 67.0, 54.3, 53.2, 50.3, 32.5, 31.3, 30.4, 26.2, 24.2, 22.8, 18.7, -5.0; HRMS (m/z) [M+H]⁺ calcd for C₁₉H₃₆NOSi, 322.2566; found, 322.2561.
2-(tert-Butyldimethylsiloxymethyl)-1,2-didehydro-cis-4-methyl-4-ethylquinolizidine (133). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 7 mL of THF and diisopropylamine (0.259 mL, 0.187 g, 1.85 mmol). The solution was cooled at 0 °C while n-BuLi (2.32 M in hexanes, 0.797 mL, 1.85 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 66a (0.270 g, 0.88 mmol) in 3 ml of THF was added dropwise over 2 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.211 mL, 0.412 g, 2.64 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 ml of water and extracted with three 30-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.281 g of orange oil that was used immediately in the next step without further purification.

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.281 g, 0.88 mmol) and 4 mL of ether. The solution was cooled at -78 °C while methylmagnesium bromide solution (3.0 M in ether, 0.88 mL, 2.64 mmol) cooled at 0 °C was added dropwise via cannula over 2 min. The resulting solution was allowed to slowly warm to rt over 4.5 h and then was diluted with 15 ml of satd aq NH₄Cl solution and 15 mL of ether. The aqueous layer was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.270 g of red oil. Column
chromatography on 10 g of silica gel (gradient elution with 5-20% EtOAc/hexanes containing 1% Et$_3$N) provided 0.176 g (63%) of 133 as a yellow oil: IR (film): 2930, 2856, 2787, 2741, 1472, 1463, 1380, 1361 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.35 (s, 1 H), 4.03 (d, $J = 13.1$ Hz, 1 H), 3.99 (d, $J = 13.1$, 1 H), 2.94 (br d, $J = 11.3$ Hz, 1 H), 2.72 (br d, $J = 8.2$ Hz, 1 H), 2.15 (d, $J = 16.5$ Hz, 1 H), 1.99 (app dt, $J = 11.5$, 2.3 Hz, 1 H), 1.61-1.78 (m, 3 H), 1.42-1.58 (m, 4 H), 1.27-1.35 (m, 2 H), 0.90 (s, 9 H), 0.88 (t, $J = 7.5$ Hz, 3 H), 0.86 (s, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 133.9, 123.5, 66.6, 56.9, 54.5, 45.2, 36.5, 33.5, 33.3, 26.9, 26.1, 25.3, 18.6, 14.6, 8.0, -5.0, -5.1; HRMS (m/z) [M]$^+$ calcd for C$_{18}$H$_{35}$NOSi, 323.2639; found, 323.2647.
2-(tert-Butyldimethylsiloxy)-1,2-didehydro-4-methyl-cis-4-ethylquinolizidine (134). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 4 mL of THF and diisopropylamine (0.202 mL, 0.146 g, 1.44 mmol). The solution was cooled at 0 °C while n-BuLi (2.20 M in hexanes, 0.654 mL, 1.44 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 66a (0.210 g, 0.69 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then methyl iodide (0.106 mL, 0.242 g, 1.71 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 ml of water and extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.226 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with crude nitrile from preceding step (0.226 g, 0.69 mmol) and 4 mL of ether. The solution was cooled at -78 °C while ethylmagnesium bromide solution (3.0 M in ether, 0.69 mL, 2.01 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 4.5 h and then was diluted with 15 ml of satd aq NH₄Cl solution and 15 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.238 g of red oil. Column chromatography on 10 g
of silica gel (elution 5% EtOAc-hexanes containing 1% Et,N) provided 0.144 g (64%) of 134 as a yellow oil: IR (film): 2930, 2856, 2785, 1462, 1379, 1360, 1333 1252 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.35 (s, 1 H), 4.00 (d, J = 13.1 Hz, 1 H), 3.97 (d, J = 13.1, 1 H), 3.04 (d, J = 11.0 Hz, 1 H), 2.80 (br d, J = 6.1 Hz, 1 H), 2.15 (dt, J = 11.3, 2.1 Hz, 1 H), 2.01 (d, J = 17.1 Hz, 1 H), 1.85 (d, J = 17.1 Hz, 1 H), 1.62-1.75 (m, 3 H), 1.46-1.58 (m, 2 H), 1.25-1.38 (m, 3 H), 1.10 (s, 3 H), 0.89 (s, 9 H), 0.79 (t, J = 7.5 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 134.1, 124.2, 66.5, 56.4, 55.1, 45.1, 35.6, 33.3, 27.0, 26.2, 26.1, 25.2, 20.1, 18.6, 9.6, -5.0, -5.1; HRMS (m/z) [M]⁺ calcd for C₁₈H₃₅NOSi, 323.2639; found [M-CH₃]⁺; 308.2405.
1-[2-(tert-Butyldimethylsiloxy)methyl]-1,2-didehydro-4-ethylindolizidinyl]ethanone (136). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.150 mL, 0.108 g, 1.07 mmol). The solution was cooled at 0 °C while n-BuLi (2.54 M in hexanes, 0.421 mL, 1.07 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 74 (0.150 g, 0.51 mmol) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.102 mL, 0.199 g, 1.28 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 8 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.153 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask containing the crude amino nitrile (0.153 g, 0.51 mmol) from the preceding step was fitted with a rubber septum and argon inlet needle, purged with argon, and charged with 3 mL of ether. The solution was cooled at -10 °C while MeLi solution (1.52 M in ether, 0.503 mL, 0.76 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred for 90 min while it slowly warmed to 0 °C and then was diluted with 10 mL of water. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to a volume of ca. 5 mL. The flask was then fitted with an argon inlet adapter and
purged with argon. Silica gel (1.5 g) was added and the resulting slurry was stirred at rt for 12 h. The mixture was then filtered, with the aid of 10 ml of ether, and concentrated to afford 0.247 g of yellow oil. Column chromatography on 8 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et$_3$N) provided 0.116 g (67%) of 136 as a yellow oil: IR (film): 2957, 2856, 1714, 1463, 1422, 1388, 1348 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.36 (s, 1 H), 4.01 (s, 2 H), 3.58 (br s, 1 H), 2.98 (s, 1 H), 2.55 (q, $J$ = 8.2 Hz, 1 H), 2.41 (d, $J$ = 16.8, 1 H), 2.19 (s, 3 H), 2.06-2.13 (m, 1 H), 1.66-1.88 (m, 5 H), 1.48-1.55 (m, 1 H), 0.91 (s, 9 H), 0.77 (t, $J$ = 7.6 Hz, 3 H), 0.07 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 211.3, 134.0, 123.8, 69.8, 66.7, 56.3, 45.4, 31.1, 30.7, 26.1, 25.0, 24.5, 22.4, 18.7, 8.5, -5.0; HRMS (m/z) [M+H]$^+$ calcd for C$_{19}$H$_{36}$NO$_2$Si, 338.2510; found, 338.2493.
2-\((\text{\textit{tert}}-\text{Butyldimethylsiloxymethyl})\)-1,2-didehydro-\textit{cis}-4-ethynyl-4-ethylindolizidine (138). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.181 mL, 0.131 g, 1.29 mmol). The solution was cooled at 0 °C while \(n\)-BuLi (2.41 M in hexanes, 0.535 mL, 1.29 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 74 (0.18 g, 0.62 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.123 mL, 0.240 g, 1.54 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 ml of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over \(K_2CO_3\), filtered, and concentrated to give 0.197 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.197 g, 0.62 mmol) and 6 mL of ether. The solution was cooled at -78 °C while ethynylmagnesium bromide solution (0.5 M in THF, 3.69 mL, 1.85 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 15 h and then was diluted with 10 mL of satd aq \(NH_4Cl\) solution and 10 mL of ether. The aqueous layer was separated and extracted with three 12-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over \(MgSO_4\), filtered, and concentrated to afford 0.191 g of red oil. Column
chromatography on 10 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 0.143 g (73%) of **138** (65:35 mixture of trans- and cis-fused indolizidines by $^1$H NMR analysis) as an orange oil. Further purification by column chromatography provided analytical samples of each pure isomer: For trans-fused conformer: IR (film): 3308, 2957, 2883, 2857, 2709, 1680, 1473, 1464, 1360, 1302, 1257 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.73 (s, 1 H), 4.05 (s, 2 H), 3.17 (br s, 1 H), 2.91 (td, $J$ = 8.7, 3.4 Hz, 1 H), 2.39 (app q, $J$ = 8.7 Hz, 1H), 2.24 (s, 1 H), 2.23 (d, $J$ = 17.0 Hz, 1 H), 2.17 (d, $J$ = 17.0 Hz, 1 H), 1.94-2.00 (m, 1 H), 1.75-1.91 (m, 3 H), 1.56-1.65 (m, 1 H), 1.45-1.53 (m, 1 H), 1.08 (t, $J$ = 7.5 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 134.4, 121.9, 83.6, 72.2, 66.6, 58.1, 56.6, 45.1, 36.9, 34.0, 28.7, 26.2, 21.4, 18.6, 8.8, -5.0; HRMS (m/z) [M+H]$^+$ calcd for C$_{19}$H$_{33}$NOSi, 320.2404; found, 320.2408. For cis-fused conformer: IR (film): 3312, 2957, 2857, 1653, 1473, 1464, 1374, 1361 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.49 (s, 1 H), 4.00 (s, 2 H), 3.62 (br s, 1 H), 3.14 (m, 1 H), 2.82 (app q, $J$ = 8.8 Hz, 1 H), 2.40 (d, $J$ = 16.8 Hz, 1 H), 2.28 (s, 1 H), 2.02-2.09 (m, 1 H), 1.97 (d, $J$ = 17.3 Hz, 1 H), 1.74-1.81 (m, 3 H), 1.56-1.67 (m, 2 H), 1.05 (t, $J$ = 7.4 Hz, 3 H), 0.92 (s, 9 H), 0.08 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 133.1, 123.5, 83.5, 71.4, 66.8, 55.6, 55.1, 48.0, 31.0, 30.5, 30.3, 26.3, 22.8, 18.8, 9.5, -5.0; HRMS (m/z) [M+H]$^+$ calcd for C$_{19}$H$_{34}$NOSi, 320.2404; found, 320.2408.
2-(tert-Butyldimethylsiloxyethyl)-1,2-didehydro-cis-4-ethynyl-4-(3-butene)quinolizidine (146). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.150 mL, 0.108 g, 1.07 mmol). The solution was cooled at 0 °C while n-BuLi (2.54 M in hexanes, 0.421 mL, 1.07 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precool (-78 °C) solution of amino nitrile 66a (0.156 g, 0.51 mmol) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then 4-bromobutene (0.057 mL, 0.076 g, 0.56 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 mL of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.186 g of orange oil that was used immediately in the next step without further purification.

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.186 g, 0.51 mmol) and 6 mL of ether. The solution was cooled at -78 °C while ethynylmagnesium bromide solution (0.5 M in THF, 3.06 mL, 1.53 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 15 h and then was diluted with 10 ml of satd aq NH₄Cl solution and 10 mL of ether. The aqueous layer was separated and extracted with three 12-mL portions of ether, and the combined organic layers were washed with 15 mL of...
brine, dried over MgSO₄, filtered, and concentrated to afford 0.191 g of red oil. Column chromatography on 10 g of silica gel (gradient elution with 5% EtOAc-hexanes) provided 0.120 g (65%) of 146 as an orange oil: IR (film): 2930, 2856, 1641, 1472, 1462, 1360, 1257 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.86 (ddt, J = 17.0, 10.3, 6.6 Hz, 1 H), 5.39 (s, 1 H), 5.06 (d, J = 17.0 Hz, 1 H), 4.98 (d, J = 10.3 Hz, 1 H), 4.04 (s, 2 H), 3.05 (br d, J = 10.9 Hz, 1 H), 2.87 (br d, J = 7.4 Hz, 1 H), 2.24 (s, 1 H), 2.19-2.30 (m, 3 H), 2.06-2.14 (m, 2 H), 1.94 (td, J = 13.4, 5.3 Hz, 1 H), 1.67-1.75 (m, 4 H), 1.53-1.58 (m, 1 H), 1.37 (app t, J = 9.5 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 132.7, 124.3, 114.8, 83.8, 71.9, 66.4, 58.1, 56.1, 46.7, 39.2, 37.5, 33.0, 28.3, 26.6, 26.2, 25.0, 18.7, -5.0; HRMS (m/z) [M+H]⁺ calcd for C₂₃H₄₂NOSi, 360.2723; found, 360.2714.
2'-(tert-Butyldimethylsiloxymethyl)-1',2'-didehydrospiro[2-vinyl-2-cyclopentene-1,4'(3'H)-quinolizidine] (148). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with Grubbs 2nd catalyst (0.014 g, 0.017 mmol) and 10 mL of toluene. A solution of quinolizidine 146 (0.120 g, 0.33 mmol) in 4 mL of toluene was added via cannula and the reaction mixture was heated at 85°C for 2 h. The reaction mixture was allowed to cool to rt and then concentrated to give 0.140 g of a black oil. Purification by column chromatography on 15 g of silica gel (gradient elution with 20-35% EtOAc-hexanes) afforded 0.097 g (81%) of the spiroquinolizidine 148 as a yellow oil: IR (film): 3081, 3035, 2929, 2855, 2795, 1680, 1610, 1462, 1360,1321 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.30 (dd, J = 17.3, 10.7 Hz, 1 H), 6.01 (s, 1 H), 5.42 (s, 1 H), 5.40 (d, J = 17.3 Hz, 1 H), 4.87 (d, J = 10.9 Hz, 1 H), 4.05 (s, 2 H), 2.93 (br s, 1 H), 2.87 (br d, J = 11.5 Hz, 1 H), 2.47 (d, J = 17.6 Hz, 1 H), 2.05-2.33 (m, 5 H), 1.91 (dt, J = 14.1, 9.0 Hz, 1 H), 1.57-1.74 (m, 4 H), 1.30 (app t, J = 11.2 Hz, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 135.0, 134.1, 128.5, 125.1, 114.0, 69.0, 66.4, 58.0, 47.0, 40.5, 39.4, 33.9, 31.3, 27.0, 26.4, 25.4, 18.9, -4.9; HRMS (m/z) [M+H]⁺ calcd for C₂₂H₃₈NOSi, 360.2717; found, 360.2713.
2′-(tert-Butyldimethylsiloxymethyl)-1′,2′-didehydrospiro[cyclopentane-1,4′(3′H)-quinolizidine] (157). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 5 mL of THF and diisopropylamine (0.184 mL, 0.133 g, 1.31 mmol). The solution was cooled at 0 °C while n-BuLi (2.54 M in hexanes, 0.516 mL, 1.31 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 66a (0.192 g, 0.63 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then 1-chloro-4-iodobutane (0.084 mL, 0.15 g, 0.69 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 ml of water and extracted with three 12-mL portions of ether. The combined organic layers were washed with 10 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.249 g of 156 as an orange oil that was used immediately in the next step without further purification.

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with LiDBB (0.4 M in THF, 9.45 mL, 3.78 mmol). The solution was cooled at -78 °C while the crude nitrile from preceding step (0.249 g, 0.63 mmol) was added dropwise via cannula. The reaction mixture was stirred at -78 °C for 1 h, and then diluted with 2 mL of MeOH and allowed to warm to rt. The reaction mixture was diluted with 10 mL of satd aq NH₄Cl solution and 20 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic layers were washed with 12 mL of brine,
dried over MgSO₄, filtered, and concentrated to give 1.211 g of a white solid. A solution of this material in CH₂Cl₂ was concentrated onto 2 g of silica gel and transferred to the top of a column of 20 g of silica gel. Gradient elution with 10-35% EtOAc-hexanes yielded 0.107 g (51%) of 157 as a yellow oil: IR (film): 2928, 2787, 2738, 1463, 1361, 1256 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.36 (s, 1 H), 4.03 (s, 2 H), 3.20 (br s, 1 H), 2.59 (br s, 1 H), 2.29 (br s, 1 H), 2.06 (br d, J = 17.2 Hz, 1 H), 1.90 (m, 2 H), 1.58-1.73 (m, 5 H), 1.24-1.39 (m, 8 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.4, 124.5, 66.4, 62.2, 59.4, 49.7, 33.0, 32.8, 31.6, 28.0, 26.5, 26.2, 24.6, 23.4, 18.7, 14.3, -5.0; HRMS (m/z) [M+H]⁺ calcd for C₂₀H₃₈NOSi, 336.2717; found, 336.2728.
Experimental Procedures for Synthesis of
Quinolizidine (−)-217A
**N-(Cyanomethyl)-N-(5-hexenyl)trifluoromethanesulfonamide (192).** A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with triphenylphosphine (15.711 g, 59.9 mmol), 80 mL of THF, and TfNHCH\(_2\)CN (10.330 g, 54.91 mmol). 5-Hexen-1-ol (6.00 mL, 5.00 g, 49.9 mmol) was then added in one portion, and then DIAD (11.60 mL, 12.11 g, 59.9 mmol) was added dropwise by syringe over 20 min. The resulting mixture was stirred at rt for 2 h and then concentrated to give 43.11 g of a yellow solid. A solution of this material in CH\(_2\)Cl\(_2\) was concentrated onto 30 g of silica gel and transferred to the top of a column of 100 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 12.357 g (92%) of 192 as a colorless oil: IR (film): 3081, 2997, 2942, 2866, 1642, 1393, 1355, 1296, 1271, 1231, 1143 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.78 (ddt, \(J=17.1, 10.1, 6.7\) Hz, 1 H), 5.01-5.08 (m, 2H), 4.35 (br s, 2 H), 3.55 (br s, 2 H), 2.13 (app q, \(J=7.0\) Hz, 2 H), 1.72 (quint, \(J=7.6\) Hz, 2 H), 1.47 (quint, \(J=7.6\) Hz, 2 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 137.1, 119.8 (q, \(J=322\) Hz), 115.8, 113.4, 49.3, 35.8, 33.0, 26.7, 25.3; Anal. Calcd for C\(_9\)H\(_{13}\)F\(_3\)N\(_2\)O\(_2\)S: C, 40.00; H, 4.85; N, 10.36. Found: C, 39.62; H, 4.81; N, 10.22.
**N-(Cyanomethyl)-N-(5-hexanal)trifluoromethanesulfonamide (193).** A 200-mL, recovery flask containing triflamide 192 (5.808 g, 21.49 mmol) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH₂Cl₂ (80 mL) was added, and the flask was cooled at -78 °C while ozone was bubbled through the solution for 25 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (5.918 g, 22.56 mmol) was added, and the solution was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 12.09 g of a cloudy, white oil. A solution of this material in CH₂Cl₂ was concentrated onto 24 g of silica gel and transferred to the top of a column of 110 g of silica gel. Elution with 25% EtOAc-hexanes provided 5.359 g (92%) of 193 as a colorless oil: IR (film): 2997, 2954, 2877, 2838, 2735, 1723, 1467, 1394, 1360, 1294, 1269, 1229, 1145 cm⁻¹; 

¹H NMR (500 MHz, CDCl₃) δ 9.80 (t, J = 1.0 Hz, 1 H), 4.39 (br s, 2 H), 3.57 (br s, 2 H), 2.59 (t, J = 6.4 Hz, 2 H), 1.69-1.78 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 201.7, 119.7 (q, J = 322 Hz), 113.5, 49.1, 42.8, 35.7, 26.4, 18.2; Anal. Calcd for C₆H₁₁F₃N₂O₃S: C, 35.29; H, 4.07; N, 10.29. Found: C, 35.42; H, 4.02; N, 10.30.
N-(Cyanomethyl)-N-(6-methyl-(E)-5-octen-7-one)trifluoromethanesulfonamide (195). A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aldehyde 193 (7.394 g, 27.16 mmol) and 54 mL of toluene. 3-(Triphenylphosphoranylidene)butan-2-one 194 (10.010 g, 30.12 mmol) was then added in one portion, and the rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter. The reaction mixture was heated at 70 °C for 7 h. Concentration by rotary evaporation afforded 17.92 g of a brown oil. A solution of this material in CH₂Cl₂ was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 20-30% EtOAc-hexanes provided 7.686 g (87%) of 195 as a yellow oil:

IR (neat): 2994, 2945, 2869, 1735, 1666, 1396, 1230 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.58 (td, J = 7.3, 1.2 Hz, 1 H), 4.38 (br s, 2 H), 3.58 (br s, 2 H), 2.33 (m, 5 H), 1.78 (m, 5 H), 1.57 (app quint, J = 7.6 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 199.7, 141.6, 138.6, 113.9, 49.5, 36.2, 28.7, 27.5, 26.0, 25.5, 11.8; Anal. Calcd for C₁₂H₁₇F₃N₂O₅S: C, 44.17; H, 5.25; N, 8.58. Found: C, 43.95; H, 5.27; N, 8.84.
N-(Cyanomethyl)-N-(7-(tert-butyl(dimethyl) siloxy)-6-methyl-(E)-5,7-octadienyl)trifluoromethanesulfonamide (196). A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NaI (6.254 g, 41.72 mmol), a solution of enone 195 (9.076 g, 27.81 mmol) in 60 mL of CH₃CN, and Et₃N (5.86 mL, 4.22 g, 41.7 mmol). tert-Butyldimethylsilyl chloride (4.611 g, 30.59 mmol) was added in one portion, and the resulting mixture was stirred at rt in the dark for 18 h. The reaction mixture was then diluted with 50 mL of satd aq NaHCO₃ solution, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 30 mL of 1M NaOH solution, 30 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 12.37 g of a yellow oil. Column chromatography on 150 g of acetone-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) provided 11.814 g (96%) of 196 as a yellow oil: IR (film): 3127, 2933, 2860, 1645, 1596, 1464, 1398, 1231, 1197 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.98 (t, J = 7.3 Hz, 1 H), 4.43 (s, 1 H), 4.28-4.44 (br s, 2 H), 4.24 (s, 1 H), 3.55 (br s, 2 H), 2.20 (app q, J = 7.3 Hz, 2 H), 1.77 (s, 3 H), 1.73 (app quint, J = 7.3 Hz, 2 H), 1.47 (app quint, J = 7.6 Hz, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 157.2, 132.2, 127.0, 119.8 (q, J = 322 Hz), 113.3, 91.7, 49.4, 35.8, 27.6, 27.2, 26.1, 25.9, 18.5, 13.5, -4.4; Anal. Calcd for C₁₈H₃₁F₃N₂O₃Si: C, 49.07; H, 7.09; N, 6.36. Found: C, 48.82; H, 6.99; N, 6.55.
7-(tert-Butyldimethylsiloxy)-6-methyl-(E)-5,7-octadienyliminoacetonitrile (191). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs₂CO₃ (19.65 g, 60.3 mmol) and 60 mL of THF. A solution of triflamide 196 (6.643 g, 15.08 mmol) in 15 mL of THF was then added in one portion, and the reaction mixture was heated at 55 °C for 1.5 h. The resulting mixture was allowed to cool to rt and then diluted with 100 mL of water. The aqueous layer was separated and extracted with three 55-mL portions of ether, and the combined organic layers were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to give 5.88 g of a yellow oil. Column chromatography on 25 g of acetone-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) afforded 4.160 g (90%) of 191 (84:16 mixture of E and Z imine isomers by ¹H NMR analysis) as a colorless oil: IR (film): 2931, 2859, 1644, 1595, 1472, 1463, 1362, 1255 cm⁻¹; For Z isomer: ¹H NMR (500 MHz, CDCl₃) δ 7.38 (t, J = 2.1 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.85 (td, J = 7.0, 2.1 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 157.4, 131.7, 131.5, 127.9, 114.7, 91.5, 59.9, 29.9, 27.9, 27.2, 26.1, 18.6, 13.5, -4.4; For E isomer: ¹H NMR (500 MHz, CDCl₃) δ 7.37 (t, J = 1.5 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.66 (td, J = 6.7, 1.5 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 157.4, 135.9, 131.7, 127.8, 114.7, 91.5, 63.2, 29.8, 28.0, 27.3, 26.1, 18.6, 13.5, -4.4; Anal. Calcd for C₁₇H₃₀N₂O₅Si: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.43; H, 9.96; N, 9.11.
2-(tert-Butyldimethylsiloxy)-1-methyl-cis-1,2-didehydro-4-cyanoquinolizidine (190a) (Thermal Cycloaddition). A threaded Pyrex tube (ca. 350-mL capacity) equipped with a rubber septum and argon inlet needle was charged with BHT (9.30 g, 42.2 mmol), imine 191 (4.312 g, 14.07 mmol), and 175 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 130 °C oil bath for 36 h and then allowed to cool to rt. Concentration by rotary evaporation afforded 13.71 g of a yellow oil. A solution of this material in CH₂Cl₂ was concentrated onto 25 g of acetone-deactivated silica gel and transferred to the top of a column of 180 g of acetone-deactivated silica gel. Elution with 7% EtOAc-hexanes containing 1% Et₃N provided 2.415 g (56%) of 190a as a white solid: mp 74-77 °C; IR (CH₂Cl₂): 2938, 2857, 2760, 1686, 1462, 1382, 1359, 1295, 1253, 1195, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.78 (dd, J = 5.5, 1.2 Hz, 1 H), 2.73-2.79 (m, 3 H), 2.52 (td, J = 11.9, 3.1 Hz, 1 H), 2.17 (dd, J = 15.6, 1.2 Hz, 1 H), 1.98-2.01 (m, 1 H), 1.82-1.85 (m, 1 H), 1.57-1.71 (m, 2 H), 1.56 (s, 3 H), 1.33-1.42 (m, 1 H), 1.08-1.17 (m, 1 H), 0.95 (s, 9 H), 0.14 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 139.0, 117.2, 113.7, 60.5, 54.6, 53.3, 34.2, 30.4, 26.1, 25.9, 24.9, 18.5, 2.4, -3.5; Anal. Calcd for C₁₇H₃₀N₂OSi: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.74; H, 9.80; N, 9.08.

(Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 191 (0.210 g, 0.69 mmol), 4Å molecular sieves (ca. 50 mg), and 7 mL of CH₂Cl₂. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.044 mL, 0.066 g, 0.69 mmol) was added.
dropwise via syringe over 1 min. The solution was stirred at -78 °C for 1 h, and then diluted with 15 mL of satd aq NaHCO₃ and 10 mL of CH₂Cl₂. The aq layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.225 g of an orange oil. This material was diluted with 5 mL of CH₃CN and stirred at 45 °C for 2 h, and then concentrated to give 0.225 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et₃N) afforded 0.142 g (68%) of 190a as a white solid.
2-(tert-Butyldimethylsiloxy)-1-methyl-trans-1,2-didehydro-4-(3-chloro-(Z)-2-propene)quinolizidine (207). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (1.68 mL, 1.28 g, 7.9 mmol) and 10 mL of THF. The solution was cooled at 0 °C while 3.38 mL of n-BuLi solution (2.35 M in hexane, 7.9 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 190a (1.015 g, 3.31 mmol) in 5 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred at -78 °C for 3.5 h, and then a precooled (-78 °C) solution of 3-bromo-1-chloropropene (1.234 g, 7.94 mmol) in 5 mL of THF was added dropwise via cannula over 1 min. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to 0 °C and stirred for an additional hour. The reaction mixture was diluted with 80 mL of ether and 30 mL of water. The aqueous layer was extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 1.917 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with NaBH₃CN (0.832 g, 13.24 mmol) and 10 mL of CH₃CN. Acetic acid (1.52 mL, 1.59 g, 26.5 mmol) was added dropwise via syringe over 4 min. The resulting solution was stirred at rt for 30 min, and then a solution of the α-amino nitrile (1.917 g) prepared in the previous step in 8 mL of CH₃CN was added over 3 min by cannula. The reaction mixture
was stirred at rt for 2 h and then diluted with 35 mL of water and 35 mL of dichloromethane. The aqueous layer was separated and extracted with three 25-mL portions of dichloromethane, and the combined organic layers were washed with 30 mL of bine, dried over MgSO₄, filtered, and concentrated onto 3.5 g of silica gel. The free-flowing powder was placed at the top of a column of 60 g of silica gel and eluted with 15% EtOAc-hexanes containing 1% Et₃N to provide 0.902 g (77%) of the quinolizidine 207 as a yellow oil: IR (neat): 2931, 2857, 2791, 2741, 1698, 1629, 1472, 1362, 1257, 1195 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.13 (app d, J = 6.60 Hz, 1 H), 5.86 (app q, J = 7.05 Hz, 1 H), 3.13 (app d, J = 11.21 Hz, 1 H), 2.40-2.54 (m, 4 H), 2.16-2.23 (m, 1 H), 1.90-2.01 (m, 3 H), 1.53-1.71 (m, 6 H), 1.20-1.34 (m, 2 H), 0.95 (s, 9 H), 0.12 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.5, 129.2, 120.6, 113.2, 65.8, 58.6, 36.7, 31.0, 30.6, 26.4, 26.2, 24.8, 18.5, 12.4, -3.5, -3.9; Anal. Calcd for C₁₉H₃₄ClNOSi: C, 64.10; H, 9.63; N, 3.93. Found: C, 64.25; H, 10.62; N, 4.03.
(1β, 4α, 10β)-4-(3-Chloro-(Z)-2-propene)-1-methyl-quinolizidin-2-one (208). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with silyl enol ether 207 (1.60 g, 4.5 mmol) and 20 mL of THF. The reaction mixture was cooled at -78 °C while 4.94 mL of TBAF solution (1.0 M in THF, 4.9 mmol) was added dropwise via syringe over 2 min. The resulting solution was stirred at -78 °C for 1.5 h and then the reaction mixture was diluted with 35 mL of ether and 15 mL of water. The aqueous layer was separated and extracted with three 20-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated onto 3 g of silica gel. The free-flowing powder was placed at the top of a column of 25 g of silica gel and eluted with 15% EtOAc-hexanes containing 1% Et₃N to provide 0.951 g (88%) of the ketone 208 as a yellow oil: IR (neat): 2934, 2859, 2794, 1718, 1629, 1443, 1337, 1237, 1112 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.17 (d, J = 7.3 Hz, 1 H), 5.87 (app q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.3 Hz, 1 H), 2.46-2.59 (m, 4 H), 2.33-2.38 (m, 2 H), 1.89-1.97 (m, 3 H), 1.70-1.78 (m, 2 H), 1.57 (qt, J = 12.8, 3.7 Hz, 1 H), 1.24-1.40 (m, 2 H), 1.01 (d, J = 6.7 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 210.3, 127.1, 120.7, 68.5, 62.8, 50.6, 49.4, 46.4, 31.7, 31.4, 26.0, 24.0, 10.4; Anal. Calcd for C₁₃H₂₀ClNO: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.79; H, 8.13; N, 6.14.
(1R, 4S, 10S)-4-(3-Chloro-(Z)-2-propene)-1-methyl-quinolizidin-2-one (208). A 100-mL, one-necked, pear-shaped flask was charged with the ketone (+)-208 (0.430 g, 1.78 mmol), (R)-(−)-1,1’-binaphthyl-2,2’-diylphosphoric acid (0.681 g, 1.96 mmol), 10 mL of CH₂Cl₂, and 25 mL of methanol. The reaction mixture was heated at 50 °C for 30 min and then allowed to cool to rt. The reaction mixture was concentrated to a volume of ca. 10 mL and then placed in a freezer at -18 °C for 15 h. The resulting crystals were collected on a sintered funnel and air-dried to yield 0.364 g of white solid. Recrystallization of the solid obtained from the mother liquor from 25 mL of methanol afforded 0.132 g of a white solid. The two crops of crystals were combined and treated with 30 mL of EtOAc and 15 mL of 10% ammonium hydroxide solution. The aqueous layer was separated and extracted with three 20-mL of portions EtOAc, and the combined organic layers were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.189 g (44% from (+)-208; i.e., 88% of theoretical) of ketone (−)-208 as a yellow oil: [α]D²² -42° (c 2.76, CHCl₃).
(1R, 4S, 10S)-4-(3-Chloro-(Z)-2-propene)-1-methyl-quinolizidine (214). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ketone 208 (0.184 g, 0.76 mmol), TsOH (0.045 g, 0.26 mmol), 1.5 mL of DMF, and 1.5 mL of sulfolane. The reaction mixture was heated at 110 °C for 2 h. NaBH₃CN (0.191 g, 3.04 mmol), t-BuSH (1.29 mL, 1.03 g, 11.4 mmol), and 3 mL of cyclohexane were added in one portion and the resulting mixture was heated at 110 °C for 5 h. The reaction mixture was allowed to cool to rt and then diluted with 15 mL of ether and 40 mL of water. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of water, 10 mL of satd NaHCO₃, 25 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.29 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 0-20% EtOAc-hexanes containing 1% Et₃N) afforded 0.144 g (66%) of the quinolizidine 214 as a pale, yellow oil: [α]D²² -60° (c 2.4, CHCl₃); IR (film): 2928, 2852, 2787, 2754, 1628, 1442, 1376, 1331, 1264 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.08 (dt, J = 7.1 Hz, 1.7 Hz, 1 H), 5.88 (q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.0 Hz, 1 H), 2.42-2.49 (m, 2 H), 2.04-2.08 (m, 1 H), 1.90-1.94 (m, 1 H), 1.60-1.78 (m, 5 H), 1.45-1.53 (m, 3 H), 1.03-1.33 (m, 4 H), 0.86 (d, J = 6.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 129.4, 119.4, 69.8, 62.9, 52.1, 36.7, 34.2, 32.2, 32.1, 30.6, 26.6, 25.0, 19.6; Anal. Calcd for C₁₃H₂₂ClN: C, 68.55; H, 9.74; N, 6.15. Found: C, 68.49; H, 9.72; N, 6.12.
(1R, 4S, 10S)-4-(Z)-(Pent-2-en-4-ynyl)-1-methyl-quinolizidine 217A (176). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with quinolizidine 214 (0.065 g, 0.29 mmol), PdCl₂(PhCN)₂ (0.011 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol), and 1 mL of piperidine. A solution of trimethylsilylacetylene (0.081 mL, 0.056 g, 0.57 mmol) in 1 mL of piperidine was added dropwise via cannula over 1 h and then the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 15 mL of ether and 10 mL of 10% ammonium hydroxide solution. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.150 g of a black oil. This material was dissolved in 2 mL of CH₂Cl₂ and stirred with charcoal (0.150 g) and 3-mercaptopropyl-functionalized silica gel (0.150 g) at rt for 18 h. Filtration through a 1-in plug of Celite in a disposable pipette gave 0.104 g of an orange oil which was used immediately in the next step without further purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with K₂CO₃ (0.040 g, 0.29 mmol), 1.5 mL of MeOH, and the quinolizidine (0.104 g) prepared in the previous step. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 15 mL of diethyl ether. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether, and the combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated onto 0.5 g of silica gel. The free-flowing powder was placed at the top of a column of 8 g of silica gel and
eluted with 0-25% EtOAc-hexanes containing 1% Et$_3$N to provide 0.051 g (82%) of quinolizidine (-)-217A 176 as a yellow oil: [α]$_D^{22}$ -14° (c 0.8, CHCl$_3$) [lit: $^2$[α]$^{20}_D$ -13.75° (c 0.4, CHCl$_3$)]; IR (film): 3312, 2973, 2852, 2784, 2097, 1615, 1452, 1376 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.10 (dt, $J$ = 10.9, 7.1 Hz, 1 H), 5.48 (ddt, $J$ = 10.9, 2.0, 1.6 Hz, 1 H), 3.29 (br d, $J$ = 11.1 Hz, 1 H), 3.09 (d, $J$ = 2.0 Hz, 1 H), 2.53-2.63 (m, 2 H), 2.05-2.10 (m, 1 H), 1.93 (br d, $J$ = 11.9 Hz, 3 H), 1.02-1.79 (m, 12 H), 0.87 (d, $J$ = 6.5 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.9, 109.6, 82.0, 81.0, 69.9, 63.4, 52.0, 36.7, 35.3, 34.2, 32.1, 30.5, 26.6, 25.0, 19.6; Anal. Calcd for C$_{15}$H$_{23}$N: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.83; H, 10.62; N, 6.42.

The enantiomeric purity of the product was determined by $^1$H NMR analysis of the salt formed by reaction with (R)-(−)-1,1'-binaphthyl-2,2'-diylphosphoric acid: the phosphoric acid (0.018 g, 0.051 mmol, 1.1 equiv) was added to a solution of 176 (0.010 g, 0.046 mmol) in ca. 0.7 mL of CDCl$_3$. The C-1 methyl group appeared as a doublet ($J$ = 6.5 Hz) at 0.69 ppm; no doublet at 0.77 ppm could be detected. Similar analysis of racemic quinolizidine 217A showed two doublets (1:1 ratio) at 0.77 and 0.69 ppm.
Experimental Procedures for Synthesis of Indolizidine (−)-235B′
A 200-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with triphenylphosphine (5.59 g, 21.3 mmol), 50 mL of THF, and TfNHCH₂CN (3.64 g, 19.4 mmol). 5-Hexen-1-ol (1.99 mL, 1.67 g, 19.4 mmol) was then added in one portion, and then DIAD (4.13 mL, 4.31 g, 21.3 mmol) was added dropwise by syringe over 20 min. The resulting mixture was stirred at rt for 1.5 h and then concentrated to give 16.11 g of a yellow solid. A solution of this material in 30 mL of CH₂Cl₂ was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 4.56 g (92%) of 251 as a colorless oil: IR (film): 3083, 2995, 2946, 1643, 1397, 1286, 1231 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.79 (ddt, J = 17.0, 10.2, 6.6 Hz, 1 H), 5.05-5.13 (m, 2H), 4.35 (br s, 2 H), 3.58 (br s, 2 H), 2.14 (app q, J = 7.0 Hz, 2 H), 1.82 (quint, J = 7.5 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 136.3, 119.8 (q, J = 32 Hz, 116.7, 113.5, 49.2, 36.0, 30.3, 26.7; Anal. Calcd for C₈H₁₁F₃N₂O₂S: C, 37.50; H, 4.33; N, 10.93. Found: C, 37.37; H, 4.27; N, 11.03.
**N-(Cyanomethyl)-N-(6-methyl-(E)-4-hepten-6-one)trifluoromethanesulfonamide**

(242). A 200-mL, recovery flask containing triflamide 241 (2.34 g, 9.13 mmol) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH₂Cl₂ (50 mL) was added, and the flask was cooled at −78 °C while ozone was bubbled through the solution for 30 min. The resulting blue solution was degassed with a stream of argon for 15 min. Triphenylphosphine (2.40 g, 9.13 mmol) was added, and the solution was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 4.81 g of a cloudy, white oil that was used immediately in the next step without further purification.

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the aldehyde (4.81 g) prepared in the previous step in 50 mL of THF. 3-(Triphenylphosphoranylidene)butan-2-one 194 (3.19 g, 9.59 mmol) was then added in one portion, and the rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter. The reaction mixture was heated at reflux for 12 h, and then allowed to cool to rt and concentrated by rotary evaporation to give 8.11 g of an orange solid. A solution of this material in 30 mL of CH₂Cl₂ was concentrated onto 15 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 20-35% EtOAc-hexanes provided 2.30 g (81%) of 242 as a yellow oil: IR (neat): 2995, 2953, 2869, 1667, 1396, 1275, 1230 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.53 (t, J = 7.3 Hz, 1 H), 4.32 (br s, 2 H), 3.56 (br s, 2 H), 2.28-2.33 (m, 2 H), 2.29 (s, 3 H), 1.89 (app quint, J = 7.5 Hz, 2 H), 1.76 (s, 3 H); ¹³C NMR (100 MHz,
CDCl₃) δ 199.7, 139.9, 139.4, 119.8, 113.3, 49.2, 36.1, 26.7, 25.8, 25.7, 11.6; Anal. Calcd for C₁₁H₁₅F₃N₂O₃S: C, 42.30; H, 4.84; N, 8.97. Found: C, 42.35; H, 4.91; N, 8.91.
N-(Cyanomethyl)-N-(6-trimethylacetoxy)-5-methyl-(E)-4,6-heptadienyl)trifluoromethanesulfonamide (250). A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with NaI (4.25 g, 28.3 mmol), a solution of enone 242 (5.90 g, 18.9 mmol) in 100 mL of CH₃CN, and trimethylacetyl chloride (3.49 mL, 3.42 g, 28.3 mmol). Et₃N (5.31 mL, 3.82 g, 37.8 mmol) was added dropwise via syringe over 5 min, and the resulting mixture was stirred at rt in the dark for 18 h. The reaction mixture was then diluted with 50 mL of satd aq NaHCO₃ solution, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed 30 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 11.72 g of a yellow oil. Column chromatography on 100 of silica gel (elution with 20% EtOAc-hexanes) provided 6.80 g (91%) of 250 as a yellow oil: IR (film): 2978, 2876, 1745, 1646, 1616, 1481, 1462, 1397, 1267 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.56 (t, J = 7.5 Hz, 1 H), 5.01 (s, 1 H), 4.72 (s, 2 H), 4.28 (br s, 1 H), 3.48 (br s, 2 H), 2.18 (app q, J = 7.3 Hz, 2 H), 1.75-1.82 (m, 2 H), 1.80 (s, 3 H), 1.27 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 176.9, 154.4, 130.5, 125.6, 119.8 (q, J = 322 Hz), 113.6, 101.8, 49.4, 39.2, 36.2, 27.4, 27.2, 24.8, 13.5; Anal. Calcd for C₁₆H₂₅F₃N₂O₄S: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.55; H, 5.81; N, 7.06.
5-Methyl-6-trimethyacetoxy-(E)-4,6-heptadienyliminoacetonitrile (251). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs$_2$CO$_3$ (18.08 g, 55.5 mmol) and 60 mL of THF. A solution of triflamide 250 (5.50 g, 13.9 mmol) in 20 mL of THF was then added in one portion, and the reaction mixture was heated at 55 °C for 1.5 h. The resulting mixture was allowed to cool to rt and then diluted with 50 mL of water. The aqueous layer was separated and extracted with three 35-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 5.91 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 20% EtOAc-hexanes containing 1% Et$_3$N) afforded 3.13 g (86%) of 251 (75:25 mixture of E and Z imine isomers by $^1$H NMR analysis) as a yellow oil: IR (film): 2975, 2873, 1747, 1645, 1618, 1480, 1416, 1368, 1263 cm$^{-1}$; For Z isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$7.36 (t, $J$ = 2.2 Hz, 1 H), 5.62 (app t, $J$ = 6.9 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.79 (td, $J$ = 6.8, 2.2 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.25 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$176.9, 154.6, 136.4, 131.8, 127.0, 114.6, 101.5, 59.3, 39.3, 29.7, 27.2, 25.9, 13.5; For E isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$7.33 (t, $J$ = 1.4 Hz, 1 H), 5.55 (app t, $J$ = 7.3 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.59 (td, $J$ = 6.8, 1.4 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.26 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$176.9, 154.6, 136.4, 129.9, 126.8, 114.6, 101.5, 62.2, 39.3, 29.5, 27.4, 25.5, 13.5; Anal. Caled for C$_{15}$H$_{22}$N$_2$O$_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.
8-Methyl-cis-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (252a) and 8-Methyl-trans-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (252b). A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine 251 (2.73 g, 10.4 mmol), 4Å molecular sieves (ca. 0.300 g), and 100 mL of CH₂Cl₂. The solution was cooled at 0 °C while methanesulfonic acid (0.676 mL, 1.00 g, 10.4 mmol) was added dropwise via syringe over 3 min. The reaction mixture was stirred at 0 °C for 30 min and then diluted with 60 mL of satd aq NaHCO₃, and the aqueous layer was separated and extracted with three 25-mL portions of CH₂Cl₂. The combined organic layers were washed with 20 mL of brine, dried over MgSO₄, filtered, and concentrated to give 2.91 g of an orange oil. A solution of this material 20 mL of CH₃CN in a 25-mL round-bottomed flask was stirred at 45 °C for 1.5 h, and then allowed to cool to rt and concentrated to give 2.91 g of an orange oil. Purification by column chromatography on 80 g of silica gel (elution with 1% Et₃N-25% EtOAc-hexanes) afforded 2.155 g (79%) of 252a and 252b (50:50 mixture by ¹H NMR analysis) as an orange oil: IR (CH₂Cl₂): 2974, 2874, 2817, 1743, 1703, 1481, 1462, 1397, 1368, 1328, 1277 cm⁻¹; For 252a: ¹H NMR (400 MHz, CDCl₃) δ 4.10 (d, J = 5.7 Hz, 1 H), 3.13 (br s, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.37 (dm, J = 16.1 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 176.4, 137.1, 122.0, 116.8, 60.0, 50.0, 47.7, 39.1, 30.6, 28.5, 27.3, 21.9, 12.1: For 252b: ¹H NMR (400 MHz, CDCl₃) δ 3.02 (dd, J = 9.2, 4.6 Hz, 1 H), 3.44 (t, J = 7.1 Hz, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.24 (d, J = 16.0 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H),
1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.6, 137.1, 122.5, 119.3, 62.3, 49.1, 47.7, 39.1, 29.3, 28.5, 27.3, 23.1, 12.2; Anal. Calcd for C$_{15}$H$_{22}$N$_2$O$_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.
(5α,8β,9β)-5-(6-heptene)-8-methyl-7-indolizidinol (255). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (0.323 mL, 0.247 g, 1.53 mmol) and 5 mL of THF. The solution was cooled at 0 °C while 0.571 mL of n-BuLi solution (2.68 M in hexane, 1.53 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile 252 (0.160 g, 0.61 mmol) in 3 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred at -78 °C for 3.5 h, and then a precooled (-78 °C) solution of 7-bromoheptene (0.102 mL, 0.119 g, 0.67 mmol) was added rapidly via syringe. The reaction mixture was stirred at 0 °C for 1 h, and then diluted with 80 mL of ether and 30 mL of water. The aqueous layer was extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K₂CO₃, filtered, and concentrated to give 0.631 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adaptor, and cold-finger condenser was charged Na (0.351 g, 15.3 mmol) and 25 mL of NH₃ at -78 °C. The resulting blue solution was stirred at -78 °C for 30 min, and then a solution of the α-amino nitrile (0.631 g) prepared in the previous step in 8 mL of THF was added over 2 min via cannula. The reaction mixture was stirred at -78 °C for 1 h, and then EtOH (0.178 mL, 0.141 g, 3.05 mmol) was added via syringe and the resulting reaction mixture was stirred at -78 °C for 30 min. NH₄Cl (0.815 g, 15.3 mmol) was added in one portion and the colorless reaction mixture
was allowed to warm to rt over 30 min. The reaction mixture was then diluted with 15 mL of satd aq NaHCO₃ solution, and the aqueous layer was separated and extracted with three 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.158 g of an orange oil. Purification by column chromatography on 5 g of Al₂O₃ (elution with 50% EtOAc-hexanes) afforded 0.099 g (65%) of 255 as a yellow semi-solid: IR (neat): 3355, 2930, 2789, 2694, 1641, 1460, 1375 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.74 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 4.93 (dm, J = 17.1 Hz, 1 H), 4.87 (dm, J = 10.2 Hz, 1 H), 3.10-3.17 (m, 2 H), 1.55-2.00 (m, 10 H), 1.19-1.45 (m, 11 H), 0.93 (t, J = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 139.2, 114.4, 75.2, 69.4, 61.0, 51.4, 44.5, 40.5, 34.4, 33.9, 29.6, 29.0, 28.9, 25.6, 21.3, 14.6.
Kevin M. Maloney

Education

Ph.D. Organic Chemistry, Massachusetts Institute of Technology May 2007
Advisor: Professor Rick L. Danheiser

B.S. Chemistry and B.S. Biochemistry, Stetson University, Summa cum laude May 2002
• Cumulative GPA: 4.0/4.0

Research Experience

Graduate Research, Massachusetts Institute of Technology January 2003 - Present
Advisor: Professor Rick L. Danheiser
• Developed an efficient total synthesis of the biologically active quinolizidine alkaloid (−)-217A
• Studies directed toward the total synthesis of indolizidine alkaloid (−)-235B' and quinolizidine alkaloid (−)-207I
• Synthetic and mechanistic studies on [4+2] cycloadditions of iminoacetonitriles
• Supervised and mentored research projects for two undergraduate students

Undergraduate Research, Stetson University September 2000 - May 2001
Advisor: Professor Dwaine D. Jackson
• Studied transcription in E. coli using molecular biology techniques

Advisor: Professor Ramee Indralingam September 2001 - May 2002
• Developed a bio-analytical teaching experiment involving the isolation and determination of the amount of iron found in chicken eggs

Howard Hughes Summer Fellow, Georgia Institute of Technology May 2001 - September 2001
Advisor: Professor Loren D. Williams
• Determined the thermodynamic properties and structural features of pseudouridine 55 synthase

Teaching and Service

Chemistry R.E.F.S., Massachusetts Institute of Technology January 2004 - Present
(Resource for Easing Friction & Stress)
• Serve as a resource for fellow graduate students to help manage adjustments, conflicts, and stress
• Massachusetts State Certified in mediation

Chemistry Outreach Coordinator, Massachusetts Institute of Technology January 2002 - Present
• Coordinate program in which MIT graduate students perform chemistry presentations at 35 local high schools each year

Teaching Assistant, Massachusetts Institute of Technology September 2002 - May 2003
• Led recitation sections and review sessions for organic chemistry

Publications and Presentations


Honors and Awards

NIH Cancer Training Fellowship, 2003
SYNLETT Star Award – Promising Young Organic Chemists, 2003
Excellence in Teaching Award – Massachusetts Institute of Technology, 2003
Chemistry Student of the Year – Stetson University, 2002
Howard Hughes Summer Fellowship – Georgia Institute of Technology, 2001
Student-Athlete of the Year – Stetson University Athletic Department, 2000
Faculty Merit Scholarship – Stetson University, 1998
ACS Polymer Award in Organic Chemistry – American Chemical Society, 1998

Affiliations

American Chemical Society, Organic Division Member