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INTERMOLECULAR AND INTRAMOLECULAR CONJUGATE ADDITION OF CARBON AND HETERO NUCLEOPHILES TO NITROSOALKENE AND AN APPROACH TO A TOTAL SYNTHESIS OF TRONOCARPINE

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by
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ABSTRACT

Novel synthetic methodology involving 1,4-conjugate additions of a variety of carbon and hetero nucleophiles to nitrosoalkenes, generated *in situ* via the Denmark protocol using $\alpha$-chloro-$O$-silyloximes has been developed. This research demonstrated that both intermolecular and intramolecular conjugate additions of various carbon and heteroatom nucleophiles to nitrosoalkenes provide a novel method to access a variety of highly functionalized systems, some of which contain vicinal quaternary centers.

In the second part of the thesis, a synthesis of the structurally unique indole alkaloid tronocarpine has been initiated. A novel intermolecular tandem Sonogashira coupling/annulation reaction was used as a key strategy to construct the indole moiety of the metabolite, resulting in establishment of three of the five rings present in this natural product.
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Chapter 1 Background on Nitrosoalkenes

1.1 Introduction

Nitrosoalkenes 1 were first proposed by Mathaipoulos in 1898 as intermediates in the reaction of α-halooximes with nucleophilic bases (Figure 1.1). These unstable and highly reactive species contain a nitroso group in conjugation with a carbon-carbon double bond. Such intermediates can participate in a wide variety of transformations including reactions with nucleophiles in conjugate additions, and in pericyclic reactions, where they most commonly function as heterodienes. The reactions of nitrosoalkenes are discussed in more detail in Section 1.3.

Figure 1.1 Structure of Nitrosoalkenes

Very few nitrosoalkenes have actually been isolated and characterized. Rather, they are usually generated and trapped in situ. Often, the presence of a nitrosoalkene in a transformation will impart a characteristic fleeting blue color to the reaction solution. Some of these unstable intermediates have been detected spectroscopically. In general, nitrosoalkenes typically have very short lifetimes, but can be stabilized via β-substitution with either sterically-demanding aryl or tert-alkyl groups, or by halogen. For example, Berndt has isolated nitrosoalkene 2 as a blue solid with a melting point of 38 °C (Figure 1.2).
1.2 Methods for the Generation of Nitrosoalkenes and Their Precursors

1.2.1 Base Promoted 1,4-Elimination from α-Heteroatom-Functionalized Oximes

The reaction of α-halo-substituted oximes 4 with a base is the most common method to generate a nitrosoalkene. In principle, these α-haloximes 4 can be prepared from the corresponding α-halocarbonyl species 3 and can serve as direct precursors to nitrosoalkenes 5 (Scheme 1). Indeed, upon exposure to base, α-haloketoximes such as 4 undergo 1,4-elimination to generate the nitrosoalkene 5 in situ. Although the most widely-encountered leaving group in such a reaction is a halogen (most commonly chlorine), examples of substrates containing α-sulfonates, α-phenylsulfinites, α-nitriles, α-sulfoxides, nitrosyl hydrogen sulfates and α-oxirane oxygens, also exist.
These reactions are typically carried out in a polar but non-nucleophilic medium to suppress solvent addition to the reactive nitrosoalkene intermediate. Additionally, the bases typically employed in these transformations are sparingly soluble inorganic compounds, such as sodium carbonate\textsuperscript{14,15} and calcium hydroxide.\textsuperscript{16} The use of these inorganic bases not only slows the elimination reaction, but also lowers the concentration of the highly reactive nitrosoalkene intermediate, thus suppressing undesired side reactions such as polymerization. On the other hand, the use of soluble organic bases such as amines\textsuperscript{11,17} or alkoxides\textsuperscript{18} accelerates the generation of the nitrosoalkene.

1.2.1.1 Synthesis of α-Chlorooximes from α-Chloroketones

Nitrosoalkene precursors, such as α-heteroatom-substituted oximes 7a and 7b, can be prepared via reaction of the corresponding α-heteroatom-substituted ketones 6a and 6b, respectively, with NH\textsubscript{2}OH\textcdot}HCl and NaOAc in MeOH (Scheme 2).\textsuperscript{8} The geometry of the oxime double bond is dependent upon steric factors, especially in cyclic systems. For example, when the α-chlorine in t-butyl cyclohexanone oxime 6a is disposed in an equatorial position, E-oxime 7a was the major product, albeit in low yield. On the other hand, if the α-chlorine was axial, the Z-oxime 7b resulted in high yield.
Scheme 2

Alternatively, when the same cyclic $\alpha$-chloroketones $6a$ and $6b$ were subjected to modified oximation conditions using KOAc under acidic conditions, the product outcome was found to be dependent on the pH of the medium (Scheme 3). Studies have shown that the optimal conditions to form the $\alpha$-halooximes is around pH 5. Under these acidic conditions, $E$-oximes $7a$ and $7c$ were produced predominately regardless of the configuration of chlorine atom.

Scheme 3
1.2.1.2 Synthesis of α-Chlorooximes via Other Methods

The reaction of olefins and nitrosyl chloride was first reported by Tilden and Shenstone in 1877 as a method to prepare crystalline derivatives of terpenes.\(^\text{19}\) This method was later extended to the generation of α-chlorooximes.\(^\text{18}\) Thus, treatment of an olefin 8 with nitrosyl chloride yields the initial nitrosochloroalkene adduct 9 (Scheme 4), \(^\text{20-22}\) which tautomerizes to form α-chloroxime 10, and may also dimerize to yield diazene dioxide 11. Both α-chlorooximes 10 and dimers 11 can be treated with a nucleophilic base to generate nitrosoalkene intermediates 12 and eventually Michael adducts 13 (\textit{vide infra}).

\[ \text{R}_1\text{R}_2 \xrightarrow{\text{NOCl}} [\text{Cl}_\text{R}_1\text{R}_2\text{NO}] \xrightarrow{\text{Cl}_\text{R}_1\text{R}_2\text{NOH} \text{and/or }} [\text{Cl}_\text{R}_1\text{R}_2\text{N}_2\text{O}_2\text{Cl}] \]

Other known methods for the formation of α-chlorooximes, such as the reaction of nitroalkenes with tin(II) chloride\(^\text{15}\) or titanium(IV) chloride,\(^\text{23}\) are also known but are limited in scope since they can only be applied to a few specific substrates.
1.2.2 Fluoride-Promoted 1,4-Elimination of α-Chloro-\(O\)-silyloximes

Although base-promoted 1,4-elimination of α-heteroatom-substituted oximes is the simplest and most frequently employed method to generate nitrosoalkenes, this approach is rather inefficient since at least two equivalents of the nucleophile are required, one of which acts as the base for the initial elimination step and the second equivalent which acts as a nucleophile (see Section 1.2.1). This protocol is especially suboptimal when valuable and expensive nucleophiles are employed.

Denmark et al. have developed a useful alternative pathway to the conventional base-promoted formation of nitrosoalkenes from α-halo oximes that avoids the use of two equivalents of nucleophile. It was shown that when an α-halo-\(O\)-silyloxime \(15\) was treated with a fluoride source under mild conditions (Scheme 5), 1,4-elimination generated the nitrosoalkene intermediate \(16\). The rate of the process was found to be approximately two to three times slower than the base-promoted method using an α-chlorooxime (\textit{vide supra}). Additionally, the nitrosoalkene species generated \textit{via} the Denmark method have half-lives of about one third to one fifth those of the species generated using the more classical method.\(^8\) These slower rates and shorter lifetimes can effectively suppress same undesired side reactions commonly observed with the other methods, thus often increasing reaction efficiency. A variety of fluoride sources of varying solubility can be used to further fine-tune the rate of nitrosoalkene formation, including tetrabutylammonium fluoride (TBAF), cesium fluoride, silver fluoride, and potassium fluoride.
Scheme 5

1.2.2.1 Synthesis of α-Chloro-O-silyloximes from α-Chloroketones

The α-chloro-O-silyloxime nitrosoalkene precursors like 19a and 19b can be prepared via the reaction of the corresponding α-chloroketones 18a and 18b with NH₂OTBS catalyzed by PPTS and activated 4Å molecular sieves (Scheme 6). Silyloximation of mixture of α-chlorocyclohexanones 18a and 18b predominantly produced E-silyloximes 19a and 19b in 82% yield. The Denmark group also found that the efficiency of nitrosoalkenes formation is independent of the silyloxime geometry or disposition of the halogen in cyclic systems (i.e. axial vs. equatorial).

Scheme 6

18a: R = E-4-hexenyl, X=H, Y=Cl
18b: R = E-4-hexenyl, X=Cl, Y=H
19a: R = E-4-hexenyl, X=H, Y=Cl
19b: R = E-4-hexenyl, X=Cl, Y=H
19 E/Z > 95:5
1.2.3. Generation of Nitrosoalkenes via Other Methods

Aside from the use of excess bases and α-haloaloximes, as well as the Denmark protocol, a number of alternative methods are available to generate nitrosoalkenes. Although these reactions are somewhat limited in their scope,\textsuperscript{24, 25} they are briefly detailed in the following section.

1.2.3.1 Generation of Nitrosoalkenes via 1,3-\(N,C\)-Elimination of Trialkysilanols

The 1,3-\(N,C\)-elimination of trialkysilanols from silyl nitronates is one alternative method to generate nitrosoalkenes. For example, methyllithium-promoted 1,3-elimination of \(t\)-butyldimethylsilyl nitronate 20 yields nitrosoalkene intermediate 22 (Scheme 7).\textsuperscript{26} When excess alkyl lithium reagent was employed, the Michael adduct oxime 23 was produced in low yield.

\textbf{Scheme 7}

Another example of a nitrosoalkene formation via 1,3-\(N,C\)-elimination of a trialkysilanol comes from the work of Ioff.\textsuperscript{27} Treatment of \(\beta\)-nitro compound 24 with \(N,O\)-bis(trimethylsilyl)acetamide (25) leads to trimethylsilylnitronate intermediate 26 (Scheme 8). This intermediate undergoes spontaneous elimination of trimethylsilanol to generate the nitrosoalkene intermediate 27. Reaction \textit{in situ} of intermediates 26 with 27 gives \(N,N\)-divinyl-\(N\)-trimethylsilyloxyamines 28 in variable yields. This alternative method for the generation of nitrosoalkenes may gain more attention in the future since it allows for formation of nitrosoalkenes containing an electron-withdrawing group at the \(\beta\)-position.
1.2.3.2 Generation of Nitrosoalkenes via the Combination of Vinyl Radicals with Nitric Oxide

In 1960, the reaction of vinyl radicals with nitric oxide was introduced as a method to synthesize nitrosoalkenes such as 30 by Griffin and coworkers (Scheme 9).\textsuperscript{28} It was found that irradiating 1,1,2-trifluoroiodoethylene (29) yielded trifluorovinyl radicals, which then react with nitric oxide to form stable, isolable nitrosoalkene 30 in low yield.

Scheme 9
Other similar reactions have been hypothesized as involving nitrosoalkenes as intermediates. For example, irradiating alkyne nitrites 31 resulted in spontaneous intramolecular cyclization followed by reaction of the incipient vinyl radical 32 with nitric oxide to form nitrosoalkene intermediate 33 (Scheme 10).\textsuperscript{25} However, further rearrangement and fragmentation of 33 led to formation of the stable products γ-butyrolactone (34) and nitriles 35. The difficulty in intercepting nitrosoalkenes generated in these free-radical methods, as well as the complication of preparing the precursors, generally limits their synthetic utility.

Scheme 10

\[ \text{Scheme 10} \]

1.2.3.3 Generation of Nitrosoalkenes via the Combination of Nitrile Oxides with Sulfoxonium Ylides

The Gilchrist group has described a method for nitrosoalkene formation which involves reaction of a nitrile oxide and a sulfoxonium ylide. For example, nitrosoalkenes such as 38 were generated from the reaction of sulfoxonium ylide 36 with benzonitrile oxide (37) with the expulsion of dimethyl sulfoxide (Scheme 11).\textsuperscript{29} The intermediate nitrosoalkene 38 then reacted with excess ylide 36 to produce isoxazoline 39 in 31\% yield.
1.2.3.4 Generation of Nitrosoalkenes via Retro-Diels Alder Reactions

In certain cases, retro-Diels Alder reactions can lead to nitrosoalkene intermediates. Typically, those compounds that undergo thermal fragmentation to produce stable products such as aromatic systems have been proposed to proceed via nitrosoalkene intermediates. In one study, indolinoxazine 40 underwent a thermal ring cleavage to form indole 41 and nitrosoacrylate 42 (Scheme 12). The latter fragment was trapped with n-pentanol to produce adduct 43 in 63% yield.
1.3 Reactions of Nitrosoalkenes

1.3.1 Unimolecular Reactions via Ring Rearrangements

Nitrosoalkenes have been shown to be highly reactive due to the presence of a carbon carbon double bond in conjugation with the electron withdrawing N=O moiety. As a result, intramolecular thermal rearrangements of nitrosoalkenes take place spontaneously but are limited to substrates containing specific structural features. For example, ring opening of oxazinones 44 and 47 with base generated nitrosoalkenes 45 and 48, respectively (Scheme 13), which underwent further rearrangement to form the corresponding products 46 and 49, respectively.

Scheme 13

1.3.2 Tautomerization

Elimination/tautomerization is the most common degradation pathway for nitrosoalkenes. As mentioned in Section 1.1, nitrosoalkenes have very short lifetimes, and evidence for their existence in solution is usually indirect, relying on the identity of products of reactions, or the characteristic blue color they impart to a solution. For example, as reported by Kisan and Przikow, the treatment of \( \alpha \)-heteroatom-substituted oxime 50 with NEt\(_3\) produced the elimination tautomers 52 and 53 in the absence of nucleophiles (Scheme 14). The formation of 2-
methyl-1-nitrosocyclohexene (51) was indicated by a blue-colored reaction mixture which faded to colorless after approximately 30 minutes. In addition, the isolated tautomer 52 can be explained as the product of a [1,5]-sigmatropic hydrogen shift on nitrosoalkene 51. In general, in systems where such tautomerization is not possible, the nitrosoalkene tends to be more stable.

Scheme 14

1.3.3 Cycloaddition Reactions of Nitrosoalkenes

Nitrosoalkenes can participate in a variety of pericyclic reactions, most-notably [4+2]-Diels-Alder-type cycloadditions, where they can function as the 4π-component in both inter- and intramolecular reactions to produce adducts 54 (Scheme 15, path A). Alternatively, these vinylnitroso species can also behave as 2π heterodienophiles, giving rise to cycloadducts 55 (path B). Theoretically, the C=C bond of nitrosoalkenes could also act as a 2π-component in [4+2]-cycloadditions (path C). However, there are no known examples of products 56 arising from this pathway. Lastly, a [3+2]-cycloaddition would generate nitrones (path D). However, no such [3+2]-periselective cycloaddition are precedent in the literature, and products like 57 only have been isolated as minor byproducts of [4+2]-cycloadditions.
1.3.3.1 [4+2]-Cycloadditions with Nitrosoalkenes as the 4π-Component (Path A)

Examples of nitrosoalkenes functioning as a 4π-component exist for both inter- and intramolecular hetero-Diels-Alder cycloadditions. Electron rich olefins, including enol ethers, enamines, allyl silanes, and alkenes have all been employed as dienophiles with a variety of nitrosoalkenes in the construction of six-membered heterocycles. One representative example, demonstrated by Reissig and coworkers, which utilizes a highly electrophilic nitrosoalkene, generated from corresponding α-bromooxime, undergoes hetero-Diels-Alder cycloaddition with a number of electron-rich dienophiles to generate 1,2-oxazine derivatives (Scheme 16).
Although formally [4+2]- cycloadditions, the degree of concertedness in the formation of heterocycles such as 66 is proposed to be rather low, with the reaction occurring instead in a stepwise manner. In 1976, Gilchrist and Faragher reported that furans and enamines, participating as dienophiles, add to nitrosoalkenes via a [4+2]-cycloaddition process. For example, nitrosoalkene 64, generated from the corresponding α-chlorooxime 63, undergoes efficient addition to enamine 65 to give formal [4+2]-cycloadduct 66 (Scheme 17). Gilchrist has proposed that such cycloaddition most likely occurs via an initial Michael-type conjugate addition producing an oximate-iminium ion species 67 and subsequent cyclization to observed product 66. Theoretical calculations on these types of reactions by Domigo and coworkers further support this hypothesis.
An intramolecular [4+2]-cycloaddition via addition of a fluoride source to an α-chloro-O-silyloxime acting as a 4π heterodiene was reported by Denmark (Scheme 18). In this example, a 1:1 $E/Z$ mixture of enol ether/α-chloro-O-silyloxime 68 was treated with cesium fluoride in acetonitrile at room temperature to generate nitrosoalkene intermediate 69, which cyclized to form a 3.4:1 diastereomeric mixture of oxazines 70 and 71. The preponderance of the cycloadduct with the methoxy group in the endo configuration observed in this intermolecular hetero-[4+2]-cycloaddition was attributed to favorable secondary orbital interactions in the endo transition state.

Scheme 18
1.3.3.2 [4+2]-Cycloadditions with Nitrosoalkenes as the $2\pi$-Component (Path B)

There are relatively few literature examples of [4+2]-cycloaddition reactions in which the nitrosoalkene N=O bond serves as the $2\pi$-component. In all known examples, the participating nitrosoalkene typically contains at least one vinylic halogen, usually at the $\beta$-position. Moreover, the cycloadducts formed from such reactions are unstable, readily undergoing rearrangement. For example, nitrosoalkene 73, generated in situ from $\alpha$-chlorooxime 72, reacts with 1,3-cyclohexadiene (74) to give unstable Diels-Alder adduct 75,\(^{42}\) which readily undergoes rearrangement to compound 76 upon warming to room temperature (Scheme 19). The formation of the transient oxazine 75 has been confirmed by low-temperature NMR experiments.

Scheme 19

1.3.3.3 [3+2]-Cycloadditions of Alkenes with Nitrosoalkenes (Path D)

Until recently, there have been few reported examples of [3+2]-cycloadditions of nitrosoalkenes. Indeed, [3+2]-cycloadducts are often observed as minor byproducts of [4+2]-hetero-Diels-Alder reactions. One such example was reported by Gilchrist who showed that treatment $\alpha$-nitrosostyrene 78, generated from the corresponding $\alpha$-chlorooxime 77, with enol ether 79 gave rise to cycloadducts 80 and 81, with the latter being the product of a formal [3+2]-cycloaddition (Scheme 20).\(^{30}\)
α-Phosphonyl- and α-phosphonyl-nitrosoalkenes have shown a proclivity for undergoing formal [3+2]-cycloadditions with electron-rich olefins such as enamines 84. One representative example, reported by Palacios and coworkers, involved the addition of α-phosphonyl-nitrosoalkene 83, generated from α-bromoxime 82, to enamines 84 furnishing formal [3+2]-cycloadduct 86 (Scheme 21). Palacios has postulated that the reaction in fact occurs in a stepwise manner via an initial Michael-type conjugate addition of nitrosoalkene 83 with enamines 84 to produce iminium oxamate 87, which then undergoes further cyclization and spontaneous aromatization via elimination of pyrrolidine to generate N-hydroxy pyrrole 86.

Scheme 20

\[
\begin{align*}
\text{\text{PhNOH}} & \quad \text{Na}_{2}\text{CO}_3 \quad \text{Ph} \quad \text{N}^\circ \text{O} \quad \text{N}^\circ \text{O} \\
\text{77} & \quad \text{CH}_2\text{Cl}_2 \quad \text{78} & \quad \text{79} \quad \text{80 (81\%)} & \quad \text{81 (11\%)}
\end{align*}
\]

Scheme 21
1.3.4 Aromatic Substitutions of Nitrosoalkenes

Electron rich aromatics and heteroaromatics can react efficiently with highly electrophilic nitrosoalkenes to afford the corresponding aromatic substitution products. This observation can be attributed to the highly electrophilic nature of the nitrosoalkene. One such example involves the addition of electron rich aromatic compound 90 to nitrosoalkene intermediate 89, generated from α-chlorooxime 88, to give regioisomeric substitution products 91 and 92 in a 4:1 ratio (Scheme 22).

Scheme 22

Indoles, pyrroles, furans, and benzofurans were all found to be suitable heteroaromatic substrates for reactions with a variety of electrophilic nitrosoalkenes. For example, pyruvate-derived nitrosoalkenes 94 reacted with 3-methylindole (95) to generate the tricyclic oxazine derivatives 96 (Scheme 23). Surprisingly, treatment of the same nitrosoalkenes 94 with 2-methylindole (97) led to the formation of 3-alkylated indoles 99. Reissig and coworkers proposed that this aromatic product 99 is likely formed via an initial [4+2]-cycloaddition to give intermediate 98, followed by ring opening.
1.3.5 Nitrosoalkenes as Enolonium Ion Equivalents in Umpolung Reactions

The α-functionalization of carbonyl compounds is a fundamental transformation in organic synthesis, but this type of reaction can often be problematic due to the presence of two adjacent electrophilic centers. For example, direct treatment of α-haloketones 100 with a nucleophile could, in principle, lead to two different products – carbonyl addition product 101 and/or α-substitution product 102 (Scheme 24).
As an example of such a process, the attempted intramolecular nucleophilic cyclization of \( \alpha \)-chloroketone \( 103 \) under a variety of basic conditions gave none of the desired nucleophilic \( \alpha \)-substitution product \( 106 \) (Scheme 25).\(^{46}\) Instead, a 1:1 mixture of diastereomeric tertiary alcohols \( 104 \) and \( 105 \) resulting from enolate addition to the carbonyl carbon were the only major products. In addition, upon occasion treatment of \( \alpha \)-haloketones with malonate anion and other nucleophilic bases can induce undesirable Favorskii rearrangements.\(^{47}\)

**Scheme 25**

![Diagram of Scheme 25](image)

\( (104 : 105 = 1 : 1) \)

One solution to this selectivity problem involves appropriate modification of a carbonyl group in order to invert its polarity, comprising an umpolung strategy for the synthesis of \( \alpha \)-functionalized carbonyls.\(^{48}\) The traditional functionalization of a carbonyl group at the \( \alpha \)-carbon is via the reaction of an enolate/azaenolate intermediate with an electrophilic reagent (Scheme 26). In contrast, an umpolung strategy for C-C bonds construction at the \( \alpha \)-carbon is via the reaction of enolonium ion equivalents and nucleophiles. In this section, various umpolung methods for the carbonyl group via enamines and related derivatives are discussed.
1.3.5.1 Umpolung Reactions via Enamines

Until recently, there have been few reported examples of umpolung \(\alpha\)-arylation and \(\alpha\)-alkylation reactions of carbonyl groups via enamine intermediates. Thus, Miyata and coworkers recently showed that treatment of ketone 107 with two equivalents of isoxazolidine (108) yielded enamine intermediate 109 (Scheme 27),\(^{49}\) which upon treatment with trialkyl- and triaryllaluminum reagents (2.0 equivalents) produced \(\alpha\)-functionalized imines 111 via intramolecular delivery of a carbon nucleophile with concomitant N-O bond cleavage. Imines 111 were easily hydrolyzed to the corresponding carbonyl compounds 112 upon aqueous workup in good yields.
1.3.5.2 Umpolung Reactions via Hydrazone Derivatives

Examples of umpolung carbonyl reactions via carbonyl derivatives such as vinyl azides,\textsuperscript{50} N-sulfonylazoalkenes,\textsuperscript{51} and enammonium salts with indolo[2,3-a]quinolizine structures\textsuperscript{52} have been carried out using nucleophilic alkylation reagents. For example, the Fuchs group has reported the successful of use \( p \)-toluenesulfonylazaalkenes like 115 as enolonium ion equivalents for the overall \( \alpha \)-arylation of ketones.\textsuperscript{53} Thus, addition of excess phenylcuprate (114) to a series of azoalkenes 115a-e, generated \textit{in situ} from \( \alpha \)-halotosylhydrazones 113a-e, led to conjugate addition products 116a-e in good yield (Scheme 28). These \( \alpha \)-phenyltosylhydrazones 116a-e were subsequently converted to the corresponding \( \alpha \)-phenylketones 117a-e using boron trifluoride etherate in acetone and water. This method was also applied to the formation of spirocyclic systems (see Scheme 55).
Another such example of an α-alkylation of ketones utilizing an umpolung strategy is the copper(I)-catalyzed addition of various Grignard reagents (119) to azaalkenes generated in situ from α-chloro-N-sulfonylhydrazones 118 to give tosylhydrazones 123 (Scheme 29). Of particular interest is the reaction of 120 with t-butylmagnesium bromide giving tosylhydrazone 123f, which contains two contiguous quaternary centers. In these reactions, the Grignard reagent not only functions as the Brønsted base in forming intermediate azoalkene 120, but also undergoes transmetalation with the Cu(I) catalyst in situ to form cuprate 121, which undergoes conjugate addition to the azoalkene 120. Aqueous work-up of 122 led to isolation of α-alkylated products 123 in moderate to good yields.

Scheme 28

Scheme 29
1.3.5.3 Umplung Reactions of Nitrosoalkenes

Another umpolung α-functionalization strategy for aldehydes and ketones that employs nitrosoalkenes as enolium ion equivalents has also been developed, although not widely explored. These transient intermediates, generated from the corresponding α-heteroatom-substituted oximes 125, allow for the α-substitution of oximes with various carbon nucleophiles and provide a practical pathway to α-substituted ketooximes 127 (Scheme 30). Facile cleavage of oximes 127 then produces the desired α-substituted ketones 128.\(^{54}\)

**Scheme 30**

\[
\begin{array}{c}
\text{R} \quad \text{X} \\
\text{124} \\
\end{array}
\xrightarrow{\text{NH}_2\text{OH}}
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \\
\text{125} \\
\end{array}
\xrightarrow{\text{B}^- \quad \text{Nu}^-}
\begin{array}{c}
\text{R} \quad \text{NO} \quad \text{CH}_2 \\
\text{126} \\
\end{array}
\xrightarrow{\text{Nu}^-}
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \\
\text{127} \\
\end{array}
\xrightarrow{\text{Nu}^-}
\begin{array}{c}
\text{O} \quad \text{Nu} \\
\text{128} \\
\end{array}
\]

1.3.5.3.1 Conjugate Additions of Carbon Nucleophiles to Nitrosoalkenes

Stabilized carbanions such as those generated from β-ketoesters such as 131 are the most commonly employed carbon nucleophiles in conjugate additions to nitrosoalkenes. One of the earliest examples of such a transformation was described by Sprio and coworkers,\(^{55,56}\) and involved treatment of mixture of β-ketoesters 131 and α-bromoketooximes 129 with sodium methoxide in methanol, leading to the formation of α-substituted oximes 132, presumably as the result of an enolate Michael addition to nitrosoalkene 130 (Scheme 31).
The enolates of 1,3-diketones can also participate in conjugate addition reactions with nitrosoalkenes. For example, the carbanion 135, generated from the corresponding 1,3-diketone upon treatment with sodium carbonate, added readily to the highly electrophilic nitrosoalkene 134 in a Michael-type fashion to generate a mixture of isomeric products 136-138 in high total yield (Scheme 32).

Similarly, it was found that enolates derived from malonates add efficiently to nitrosoalkenes to provide the corresponding Michael adducts. For example, Ohno et al. reported
exposure of α-chlorooximes 139 and 143 to large excesses of carbanions 140 and 144 generate the corresponding α-malonylate oximes 142 and 146, respectively (Scheme 33).\(^\text{57}\)

Notably, Ohno and coworkers observed that the stability of the cyclic vinyl nitroso compounds was dependent upon ring size. In general, the macrocyclic α-chloroximes such as 143 appeared to more efficiently undergo nucleophilic Michael additions compared to smaller ring α-chloroximes. In addition, the same group reported examples of the Michael addition of various carbon and heteronucleophiles to nitrosoalkene 145. It was found that morpholine (entry 1), sodium azide (entry 2), silver nitrite (entry 3), Grignard reagents (entry 4), diethyl malonate sodium salt (entry 5), and acetylacetone sodium salt (entry 6) were all compatible with this methodology, generating the corresponding Michael adducts 146 in moderate to good yields.

Scheme 33

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R Group</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Morpholine, EtOH, rt</td>
<td>N-morpholino</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>NaN(_3), MeCN, reflux</td>
<td>N(_3)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>AgNO(_2), ether, rt</td>
<td>NO(_2)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>PhMgBr, THF</td>
<td>Ph</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>NaHC(CO(_2)Et(_2)), ether</td>
<td>CH(CO(_2)Et(_2))</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>NaHC(COCH(_3))(_2), ether</td>
<td>CH(COCH(_3))(_2)</td>
<td>98</td>
</tr>
</tbody>
</table>
1.3.5.3.2 Conjugate Additions of Carbon Nucleophiles to Nitrosoalkenes Generated via the Denmark Protocol

As mentioned previously, the hitherto relatively limited use of nitrosoalkene Michael additions in organic synthesis may be due in part to the necessity to use more than two equivalents of a nucleophile in the classical generation method. Fortunately, this problem has been circumvented by generating nitrosoalkenes via the Denmark protocol, in which only one equivalent of nucleophiles is needed in principle. For example, in 2005, Barrett and coworkers reported that in the presence of one equivalent of TBAF, one equivalent of the valuable anomeric alcohol 148 successfully adds to one equivalent of the nitrosoalkene intermediates 149 and 152, generated in situ from α-chloro-O-TBS-oximes 147 and 151, to yield corresponding glycosides 150 and 153, respectively, as mixtures of stereoisomers (Scheme 34).58

Scheme 34
1.4 Previous Studies of Nitrosoalkenes in the Weinreb Group

1.4.1 Intramolecular Michael Cyclizations of Nitrosoalkenes

Although several examples of intermolecular conjugate additions of various nucleophiles to nitrosoalkenes have been reported,\textsuperscript{2,9,15} no such intramolecular reactions had been reported in the literature. In 2007, Ilia Korboukh in our group furnished the first intramolecular conjugate additions of tethered nucleophiles to nitrosoalkene intermediates to form fused and bridged ring systems.\textsuperscript{59} In order to access the requisite substrates, methodology for the ring closing metathesis (RCM) of vinyl chlorides\textsuperscript{60,61} and the subsequent regioselective oxidation of vinyl chlorides to \(\alpha\)-chloroketones,\textsuperscript{62} developed in our lab, were employed. Thus, diene 154 was converted to vinyl chloride 155 using the Grubb’s 2nd generation catalyst in 74% yield (Scheme 35). Treatment of vinyl chloride 155 with sodium hypochlorite and glacial acetic acid in acetone yielded \(\alpha\)-chloroketone 156 in 67% yield. Oximation of \(\alpha\)-chloroketone 156 with \(O\)-TBS hydroxylamine (TBSONH\textsubscript{2}) gave the desired cyclization precursor 157 as a complex mixture of diastereomers and oxime geometric isomers. Deprotonation of the malonate moiety in 157 using NaHMDS at low temperature followed by treatment with TBAF, promoted an intramolecular cyclization via nitrosoalkene intermediate 158 to form the desired bicyclic oxime 159 as a single oxime geometric isomer in nearly quantitative yield.
Additional examples of the formation of bridged ring systems are shown in Table 1.1. It was found that enolates of \( \beta \)-ketoesters (entries 1-3), and simple monoesters (entry 4) are both compatible with this methodology to generate various ring systems. It is worth mentioning that KHMDMS was also compatible with this methodology for formation of carbanions (entries 4). In general, however, the use of NaHMDS or KHMDMS led to better results than LiHMDS.

**Table 1.1 Examples of Intramolecular Michael Cyclizations of Nitrosoalkenes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="" /></td>
</tr>
</tbody>
</table>
Owing to the success in carrying out the intramolecular nitrosoalkene cyclizations described above, we became interested in exploring the possibility of extending these intramolecular nitrosoalkene conjugate additions to a wider range of stabilized carbanions as nucleophiles. This phase of the study was conducted by Praveen Kumar of our group employing vinyl chloride metathesis and the oxidation of vinyl chlorides to access the requisite cyclization precursors. Specifically, alkyl iodide 160 was reacted with a number of active methylene compounds to produce alkylated products 161 (Scheme 36). These chlorodienes underwent ring closing metathesis to afford vinyl chlorides 162 in the presence of Grubbs 2nd generation catalyst. Treatment of vinyl chlorides 162 with sodium hypochlorite and acetic acid in acetone yielded α-chloroketones 163, which were transformed into the requisite α-chloro-O-silyloxime cyclization precursors 164.
With various cyclization substrates in hand, cyclization studies were initially conducted on the symmetrical 1,3-diketone 163a and diphenylsulfone 163b (Table 1.2, entries 1 and 2). First, α-chloro-O-silyloximes 164a and 164b were deprotonated with KHMDS, followed by treatment with TBAF to generate the reactive nitrosoalkene intermediate. Thus, intramolecular cyclization furnished bicycle[2.2.1]heptanes 165a and 165b, respectively, in 78% and 61% yields. Both bridged bicyclic compounds were found to exist as single oxime isomers which were assumed to have the more stable E-configuration as shown. In addition, treatment of unsymmetrically-substituted esters 164c and 164d under the standard reaction conditions, provided bicycles 165c and 165d, respectively, as single stereoisomers (entries 3 and 4). Moreover, it was found that other carbon nucleophiles, such as β-ketoesters (entry 5),
phosphonate esters (entry 6) and phenylsulfone nitriles (entry 7), participated in these cyclizations. In each of these examples, the products appeared to be single oxime isomers, which are assumed to exist in the $E$-configuration. However, the configuration of products at the quaternary carbon could not be determined.

**Table 1.2 More Examples of Intramolecular Michael Cyclizations of Nitrosoalkenes Performed in Our Group**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Reaction 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Reaction 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Reaction 3" /></td>
</tr>
</tbody>
</table>
One limitation of these studies is that the hypochlorite-induced halogenation of vinyl chlorides often led to a variety of undesired side products, thereby lowering the yield of the desired α-chloroketone. One competitive reaction was the chlorination of the activated methylene...
portion of the substrate,\textsuperscript{64} which often occurs preferentially over the reaction with the electron-deficient olefinic double bond.

Thus, in a related study,\textsuperscript{64} reaction of vinyl chloride malonate 166 with NaOCl led to chemoselective $\alpha,\alpha$-dichlorination, with the desired $\alpha$-chloroketone 170 not formed at all (Scheme 37). Instead, a mixture of trichloroacetate 167, dichloroketone 168, and compound 169 was generated. Therefore, we sought to explore the possibility of using more electron rich enol ethers as an alternative to vinyl chlorides as precursors to the desired $\alpha$-chloroketones. This part of the work is discussed in Section 2.2.1.

Scheme 37
Chapter 2 Results and Discussion

2.1 Intermolecular Conjugate Additions of Nitrosoalkenes

As discussed previously, nitrosoalkenes can be used as enolonium ion equivalents in organic synthesis. Although intermolecular alkylation of nitrosoalkenes with carbon nucleophiles is known, the methodology had not been widely explored. As noted above, the traditional method for forming nitrosoalkenes involves the 1,4-elimination of α-halooximes to produce nitrosoalkenes in situ, but this method typically requires at least two equivalents of a nucleophile, one of which acts as the base, for the initial elimination step. Thus, such a procedure is inefficient and not practical when the nucleophiles are valuable. Fortunately, Demark has demonstrated a useful alternative pathway to generate nitrosoalkenes in which, in principle, only one equivalent of the nucleophile is required. However, this methodology had not been explored to any significant extent for forming C-C bonds. Therefore, we were prompted to investigate the scope of intermolecular conjugate addition reactions of carbon nucleophiles involving nitrosoalkenes generated via the Denmark protocol.

2.1.1 1,4-Conjugate Additions of Nitrosoalkenes with Carbon Nucleophiles

Preliminary results by Max Majireck in our group demonstrated the possibility of generating α-alkylated oxime 173 via an intermolecular process using the Denmark method with an α-chloro-O-TBS-oxime 174 serving as the nitrosoalkene precursor (Scheme 38). Thus, ester 171 (1.2 equiv) was treated with KHMDS at -78 °C, followed by addition of 1.0 equiv of α-chloro-O-silyloxime 174, and then slow addition of TBAF to afford the alkylation product 172 in good yield. It should be noted that allowing the reaction mixture to warm to room temperature before aqueous workup led to the isolation of the undesired intramolecular cyclization product 173 in low yield.
Scheme 38

Encouraged by this one result, we initiated an investigation of the scope and limitations of this intermolecular alkylation methodology utilizing nitrosoalkenes.\textsuperscript{65-67} Thus, we synthesized \(\alpha\)-chloro-O-TBS-oximes \textbf{174-179} under standard reaction conditions starting from commercially available or known \(\alpha\)-chloroketones and aldehydes\textsuperscript{68,69} (Scheme 39). This process gave the desired silyloximes in good yields and as mixtures of geometric isomers.

Scheme 39
We then developed a general experimental procedure to effect the conjugate addition of carbon nucleophiles to nitrosoalkenes generated from these substrates (Scheme 40). Thus, an ester derivative \( \text{182} \) (1.2 equiv) was converted into its potassium enolate with KHMDS (1.2 equiv) in THF at \(-78^\circ\text{C}\). The \( \alpha \)-chloro-\( O \)-silyloxime (1.0 equiv) was then added to this enolate solution, followed by slow addition of TBAF in THF (1.2 equiv). The mixture was then slowly warmed to \( 0^\circ\text{C} \). After two hours, the reaction was subjected to an aqueous workup to yield the desired alkylation products \( \text{183} \).

**Scheme 40**

\[
\begin{align*}
\text{R}_1\text{O}_2\text{C} & \quad \quad \quad 1) \text{KHMDS (1.2 equiv), THF, -78}^\circ\text{C} \\
\text{182} & \quad \quad \quad 2) \text{Cl} \quad \text{N=OTBS} \\
\quad (1.0 \text{ equiv}) \quad \text{then TBAF (1.2 equiv)} \\
\quad \text{-78}^\circ\text{C to 0}^\circ\text{C} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qua
Table 2.1 Intermolecular Michael Additions to Cyclic Nitrosoalkenes

<table>
<thead>
<tr>
<th>Ester Derivative</th>
<th>Entry</th>
<th>Product (Isolated Yield)</th>
<th>Entry</th>
<th>Product (Isolated Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtO₂C₂H₅CO₂Et</td>
<td>1</td>
<td>EtO₂C₂H₅N-OH</td>
<td>9</td>
<td>EtO₂C₂H₅N-OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95%</td>
<td></td>
<td>59%, 85% b,c</td>
</tr>
<tr>
<td>EtO₂C₂H₅CO₂EtCH₃</td>
<td>2</td>
<td>EtO₂C₂H₅N-OH</td>
<td>10</td>
<td>EtO₂C₂H₅N-OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84%</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>EtO₂C₂H₅CO₂EtEt</td>
<td>3</td>
<td>EtO₂C₂H₅N-OH</td>
<td>11</td>
<td>EtO₂C₂H₅N-OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69%</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>EtO₂C₂H₅NO₂</td>
<td>4</td>
<td>EtO₂C₂H₅N-OH</td>
<td>12</td>
<td>EtO₂C₂H₅N-OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57% a</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>EtO₂C₂H₅CO₂CH₃</td>
<td>5</td>
<td>EtO₂C₂H₅N-OH</td>
<td>13</td>
<td>decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71% a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO₂C₂H₅SO₂Ph</td>
<td>6</td>
<td>PhO₂S₂H₅N-OH</td>
<td>14</td>
<td>PhO₂S₂H₅N-OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% a</td>
<td></td>
<td>82% a</td>
</tr>
</tbody>
</table>
To determine whether the counterion from the base had any effect on the product yield, both LiHMDS and NaHMDS were screened using ethyl nitroacetate. Interestingly, neither base provided the desired product (entry 4), which was formed cleanly with KHMDS. On the other hand, when diethyl malonate was deprotonated with LiHMDS and NaHMDS, the yield of the alkylation product differed only very slightly from that obtained using KHMDS. In any event, KHMDS was found to be the most generally compatible base for these intermolecular alkylations of nitrosoalkenes with carbon nucleophiles.

All of the carbon nucleophiles tested also reacted with nitrosocyclopentene, derived from oxime 175, to yield the corresponding alkylation products (entries 9-15) except for the β-ketoester enolate. Additionally, increasing the amount of ester enolate to two equivalents was found to improve the yields (Table 2.1, entries 9, 15). In general, the corresponding reactions of nitrosocyclopentene gave lower yields than those with nitrosocyclohexene.

In most cases, a single oxime geometric isomer product was formed, which was assumed to have the lower energy E-configuration. Occasionally, mixtures of oxime stereoisomeric products were produced, but stereochemical assignments were not made since these compounds...
were not only mixtures of $E$ and $Z$ isomers but also were mixtures of diastereomers, which were inseparable by flash column chromatography.

Treatment of phenylsulfonylacetonitrile (184) with nitrosocyclohexene under the above standard conditions did not provide the desired Michael-type product and only the unstable compound 186 was isolated, resulting from an intramolecular cyclization of the oxime anion onto the cyano group of intermediate 15 (Scheme 41).\textsuperscript{70-72}

**Scheme 41**

\[
\text{PhSO}_2\text{CN} \quad \begin{array}{c}
\text{OTBS} \\
\text{Cl}
\end{array}
\xrightarrow{1) \text{KHMDS (1.2 equiv), THF, -78 °C} \atop 2) \text{TBAF (1.2 equiv), -78 °C-0 °C}} \begin{array}{c}
\text{OTBS} \\
\text{N}^\ominus
\end{array}
\xrightarrow{54\%} \begin{array}{c}
\text{PhSO}_2\text{CN} \\
\text{N}^\ominus
\end{array}
\xrightarrow{\text{H}_2\text{N}^\ominus \text{O} \text{N}} \\
\text{PhSO}_2\text{CN}
\]

We also examined intermolecular conjugate additions with nitrosoalkene 187, derived from $\alpha$-chlorosilyloxime 176, as a means to form $\alpha$-quaternary centers. Unfortunately, all these attempted reactions only led to the formation of the elimination tautomer $\alpha,\beta$-unsaturated oxime 188 (Scheme 42). This is probably due to steric effects of the methyl group slowing the nucleophilic addition and allowing tautomerization to occur.

**Scheme 42**

\[
\begin{array}{c}
\text{N}^\ominus \\
\text{Cl}
\end{array}
\xrightarrow{\text{186}} \\
\]
We next investigated reactions of various carbon nucleophiles with aldoximes 177 and 178 (Table 2.2) since conjugate additions to such species are not well studied and the direct alkylation of aldehydes by conventional enolate chemistry usually leads to side reactions such as self condensation and polymerization. Various ester enolates were reacted with both substrates under the optimized standard conditions (entries 1-3, 8-10). Interestingly, the reaction of α–methyl and α–ethyl diethyl malonate enolate with aldoxime 177 proceeded smoothly to give alkylation products with two adjacent quaternary carbons in moderate yields (entries 2 and 3). Addition of methyl phenylacetate to both oximes yielded the desired products, also in moderate yields (entries 7 and 14). However, the α-nitroester, β-ketoester, and α-sulfonylester enolates did not add to the nitrosoalkenes derived from oximes 177 and 178 (entries 4-6, 11-13). These reactions either led to complete decomposition or starting material was recovered.

Table 2.2 Intermolecular Michael Additions to Nitrosoalkenes Derived from Aldoximes

<table>
<thead>
<tr>
<th>Ester Derivative</th>
<th>Entry</th>
<th>Product (Isolated Yield)</th>
<th>Entry</th>
<th>Product (Isolated Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtO₂C–CO₂Et</td>
<td>1</td>
<td>H</td>
<td>8</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtO₂C–CO₂Et</td>
<td></td>
<td>EtO₂C–CO₂Et</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%, 64% bc</td>
<td></td>
<td>51% c</td>
</tr>
<tr>
<td>CH₃</td>
<td>2</td>
<td>H</td>
<td>9</td>
<td>Ph</td>
</tr>
<tr>
<td>EtO₂C–CO₂Et</td>
<td></td>
<td>EtO₂C–CH₃–CO₂Et</td>
<td></td>
<td>EtO₂C–CO₂Et</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48%, 74% b</td>
<td></td>
<td>69%</td>
</tr>
</tbody>
</table>
Similarly, some ester enolate nucleophiles were also added to the nitrosoalkene formed from acyclic ketoxime 179 (Table 2.3). Surprisingly, α-substituted diethyl malonates generated the desired products, with formation of vicinal quaternary carbon centers, in higher yield than with diethyl malonate itself. One possible explanation for this result is the greater solubility of the α-substituted ester enolates in THF at -78 °C, increasing the efficiency of the latter reactions.
Table 2.3 Intermolecular Michael Additions to Terminal Nitrosoalkenes

<table>
<thead>
<tr>
<th>Ester Derivative</th>
<th>Entry</th>
<th>Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtO₂C—CO₂Et</td>
<td>1</td>
<td>EtO₂C</td>
<td>30% (^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N—OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td></td>
</tr>
<tr>
<td>EtO₂C—CO₂Et</td>
<td>2</td>
<td>EtO₂C</td>
<td>88%</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>N—OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td></td>
</tr>
<tr>
<td>EtO₂C—CO₂Et</td>
<td>3</td>
<td>EtO₂C</td>
<td>71%</td>
</tr>
<tr>
<td>Et</td>
<td></td>
<td>N—OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Et</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td></td>
</tr>
<tr>
<td>H₂CO₂C—Ph</td>
<td>4</td>
<td>H₂CO₂C</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N—OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The deprotonation step was performed at 0 °C to prevent freezing of the reaction mixture.
2.2 Studies on Intramolecular Michael Cyclizations of Nitrosoalkenes

We next became interested in exploring the possibility of effecting additional types of intramolecular nitrosoalkene conjugate additions using a range of malonates and stabilized carbanions as nucleophiles. We sought to develop protocols for three types of ring formation using this method: 1) bridged rings, 2) fused rings, and 3) spirocyclic rings.

2.2.1 Bridged Ring Formation

Since the hypochlorite-induced halogenation of vinyl chlorides often led to a variety of undesired side products (Cf Scheme 36), we decided to modify the formation of the nitrosoalkene precursor α-chloroketones using more electron rich enol ethers. We expected this new strategy would provide greater flexibility toward the preparation of substrates for the intramolecular nitrosoalkene conjugate addition methodology.

Thus, known enol ether alcohol 192 was prepared via the Diels-Alder reaction of 2-methoxybutadiene (190)\(^{73}\) with ethyl acrylate followed by ester reduction\(^{74}\) (Scheme 43). The alcohol in 192 was converted to tosylate 193, which was displaced with dimethyl malonate to form enol ether 194. Enol ether 194, upon treatment with \(N\)-chlorosuccinimide (NCS)\(^{75}\) afforded the desired α-chloroketone 156 in reasonable yield as a mixture of diastereomers. This α-chloroketone 156 had previously been shown to be a good cyclization precursor for the formation of bridged oxime 159 (Cf Scheme 35).
Similarly, unsymmetrically-substituted phenylsulfone methyl ester 192 was synthesized from tosylate 192 employing the same set of conditions used for the synthesis of α-chloroketone 197. Thus, alkylation of α-phenylsulfonylacetate (195) with tosylate 192 led to enol ether 196 as a mixture of diastereomers in 65% yield based on alcohol 191. Chlorination of enol ether 196 with N-chlorosuccinimide, followed by oximation with NH₂OTBS generated the cyclization precursor 198. Treatment of silyloxime 198 with KHMDS, followed by TBAF, provided the desired bicyclo[3.2.1]octane 200 in 83% yield as a single diastereomer. The configuration and (E)-oxime geometry of this product was elucidated by conversion to the crystalline oxime tosylate 201 and subsequent X-ray analysis showed the methyl ester moiety of 201 to be disposed above the face of the tosyl aromatic ring. (Figure 2.1). This result agrees with the upfield shift observed for the ¹H NMR resonances of the O-methyl groups in 200 and 201 (0.21 and 0.42 ppm, respectively) relative to the corresponding α-chlorosilyloxime 198. Therefore, we believe that this cyclization occurs through an ester enolate intermediate in a conformation 199.
this point it is not clear if the preference for having the ester enolate group syn to the oxime is a consequence of steric factors, or possibly some type of dipole effect which controls the stereochemical outcome of the cyclization.

Scheme 44
We next sought to investigate whether nitrogen nucleophiles could participate in these intramolecular nitrosoalkene Michael reactions to form bridged azaheterocycles. Thus, system 208 containing a pendant sulfonamide was prepared. A Diels-Alder cycloaddition of 2-methoxybutadiene (189) with acrylonitrile (202) gave an inseparable 8:1 mixture of regioisomers with adduct 203 being the major product (Scheme 45). Reduction of 203 with LiAlH₄ provided the corresponding amine 204, which was then treated with tosyl chloride afforded sulfonamide 205. The enol ether moiety of 205 was transformed to the α-chloroketone 206 as a mixture of diastereomers in high yield using sodium acetate and NCS. It is worth mentioning that halogenation of vinyl chloride systems similar to enol ether 205 using the sodium hypochlorite/acetic acid method led to significantly lower yields of the corresponding α-
chloroketone.\textsuperscript{76} Subsequent oximation of 206 provided the desired $\alpha$-chloro-$O$-silyloxime 207. At this time, we noted that TBAF was a sufficiently strong base to deprotonate the sulfonamide. As a result, compound 207 was simply treated with 2.5 equivalents of TBAF in acetonitrile at 0 °C to provide the desired 6-azabicyclo[3.2.1]octane in 84% yield as a separable 5:1 mixture of oxime geometric isomers. X-ray crystallographic analysis confirmed that the major isomer of 208 possessed the (E)-geometry. In order to further showcase the synthetic utility of this procedure, the oxime moiety in 208 was oxidatively cleaved to afford bridged ketone 209.\textsuperscript{77}

\textbf{Scheme 45}
2.2.2 Attempted Fused Ring Formation

As discussed above, intramolecular Michael-type conjugate additions of carbon nucleophiles to nitrosoalkenes generally proceed in a good yields to generate a variety of bridged ring systems. Encouraged by these results, we next turned our attention towards the synthesis of a fused ring system such as 217, which we postulated could be prepared from an intramolecular cyclization precursor such as 216.

Toward this end, treatment of commercially available β-ethoxyenone 210 with the lithium reagent formed from THP-protected iodoalcohol 211, in turn prepared from 3-iodopropan-1-ol, produced the desired enone THP ether 212. Ether 212 was then converted to tosylate 214 via alcohol 213. However, all attempted alkylations of 214 with diethyl malonate anion failed to provide the desired enone diester 215.
Failure to form the cyclization precursor 216 prompted us to investigate an alternative pathway relying on the mono-ester α-chloroketone 225. Thus, alkylation of commercially available β-ethoxyenone 210 and the Grignard reagent from 6-bromohex-1-ene (218) afforded the desired enone olefin 219 (Scheme 47). Using the ruthenium-catalyzed oxidative cleavage conditions described by Zhang et al., the terminal olefin in 219 was converted into the corresponding aldehyde 220 in 44% yield. Oxidation of 220 with Jones reagent, followed by Fischer esterification with MeOH furnished enone ester 222. Next, as reported by Keith and coworkers, exposure of enone 222 to a catalytic amount of [CuH(PPh₃)]₆ in the presence of dimethylphenylsilane (223) led to silylenol ether intermediate 224, which then underwent α-chlorination with NCS to generate the cyclization precursor α-chloroketone 225.
The α-chloroketone 225 was then converted to the α-chloro-O-silyloxime 227 (Scheme 48). Unfortunately, subjection of silyloxime 227 with KHMDS, followed by addition of TBAF failed to provide the desired fused ring system 226 but instead led to the elimination tautomer oxime 229. Alternatively, α-chloroketone 225 was converted to α-chlorooxime 228. However, regardless of the base used, treatment of oxime 228 failed to produce any of the desired cyclization product 226, rather only the starting oxime 228 was recovered.
2.2.3 Attempted Spirocyclic Ring Formation

Due to our failure to synthesize the fused ring system 226 despite many attempts, we decided to focus on intramolecular nitrosoalkene conjugate additions of enolates to produce spirocyclic ring systems, which are commonly found many in terpenes and alkaloids.\textsuperscript{80} In principle, spirocycles such as 230 could be accessed from a O-silylketoxime precursor such as 232 employing the strategy described in Scheme 49.
Our original plan was to apply our vinyl chloride ring closing metathesis/oxidation methodology to access the requisite cyclization precursor 240. This phase of the study was initially conducted by Praveen Kumar of our group beginning with Michael addition of malonate 234 to known enone 233, followed by Wittig olefination to give chlorodiene 236. The chlorodiene 236 was converted to corresponding iodide derivative 238, which was then alkylated with dimethyl malonate to generate desired RCM precursor 239. However, ring closing metathesis of chlorodiene 239 with Grubbs catalyst only gave a trace amount of desired tetrasubstitued vinyl chloride 240, which could not be purified via flash chromatography.

Scheme 50
The failure to access the desired tetrasubstituted vinyl chloride 240 prompted us to investigate an alternative pathway relying instead upon a simple cyclization precursor 248 (Scheme 51). Therefore, in order to access the requisite cyclization precursor 248 for the construction of spirocycle 249, commercially available ethyl 2-oxocyclopentanecarboxylate (242) was alkylated with ethyl 5-bromopentanoate (243) to provide ester 244 in good yield. Alkoxycarboxylation of ester 244, followed by Fischer esterification with EtOH and PTSA, generated the desired keto ester 246 in excellent yield. The α-substituted silylenol ether 247 was then prepared via reaction of ketoester 246 with TMSCl and base. Unfortunately, attempted chlorination of silylenol ether 247 under various conditions did not provide any of the desired α-chloroketone 248. Rather, when either ketone 246 or silylenol ether 247 was chlorinated with NCS, cyclopentenone 250 was produced as the major product. Furthermore, treating 247 with CuCl$_2$ led to desilylation, leading to the reformation of ketone 246.

Scheme 51

\[
\begin{align*}
\text{242} & \xrightarrow{1) \text{NaH, THF, } -78 \, ^\circ \text{C}} \text{243} & \xrightarrow{2) \text{NaI, Br(CH}_2)_4\text{CO}_2\text{Et}} \text{244} & \xrightarrow{\text{CH}_3\text{COOH 3 M HCl, reflux}} \text{245} \\
\text{244} & \xrightarrow{\text{PTSA, ROH reflux}} \text{246a R = Et, 88\%} & \xrightarrow{\text{TMSCl, NaI, CH}_3\text{CN, NEt}_3} \text{247} \\
\text{246b R = CH}_3, 76\% & & \text{248} & \xrightarrow{\text{Cl}(\text{CH}_2)_4\text{CO}_2\text{Et}} \text{249} & \xrightarrow{\text{HO-}} \text{250}
\end{align*}
\]
Alternatively, direct regioselective chlorination of ketoester 246 with SO₂Cl₂ provided the desired α-chloroketone 248, albeit in low yield (Scheme 52). This α-chloroketone 248 could be successfully converted to the corresponding O-silyloxime 251 in low yield. However, attempted cyclization under standard conditions failed to afford the desired spiro product 249 but rather gave only the elimination tautomer 252 as the major product in 72% yield.

Scheme 52

\[
\begin{array}{c}
\text{246} \xrightarrow{\text{SO₂Cl₂, CO₂Et, 0 °C, 24%}} \text{248} \\
\text{248} \xrightarrow{\text{TBSOHN₂, PPTS, 4A MS, CH₂Cl₂, rt, 10%}} \text{251}
\end{array}
\]

In light of our failure to effect a sirocyclization with the α-chloro-O-silyloxime 249, we hypothesized that modification of the nucleofuge to Br might allow generation of a spirocyclic system (Scheme 53). Thus, ketone 246 was treated with acetic anhydride in the presence of PTSA to generate enol acetate 253 in 69% yield, accompanied by 6% of recovered 246. Bromination of enol acetate 253 gave the desired α-bromoketone 254 in good yield. Oximation of α-bromoketone 254 with NH₂OTBS provided the desired product 255 in 50% yield. However, attempted cyclization of 255 under our standard conditions failed to afford the desired spirocyclization product 249, giving only the elimination tautomer 252 as the major product. This failure prompted us investigate an alternative method of generating the nitrosoalkene intermediate.
Since Trost and coworkers had previously shown that \( \alpha \)-ketoxime sulfones can be used to generated nitroalkenes,\(^{10}\) we sought to prepare ketoxime \( \alpha \)-sulfone 258 as a substrate for a spirocyclization (Scheme 54). Oximation of known \( \alpha \)-ketsulfone 253 with \( \text{NH}_2\text{OTBS} \), followed by alkylation with alkyl iodide 257 gave the desired cyclization precursor 258. However, deprotonation of ketoxime \( \alpha \)-sulfone 258 under standard conditions at low temperature followed by treatment with TBAF, led to only the dimeric product 259 and elimination tautomer 252 rather than the desired spirocyclic oxime 249.
A related conjugate addition to an azoalkene generated from a hydrazone derivative (Cf Scheme 28) was also investigated as a method for synthesizing spirocyclic systems such as 262 (Scheme 55). Thus, cyclization precursor 261 was prepared from α-ketosulfone 253 in two steps. However, treatment of hydrazone 261 with two or more equivalents of bases such as KHMDS failed to provide any of the desired spirocyclic hydrazone 262, giving only the elimination tautomer 263. At this point, we decided to abandon this project.

Scheme 55

![Scheme 55](image)

2.3 Conclusions

In summary, novel synthetic methodology involving both inter- and intramolecular conjugate addition of nucleophiles to nitrosoalkenes, generated in situ via the Denmark protocol using α-chloro-O-silyloximes, has been developed. A variety of ester enolates and carbanions have been found to participate in intermolecular reactions with nitrosoalkenes. In addition, intramolecular reactions of nitrosoalkenes provide approach to a wide array of highly functionalized systems.
Chapter 3 Experimental Section

General Methods. All non-aqueous reactions were carried out under an inert atmosphere of argon in flame-dried glassware using standard Schlenk techniques unless otherwise indicated. Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, dimethylformamide, and toluene were obtained from a solvent dispensing system equipped with alumina drying columns. Additional solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). Analytical and preparative thin layer chromatography (TLC) were performed using 0.5 or 1.0 mm EM Science silica gel 60 PF<sub>254</sub> plates. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker CDPX-300, DPX-300, AMX-360, or DRX-400 MHz spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR. Nominal mass spectral data (MS) were obtained on an Applied Biosystems 150EX instrument. High resolution mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. X-Ray data was collected on a Bruker SMART APEX CCD area detector system. We thank Hemant Yennawar of the Penn State X-Ray Small Molecule Crystallographic Facility for structure determinations of compounds 201 and 208.
General Procedure for Conversion of α-Chloroketones to α-Chloro-O-TBS-oximes

To a stirred solution of the α-chloroketone in CH₂Cl₂ was added PPTS, 4Å powdered molecular sieves, followed by O-TBS-hydroxylamine. The resulting mixture was stirred until complete consumption of the starting α-chloroketone was observed (typically 24 h) and then filtered through a Celite pad washing with CH₂Cl₂. The filtrate was concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes to give the α-chloro-O-TBS-oximes 174 - 179.

2-Chlorocyclohexanone O-(tert-Butyldimethylsilyl) Oxime (174). The title compound was obtained using the above general experimental procedure with the following quantities: α-chlorocyclohexanone (1.0 mL, 8.19 mmol), and O-TBS-hydroxylamine (2.54 g, 16.4 mmol), and CH₂Cl₂ (15 mL). Purification: EtOAc:hexanes = 1:10. Yield: 2.18 g, 100% (~ 2:1 mixture of oxime isomers). ¹H NMR (400 MHz, CDCl₃) δ 5.69 (s, 0.33H), 4.77 (s, 0.67H), 3.27 (J = 14.6 Hz, d, 0.67H), 2.56 (J = 13.9, 4.7, td, 0.33H), 2.35 (J = 14.2 Hz, d, 0.33H) 2.22-1.81 (m, 4.67 H), 1.66-1.63 (m, 1H), 1.43-1.32 (m, 1H), 1.09-0.95 (m, 9H), 0.18 (s, 6H).
2-Chlorocyclopentanone O-(tert-Butyldimethylsilyl) Oxime (175). The title compound was obtained using the above general experimental procedure with the following quantities: α-chlorocyclopentanone (2.0 g, 16.946 mmol), O-TBS-hydroxylamine (2.39 g, 16.246 mmol), and CH₂Cl₂ (15 mL). Purification: EtOAc:hexanes = 1:8. Yield: 3.48 g, 83% (~ 2:1 mixture of oxime isomers). ^1H NMR (300 MHz, CDCl₃) δ 4.82 (J = 2.6, 0.8 Hz, dd, 0.33H), 4.59 (J = 4.6, 2.8 Hz, dd, 0.67H), 2.51-2.45 (m, 1H), 2.26-2.15 (m, 1H), 1.93-1.88 (m, 3H), 1.70-1.67 (m, 1H), 0.79-0.76 (m, 9H), 0.00--0.02 (m, 6H); LRMS-ES+ m/z (relative intensity) 248 (MH⁺, 30).

2-Chloro-2-Methylcyclohexanone O-(tert-Butyldimethylsilyl) Oxime (176). The title compound was obtained using the above general experimental procedure with the following quantities: 2-methylcyclohexanone (136 mg, 0.931 mmol), O-TBS-hydroxylamine (137 mg, 0.931 mmol), and CH₂Cl₂ (1 mL). Purification: EtOAc:hexanes = 1:20. Yield: 120 mg, 47%. ^1H NMR (300 MHz, CDCl₃) δ 1.93 (s, 3H), 1.85-1.40 (m, 8H), 0.76 (s, 9H), 0.00 (s, 6H); LRMS-ES+ m/z (relative intensity) 248 (MH⁺, 30).

(E)-1-Chlorocyclohexanecarboxaldehyde O-(tert-Butyldimethylsilyl) Oxime (177). The title compound was obtained using the above general experimental procedure with the following quantities: 1-chlorocyclohexanecarboxaldehyde (136 mg, 0.931 mmol), O-TBS-
hydroxylamine (137 mg, 0.931 mmol), and CH₂Cl₂ (1 mL). Purification: EtOAc:hexanes = 1:15. Yield: 120 mg, 47%. ¹H NMR (300 MHz, CDCl₃) δ 7.36 (s, 1H), 1.85-1.40 (m, 10H), 0.77 (s, 9H), -0.01 (s, 6H); LRMS-ES+ m/z (relative intensity) 276 (MH⁺, 15).

![2-Chloro-3-phenylpropanal O-(tert-Butyldimethylsilyl) Oxime (178).](image)

2-Chloro-3-phenylpropanal O-(tert-Butyldimethylsilyl) Oxime (178). The title compound was obtained using the above general experimental procedure with the following quantities: 2-chloro-3-phenylpropanal (1.0 g, 5.93 mmol), O-TBS-hydroxylamine (1.0 g, 6.52 mmol), and CH₂Cl₂ (10 mL). Purification: EtOAc:hexanes = 1:15. Yield: 1.24 g, 70% (~ 2:1 mixture of oxime isomers). ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.08 (m, 6H), 5.30 (m, 0.33H) 4.59 (J = 7.2 Hz, q, 0.67H), 3.12-3.02 (m, 2H), 0.77-0.75 (m, 9H), 0.05-0.00 (m, 6H).

![1-Chloro-4-phenylbutan-2-one O-(tert-Butyldimethylsilyl) Oxime (179).](image)

1-Chloro-4-phenylbutan-2-one O-(tert-Butyldimethylsilyl) Oxime (179). The title compound was obtained using the above general experimental procedure with the following quantities: 1-chloro-4-phenylbutan-2-one⁶⁹ (80 mg, 0.476 mmol), O-TBS-hydroxylamine (81 mg, 0.524 mmol) and CH₂Cl₂ (1 mL). Purification: EtOAc:hexanes = 1:20. Yield: 81 mg, 60% (~ 2:1 mixture of oxime isomers). ¹H NMR (300 MHz, CDCl₃) δ 7.17-7.02 (m, 5H), 4.12 (s, 1.3H), 3.83 (s, 0.7H), 2.77-2.54 (m, 4H), 0.81 (s, 3H), 0.77 (s, 6H), 0.04 (s, 2H), -0.01 (s, 4H); LRMS-ES+ m/z (relative intensity) 312 (MH⁺, 25).
General Procedure for Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes.

To a solution of ester derivative 182 in THF at -78 °C was added KHMDS. The resulting solution was stirred at -78 °C for 45 min. The O-TBS-oxime 174 - 179 dissolved in THF was added slowly dropwise, followed by the slow addition of TBAF in THF. The resulting solution was immediately transferred to a 0 °C ice bath and stirred for an additional 2 h. Saturated NH₄Cl was added and the mixture was extracted with EtOAc. The combined organics were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes to give the conjugate addition products 183.

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)acetate (Table 2.1, entry 1).

The title compound was obtained using the above general experimental procedure with the following quantities: diethyl malonate (74 mg, 0.458 mmol), KHMDS (0.5 M in toluene, 0.46 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes=1:3. Yield: 98 mg, 95%. ¹H NMR (300 MHz, CDCl₃) δ 8.09 (br s, 1H), 4.22-4.11 (m, 4H), 3.69 (J = 10.2 Hz, d, 1H), 3.20-3.16 (m, 1H),
3.01 (J = 10.6, 4.0 Hz, td, 1H), 1.93-1.78 (m, 4H), 1.60-1.42 (m, 3H), 1.28-1.20 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.1, 168.7, 160.4, 61.83, 61.82, 53.8, 42.6, 31.2, 26.3, 25.2, 24.7, 14.5, 14.1; LRMS-ES+ $m/z$ (relative intensity) 272 (MH$^+$, 100).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)-2-methylacetate (Table 2.1, entry 2). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-methylmalonate (80 mg, 0.458 mmol), KHMD$_3$ (0.5 M in toluene, 0.92 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF, 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:5. Yield: 92 mg, 84%.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54 (br s, 1H), 4.13-4.00 (m, 4H), 3.30-3.25 (m, 1H), 3.09-3.01 (m, 1H), 1.85-1.72 (m 3H), 1.59-1.26 (m, 7H), 1.18-1.08 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.9, 171.8, 158.9, 61.8, 61.7, 56.1, 47.5, 30.2, 26.4, 26.3, 25.1, 17.0, 14.4, 14.3; LRMS-ES+ $m/z$ (relative intensity) 286 (MH$^+$, 80).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)-2-ethylacetate (Table 2.1, Entry 3). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-ethylmalonate (86 mg, 0.458 mmol), KHMD$_3$ (0.5 M in toluene, 0.92 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF, 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:5. Yield: 103 mg,
69%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (br s, 1H), 4.12-3.99 (m, 4H), 3.20 ($J = 13.5, 4.0$ Hz, dt, 1H), 2.74 ($J = 11.4, 3.9$ Hz, dd, 1H), 2.16-2.07 (m, 1H), 1.95-1.30 (m, 8H), 1.19-1.13 (m, 6H), 0.84 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.8, 171.7, 159.0, 61.3, 61.1, 59.5, 48.6, 31.4, 28.1, 26.70, 26.69, 25.4, 14.44, 14.35, 10.3; LRMS-ES+ $m/z$ (relative intensity) 300 (MH$^+$, 50).

(E)- and (Z)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-nitroacetate (Table 2.1, entry 4). The title compound was obtained using the above general experimental procedure with the following quantities: ethyl 2-nitroacetate (61 mg, 0.458 mmol), KHMDS (0.5 M in toluene, 0.93 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:8. Yield: 53 mg, 57% (~ 1:1 mixture of oxime isomers). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.00 (br s, 1H), 5.38 ($J = 9.9$ Hz, d, 0.5H), 5.34 ($J = 9.8$ Hz, d, 0.5H), 4.30-4.15 (m, 2H), 3.31-3.13 (m, 2H), 1.86-1.71 (m, 4H), 1.48-1.17 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.7, 163.7, 159.0, 158.4, 90.0, 88.0, 63.4, 63.3, 43.3, 43.1, 29.6, 29.2, 25.94, 25.88, 25.4, 25.1, 24.7, 14.2; LRMS-ES+ $m/z$ (relative intensity) 245 (MH$^+$, 75).
**Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-3-oxobutanoate (Table 2.1, entry 5).** The title compound was obtained using the above general experimental procedure with the following quantities: ethyl 3-oxobutanoate (60 mg, 0.458 mmol), KHMD (0.5 M in toluene, 0.93 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF, 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:3. Yield: 65 mg, 71% (~ complex mixture of diastereomers and/or oxime isomers). 1H NMR (300 MHz, CDCl3) δ 4.58-4.25 (m, 2H), 3.00-2.71 (m, 3H), 2.45-2.03 (m, 4H), 1.82-1.31 (m, 9H); LRMS-ES+ m/z (relative intensity) 242 (MH+, 75).

**E**-Methyl 2-(Phenylsulfonyl)-2-(2-(hydroxyimino)cyclohexyl)acetate (Table 2.1, entry 6). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-(phenylsulfonyl)acetate (98 mg, 0.458 mmol), KHMDS (0.5 M in toluene, 0.93 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 2:3. Yield: 117 mg, 95% (~ 2:1 mixture of oxime isomers). 1H NMR (300 MHz, CDCl3) δ 8.00 (br s, 1H), 7.95-7.85 (m, 2H), 7.69-7.64 (m, 1H), 7.57-7.51 (m, 2H), 4.62 (J = 6.5 Hz, d, 0.33H), 4.29 (J = 11.0 Hz, d, 0.67H), 3.60 (s, 1H), 3.27 (s, 2H), 3.23-3.11 (m, 2H), 2.85-2.63 (m, 1H), 2.20-2.15 (m, 1H), 1.89-1.49 (m, 5H); 13C NMR (75 MHz, CDCl3) δ 167.0, 165.9, 160.3, 159.2, 138.8, 138.4, 134.7,
(E)- and (Z)-Methyl 2-(2-(Hydroxyimino)cyclohexyl)-2-phenylacetate (Table 2.1, entry 7). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-phenylacetate (69 mg, 0.46 mmol), KHMDS (0.5 M in toluene, 0.46 mL, 0.458 mmol), O-TBS-oxime 174 (100 mg, 0.382 mmol), TBAF (1 M in THF 0.46 mL, 0.458 mmol), and THF (1 mL). Yield: 79mg, 79% (3:1 mixture of oxime isomers).^1H NMR (300 MHz, CDCl₃) δ 8.09 (br s, 1H), 7.40-7.26 (m, 5H), 4.09 (J = 10.6 Hz, d, 0.25H), 3.78 (J = 11.3 Hz, d, 0.75H), 3.68 (s, 1H), 3.59 (s, 2H), 3.30 (J = 12.4, 3.0 Hz, dt, 0.75H), 3.16-3.09 (m, 0.25H), 3.00 (J = 11.1, 4.0 Hz, td, 0.75H), 2.62-2.57 (m, 0.25H), 1.99-1.39 (m, 7H); ^13C NMR (75 MHz, CDCl₃) δ 174.4, 173.8, 161.9, 160.1, 137.6, 137.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0, 127.8, 52.5, 52.2, 45.8, 45.1, 31.5, 30.9, 26.7, 26.5, 25.4, 25.0, 23.4, 23.2; LRMS-ES+ m/z (relative intensity) 262 (MH+, 80).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)acetate (Table 2.1, entry 9). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl malonate (130 mg, 0.810 mmol), KHMDS (0.5 M in toluene, 1.62 mL, 0.810 mmol), O-TBS-oxime 175 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.48 mL, 0.485 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes=1:3. Yield: 88 mg, 85%. ^1H NMR
(300 MHz, CDCl$_3$) $\delta$ 8.15 (br s, 1H), 4.18-4.01 (m, 4H), 3.53 ($J$ = 8.0 Hz, d, 1H), 3.15-3.09 (m, 1H), 2.55-2.50 (m, 1H), 2.34-2.28 (m, 1H), 1.95-1.79 (m, 2H), 1.64-1.55 (m, 2H), 1.20-1.14 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.8, 168.5, 166.2, 62.0, 61.8, 53.8, 42.7, 29.5, 27.5, 22.7, 14.44, 14.37; LRMS-ES+ m/z (relative intensity) 258 (MH$^+$, 90).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)-2-methylacetate (Table 2.1, entry 10). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-methylmalonate (85 mg, 0.486 mmol), KHMDS (0.5 M in toluene, 0.97 mL, 0.486 mmol), O-TBS-oxime 175 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.49 mL, 0.486 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:3. Yield: 79 mg, 72%.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 (br s, 1H), 4.13-4.00 (m, 4H), 3.29-3.22 (m, 1H), 2.65-2.55 (m, 1H), 2.23-2.14 (m, 1H), 1.93-1.85 (m, 1H), 1.79-1.73 (m, 1H), 1.54-1.42 (m, 2H), 1.34 (s, 3H), 1.15-1.05 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.7, 171.5, 165.4, 61.9, 61.8, 56.2, 47.5, 28.9, 28.4, 22.6, 17.6, 14.4, 14.3; LRMS-ES+ m/z (relative intensity) 272 (MH$^+$, 90).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)-2-ethylacetate (Table 2.1, entry 11). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-ethylmalonate (91 mg, 0.486 mmol), KHMDS (0.5 M in toluene, 0.97 mL, 0.486 mmol), O-TBS-oxime 175 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.49 mL, 0.486 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:4. Yield: 84 mg, 73%.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 8.04\) (br s, 1H), 4.13-3.99 (m, 4H), 3.10-3.05 (m, 1H), 2.62 \((J = 18.5, 8.1\) Hz, dd, 1H), 2.20-2.14 (m, 1H), 2.00-1.88 (m, 3H), 1.74-1.64 (m, 2H), 1.50-1.38 (m, 1H), 1.17-1.12 (m, 6H), 0.86 (t, \(J = 7.4\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 171.23, 171.15, 61.5, 61.4, 60.7, 47.2, 29.1, 28.5, 28.3, 22.7, 14.4, 10.2\); LRMS-ES+ \(m/z\) (relative intensity) 286 (MH\(^+\), 70).

(E)- and (Z)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-nitroacetate (Table 2.1, entry 12). The title compound was obtained using the above general experimental procedure with the following quantities: ethyl 2-nitroacetate (65 mg, 0.486 mmol), KHMDMS (0.5 M in toluene, 0.97 mL, 0.486 mmol), \(O\)-TBS-oxime 175 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.49 mL, 0.486 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:4. Yield: 37 mg, 40\% (~ 1:5 mixture of oxime isomers). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 6.27–6.17\) (m, 0.2H), 5.37-5.27 (m, 1H), 4.27-4.18 (m, 2.4H), 3.48-3.42 (m, 1.2H), 2.59-2.01 (m, 2.4H), 1.98-1.63 (m, 5.4H), 1.28-1.19 (m, 4.2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 164.3, 164.1, 164.0, 163.8, 88.7, 88.5, 63.6, 63.5, 43.8, 43.6, 28.4, 28.3, 27.6, 27.4, 22.7, 22.6, 14.3, 14.3\); LRMS-ES+ \(m/z\) (relative intensity) 231 (MH\(^+\), 70).

(E)- and (Z)-Methyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(phenylsulfonyl) Acetate (Table 2.1, entry 14). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-(phenylsulfonyle)acetate (104 mg, 0.458 mmol),
KHMD (0.5 M in toluene, 0.92 mL, 0.458 mmol), O-TBS-oxime 175 (100 mg, 0.402 mmol), TBAF (1 M in THF, 0.46 mL, 0.458 mmol), and THF (1 mL). Purification: EtOAc:hexanes:CHCl$_2$ = 1:2:1. Yield: 102 mg, 82% (~1:1 mixture of oxime isomers). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.88-7.45 (m, 6H), 4.51 ($J = 4.1$ Hz, d, 0.5H), 3.97 ($J = 10.3$ Hz, d, 0.5H), 3.44 (s, 1.5H), 3.33 (s, 1.5H), 3.29-3.23 (m, 1H), 2.58-2.16 (m, 3H), 1.91-1.51 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.6, 166.5, 165.8, 165.2, 139.1, 138.2, 134.7, 134.6, 129.51, 129.46, 129.2, 73.1, 70.0, 53.2, 53.0, 41.9, 40.9, 30.7, 28.0, 27.2, 26.7, 23.2, 22.9.

(E)- and (Z)-Methyl 2-(2-(Hydroxyimino)cyclopentyl)-2-phenylacetate (Table 2.1, entry 15). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-phenylacetate (73 mg, 0.486 mmol), KHMD (0.5 M in toluene, 0.97 mL, 0.486 mmol), O-TBS-oxime 175 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.49 mL, 0.486 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:3. Yield: 48 mg, 40%, ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.05 (br s, 1H), 7.24-7.14 (m, 5H), 3.88 ($J = 7.4$ Hz, d, 0.33H), 3.57 (s, 2H), 3.56 (s, 1H), 3.47 ($J = 10.4$ Hz, d, 0.67H), 3.45-3.27 (m, 0.67H), 3.05-2.95 (m, 0.33H), 2.56-2.47 (m, 1H), 2.40-2.30 (m, 1H), 1.81-1.60 (m, 2H), 1.50-1.44 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.2, 173.4, 167.2, 167.1, 137.84, 137.81, 129.1, 129.0, 128.7, 127.9, 127.7, 54.3, 52.8, 52.6, 52.4, 46.8, 46.3, 30.6, 29.6, 27.9, 27.6, 22.6, 22.4; LRMS-ES$^+$ m/z (relative intensity) 248 (MH$^+$, 50).
4-(Phenylsulfonyl)-5,6,7,8-tetrahydro-4aH-benzo[c][1,2]oxazin-3-amine (186). The title compound was obtained using the above general experimental procedure with the following quantities: 2-(phenylsulfonyl)acetonitrile (88 mg, 0.486 mmol), KHMDS (0.5 M in toluene, 0.97 mL, 0.486 mmol), O-TBS-oxime 174 (100 mg, 0.405 mmol), TBAF (1 M in THF, 0.49 mL, 0.486 mmol), and THF (1 mL). Yield: 54 mg. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.90-7.83\) (m, 2H), 7.55-7.43 (m, 3H), 4.90 (br s, 2H), 2.41-2.06 (m, 4 H), 1.67-1.59 (m, 5H); LRMS-ES+ \(m/z\) (relative intensity) 293 (MH\(^+\), 60).

\(E\)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)malonate (Table 2.2, entry 1). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl malonate (116 mg, 0.726 mmol), KHMDS (0.5 M in toluene, 1.45 mL, 0.726 mmol), O-TBS-oxime 177 (100 mg, 0.363 mmol), TBAF (1 M in THF, 0.44 mL, 0.436 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes = 1:3. Yield: 66 mg, 64%. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 8.01\) (br s, 1H), 7.63 (s, 1H), 4.15-4.07 (m, 4H), 3.51 (s, 1H), 1.99-1.82 (m, 2H), 1.58-1.40 (m, 8H), 1.19 (t, \(J = 7.1\) Hz, 6H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 167.7, 155.8, 61.7, 60.6, 42.1, 33.2, 26.0, 22.3, 14.5\); LRMS-ES+ \(m/z\) (relative intensity) 286 (MH\(^+\), 60).
(E)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-methylmalonate (Table 2.2, entry 2). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-methylmalonate (126 mg, 0.726 mmol), KHMDS (0.5 M in toluene, 1.45 mL, 0.726 mmol), O-TBS-oxime 177 (100 mg, 0.363 mmol), TBAF (1 M in THF, 0.44 mL, 0.436 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes = 1:5. Yield: 79 mg, 74%. 1H NMR (300 MHz, CDCl3) δ 7.92 (s, 1H), 7.43 (s, 1H), 4.07 (J = 7.1 Hz, q, 4H), 1.99 (J = 12.4 Hz, d, 2H), 1.53-1.44 (m, 6H), 1.34-1.23 (m, 5H), 1.13 (J = 7.1 Hz, t, 6H); 13C NMR (75 MHz, CDCl3) δ 171.3, 158.5, 61.8, 61.6, 45.4, 30.1, 26.1, 22.9, 18.7, 14.4; LRMS-ES+ m/z (relative intensity) 300 (MH+, 60)

(E)- and (Z)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-ethylmalonate (Table 2.2, entry 3). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-ethylmalonate (137 mg, 0.726 mmol), KHMDS (0.5 M in toluene, 1.45 mL, 0.726 mmol), O-TBS-oxime 177 (100 mg, 0.363 mmol), TBAF (1 M in THF 0.44 mL, 0.436 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes = 1:5. Yield: 64 mg, 56% (~ 3:1 mixture of oxime isomers). 1H NMR (300 MHz, CDCl3) δ 7.78 (s, 0.75H), 7.72 (s, 0.25H), 7.37 (s, 0.75H), 7.17 (s, 0.25H), 4.18-4.06 (m, 4H), 1.96-1.80 (m, 4H), 1.57-1.38 (m, 8H), 1.21-1.17 (m, 6H), 0.82-0.76 (m, 3H); LRMS-ES+ m/z (relative intensity) 314 (MH+, 60).
(E)-Methyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-phenylacetate (Table 2.1, entry 7). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-phenylacetate (109 mg, 0.726 mmol), KHMDS (0.5 M in toluene, 1.45 mL, 0.726 mmol), O-TBS-oxime 177 (100 mg, 0.363 mmol), TBAF (1 M in THF, 0.44 mL, 0.436 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes = 1:5. Yield: 62 mg, 63%. 1H NMR (300 MHz, CDCl3) δ 7.99 (s, 1H), 7.42 (s, 1H), 7.24-7.13 (m, 5H), 3.59 (s, 1H), 3.55 (s, 3H), 1.80-1.20 (m, 10H); 13C NMR (75 MHz, CDCl3) δ 170.9, 153.5, 132.7, 128.6, 126.4, 126.1, 59.7, 50.3, 41.5, 32.2, 30.7, 24.2, 20.8, 20.3; LRMS-ES+ m/z (relative intensity) 276 (MH+, 40).

(E)-Diethyl 2-(1-(Hydroxyimino)-3-phenylpropan-2-yl)malonate (Table 2.2, entry 8). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl malonate (130 mg, 0.810 mmol), KHMDS (0.5 M in toluene, 0.81 mL, 0.404 mmol), O-TBS-oxime 178 (100 mg, 0.337 mmol), TBAF (1 M in THF 0.41 mL, 0.404 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:5. Yield: 53 mg, 51%. 1H NMR (300 MHz, CDCl3) δ 7.91 (br s, 1H), 7.54-7.51 (m, 1H), 7.34-7.18 (m, 5H), 4.26-4.19 (m, 4H), 3.59 (d, J = 7.1 Hz, 1H), 3.40-3.35 (m, 1H), 2.93-2.89 (m, 2H), 1.32-1.26 (m, 6H); 13C NMR (90 MHz, CDCl3) δ 168.1, 167.8, 151.4, 137.9, 129.3, 129.2, 128.62, 128.56, 126.74, 126.70, 61.8, 61.7, 53.7, 41.2, 36.7, 14.1.
(E)-Diethyl 2-(1-(Hydroximino)-3-phenylpropan-2-yl)-2-methylmalonate (Table 2.2, entry 9). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-methylmalonate (70 mg, 0.404 mmol), KHMDS (0.5 M in toluene, 0.81 mL, 0.404 mmol), O-TBS-oxime 178 (100 mg, 0.337 mmol), TBAF (1 M in THF 0.41 mL, 0.404 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:5. Yield: 74 mg, 69%.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.76 (br s, 1H), 7.24-7.04 (m, 6H), 4.15-3.99 (m, 4H), 3.14 ($J$ = 10.9, 7.9, 3.0 Hz, ddd, 1H), 2.85-2.62 (m, 2H), 1.40 (s, 3H), 1.19-1.01 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.3, 171.2, 150.9, 139.5, 129.6, 129.0, 128.9, 128.5, 126.8, 126.7, 126.1, 62.14, 62.10, 57.2, 47.1, 35.4, 18.6, 14.5, 14.4; LRMS-ES $m/z$ (relative intensity) 322 (MH$^+$, 60).

(E)-Diethyl 2-(1-(Hydroximino)-3-phenylpropan-2-yl)-2-ethylmalonate (Table 2.2, entry 10). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-ethylmalonate (127 mg, 0.673 mmol), KHMDS (0.5 M in toluene, 1.35 mL, 0.673 mmol), O-TBS-oxime 178 (100 mg, 0.337 mmol), TBAF (1 M in THF 0.41 mL, 0.404 mmol), and THF (1.5 mL). Purification: EtOAc:hexanes = 1:5. Yield: 65 mg, 58%.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.67 (br s, 1H), 7.29-7.09 (m, 6H), 4.25-4.16 (m, 4H), 3.14-3.03 (m, 2H), 2.55-2.46 (m, 1H), 2.02-1.84 (m, 2H), 1.32-1.17 (m, 6H), 0.83 (t, $J$ = 7.4 Hz, 3H);
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.9, 170.8, 151.0, 139.7, 129.7, 129.0, 128.8, 126.7, 61.8, 61.1, 45.6, 36.1, 27.9, 14.6, 9.0; LRMS-ES+ \(m/z\) (relative intensity) 336 (MH\(^+\), 40).

\((E)\)- and \((Z)\)-Methyl 3-Benzyl-4-(hydroxyimino)-2-phenylbutanoate (Table 2.2, entry 14). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-phenylacetate (61 mg, 0.404 mmol), KHMDS (0.5 M in toluene, 0.81 mL, 0.404 mmol), O-TBS-oxime 178 (100 mg, 0.337 mmol), TBAF (1 M in THF, 0.41 mL, 0.404 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:3. Yield: 68 mg, 68% (~ 2:1 mixture of oxime isomers). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.91 (br s, 0.66H), 7.65 (br s, 0.33H), 7.25-6.84 (m, 11H), 3.60-3.55 (m, 1H), 3.49 (s, 1H), 3.43 (s, 2H), 3.25-3.16 (m, 1H), 2.71-2.49 (m, 2H), 2.36-2.24 (m, 1H); LRMS-ES+ \(m/z\) (relative intensity) 298 (MH\(^+\), 75).

\((E)\)-5,5-Bis(ethyl ester)-1-phenylhexan-3-one Oxime (Table 2.3, entry 1). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl malonate (62 mg, 0.386 mmol), KHMDS (0.5 M in toluene, 0.77 mL, 0.386 mmol), O-TBS-oxime 179 (100 mg, 0.321 mmol), TBAF (1 M in THF, 0.39 mL, 0.386 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:5. Yield: 30 mg, 30%. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.92-7.01 (m, 5H), 4.13-4.03 (m, 4H), 3.67 \((J = 7.5 \text{ Hz}, \text{t}, 2\text{H})\), 2.77-2.51 (m, 6H), 1.29-1.09 (m, 6H).
(E)-5,5-Bis(ethyl ester)-1-phenylhexan-3-one Oxime (Table 2.3, entry 2). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-methylmalonate (67 mg, 0.386 mmol), KHMDS (0.5 M in toluene, 0.77 mL, 0.386 mmol), O-TBS-oxime 179 (100 mg, 0.321 mmol), TBAF (1 M in THF 0.39 mL, 0.386 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:4. Yield: 95 mg, 88%. ¹H NMR (300 MHz, CDCl₃) δ 8.81 (br s, 1H), 7.19-7.05 (m, 5H), 4.17-3.94 (m, 4H), 2.73-2.62 (m, 4H), 2.46 (J = 8.8, 5.6 Hz, dd, 2H), 1.35 (s, 3H), 1.16-1.08 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 172.3, 157.1, 141.6, 128.8, 128.7, 126.5, 62.1, 61.9, 52.7, 39.6, 31.8, 31.2, 25.1, 20.5, 14.4; LRMS-ES+ m/z (relative intensity) 336 (MH⁺, 75).

(E)-5,5-Bis(ethyl ester)-1-phenylheptan-3-one Oxime (Table 2.3, entry 3). The title compound was obtained using the above general experimental procedure with the following quantities: diethyl 2-ethylmalonate (73 mg, 0.386 mmol), KHMDS (0.5 M in toluene, 0.77 mL, 0.386 mmol), O-TBS-oxime 179 (100 mg, 0.321 mmol), TBAF (1 M in THF 0.39 mL, 0.386 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:4. Yield: 80 mg, 71%. ¹H NMR (300 MHz, CDCl₃) δ 8.01 (br s, 1H), 7.21-7.07 (m, 5H), 4.10-4.01 (m, 4H), 2.78-2.70 (m, 4H), 2.47 (J = 8.7, 5.5 Hz, dd, 2H), 1.95 (J = 7.6 Hz, q, 2H), 1.16-1.10 (m, 6H), 0.70 (J = 7.6 Hz, t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 157.3, 141.6, 128.9, 128.7, 126.5, 61.8, 57.0, 36.1, 31.9, 31.4, 31.1, 25.8, 14.6, 14.4, 9.1; LRMS-ES+ m/z (relative intensity) 350 (MH⁺, 80).
(E)-Methyl 4-(Hydroxyimino)-2,6-diphenylhexanoate (Table 2.3, entry 4). The title compound was obtained using the above general experimental procedure with the following quantities: methyl 2-phenylacetate (58 mg, 0.386 mmol), KHMDS (0.5 M in toluene, 0.77 mL, 0.386 mmol), O-TBS-oxime 179 (100 mg, 0.321 mmol), TBAF (1 M in THF 0.39 mL, 0.386 mmol), and THF (1 mL). Purification: EtOAc:hexanes = 1:3. Yield: 75 mg, 75%. ¹H NMR (300 MHz, CDCl₃) δ 8.20 (br s, 1H), 7.22-7.09 (m, 10H), 3.88 (J = 10.2, 4.8 Hz, dd, 1H), 3.55 (s, 3H), 2.95 (J = 16.6, 10.2 Hz, dd, 1H), 2.72 (J = 10.6, 6.8 Hz, dd, 2H), 2.52 (J = 9.2, 5.9 Hz, dd, 2H), 2.36 (J = 16.6, 4.8 Hz, dd, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 174.2, 159.1, 141.6, 139.0, 129.2, 128.9, 128.7, 128.2, 128.0, 126.6, 52.7, 48.3, 38.6, 31.8, 31.1; LRMS-ES+ m/z (relative intensity) 312 (MH⁺, 50).

Ethyl 4-Methoxycyclohex-3-ene-carboxylate (191).²⁴ To a pressure flask containing 2-methoxy-1,3-butadiene²³ (1.46 g, 17.4 mmol) in toluene (10 mL) was added ethyl acrylate (2.04 mL, 19.2 mmol). The flask was sealed tightly and the mixture was stirred for 18 h at 145 °C. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (1:15 EtOAc:hexanes) to afford the title compound 191 as a clear oil (1.74 g, 54% yield). ¹H NMR (300 MHz, CDCl₃) δ 4.28 (J = 3.9 Hz, t, 1H), 4.08 (J = 7.1 Hz, q, 2H), 3.44 (s, 3H), 2.47-2.40 (m, 1H), 2.27-2.23 (m, 2H), 2.10-2.05 (m, 2H), 2.00-1.95 (m, 1H), 1.78-1.64 (m, 1H), 1.21 (J = 7.1 Hz, t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 153.9, 90.5, 59.5, 53.2, 38.7, 26.0, 25.1, 24.4, 13.4.
(4-Methoxycyclohex-3-enyl)methanol (192). To a stirred suspension of LiAlH₄ (124 mg, 3.26 mmol) in THF (8 mL) at 0 °C was added ester 191 (290 mg, 1.63 mmol) in THF (2 mL) dropwise. The mixture was stirred at rt for 2 h. The reaction was quenched by slow addition of a 5:1 mixture of THF:H₂O at 0 °C, followed by addition of 1 M NaOH with stirring. The solids were filtered off and washed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title compound 192 as a clear oil (158 mg, 70% yield). ^1H NMR (300 MHz, CDCl₃) δ 4.53 (br s, 1H), 3.51-3.46 (m, 2H), 3.44 (s, 3H), 2.14-2.01 (m, 3H), 1.82-1.66 (m, 3H), 1.50 (s, 1H), 1.33-1.26 (m, 1H); ^13C NMR (75 MHz, CDCl₃) δ 153.9, 90.4, 66.0, 52.6, 35.2, 25.6, 25.0, 24.0.

Diethyl 2-((4-Methoxycyclohex-3-enyl)methyl)malonate (194). To a solution of alcohol 192 (465 mg, 3.27 mmol) in pyridine (8 mL) was added tosyl chloride (1.25 g, 6.54 mmol). The mixture was stirred at rt for 18 h, and washed with saturated NaHCO₃. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:6 EtOAc:hexanes) to afford the corresponding tosylate as a clear oil (848 mg, 88% yield). ^1H NMR (300 MHz, CDCl₃) δ 7.72 (J = 8.3 Hz, d, 2H), 7.28 (J = 8.3 Hz, d, 2H), 4.434 (br s, 1H), 3.84 (J = 6.8 Hz, d, 2H), 3.40 (s, 3H), 2.34 (s, 3H), 2.11-1.66 (m, 7H).
Diethyl malonate (0.8 mL, 5.32 mmol) was added to a stirred solution of sodium hydride (127 mg, 5.32 mmol, 60% dispersion in mineral oil) in DMF (8 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. A solution of tosylate 193 (787 mg, 2.66 mmol) in DMF (4 mL) and NaI (159 mg, 1.06 mmol) were added at rt. The resulting mixture was heated at 65 °C for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:15 EtOAc:hexanes) to afford the title compound 194 as a clear oil (381 mg, 51% yield).

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \delta 4.47 \text{(br s, 1H), 4.12 \text{(} J = 7.2 \text{ Hz, q, 4H), 3.41 \text{(s, 3H), 3.38 \text{(} J = 7.8 \text{ Hz, t, 1H), 2.14-1.97 \text{(m, 3H), 1.85-1.62 \text{(m, 4H), 1.43-1.22 \text{(m, 2H), 1.19 \text{(} J = 7.1 \text{ Hz, t, 6H); 13C NMR (75 MHz, CDCl}_3\text{)} \delta 170.0, 169.9, 155.5, 92.2, 61.7, 54.3, 50.3, 35.0, 32.1, 30.0, 29.0, 27.6, 14.5.} \]

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\[ \text{N-(3-Chloro-4-oxocyclohexylmethyl)-4-methylbenzenesulfonamide (156). To a solution of sulfonamide 194 (950 mg, 3.22 mmol) in THF:H}_2\text{O (4:3, 35 mL) was added NaOAc (26 mg, 0.32 mmol) and N-chlorosuccinimide (475 mg, 3.54 mmol). The reaction mixture was stirred at rt for 1 h and then was extracted with EtOAc. The combined organic extracts were dried over Na}_2\text{SO}_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford the title compound 156 as two diastereomers (clear oil, 935 mg, 92%). A sample of the mixtures was separated by chromatography for characterization purposes. Less polar major diastereomer of 156: 1H NMR (300 MHz, CDCl}_3\text{)} \delta 7.68 \text{(} J = 8.3 \text{ Hz, d, 2H) 7.25 \text{(} J = 7.9 \text{ Hz, d, 2H), 5.35 \text{(} J = 6.6Hz, t, 1H), 4.14-4.11 \text{(m, 1H), 2.86-2.76 \text{(m, 3H), 2.36 \text{(s, 3H), 2.25-2.16 \text{(m, 3H), 1.98-1.93 \text{(m, 1H), 1.82-}} \]

\[ \text{}\]
1.74 (m, 1H), 1.35 -1.13 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 204.6, 144.2, 137.1, 130.3, 127.4, 59.7, 47.5, 38.6, 35.5, 31.5, 30.1, 22.0. More polar minor diastereomer of 156: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.68 ($J = 10$ Hz, d, 2H) 7.26 ($J = 8.2$ Hz, d, 2H), 5.38 ($J = 6.6$ Hz, t, 1H), 4.44-4.39 (m, 1H), 2.82-2.77 (m, 2H), 2.51-2.48 (m, 1H), 2.36 (s, 3H), 2.33-2.00 (m, 3H), 2.02-1.98 (m, 1H), 1.60-1.48 (m, 1H), 1.36-1.28 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.3, 144.3, 137.0, 130.3, 127.4, 63.2, 47.6, 42.1, 39.9, 37.8, 30.7, 22.0. Spectral data were consistent with literature values.$^{59}$

![Diagram](attachment:image.png)

**Diethyl 2-(((4-((tert-Butyldimethylsilyl)oxy)imino)-3-chlorocyclohexyl) Methyl) malonate (157).** To a solution of α-chloroketones 156 (65 mg, 0.21 mmol) in CH$_2$Cl$_2$ (5 mL) were added $O$-(t-butyldimethylsilyl)-hydroxylamine (35 mg, 0.24 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 72 h and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give the residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 157 as a clear oil containing a mixture of two oxime isomers in a 1.5:1 ratio (64 mg, 70%). $^1$H NMR (300 MHz, CDCl$_3$) δ5.62 (br s, 0.4H) 4.73 (br s, 0.6H), 4.15 ($J = 7.2$ Hz, q, 4H), 3.38 ($J = 7.8$ Hz, t, 1H), 3.31-3.16 (m, 0.6H), 2.58-2.48 (m, 0.4H), 2.30-1.78 (m, 6H), 1.60-1.47 (m, 2H), 1.24 ($J = 7.2$ Hz, t, 6H), 1.07-0.99 (m, 1H), 0.94-0.94 (m, 9H), 0.14-0.12 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.8, 169.7, 161.6, 160.3, 62.0, 59.3, 50.0, 47.3, 41.4, 40.2, 34.9, 32.3, 31.5, 30.1, 29.7, 29.7, 27.2, 26.4, 20.1, 18.6, 18.6, 14.5, -4.9. Spectral data were consistent with literature values.$^{59}$
4-Hydroxyiminobicyclo[3.2.1]octane-6,6-dicarboxylic Acid Diethyl Ester (159). To a stirred solution of oxime 157 (60 mg, 0.14 mmol) in THF (2 mL) at -78 °C was added KHMDS (0.5 M in toluene, 0.42 mL, 0.21 mmol) dropwise. After stirring the mixture for 1 h at -78 °C, TBAF (1 M in THF, 0.21 mL, 0.21 mmol) was added and reaction mixture was stirred at 0 °C for 3 h. Saturated NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 159 as a colorless crystalline solid (30 mg, 77% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.54 (br s, 1H), 4.20-4.00 (m, 4H), 3.39 (J = 4.4 Hz, d, 1H), 3.00-2.91 (m, 1H), 2.54-2.48 (m, 1H), 2.35 (s, 1H), 2.22-2.15 (m, 1H), 2.08-1.90 (m, 2H), 1.73-1.50 (m, 3H), 1.19-1.10 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 172.0, 170.2, 160.0, 63.5, 62.1, 62.0, 49.3, 38.3, 36.3, 34.4, 30.4, 18.4, 14.5, 14.4. Spectral data were consistent with literature values.³⁹

Methyl 3-(4-Methoxycyclohex-3-enyl)-2-(phenylsulfonyl)propanoate (196). To a solution of alcohol 191 (230 mg, 1.62 mmol) in pyridine (10 mL) was added tosyl chloride (617 mg, 3.24 mmol). The mixture was stirred at rt for 18 h and washed with saturated NaHCO₃. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give the tosylate 192 as a yellow oil. The compound was used for the next step without purification. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (J = 8.3 Hz, d, 2H), 7.28 (J = 8.3 Hz, d, 2H), 4.434 (br s, 1H), 3.84 (J = 6.8 Hz, d, 2H), 3.40 (s, 3H), 2.34 (s, 3H), 2.11-1.66 (m, 7H).
Methyl phenylsulfonylacetate (0.29 mL, 1.62 mmol) was added to a stirred solution of sodium hydride (77 mg, 1.94 mmol, 60% dispersion in mineral oil) in DMF (8 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. A solution of crude tosylate 192 in DMF (2 mL) and NaI (98 mg, 0.65 mmol) were added at rt. The resulting mixture was heated at 65 °C for 18 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3:0.01 EtOAc:hexanes:triethylamine) to afford the title compound 196 as a clear oil containing a mixture of diastereomers in a 1:1 ratio (290 mg, 53% yield for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.89-7.81 (m, 2H), 7.68-7.62 (m, 1H), 7.60-7.51 (m, 2H), 4.47 (br s, 1H), 4.08-3.98 (m, 1H), 3.61-3.61 (m, 3H), 3.46-3.42 (m, 3H), 2.12-1.95 (m, 6H), 1.94-1.66 (m, 4H), 1.661.21 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 165.9, 154.4, 154.2, 136.3, 136.2, 133.6, 128.6, 128.4, 90.9, 90.5, 68.6, 68.4, 53.3, 52.3, 52.3, 32.0, 31.2, 30.8, 30.2, 29.3, 28.6, 28.2, 27.0, 26.4, 26.2; HRMS-EI [M+H]⁺ calcd for C₁₇H₂₂O₅S, 339.1266; found, 339.1259.

Methyl 3-(3-Chloro-4-oxocyclohexyl)-2-(phenylsulfonyl)propanoate (197). To a solution of enol ether 196 (110 mg, 0.33 mmol) in THF:H₂O (4:3, 3 mL) was added NaOAc (29 mg, 0.36 mmol) and N-chlorosuccinimide (48 mg, 0.36 mmol). The reaction mixture was stirred at 0 °C for 5 h and then extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 197 as clear oil containing a complex diastereomer mixture (74 mg, 64%). ¹H NMR (300 MHz,
CDCl$_3$ $\delta$ 7.89-7.82 (m, 2H), 7.71-7.66 (m, 1H), 7.58-7.54 (m, 2H), 4.16 (br s, 1H), 3.98 ($J = $ 11.0, 4.2 Hz, dd, 1H), 3.65-5.60 (m, 3H), 3.13-2.84 (m, 1H), 2.29-2.12 (m, 3H), 2.07-1.97 (m, 3H), 1.89-1.75 (m, 1H), 1.48-1.30 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.4, 204.0, 203.9, 166.7, 166.6, 137.2, 137.1, 135.0, 129.7, 129.7, 129.6, 69.3, 69.2, 59.6, 59.3, 53.9, 53.7, 53.6, 41.3, 40.1, 35.7, 35.5, 32.9, 31.8, 31.7, 31.7, 31.3, 29.2, 29.1.

![Methyl 3-(4-((tert-Butyldimethylsilyl)oxy)imino)-3-chlorocyclohexyl)
2-(phenylsulfonyl)propanoate (198)](image)

Methyl 3-(4-((tert-Butyldimethylsilyl)oxy)imino)-3-chlorocyclohexyl)
2-(phenylsulfonyl)propanoate (198). To a solution of $\alpha$-chloroketones 197 (19 mg, 0.05 mmol) in CH$_2$Cl$_2$ (5 mL) were added O-(t-butyldimethylsilyl)-hydroxylamine (16 mg, 0.11 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 84 h and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give the residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford compound 198 as a clear oil containing a complex mixture of diastereomers including oxime geometric isomers (17 mg, 66%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.89-7.82 (m, 2H), 7.73-7.64 (m, 1H), 7.62-7.52 (m, 2H), 5.60-4.70 (m, 1H), 4.07-3.97 (m, 1H), 3.63-3.60 (m, 3H), 3.28-1.83 (m, 7H), 1.84-1.03 (m, 2H), 0.92-0.87 (m, 9H), 0.13-0.03 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$166.9, 166.8, 161.0, 159.7, 137.2, 134.8, 129.8, 129.7, 129.5, 69.3, 69.1, 59.0, 58.9, 53.6, 53.5, 47.0, 46.8, 41.9, 40.7, 32.7, 32.7, 32.6, 31.8, 30.8, 30.0, 29.7, 27.1, 26.4, 20.0, 19.8, 18.6, -4.9; HRMS-EI [M+H]$^+$ calcd for C$_{22}$H$_{34}$ClNO$_5$Si, 488.1694; found, 488.1691.
Methyl 4-(Hydroxyimino)-6-(phenylsulfonyl)bicyclo[3.2.1]octane-6- Carboxylate (200). To a stirred solution of oxime 198 (40 mg, 0.08 mmol) in THF (2 mL) at -78 °C was added KHMS (0.5 M in toluene, 0.24 mL, 0.12 mmol) dropwise. After stirring the mixture for 1 h at -78 °C, TBAF (1 M in THF, 0.13 mL, 0.12 mmol) was added and reaction mixture was stirred at 0 °C for 3 h. Saturated NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to afford the title compound 200 as a white solid (23 mg, 83% yield). "H NMR (300 MHz, CDCl₃) δ 7.71-7.67 (m, 2H), 7.56-7.50 (m, 1H), 7.43-7.38 (m, 2H), 3.40 (s, 3H), 3.38-3.29 (m, 1H), 2.97-2.87 (m, 2H), 2.58-2.39 (m, 3H), 1.63-1.42 (m, 4H), 1.21-1.04 (m, 1H); "C NMR (75 MHz, CDCl₃) δ168.0, 158.8, 137.0, 134.7, 130.4, 129.3, 83.0, 53.3, 49.6, 37.5, 35.0, 33.4, 30.5, 18.5; HRMS-EI [M+H]+ calcd for C₁₆H₁₉NO₅S, 338.1062; found, 338.1061.

Methyl 6-(Phenylsulfonyl)-4-((tosyloxy)imino)bicyclo[3.2.1]octane-6- Carboxylate (201). To a stirred mixture of triethylamine (0.02 mL, 0.11 mmol), tosyl chloride (20 mg, 0.11 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH₂Cl₂ (1 mL) was added a solution of oxime 200 (12 mg, 0.036 mmol) in CH₂Cl₂ (2 mL) at rt. The resulting mixture was stirred at rt for 2 h, and washed with saturated NaHCO₃. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a residue which was purified by
flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford compound 201 as a white solid (11 mg, 63%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.77-7.71 (m, 4H), 7.71-7.65 (m, 1H), 7.60-7.47 (m, 2H), 7.28-2.25(m, 2H), 3.61 ($J = 4.8$ Hz, d, 1H), 3.19 (s, 3H), 3.06-2.92 (m, 2H), 2.70-2.58 (m, 2H), 2.42 (s, 3H), 1.76-1.51 (m, 4H), 1.55-1.15 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.3, 166.2, 143.8, 135.5, 133.4, 131.6, 128.8, 128.4, 128.0, 81.1, 51.8, 47.2, 36.3, 33.0, 32.6, 29.2, 20.66, 19.3; HRMS-EI [M+H]$^+$ calcd for C$_{23}$H$_{25}$NO$_7$S$_2$, 492.1151; found, 492.1134.

![4-Methoxycyclohex-3-ene Carbonitrile (203) and 3-Methoxycyclohex-3-ene Carbonitrile.](image)

4-Methoxycyclohex-3-ene Carbonitrile (203) and 3-Methoxycyclohex-3-ene Carbonitrile. $^1$ To a pressure flask containing 2-methoxy-1,3-butadiene$^{73}$ (3.21 g, 38.2 mmol) in toluene (12 mL) was added acrylonitrile (2.75 mL, 42.0 mmol). The flask was sealed tightly and the mixture was stirred for 16 h at 145 °C. The solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title adducts 203 as an inseparable clear oil containing a mixture of regioisomers in an 8:1 ratio (2.93 g, 56% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 4.60 ($J = 3.9$ Hz, t, 0.11H), 4.49 ($J = 12.9$ Hz, t, 0.88H), 3.44 (s, 3H), 2.72-2.69 (m, 0.88H), 2.38-2.35(m, 0.11H), 2.35-2.18 (m, 2H), 2.18-2.11 (m, 1H), 2.11-1.96 (m, 1H), 1.96-1.74 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.1, 152.0, 122.7, 93.2, 90.2, 54.5, 30.9, 27.3, 26.0, 25.9, 25.7, 25.3, 21.6; HRMS-EI [M]$^+$ calcd for C$_8$H$_{13}$NO, 138.0919; found, 138.0921.
(4-Methoxycyclohex-3-enyl) methanamine (204) and (3-Methoxycyclohex-3-enyl) methanamine. To a stirred suspension of LiAlH₄ (276 mg, 7.29 mmol) in THF (10 mL) at 0 °C was added nitriles 203 (500 mg, 3.64 mmol) in THF (2 mL) dropwise and the mixture was stirred at rt for 2 h. The reaction was quenched by slow addition of a 5:1 mixture of THF:H₂O at 0 °C, followed by addition of 1 M NaOH with stirring. The solids were filtered and washed with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄, and the solvent was removed under reduced pressure to afford the title compounds 204 as yellow oil. The mixture was used for the next step without purification. Major regioisomers 204: ¹H NMR (300 MHz, CDCl₃) δ 4.51 (br s, 1H), 3.44 (s, 3H), 2.56 (J = 6.5 Hz, d, 2H), 2.15-1.92 (m, 5H), 1.76-1.64 (m, 2H), 1.64-1.36 (m, 1H), 1.36-1.06 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 92.3, 54.4, 47.8, 37.6, 28.1, 27.7, 26.9; HRMS-EI [M⁺] calcd for C₇H₁₆NO, 142.1232; found, 142.1240.

N-(4-Methoxycyclohex-3-enylmethyl)-4-methylbenzenesulfonamide (205). To a solution of crude amines 204 (513 mg, 3.64 mmol) in CH₂Cl₂ (12 mL) was added triethylamine (0.5 mL, 3.59 mmol), tosylic chloride (2 g, 10.5 mmol), and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at rt for 18 h, and washed with saturated NaHCO₃. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:4 EtOAc:hexanes) to afford the title compound 205 as a white solid (617 mg, 57% for 2 steps). ¹H
NMR (300 MHz, CDCl$_3$) $\delta$ 7.68 ($J = 8.3$ Hz, d, 2H) 7.23 ($J = 8.0$ Hz, d, 2H), 4.90 ($J = 10.7$ Hz, t, 1H), 4.42 (br s, 1H), 3.40 (s, 3H), 2.77 ($J = 6.0$ Hz, t, 2H), 2.35 (s, 3H), 2.07-1.90 (m, 3H), 1.73-1.55 (m, 3H), 1.25-1.16 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.4, 143.8, 137.4, 130.1, 127.5, 112.1, 109.6, 91.8, 54.4, 48.5, 34.4, 27.8, 27.2, 26.6, 22.0; HRMS-EI [M]$^+$ calcd for C$_{15}$H$_{21}$NO$_3$S, 296.1320; found, 296.1316.

$N$-(3-Chloro-4-oxocyclohexylmethyl)-4-methylbenzenesulfonamide (206). To a solution of sulfonamide 205 (950 mg, 3.22 mmol) in THF:H$_2$O (4:3, 35 mL) was added NaOAc (26 mg, 0.32 mmol) and $N$-chlorosuccinimide (475 mg, 3.54 mmol). The reaction mixture was stirred at rt for 1 h and then was extracted with EtOAc. The combined organic extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford the title compound 206 as two diastereomers in 1:4 ratio (clear oil, 935 mg, 92%). A sample of the isomers was separated by chromatography for characterization purposes. Less polar major diastereomer of 206: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.68 ($J = 8.3$ Hz, d, 2H) 7.25 ($J = 7.9$ Hz, d, 2H), 5.35 ($J = 6.6$ Hz, t, 1H), 4.14-4.11 (m, 1H), 2.86-2.76 (m, 3H), 2.36 (s, 3H), 2.25-2.16 (m, 3H), 1.98-1.93 (m, 1H), 1.82-1.74 (m, 1H), 1.35 -1.13 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 204.6, 144.2, 137.1, 130.3, 127.4, 59.7, 47.5, 38.6, 35.5, 31.5, 30.1, 22.0. More polar minor diastereomer of 206: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.68 ($J = 10$ Hz, d, 2H) 7.26 ($J = 8.2$ Hz, d, 2H), 5.38 ($J = 6.6$ Hz, t, 1H), 4.44-4.39 (m, 1H), 2.82-2.77 (m, 2H), 2.51-2.48 (m, 1H), 2.36 (s, 3H), 2.33-2.00 (m, 3H), 2.02-1.98 (m, 1H), 1.60-1.48 (m, 1H), 1.36-1.28 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.3, 144.3, 137.0, 130.3, 127.4, 63.2, 47.6, 42.1, 39.9, 37.8, 30.7, 22.0.
**N-((4-((tert-Butyldimethylsilyl)oxy)imino)-3-chlorocyclohexyl)methyl)-4-methylbenzenesulfonamide (207).** To a solution of α-chloroketones 206 (128 mg, 0.41 mmol) in CH₂Cl₂ (5 mL) were added O-(t-butyldimethylsilyl)-hydroxylamine (66 mg, 0.45 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 48 h, and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 207 as a clear oil which was an inseparable complex mixture of diastereomers and oxime isomers (121 mg, 67% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.60 (J = 8.3 Hz, d, 2H) 7.16 (J = 8.3 Hz, d, 2H), 5.55-4.48 (m, 2H), 4.00-3.11, (m, 1H), 2.66-2.29 (m, 2H), 2.2 1 (s, 3H), 2.08-1.94 (m, 3H), 1.89-1.08 (m, 2H), 0.91-0.78 (m, 1H), 0.78-0.69 (m, 9H), 0.04-0.0 0 (m, 6H); HRMS-EI [M]⁺ calcd for C₂₀H₃₇N₂O₃SiCl, 445.1748; found, 445.1751.

![Chemical structure of 6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one Oxime (208).](image)

**6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one Oxime (208).** To a solution of oxime 207 (190 mg, 0.43 mmol) in acetonitrile (5 mL) was added TBAF (1 M in THF, 1.07 mL, 1.07 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. Saturated NH₄Cl was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title compound 208 as a white solid (106 mg, 84%) containing a mixture of E/Z oxime isomers in a
5:1 ratio. The solid was recrystallized from chloroform to afford colorless crystals of the (E)-isomer suitable for X-ray analysis. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69-7.57 (m, 2H), 7.19 ($J$ = 8 Hz, d, 2H), 5.38 ($J$ = 5.8 Hz, d, 0.17H), 4.42 ($J$ = 5.6 Hz, d, 0.83H), 3.41-3.33 (m, 1H), 3.22 ($J$ = 9.5 Hz, d, 0.17H), 3.06 ($J$ = 13.2 Hz, d, 0.83H), 2.82 ($J$ = 16.5, 6.6 Hz, dd, 1H), 2.45 (br s, 1H), 2.3 (s, 3H), 1.73-1.40 (m, 4H), 1.47-1.13 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.1, 142.7, 142.6, 134.8, 128.9, 128.8, 128.6, 126.9, 126.4, 126.2, 59.6, 51.9, 50.8, 50.4, 49.3, 48.5, 36.7, 36.3, 34.2, 33.4, 29.7, 27.8, 25.6, 24.3, 20.7, 17.0; HRMS-EI [M]$^+$ calcd for C$_{14}$H$_{18}$N$_2$O$_3$S, 295.1116; found, 295.1107.

$\text{Ts}$

![6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one (209)](image)

To a stirred solution of oxime 208 (40 mg, 0.14 mmol) in 2:1 acetonitrile:H$_2$O (4 mL) was added KMnO$_4$ (43 mg, 0.272 mmol). The mixture was refluxed for 2.5 h and then cooled to rt. The mixture was extracted with CH$_2$Cl$_2$, and the aqueous layer was washed with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title compound 209 as a white crystalline solid (29 mg, 76% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.63 ($J$ = 8.3 Hz, d, 2H), 7.25 ($J$ = 7.9 Hz, d, 2H), 4.07 ($J$ = 6.0 Hz, d, 1H), 3.51-3.46 (m, 1H) 3.39 ($J$ = 9.7 Hz, d, 1H), 2.54 (m, 1H), 2.36 (s, 3H), 2.30-2.21 (m, 1H), 2.13-2.05 (m, 1H), 1.91-1.79 (m, 2H), 1.72-1.51 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.3, 144.2, 136.0, 130.3, 127.4, 66.2, 52.3, 37.9, 34.8, 34.7, 30.7, 22.0; HRMS-EI [M]$^+$ calcd for C$_{14}$H$_{17}$NO$_3$S, 280.1007; found, 280.0984.
3-(3-((Tetrahydro-2H-pyran-2-yl)oxy)propyl)cyclohex-2-enone (212). To a solution of lithium (12 mg, 1.780 mmol) in THF (1 mL) was added a catalytic amount of I₂ and iodide 211 (250 mg, 0.927 mmol). The mixture was stirred at rt for 5 min. To the resulting mixture was added enone 210 (0.10 mL, 0.713 mmol). The mixture was stirred at rt for 4 h and then filtered through a Celite pad. 2 M HCl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title compound 212 (70 mg, 42%). ¹H NMR (300 MHz, CDCl₃) δ 5.84 (s, 1H), 4.51 (s, 1H), 3.79-3.67 (m, 2H), 3.46-3.31 (m, 2H), 2.32-1.95 (m, 6H), 1.95-1.45 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 200.3, 166.5, 126.1, 99.4, 67.1, 62.9, 37.8, 35.2, 31.1, 30.1, 27.4, 25.8, 23.1, 20.1.

3-(3-Oxocyclohex-1-enyl)propyl 4-Methylbenzenesulfonate (214). The ether 212 (35 mg, 0.149 mmol) in 2 M HCl:THF (1:1, 6 mL) was stirred at rt overnight. Saturated NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure to give the alcohol 213. The compound was used for the next step without purification.

To a solution of crude alcohol 213 in CH₂Cl₂ (1 mL) was added tosyl chloride (85 mg, 0.447 mmol), TEA (0.06 mL, 0.447 mmol), and a catalytic amount of DMAP. The mixture was stirred at rt for 12 h, and washed with saturated NaHCO₃. The organic layer was removed and the
aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford tosylate 214 as a clear oil (25 mg, 54% yield for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.70 (m, 2H), 7.28 (J = 8.0 Hz, d, 2H), 5.68 (s, 1H), 3.97 (J = 6.1 Hz, t, 2H), 2.39 (s, 3H), 2.28-2.15 (m, 6H), 1.93-1.77 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 200.0, 164.4, 145.5, 133.2, 130.4, 128.3, 126.4, 69.8, 37.7, 34.1, 30.0, 26.5, 23.0, 22.1.

3-(Hex-5-enyl)cyclohex-2-enone (219). To a solution of magnesium turnings (22 mg, 0.919 mmol) in THF (1 mL) was added 6-bromo-1-hexene (218) (0.08 mL, 0.613 mmol). The mixture was stirred at 50 °C for 2 h and then cooled to rt. 3-Ethoxycyclohex-2-enone (210) was added, and the resulting mixture was stirred at rt for 2 h. Saturated NH₄Cl was added and the mixture was extracted with EtOAc. The reaction was quenched by slow addition of the saturated NH₄Cl solution. The organic layer was separated, the aqueous layer was extracted with EtOAc, and the combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 219 (98 mg, 90% yield). ¹H NMR (300 MHz, CDCl₃) δ 5.80-5.64 (m, 2H), 4.97-4.86 (m, 2H), 2.30-2.12 (m, 6H), 2.04-1.89 (m, 4H), 1.48-1.18 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 200.3, 166.9, 138.8, 126.1, 115.2, 38.3, 37.7, 33.8, 30.1, 28.8, 26.7, 23.1.
5-(3-Oxocyclohex-1-enyl)pentanal (220). To a solution of alkene 219 (86 mg, 0.483 mmol) in CH$_3$CN:H$_2$O 6:1 (2 mL) was added RuCl$_3$ (3 mg, 0.014 mmol) and NaIO$_4$ (206 mg, 0.966 mmol). The mixture was stirred at rt overnight. Saturated Na$_2$S$_2$O$_3$ was added and the mixture was extracted with EtOAc. The combined organics were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc:hexane) to afford the title compound 220 (38 mg, 44% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.71 (s, 1H), 5.85 (s, 1H), 2.46-2.39 (m, 2H), 2.30-2.11 (m, 6H), 1.98-1.88 (m, 2H), 1.64-1.43 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.4, 200.1, 166.1, 126.2, 43.9, 38.1, 37.7, 30.0, 26.7, 23.1, 21.9.

Methyl 5-(3-Oxocyclohex-1-enyl)pentanoate (222). To a solution of aldehyde 220 (52 mg, 0.288 mmol) in actone (1 mL) was added Jones’ reagent (0.1 mL). The mixture was stirred at rt for 15 min and then filtered through a pad of Celite which was washed with isopropanol. The organics were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure to give the acid 221. The compound was used for the next step without purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.85 (s, 1H), 5.27 (s, 1H), 2.38-2.19 (m, 8H), 2.01-1.91 (m, 2H), 1.68-1.51 (m, 4H), 1.24-1.18 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.1, 177.5, 165.0, 124.8, 36.6, 36.3, 32.5, 28.6, 25.2, 23.2, 21.7.
To a solution of crude acid 221 in MeOH (1 mL) was added concentrated H$_2$SO$_4$ (1 drop). The resulting mixture was heated at 55 °C for 12 h and then cooled to rt. The solvent was removed under reduced pressure. H$_2$O was added and the mixture was extracted with EtOAc. The combined organics were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc:hexane) to afford the title compound 222 (34 mg, 56% yield for 2 steps). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.80-5.79 (m, 1H), 3.61 (s, 3H), 2.31-2.14 (m, 8H), 1.97-1.87 (m, 2H), 1.63-1.44 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 200.3, 174.2, 166.2, 126.3, 52.0, 38.1, 37.7, 34.1, 30.0, 26.7, 24.9, 23.1.

![Methyl 5-(2-Chloro-3-oxocyclohexyl)pentanoate](image)

**Methyl 5-(2-Chloro-3-oxocyclohexyl)pentanoate (225).** To a solution of CuH(PPh$_3$)$_6$ (11 mg, 0.005 mmol) in toluene (3 mL) was added dimethyldiphenylsilane (0.42 mL, 2.723 mmol). The mixture was stirred at rt for 5 min. To the resulting solution was added enone 222 (229 mg, 1.089 mmol). The mixture was stirred at rt overnight. In a separate flask containing BF$_3$.Et$_2$O (0.17 mL, 1.416 mmol) in CH$_2$Cl$_2$ (1 mL) at -78 °C was added N-chlorosuccinimide (290 mg, 2.178 mmol). The mixture enone/silane mixture was carefully transferred to the BF$_3$.Et$_2$O/NCS mixture, and the resulting mixture was slowly warmed to rt over 3 h. Saturated NaHCO$_3$ was added and the mixture was extracted with EtOAc. The combined organics were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford the α-chloroketone 225 as an inseparable mixture of two diastereomers as clear oil (238 mg, 88% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.80 (s, 1H), 3.61 (s, 3H), 2.31-2.14 (m, 8H), 1.94-1.46 (m,
\[ \text{Methyl 5-((\text{tert-Butyldimethylsilyl})oxyimino)-2-chlorocyclohexyl) Pentanoate (227).} \]

To a solution of α-chloroketones 225 (40 mg, 0.163 mmol) in CH\(_2\)Cl\(_2\) (4 mL) were added \(O\)-(t-butyldimethylsilyl)-hydroxylamine (26 mg, 0.178 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 72 h and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give the residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 227 as a clear oil containing a mixture of two oxime isomers in a 1:1 ratio (64 mg, 70%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.62 (s, 0.5H), 5.92 (s, 0.5H), 3.63 (s, 3H), 2.52-2.04 (m, 8H), 1.68-1.22 (s, 7H), 0.90-0.84 (s, 9H), 0.13 (s, 6H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.0, 173.0, 159.8, 126.8, 151.7, 147.9, 118.8, 112.3, 50.5, 36.9, 36.5, 32.9, 32.8, 28.0, 27.3, 25.8, 25.6, 25.2, 25.1, 23.6, 23.5, 21.6, 21.5, 20.3, 17.1, -6.2.

\[ \text{Methyl 5-(2-Chloro-3-(hydroxyimino)cyclohexyl)pentanoate (228).} \]

To a solution of α-chloroketone 225 (160 mg, 0.651 mmol) in EtOH (5 mL) was added NH\(_2\)OH.HCl (100 mg, 1.430 mmol), and the mixture was stirred overnight at rt. Water was added and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined organics were dried over Na\(_2\)SO\(_4\), and the solvent was removed under reduced pressure to give the title compound as clear oil containing a mixture of
two α-chlorooxime isomers in a 1:1.5 ratio (80 mg, 48%). $^1$H NMR (300 MHz, CDCl$_3$) δ 11.91 (s, 1H), 6.56 (s, 0.4H), 6.00 (s, 0.6H), 3.58 (s, 3H), 2.56-2.42 (m, 2H), 2.27-2.06 (m, 6H), 1.81-1.38 (m, 7H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.3, 174.2, 161.5, 158.0, 155.4, 155.0, 117.5, 112.8, 53.9, 52.0, 52.0, 38.6, 38.2, 34.1, 34.1, 30.4, 29.2, 27.1, 27.0, 24.9, 22.6, 22.3, 21.1, 14.6.

Methyl 5-(3-(Hydroxyimino)cyclohex-1-en-1-yl)pentanoate (229). To a stirred solution of α-chlorosilyloxime 227 (30 mg, 0.080 mmol) in THF (2 mL) at -78 °C was added KHMDS (0.5 M in toluene, 0.12 mL, 0.080 mmol) dropwise. After stirring the mixture for 1 h at -78 °C, TBAF (1 M in THF, 0.12 mL, 0.12 mmol) was added and reaction mixture was stirred at 0 °C for 3 h. Saturated NH$_4$Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford the title compound 229. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.55 (s, 0.4H), 5.84 (s, 0.6H), 3.60 (s, 3H), 2.51-2.23 (m, 4H), 2.13-2.01 (m, 4H), 1.77-1.40 (m, 7H).

Ethyl 1-(4-(Ethoxycarbonyl)butyl)-2-Oxocyclopentanecarboxylate (244). To a stirred solution of NaH (299 mg, 12.464 mmol) in THF (40 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (242, 1.43 mL, 9.604 mmol). The reaction mixture was then stirred at rt for 30 min. 5-Bromovaleronitrile (243, 1.97 mL, 12.464 mmol) and NaI (287 mg, 1.921 mmol) were added to the stirred solution. The mixture was refluxed for 24 h and then cooled to rt.
Saturated NH$_4$Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:8 EtOAc:hexanes) to afford the title compound 244 (2.337 g, 87% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.11-4.01 (m, 4H), 2.40-2.18 (m, 2H), 2.16-2.13 (m, 3H), 1.89-1.76 (m, 4H), 1.53-1.42 (m, 3H), 1.24-1.13 (m, 8H).

Ethyl 5-(2-Oxocyclopentyl)pentanoate (246a) and Methyl 5-(2-Oxocyclopentyl)pentanoate (246b). To a stirred solution of carboxylate 244 (256 mg, 0.901 mmol) in MeOH (4 mL) was added 3 M HCl (7 mL). The mixture was heated at 98 °C for 24 h and then cooled to rt. The mixture was extracted with EtOAc, and the aqueous layer was washed with EtOAc. The combined organic extracts were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give the acid 245. The compound was used for the next step without purification.

To a stirred solution of crude acid 245 in EtOH (2 mL) was added a catalytic amount of PTSA. The mixture was heated at 76 °C for 24 h and then cooled to rt. The mixture was extracted with EtOAc, and the aqueous layer was washed with EtOAc. The combined organics were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:9 EtOAc:hexanes) to afford the title compound 246a (169 mg, 88% yield for 2 steps). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.03 ($J = 7.1$ Hz, q, 2H), 2.25-1.91 (m, 7H), 1.72-1.26 (m, 8H), 1.19 ($J = 7.2$ Hz, t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 220.8, 173.5, 60.3, 49.0, 38.2, 34.2, 29.8, 29.5, 27.2, 25.0, 21.0, 14.4.

To a stirred solution of crude acid 245 (120 mg) in MeOH (1 mL) was added a catalytic amount of PTSA. The mixture was heated at 64 °C for 24 h and then cooled to rt. The mixture
was extracted with EtOAc, and the aqueous layer was washed with EtOAc. The combined organics were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:9 EtOAc:hexanes) to afford the title compound 246b (169 mg, 76% yield for 2 steps). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.59 (s, 3H), 2.27-1.92 (m, 7H), 1.72-1.26 (m, 8H).

![Image of organic structure]

**Ethyl 5-(2-((Trimethylsilyl)oxy)cyclopent-1-en-1-yl)pentanoate (247).** To a stirred solution of ester 246a (83 mg, 0.419 mmol) in CH$_3$CN (2 mL) was added NaI (63 mg, 0.419 mmol), NEt$_3$ (0.29 mL, 2.095 mmol), followed by TMSCl (0.16 mL, 1.257 mmol). The resulting mixture was stirred at rt overnight. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with hexane. The combined organic extracts were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give TMS enol ether 247. The compound was used for the next step without purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.95 ($J = 7.1$ Hz, q, 2H), 2.16-2.08 (m, 4H), 2.01 ($J = 7.2$ Hz, t, 2H), 1.85 ($J = 7.5$ Hz, q, 2H), 1.66-1.59 (m, 2H), 1.49-1.38 (m, 2H), 1.26-1.08 (m, 3H), 1.08 ($J = 7.3$ Hz, t, 2H), 0.00 (s, 9H).

![Image of organic structure]

**Ethyl 5-(1-Chloro-2-oxocyclopentyl)pentanoate (248).** To a stirred solution of ketoester 246 (197 mg, 0.98 mmol) in CCL$_4$ (2 mL) was added SO$_2$Cl$_2$ (0.086 mL, 1.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was washed with water, saturated aqueous NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give a residue which was purified by flash
column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 248 as colorless oil (55 mg, 24% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 4.07-4.01 (m, 2H), 2.54-2.46 (m, 1H), 2.29-1.87 (m, 6H), 1.64-1.22 (m, 6H), 1.21-1.15 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 211.3, 173.7, 72.8, 60.6, 38.2, 36.3, 35.4, 34.4, 25.3, 24.4, 18.6, 14.6.

![Ethyl 5-(5-Oxocyclopent-1-enyl)pentanoate (250)](image)

**Ethyl 5-(5-Oxocyclopent-1-enyl)pentanoate (250).** To a stirred solution of TMS enol ether 247 (170 mg, 0.598 mmol) in CH$_2$Cl$_2$ (3 mL) was added N-chlorosuccinimide (88 mg, 0.657 mmol). The mixture was refluxed for 4 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 250 (79 mg, 63% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 4.00 ($J$ = 7.1 Hz, q, 2H), 2.48-2.45 (m, 2H), 2.29-2.26 (m, 2H), 2.25-2.22 (m, 2H), 2.10-2.05 (m, 2H), 1.57-1.35 (m, 5H), 1.16 ($J$ = 7.1 Hz, t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 210.2, 173.9, 160.0, 146.2, 60.5, 34.9, 34.3, 30.0, 27.5, 26.8, 25.0, 14.6.

![Ethyl 5-(2-(tert-Butyldimethylsilyloxyimino)-1-chlorocyclopentyl)pentanoate (251)](image)

**Ethyl 5-(2-(tert-Butyldimethylsilyloxyimino)-1-chlorocyclopentyl)pentanoate (251).** To a solution of α-chloroketones 248 (55 mg, 0.22 mmol) in CH$_2$Cl$_2$ (5 mL) were added O-(t-butyldimethylsilyl)-hydroxylamine (36 mg, 0.24 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 48 h, and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:6
ether:hexanes) to afford the title compound 251 as a clear oil which was an inseparable complex mixture of oxime isomers (8.3 mg, 10% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.00-3.92 (m, 2H), 2.38-2.00 (m, 5H), 1.82-1.40 (m, 7H), 1.29-1.25 (m, 2H), 1.12-1.07 (m, 3H), 0.79-0.72 (m, 9H), 0.01-0.00 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.9, 169.9, 76.9, 60.6, 41.6, 39.1, 34.6, 26.7, 26.5, 26.4, 25.4, 25.2, 20.7, 18.5, 14.6, -4.8.

**Ethyl 5-(2-Acetoxy-3cyclopent-1-enyl)pentanoate (253).** To a stirred solution of ester 246 (260 mg, 1.226 mmol) in acetic anhydride (10 mL) was added PTSA (40 mg, 0.232 mmol). The mixture was refluxed for 12 h and then cooled to rt. Ice-cold saturated NaHCO\(_3\) was added and the mixture was extracted with hexane. The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 253 (199 mg, 69% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.05 \((J = 7.1 \text{ Hz, q, } 2\text{H}), 2.42-2.37 \text{ (m, } 2\text{H}), 2.24-2.19 \text{ (m, } 4\text{H}), 2.07 \text{ (s, } 3\text{H}), 1.93 \((J = 7.4 \text{ Hz, q, } 2\text{H}), 1.85-1.78 \text{ (m, } 2\text{H}), 1.57-1.47 \text{ (m, } 2\text{H}), 1.37-1.29 \text{ (m, } 2\text{H}), 1.18 \((J = 7.1 \text{ Hz, t, } 3\text{H}); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.1, 169.3, 144.6, 126.6, 60.6, 34.5, 31.4, 31.3, 27.0, 26.4, 25.1, 21.2, 20.2, 14.6.

**Ethyl 5-(1-Bromo-2-oxocyclopentyl)pentanoate (254).** To a stirred solution of CaCO\(_3\) in chloroform (2 mL) at 0 °C was added enol ether 253 (48 mg, 0.189 mmol), Br\(_2\) (0.0052 mL, 0.208 mmol) and CCl\(_4\) (0.023 mL, 0.236 mmol). The reaction mixture was stirred at 0 °C for 5 min, followed by slow addition of saturated Na\(_2\)S\(_2\)O\(_3\) solution. The organic layer was separated,
and the aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \). The combined organics were dried over \( \text{Na}_2\text{SO}_4 \). The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 254 (20 mg, 83% yield along with 27 mg of recovered enol ether 253). \(^1\)H NMR (300 MHz, \( \text{CDCl}_3 \)) \( \delta \) 4.07 \((J = 7.2 \text{ Hz, q, 2H})\), 2.49-2.45 \((m, 1H)\), 2.33-2.25 \((m, 3H)\), 2.10-1.91 \((m, 5H)\), 1.66-1.58 \((m, 4H)\), 1.34-1.29 \((m, 1H)\), 1.18 \((J = 7.2 \text{ Hz, t, 3H})\); \(^{13}\)C NMR (75 MHz, \( \text{CDCl}_3 \)) \( \delta \) 210.9, 173.8, 69.7, 60.7, 39.0, 37.3, 35.2, 34.4, 25.7, 25.3, 19.2, 14.7.

**Ethyl 5-(1-Bromo-2-(tert-butyldimethylsilyloxyimino)cyclopentyl)pentanoate (255).**

To a solution of \( \alpha \)-bromoketones 254 (20.0 mg, 0.069 mmol) in \( \text{CH}_2\text{Cl}_2 \) (1.5 mL) were added \( O-(t\text{-butyldimethylsilyl})\)-hydroxylamine (20.2 mg, 0.14 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 48 h, and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:20 EtOAc:hexanes) to afford the title compound 255 as a clear oil (15 mg, 50% yield). \(^1\)H NMR (300 MHz, \( \text{CDCl}_3 \)) \( \delta \) 4.01-3.92 \((m, 2H)\), 2.52-2.48 \((m, 1H)\), 2.26-2.06 \((m, 5H)\), 1.72-1.39 \((m, 6H)\), 1.12-1.07 \((m, 5H)\), 0.81-0.69 \((m, 9H)\), 0.00 \((s, 6H)\).
2-(Phenylsulfonyl)cyclopentanone \textit{O-}\textit{tert}-Butyldimethylsilyl Oxime (256). To a solution of ketosulphone 253\textsuperscript{89} (510 mg, 2.27 mmol) in \textit{CH}_2\textit{Cl}_2 (5 mL) were added \textit{O-}\textit{tert}-butyldimethylsilyl)-hydroxylamine (368 mg, 2.5 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 48 h, and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:4 ether:hexanes) to afford the title compound 256 (800 mg, 100% yield). \textit{H} NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.89-7.85 (m, 2H), 7.67-7.61 (m, 1H), 7.56-7.51 (m, 2H), 4.13-4.09 (m, 1H), 2.75-2.52 (m, 3H), 2.25-2.07 (m, 2H), 1.87-1.78 (m, 1H), 0.85-0.83 (m, 9H), 0.01-0.00 (m, 6H); \textit{C} NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 163.8, 138.6, 133.8, 129.4, 129.2, 67.1, 27.8, 27.0, 26.2, 22.4, 18.2, -4.7, -4.9.

\textbf{Ethyl 5-} \textit{O-}\textit{tert}-Butyldimethylsilyloxyimino-1-(phenylsulfonyl)cyclopentyl)pentanoate (258). To a stirred solution of \textit{O-silylketoxime} 253 (826 mg, 2.33 mmol) in THF (10 mL) was added dropwise n-BuLi (2.5 M in hexanes, 1.1 mL, 2.75 mmol) at -78 oC. The reaction mixture was stirred at -78 oC for 30 min and iodoester 257 (660 mg, 2.75 mmol) in THF (2 mL) was added. The mixture was warmed to rt over 5 h and stirred at rt for 96 h. The reaction was quenched by slow addition of the saturated NH\textsubscript{4}Cl solution. The organic layer was separated, the aqueous layer was extracted with CH2Cl2, and the combined organics were dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:4
ether:hexanes) to afford the title compound 258 (758 mg, 68% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.75-7.71 (m, 2H), 7.60-7.54 (m, 1H), 7.45 (\(J = 7.6\) Hz, t, 2H), 4.04 (\(J = 7.1\) Hz, q, 2H), 2.76-2.66 (m, 1H), 2.55-2.48 (m, 2H), 2.16 (\(J = 7.4\) Hz, t, 2H), 2.08-1.82 (m, 3H), 1.73-1.64 (m, 2H), 1.53-1.41 (m, 3H), 1.15 (\(J = 7.1\) Hz, t, 4H), 0.86-0.79 (m, 9H), 0.04-0.00 (m, 6H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.7, 165.7, 136.1, 133.9, 131.2, 128.8, 60.7, 34.4, 33.4, 31.2, 28.9, 26.3, 25.6, 24.1, 21.6, 18.3, 14.6, -4.6, -4.6.

![Ethyl (2Z)-2-(1-(5-Ethoxy-5-oxopentyl)-2-(hydroxyimino) cyclopentyloxyimino)-1-(phenylsulfonyl)cyclopentylpentanoate (259) Diagram](image)

Ethyl (2Z)-2-(1-(5-Ethoxy-5-oxopentyl)-2-(hydroxyimino) cyclopentyloxyimino)-1-(phenylsulfonyl)cyclopentylpentanoate (259). To a stirred solution of oxime 258 (20 mg, 0.041 mmol) in THF (3 mL) at -78 °C was added KHMDS (0.5 M in toluene, 0.13 mL, 0.065 mmol) dropwise. After stirring the mixture for 1 h at -78 °C, TBAF (1 M in THF, 0.062 mL, 0.062 mmol) was added and reaction mixture was stirred at 0 °C for 3 h. Saturated NH\(_4\)Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:2 ether:hexanes) to afford the title compound 259 as clear oil (55 mg) as a mixture of oxime isomers. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.65-7.61 (m, 2H), 7.47 (\(J = 7.3\) Hz, t, 1H), 7.36 (\(J = 7.1\) Hz, q, 2H), 4.00-3.91 (m, 4H), 2.70-2.45 (m, 1H), 2.36 – 2.07 (m, 9H), 1.87-1.27 (m, 19H), 1.11-0.94 (m, 6H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.9, 173.7,173.3, 165.7, 164.4, 160.6, 159.6, 135.4, 135.3, 133.2, 133.1, 130.5, 130.4, 128.1, 128.1, 88.6, 75.0, 74.9, 60.2, 59.8, 35.6, 35.0, 33.9, 33.9, 33.9, 33.7, 30.0, 28.1, 26.3, 25.0, 24.7, 23.3, 23.0, 13.9, 13.8; HRMS-EI [M+H]\(^+\) calcd for C\(_{50}\)H\(_{45}\)N\(_2\)O\(_8\)S, 593.3; found, 593.4.
Ethyl 5-(2-Oxo-1-(phenylsulfonyl)cyclopentyl)pentanoate (260). To a solution of ketosulfone 253 (100 mg, 0.44 mmol) and Cs₂CO₃ (175 mg, 0.57 mmol) in acetone (2 mL) was added iodide 257 (135 mg, 0.53 mmol) and the resulting mixture was stirred at reflux for 2 h. Saturated NH₄Cl was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:2 ether:hexanes) to afford the title compound 260 as clear oil (150 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.69 (m, 2H), 7.48 (J = 7.7 Hz, t, 2H), 7.29-7.18 (m, 2H), 4.11 (J = 7.1 Hz, q, 2H), 2.91-2.81 (m, 1H), 2.55-2.43 (m, 1H), 2.24-2.06 (m, 5H), 1.83-1.57 (m, 3H), 1.48-1.29 (m, 3H), 1.15 (J = 7.1 Hz, t, 3H), 1.03-0.90 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 211.8, 173.4, 135.7, 134.6, 130.9, 129.1, 75.4, 60.7, 39.5, 34.1, 32.6, 28.9, 25.3, 23.9, 19.4, 14.6.

Synthesis of Tosylhydrazone 261. To a stirred solution of β-ketosulfone 253 (119 mg, 0.34 mmol) in toluene (2 mL) was added p-TsNHNH₂ (65 mg, 0.34 mmol). The resulting mixture was stirred at reflux for 14 h. The reaction mixture was cooled to rt and filtered though a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to afford the title compound 261 (88 mg, 50%). ¹H NMR (300 MHz, CDCl₃) δ 8.10 (br s, 1H), 7.71 (J = 7.4 Hz, d, 2H), 7.67-7.55 (m, 3H), 7.48 (J = 7.7 Hz, t, 2H), 7.29-7.18 (m, 2H), 4.11 (J = 7.1 Hz, q, 2H), 2.76-2.65 (m, 1H), 2.48-2.44 (m, 1H), 2.39 (s, 3H), 2.35-2.26 (m, 2H), 2.08-1.93 (m, 5H), 1.79-1.71 (m, 2H), 1.60-
1.35 (m, 3H), 1.26 (J = 7.1, t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.7, 159.2, 143.7, 134.7, 134.6, 133.2, 130.4, 128.9, 128.1, 127.6, 75.0, 59.9, 33.3, 32.6, 29.7, 28.3, 24.5, 22.9, 21.0, 21.0, 13.8; HRMS-EI [M+H]$^+$ calcd for C$_{25}$H$_{33}$N$_2$O$_6$S$_2$, 521.2; found, 521.0.

**Synthesis of α,β- Unsaturated Hydrazione Ester 263.** To a stirred solution of oxime 261 (23.9 mg, 0.046 mmol) in THF (3 mL) at -78 °C was added KHMDS (0.5 M in toluene, 0.22 mL, 0.11 mmol) dropwise. Saturated NH$_4$Cl was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 263 (10.7 mg, 62%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.79 (J = 8.2 Hz, d, 2H), 7.25-7.19 (m, 3H), 6.23 (s, 1H), 4.06 (J = 7.1 Hz, q, 2H), 2.38-2.29 (m, 7H), 2.24-2.10 (m, 4H), 1.64-1.46 (m, 2H), 1.42-1.32 (m, 2H), 1.19 (J = 7.1 Hz, t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.8, 166.6, 144.0, 143.0, 142.2, 135.5, 129.5, 128.2, 60.4, 34.2, 29.0, 26.9, 26.0, 25.7, 24.8, 21.7, 14.1; HRMS-EI [M+H]$^+$ calcd for C$_{19}$H$_{27}$N$_2$O$_4$S, 379.2; found, 379.2.
3.1 References and Notes


(48) Miyata, O.; Miyoshi, T.; Ueda, M. *ARKIVOC* 2013, 60.


(60) Chao, W.; Weinreb, S. M. *Org. Lett.* 2003, 5, 2505.


Chapter 4 Introduction and Background of Tronocarpine

4.1 Tronocarpine and Biogenetically Related Alkaloids

Tronocarpine (1) was isolated in 1999 by Lim and coworkers from a stem-bark extract of the Malayan plant *Tabernaemontana corymbosa.* The structure of tronocarpine represents a new addition to the post-secodine skeletal class of indole alkaloids. These indole alkaloids contain scaffolds of varying connectivity, typically with a bond to the indole nitrogen. Tronocarpine is biogenetically related to the tacaman group of alkaloids, exemplified by tacamine (2), a molecule in itself of synthetic and biological interest.

Figure 4.1 Tronocarpine and Tacamine

![Structure of Tronocarpine and Tacamine](image)

The carbon connectivity and relative stereochemistry of tronocarpine (1) was established by a combination of spectrometric and spectroscopic methods. High-resolution mass spectrometry was used to establish a molecular formula of $C_{20}H_{20}N_2O_3$ requiring 12 degrees of unsaturation. The IR spectrum indicated a hydroxyl and/or amine absorption peak at 3315 cm$^{-1}$. Additionally, the IR spectrum indicated olefinic and carbonyl stretching vibrations at 1633 and 1661 cm$^{-1}$, respectively. Analysis of the $^{13}$C NMR spectrum confirmed the presence of a oxymethine (80.5 ppm), a trisubstituted double bond (137.9 and 139.7 ppm), and ketogenic and lactam carbonyl moieties (198.2 and 174.5 ppm). In addition, the $^1$H NMR spectrum indicated the presence of an indole moiety, an NH function, an acetyl group, and a deshielded vinylic hydrogen (7.05 ppm). Moreover, polarimetry showed a rotation of $[\alpha]_D = +231$ in CH$_2$Cl$_2$ for the alkaloid.
4.2 Proposed Biosynthesis of Tronocarpine from Iboganes

Although the exact biosynthetic pathway for tronocarpine (1) has not been definitively established, Hájíček has proposed a possible route by drawing analogy to known biosyntheses of related alkaloid iboganes (3, Scheme 1). Thus, oxidative cleavage of the C-3/N-4 of iboganes (3), followed by cyclization of the resulting aldehyde 4 onto the N-1 nitrogen, is proposed to generate the well known chippine/dippinine class of alkaloids 5. Cleavage of the N-4/C-21 bond in 5, followed by formation of the N-4/C-22 bond in 6, would furnish the skeleton of tronocarpine 7.

Scheme 1
4.3 Previous Synthetic Approaches to Tronocarpine

Tronocarpine is an attractive target for total synthesis because of its unique structure, which includes a six-membered ring fused to the indole 1,2-positions and a lactam fused to the indole 2,3-positions. The molecule also contains an all-carbon quaternary center adjacent to an enone moiety. Almost 13 years after the discovery of tronocarpine (1), there have been no total syntheses reported. The tetracyclic compounds 8, which contain four of the five rings of tronocarpine (1), represent the most advanced intermediates prepared to date. In this section, the strategies hitherto utilized to access the skeleton of tronocarpine will be discussed.

Scheme 2
4.3.1 Mahboobi’s Approach to the Tronocarpine Core

The Mahboobi group has prepared the most advanced intermediate to tronocarpine 8a utilizing an approach that commenced with the introduction of a nitroethylene moiety into indole 9 to yield malonate 11 (Scheme 3).\(^3\) Cyclization of malonate 11 with acrolein using a catalytic amount of Triton B led to pyridoindole 13, along with the regioisomeric undesired carbazole carboxaldehyde 12. The desired regioisomer 13 was oxidized using CrO\(_3\) and pyridine to generate lactam 14, which underwent nitroalkene reduction, hydrogenation of the corresponding nitro compound. Cyclization of the resulting amine afforded bis-lactam 8a, which contains four of five rings of tronocarpine (1).

\[ \text{Scheme 3} \]
4.3.2 Wang’s Approach to the Tronocarpine Core

In 2009, Wang and coworkers developed an N-heterocyclic carbene-catalyzed cyclization as the key strategy in their synthesis of the tetracyclic core 8a of tronocarpine (Scheme 4). This approach began with the formation of a carbene 17 upon the treatment of triazolium salt 15 with DBU, which reacted with cyclopropane carboxaldehyde 16 to give substituted vinylcyclopropane intermediate 18. Ring opening of this intermediate in situ and subsequent N-acyl substitution of indole aldehyde 19 furnished malonate anion intermediate 20, which underwent intramolecular cyclization with the indole C2-halogen to construct lactam aldehyde 21. Treatment of 21 with nitromethane in the presence of NH₄OAc gave nitroalkene 14, which had previously been elaborated to tetracycle 8a by Mahboobi (Cf Scheme 3).

Scheme 4
4.3.3 Kerr’s Approach to the Tronocarpine Core

In a synthetic route devised by the Kerr group, a Mn(OAc)$_3$-mediated radical cyclization of 24 was applied as the key strategy to construct the tetracyclic core of tronocarpine (Scheme 5). The synthesis began with the N-acylation of commercially available indole-3-acetonitrile (22) with acid chloride 23 affording cyclization precursor 24. The single-electron oxidation of the malonic enolate derived from acetonitrile 24 yielded a malonate radical 25. Subsequent cyclization at the 2-position of the indole resulting in benzylic radical 26, which underwent further oxidation and aromatization to produce nitrile indole 27. Treatment of 27 with H$_2$ over Raney nickel resulted in nitrile reduction to the tryptamine derivative which spontaneously cyclized to give the tronocarpine lactam core 8a.
4.3.4 Miranda’s Approach to the Tronocarpine Core

The Miranda group has also published a synthetic route to the tetracyclic core of tronocarpine 8b, which commenced with an intermolecular radical oxidative substitution of known N-Boc tryptamine 28 and malonate xanthate 29 to generate C2-alkylated tryptamine derivative 30 (Scheme 6). Treatment of malonate 30 with sodium hydride resulted in annulation with ethyl acrylate to furnish tricycle 31. Subsequent N-Boc deprotection of 31 furnished the tryptamine trifluoroacetate salt 32, which then underwent lactamization to provide the tronocarpine core 8b.

Scheme 6
Chapter 5 Results and Discussion

5.1 First Generation Retrosynthetic Plan for the Synthesis of Tronocarpine

In our first generation retrosynthesis, we envisioned that the hemiaminal moiety in tronocarpine (1) could be installed via an intramolecular cyclization of the indole nitrogen with the C16 aldehyde in 33 (Scheme 7). It should be noted that only the stereoisomer shown can cyclize to afford aminal 1. An aldehyde epimerization step at C17 may be necessary at this stage to achieve formation of the desired stereochemistry for cyclization.

The C16 aldehyde functionality in tetracycle 33 could be accessed via oxidation of the corresponding C16 alcohol in tetracycle 34. The enone moiety in tetracycle 34 would be accessible from the ester moiety in tetracycle 35, containing an ε-lactam that we proposed could arise via a reduction and selective cyclization of tricyclic nitroethylene ester 36. The nitroethylene moiety in tricycle 36 could be installed via conjugate addition of nitroethylene 10 with the indole 37, which could in turn be obtained via a key intermolecular Pd-catalyzed α-arylation of the 2-bromoindole 38 and the enolate of ene diester 39.
5.1.1 Background on the Key Ester Enolate α-Arylation Methodology

The formation of carbon-carbon bonds is of singular importance in organic synthesis. In the past several decades, the use of transition metal-catalyzed cross coupling reactions to accomplish this task has reached new levels of sophistication and practical importance. In particular, metals such as Pd, Ni, Cu, Zn, Co, Rh, Ru and Mo have been utilized to accomplish a wide array of reactions. Despite the aforementioned variety of available metals, the vast majority of these such transformations have utilized Pd despite its relatively higher unit cost than many of other catalysts. This phenomenon is undoubtedly due high activity and turnover numbers of Pd-metal catalysts which permit the efficient cross-coupling of even low reactivity species such as aryl halides at relatively benign temperature.
In recent years, there has been considerable interest in the Pd-catalyzed synthesis of α-aryl-substituted carboxylic acid derivatives due in large part to their prevalence in pharmacologically active agents such as ibuprofen and ketoprofen, as well as many natural products. Our synthetic effort towards tronocarpine (1) initially relied on intermolecular α-arylation of ester enolates, which was first introduced in 1991 by Musco and Santi. Thus, it was reported that the Pd-catalyzed coupling reaction of aryl triflates with ketene trimethylsilyl acetics yields alkyl-2-arylalkanoates in the presence of LiOAc (Scheme 8). The substrate scope of this reaction has since been expanded to the enolates of amides, esters, nitriles, cyano esters, β-keto esters and malonates.

Scheme 8

The mechanism for α-arylation of esters was proposed by Hartwig and Culkin in 2001 (Scheme 9). Thus, oxidative addition of aryl halide to the active Pd(0) species generates complex, which, in turn coordinates to the enolate generated from ester with base to give intermediate metal enolates and . A subsequent proton transfer and reductive elimination achieves the C-C coupling and regenerates the active catalyst.
Examples of such intermolecular Pd-catalyzed α-arylations of ester enolates with aryl bromides were reported by Moradi and Buchwald (Scheme 10). Thus, in the presence of a catalytic amount of Pd(OAc)$_2$ and DavePhos, the lithium enolate of ester 51 underwent cross-coupling with aryl bromides 50 (-10 °C followed by slow warming) leading to the desired monoarylation products 52 in good yields (entries 1-5). Of particular interest to our synthetic endeavors toward tronocarpine (Cf. Scheme 7) are the reactions with ethyl 2-methylbutanoate which give rise to cross-coupled products containing newly formed quaternary centers (entries 4-5).
Hartwig and coworkers have published other examples of intermolecular Pd-catalyzed α-arylations of ester enolates with aryl bromides 54 and 57.\textsuperscript{28} Treatment of aryl bromide 54 and malonate 53 with LiHMDS at room temperature in the presence of a 1:1 mixture of Pd(dba)$_2$ and P($t$-Bu)$_3$ led to formation of the desired α-aryl ester 55 in good yield. Similarly, α-amino acetate ester 58 was obtained via α-arylation of ester 56 with aryl bromide 57 using the same catalyst with K$_3$PO$_4$ as the base.
Sole and coworkers have published intramolecular Pd-catalyzed enolate arylation methodology with β-(2-iodoanilino) esters 59 in the presence of a Pd(0) catalyst (Scheme 12).29 In this example, the β-(2-iodoanilino)ester 59 was converted to the corresponding indole derivative 60 in the presence of a catalytic amount of Pd(PPh₃)₂ and phenol, using K₂PO₄ as base in DMF in moderate yields. In general, substrates containing electron donating groups such as OCH₃ and CH₃ on the arene ring appeared to undergo the α-arylation reaction more efficiently than those substrates containing electron-withdrawing groups such as Cl, F, and CO₂CH₃. In addition, it was believed that the use of a catalytic amount of phenol served not only to ligate palladium by displacing the iodide at the metal center, but also formed a transient palladium phenoxide complex, thus suppressing potentially undesirable side reactions such as nucleophilic attack at the carbonyl.
5.1.2 Studies on Pd-Catalyzed Intermolecular α-Arylation Approaches to the Tronocarpine Core

Since no examples of Pd-catalyzed α-arylations of the enolate of known diester alkene 65 with an aryl halide had been previously reported, we decided that a model study for Scheme 7 should first be performed to determine the feasibility of this reaction. Since bromobenzene is far more available and stable than the requisite 2-bromoindole 38, the former was chosen as a model substrate for initial exploratory reactions.

Our synthetic efforts began with synthesis of the model diester substrate via dialkylation of 61 with dibromo compound 62 promoted by magnesium methoxide to afford diester ketone 63, followed by ketone reduction and alcohol elimination to give known diester alkene 65 (Scheme 13). With the desired compound 65 in hand, α-arylation of diester alkene 65 with bromobenzene was next examined in toluene, using a variety of combinations of catalyst and ligand (Table 5.1). Attempted Pd-catalyzed coupling reactions using Pd(OAc)$_2$ as catalyst and LiHMDS led to the recovery of starting materials, irrespective of the additive and temperature used (entries 1-6). A different soluble base, KHMDS, provided similar disappointing results (entry 7).
Due to the poor results with Pd(OAc)$_2$, a different catalyst, Pd(dba)$_2$, was next examined (entries 8-13). Attempted $\alpha$-arylation using P($t$-Bu)$_3$ as additive and NaHMDS as base, irrespective of the temperature used (entries 8 and 9), yielded no desired product 67. Substituting KHMDS with LiHMDS led to the recovery of the starting material only at room temperature (entry 10). Raising the reaction temperature to 40 °C provided a small amount of desired product but the majority of the mass balance was recovered starting material (entry 11). However, we were pleased to find that further increasing the reaction temperature to 60 °C gave the desired coupled product in 70% yield (entry 12). Higher temperatures led to decomposition products (entry 13).

Scheme 13

Table 5.1 Attempted $\alpha$-Arylation of Diester Alkene 65 with Bromobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>$t$-Bu$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>$t$-tol$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>$p$-tol$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>Ph$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>68</td>
<td>LiHMDS</td>
<td>rt</td>
<td>SM</td>
</tr>
</tbody>
</table>
To determine whether the nature of the aryl halide had any effect on the product yield, iodobenzene was reacted with diester alkene 65 under the optimized reaction conditions (Table 5.1, entry 12). Interestingly, iodobenzene provided the coupling adduct 67, but at a slower rate relative to bromobenzene (by TLC). Thus, we decided that aryl bromides were the most appropriate substrates to probe the coupling reaction.

At this stage, we decided to attempt the Pd-catalyzed coupling reaction with more sterically hindered substrates such as 1,2-disubstituted bromobenzenes 69a and 69b (Scheme 14). The coupling reaction of 69a with ester 65 using catalytic amounts of Pd(dba)$_2$ with P(t-Bu)$_3$ as an additive and LiHMDS as base provided only unreacted starting materials (Table 5.2, entry 1). Neither changing the catalyst to Pd(OAc)$_2$ nor changing the base and additive led to any of the desired products (entry 2-4). Likewise, depending upon the base and reaction temperature, using $\{$(P(t-Bu)$_3$)PdBr$_2$$\}_2$ as catalyst led either to complete decomposition or starting material recovery (entry 5 and 6). Similar combinations of Pd catalysts, additives, bases, solvents and temperatures were attempted using bromobenzene 69b (entries 7-12). Unfortunately, recovery of starting material or decomposition was the only outcome of the reaction. We postulated that the failure of this coupling reaction might be due to the more sterically demanding environment surrounding the quaternary center in adduct 70.
Since the 1,2-disubstituted bromobenzenes 69 did not appear to participate in the desired Pd-catalyzed α-arylation with diester alkene 65, our focus shifted to the use of bromoindoles 71 as coupling partners (Scheme 15). To probe the reaction, the cross coupling of ester 65 with free 2-bromoindole 71 was attempted using LiHMDS as base (Table 5.3, entry 1 and 4). However, this experiment resulted in only decomposition. The use of a weaker base, NEt₃, also led only to the decomposition (entries 2, 3, and 5). Accordingly, the analogous transformation with N-methyl-2-bromoindole (71b) was examined under various conditions (entries 6-12).
Unfortunately, these reactions either led to complete decomposition or recovery of starting material. In addition, the attempted coupling reaction with \textit{N}-Bs bromoindole $71c$ led only to decomposition (entries 13-17).

We reasoned that these failures might again be the result of steric crowding at the newly formed quaternary center adjacent to the indole nitrogen. Moreover, although we could synthesize 2-bromoindoles $71$ using known methods, these substrates are unstable due to their electron-rich nature.\cite{33} Thus, the failures might also due to the unstable nature of 2-bromoindoles $71$. Hence, we modified our strategy to access the tronocarpine core $37$ via a strategy involving an intramolecular $\alpha$-arylation of an ester enolate.

**Scheme 15**

![Scheme 15](image)

**Table 5.3 Attempted $\alpha$-Arylation of Diester Alkene 65 with Various Bromoindoles 71**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Temperature</th>
<th>Result</th>
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<td>$R = H$</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>LiHMDS</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>NEt$_3$</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>NEt$_3$</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>NEt$_3$</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>$R = CH_3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>LiHMDS</td>
<td>60 °C</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>8</td>
<td>Pd(dba)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>NaHMDS</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>LiHMDS</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>P(t-Bu)$_3$</td>
<td>NaHMDS</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
</tbody>
</table>
5.1.3 Studies on Pd-Catalyzed Intramolecular α-Arylation Approaches to the Tronocarpine Core

Since the intermolecular Pd-catalyzed ester α-arylation route to the tronocarpine core was problematic (vide supra), we instead envisioned that we could construct the tetracyclic core 35 using an intramolecular Pd-catalyzed coupling of substrate 73, which could in turn be prepared via coupling of tryptamine 74 with diester 39 (Scheme 16).

**Scheme 16**
To examine the feasibility of this intramolecular route, we chose first to investigate aryl bromide amide 78 as a model system (Scheme 17). Our synthetic efforts toward 78 began with the borane reduction of commercially available 2-bromobenzyl cyanide (69b) to amine 75, which was then converted to known N-methylamine 76 in 3 steps.\textsuperscript{34} Using previous Weinreb group methodology, trimethylaluminum was expected to react with the secondary amine 76 providing dimethylaluminum amide intermediate 77.\textsuperscript{35} However, this compound failed to undergo coupling with ester 65 upon gentle warming.\textsuperscript{34,36} Additionally, the use of CaCl\textsubscript{2}, Mg(OCH\textsubscript{3})\textsubscript{2} and MgCl\textsubscript{2} failed to form the amide in 78 with N-methylamine 76.\textsuperscript{37}

As an alternative model, we believed that an amide like 78 might be more easily accessed by direct acylation of 76 (Scheme 18).\textsuperscript{38,39} Interestingly, treatment of amine 76 with acid 79 in the presence of EDC·HCl and NEt\textsubscript{3}, with or without HOBr·H\textsubscript{2}O, failed to produce any of the desired amide 78.\textsuperscript{40} Alternatively, the acid 79 was treated with oxalyl chloride to form the corresponding
acid chloride 80. Crude acid chloride 80 was then treated with secondary amine 76 but unfortunately the desired amide 78 could not be detected. These failures might be due to the steric bulk of the amine 76, slowing the acylation. Faced with this impasse, our focus shifted to the use of primary amine as the coupling partner. Thus, crude acid chloride 80 was treated with primary amine 75 in the presence of NEt$_3$ in CH$_2$Cl$_2$, which yielded the corresponding amide 81 in excellent yield. However, all attempted N-methylations of amide 81 failed to provide the methyl amide 78.

Scheme 18
At this point, we attempted an intramolecular Pd-catalyzed $\alpha$-arylation of substrate $81$ to see if the desired cyclization product $82$ could be obtained (Scheme 19). The reaction was initially attempted with a catalytic amount of Pd(OAc)$_2$ with a variety of additives, bases, solvents and temperatures (Table 5.4, entry 1-12). However, none of the cyclized lactam $82$ was detected. The use of Pd(dba)$_2$ as catalyst with a similar array of additives and bases, such as Na‘OBu (entry 13), NaHCO$_3$ (entry 14), LiHMDS (entry 15), K‘OBu (entry 16), and Cs$_2$CO$_3$ (entry 17), led either to the recovery of starting material or decomposition. When K$_2$CO$_3$ was employed as the base, a small amount of a compound with the correct molecular weight was detected by mass spectrometry. However, after careful study by NMR, it was determined that the product was in fact lactam $83$. We propose that cyclization product $83$ forms preferentially over $82$ via a Heck reaction due to steric inhibition of the formation of the quaternary center in $82$. Different additives, such as BINAP$^4$ (entries 20-22) and PPh$_3$ (entry 23), provided similarly disappointing results. In view of these failures, this route was abandoned.

Scheme 19

Table 5.4 Attempted Intramolecular $\alpha$-Arylation of Amide 81

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
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</thead>
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<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>NEt$_3$</td>
<td>CH$_3$CN</td>
<td>80°C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>NEt$_3$</td>
<td>CH$_3$CN</td>
<td>90°C</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>NEt$_3$</td>
<td>CH$_3$CN</td>
<td>125°C</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>70°C</td>
<td>comp</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>80°C</td>
<td>comp</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>LiHMDS</td>
<td>toluene</td>
<td>80°C</td>
<td>comp</td>
</tr>
</tbody>
</table>
5.2 Revision of the Retrosynthesis of the Tronocarpine Core

Since the ester enolate $\alpha$-arylation route to the tronocarpine core 35 described in the previous sections appeared to be problematic, we instead envisioned that indole could be formed through a Larock/Sonogashira indole synthesis (Scheme 20). Thus, the key indole moiety of the tricyclic skeleton 37 could arise via a Pd-catalyzed cross coupling reaction of iodoaniline 84 with the acetylene moiety in a $\beta$-ketoester such as 85.
5.2.1 Background on the Key Palladium-Catalyzed Annulation of Terminal Alkynes

The impetus for the development of the many recent methods for the efficient construction of the indole moiety has undoubtedly been its prominence in a wide array of natural products, agrochemicals, molecular materials, and pharmaceuticals.26 In contrast to the classical methods for indole preparation, which are severely limited by the nature of the substituents on the ring,42,43 these modern methods, especially Pd-catalyzed cross coupling, allow for greater substrate diversity and regiocontrol (vide infra).

5.2.1.1 Larock Indole Synthesis

Larock and coworkers have developed a method for preparing 2,3-disubstituted indoles using an intermolecular palladium-catalyzed cross coupling reaction of 2-iodoanilines with disubstituted alkynes (Scheme 21, entries 1-4).44,45 Particularly noteworthy are examples that allow for the generation of all-carbon quaternary centers in good yields (entries 1-3). In these reactions, the more hindered substituent of the alkyne aligns with the nitrogen of 84, becoming the C2 substituent of the incipient indole.
The proposed catalytic cycle for the Larock process involves reduction of Pd(OAc)$_2$ to Pd(0) which coordinates with the chloride ion to form ligated Pd(0) species 88, as proposed by Amatore. Oxidative addition of aryl iodide 89 to Pd complex 88 results in metallated intermediate 90, which in turn coordinates alkyne 86 to give intermediate 91. A subsequent regioselective syn-insertion of 86 into the aryl palladium bond gives rise to vinylic palladium intermediate 91, which then undergoes nitrogen displacement of the halide to form the six-membered heteroatom-containing palladacyclic intermediate 92. Reductive elimination regenerates the active catalyst chloride-ligated Pd(0) 88, and liberates the indole 87. The
regioselectivity of the insertion step (90 to 91) likely derives from the more favorable orientation of the aniline ring syn to the less bulky alkyne substituent in vinylic palladium species 93.

The Hideg group has extended the scope of this methodology to terminal alkynes in order to generate 2-substituted indoles.47 Thus, terminal alkyne 96 was reacted with 2-iodoaniline (95) leading to 2-substituted indole 97 (Scheme 23) using a set of conditions similar to those reported by Larock.
5.2.1.2 Indole Synthesis via Sonogashira Coupling

The palladium-catalyzed cross coupling of terminal alkynes 99 with aryl and vinyl halides 98 was first reported by Sonogashira and Hagihara in 1975 (Scheme 25). A copper (I) cocatalyst is generally also employed in these reactions. The coupling of electron-rich alkynes generally proceeds under milder conditions than electron-poor derivatives. Sonogashira coupling reactions of iodoanilines have also been utilized to prepare the indole moiety in substrates that can undergo subsequent 5-endo-dig cyclization (vide infra).

Scheme 25

Sakamoto et al. showed that subjection of a mixture of 2-iodoaniline 101 and terminal alkyne 102 to a combination of Pd(PPh3)Cl2 and CuI provided the corresponding Sonogashira coupling product 103 (Scheme 26). Cyclization of the resulting 2-alkynylaniline 103 with TBAF resulted in formation of the 2-substituted indole 104 with excellent functional groups tolerance.
Another such two-step indole formation method was reported Rutjes and coworkers in their efforts toward synthesis of isotryptophan.\textsuperscript{50} When 2-iodoaniline (105) and alkyne 106 were treated with the typical Sonogashira catalytic mixture of Pd(PPh)\textsubscript{3}Cl\textsubscript{2}/CuI in the presence of NHEt\textsubscript{3} in Et\textsubscript{2}O, the corresponding 2-alkynylanilines 107 were obtained in good yields (Scheme 27). The 2-alkynylaniline 107a cyclized spontaneously in refluxing acetonitrile in the presence of PdCl\textsubscript{2}(MeCN)\textsubscript{2} to form indole 108a in moderate yield. An alternative cyclization method for 107b and 107c involved treatment with AgOTf in refluxing acetonitrile, which led to regioselective formation of cyclization products 108b and 108c, respectively. The high degree of regioselectivity in the cyclization likely is due to the higher affinity of AgOTf for triple bonds over heteroatoms such as nitrogen.
Despite detailed studies by many groups, the exact mechanism for the homogeneous Pd-catalyzed Sonogashira reaction remains unknown due to the difficulty in isolating and characterizing the organometallic intermediates. The generally accepted hypothesis, proposed by Nájera and Chinchilla (Scheme 28), is similar to the proposed mechanism of Larock’s indole synthesis (Cf. Scheme 22). Thus, the oxidative addition of 98 to the active catalyst 109 results in palladium complex 110, which undergoes complexation with alkyne 99 via ligand displacement to give Pd-alkyne complex 111. The acidic terminal alkylic proton is removed by the amine base 112, resulting in intermediate 113. Subsequent reductive elimination of 113 provides coupling product 100 and regenerates the active catalyst 109.
The construction of heteroaromatic rings using copper co-catalyzed Sonogashira cross coupling and subsequent cyclization has been applied to several total syntheses. One such example is an approach to ibogamine (118) by Sinha and coworkers (Scheme 29). Thus, Sonogashira coupling of Boc-protected 2-iodoaniline 114 with terminal alkyne 115 followed by TBAF-mediated annulation afforded 2-substituted indole 117 in acceptable yield. Several subsequent steps led to ibogamine (118).
Scheme 29

The Sonogashira coupling in this indole synthesis method is generally performed under rather mild conditions. However, the subsequent intramolecular heteroannulation often requires the use of strong bases such as metal alkoxides\textsuperscript{53} at high temperatures to achieve the desired conversion. Although mild reaction conditions using palladium,\textsuperscript{54} copper,\textsuperscript{55} fluorides,\textsuperscript{49} Lewis acids,\textsuperscript{56} gold(III),\textsuperscript{57} iodine,\textsuperscript{58} and electrophilic reagents\textsuperscript{59,61} to achieve intramolecular cyclization do exist, they present additional difficulties due to the high costs of handling, separation and refining procedures.\textsuperscript{62} However, a more elegant solution to the aforementioned reactivity/selectivity issues in which the base additive to the Sonogashira coupling also assists in the desired cyclization has been found (\textit{vide infra}).

5.2.1.3 Indole Synthesis via Tandem Sonogashira Coupling/Cyclization

Various indole derivatives can be accessed utilizing a tandem Sonogashira coupling/annulation reaction between \textit{o}-haloanilines and terminal alkynes.\textsuperscript{63} The reactions utilize standard Sonogashira conditions with a Pd-catalyst and CuI as cocatalyst to achieve the cross-coupling, which is followed by spontaneous 5-\textit{endo}-dig cyclization \textit{in situ}. Thus, reaction of 2-indoaniline or protected iodoaniline \textbf{101} with ethynylbenzene (\textbf{119}) afforded the corresponding 2-substituted indole \textbf{121} via Sonogashira coupled intermediate \textbf{120} (Scheme \textbf{30}).\textsuperscript{64} Moreover,
although reactions of aryl iodides comprise the majority of published examples, aryl bromides have also been employed with a similar level of success.

Scheme 30

Just as the standard the Sonogashira coupling can take place with or without the copper cocatalyst, Srinivasan and coworkers have reported a copper-free tandem Sonogashira/cyclization reaction for the synthesis of various C-2 functionalized indole derivatives. Thus, when various substituted or unsubstituted \(N\)-p-toluenesulfonyl- or methanesulfonyl- protected 2-iodoanilines 122 were combined with terminal alkynes 123 in the presence of a catalytic amount of Pd(OAc)\(_2\) and Bu\(_4\)NOAc as base, the corresponding 2-substituted indoles 124 were generated in good yields (Scheme 31). Particularly noteworthy are the examples involving 2-iodoanilines containing electron withdrawing substituents (124\textsuperscript{d}-124\textsuperscript{i}) in which the tandem Sonogashira/cyclization reaction still proceeds in acceptable yields.
Srinivasan and coworkers also utilized a tandem copper-free Sonogashira/cyclization process to access KDR kinase inhibitor 128, which is used in the treatment of certain types of cancer. Thus, iodoaniline 125 and terminal alkyne 126 underwent tandem Pd(OAc)$_2$-catalyzed Sonogashira coupling and cyclization using Bu$_4$NOAc as base in a ligand-, copper-, and amine additive-free reaction to furnish the indole-chloroquinoline 127 (Scheme 32). Subsequent hydrolysis of the 2-chloroquinoline moiety under acidic conditions provided the KDR kinase inhibitor 128 in excellent yield.
Although the Larock indole synthesis and the Sonogashira method are both Pd-catalyzed reactions for indole synthesis, there are three major differences between them. First, the Larock indole synthesis involves the heteroannulation of a 2-iodoaniline with either a terminal alkyne or disubstituted alkyne to provide a 2-substituted indole or a 2,3-disubstituted indole. In contrast, the Sonogashira process is characterized by the coupling of an aryl or vinyl halide with a terminal alkyne to give an enyne or 2-substituted indole. Thus, the Larock heteroannulation is limited to the synthesis of indoles, while Sonogashira coupling is not. Moreover, although both reactions are Pd-catalyzed, and the use of Cl ion was found to be necessary for the reproducibility of the Larock indole synthesis, while the Sonogashira reaction usually requires Cu as a cocatalyst. Finally, the Sonogashira coupling reaction is usually conducted at a lower temperature compared to the Larock indole synthesis.

5.2.2 Pd-Catalyzed Coupling Approaches to the Tronocarpine Core

Due to the broad synthetic utility of palladium-catalyzed annulation methods, we decided to attempt to utilize this approach to construct the indole moiety of the tronocarpine core 37. To this end, we first sought to prepare an appropriately functionalized alkyne to couple with 2-iodoaniline. Thus, we reasoned a model keto diester alkyne 131 could be accessed from keto diester 129 via alkynylation, decarboxylation, and reduction/elimination of the ketone.

Scheme 33
Alkynyl halides have been shown by Jørgensen and coworkers to be effective coupling partners in nucleophilic acetylenic substitution reactions when paired with an appropriate base and chiral phase transfer catalyst and a β-keto ester. For example, it was shown that halo alkyne 133 coupled with β-keto ester 132 in the presence of a phase transfer catalyst O-1-Adamantoyl-N-9-anthracenylmethyl dihydrocinchonium chloride and base to afford the alkynylated products 134 in high yields at -20 °C (Scheme 34).

Scheme 34

Thus, we sought to prepare alkynyl diester olefin 131 via a variation of Jørgensen’s method. However, treatment of keto diester 129 with methyl bromopropionate (135), prepared from commercially available methyl propionate, along with NBu₄Br using a variety of inorganic bases at -20 °C failed to provide any of the desired α-alkynyl-β-ketodiester 130. Increasing the reaction temperature had no measurable effect on the reaction.
Since α-alkynylation of ketoester 129 did not provide alkynylated product 130, alkynylation of corresponding ester alkene 65 was also briefly examined (Scheme 36). Accordingly, diester alkene 65 was treated with methyl 3-bromopropiolate (135) in the presence of various bases in attempts to generate alkynylated product 136. However, the desired coupling product 136 could not be generated under any conditions.

We therefore sought an alternative preparation for alkyne 140. Waser and coworkers have reported that ethynyl-1,2-benziodoxol-3(1H)-one (EBX, 138), which is generated in situ from corresponding silyl-protected reagent (TMS-EBX, 137), is a good reagent for the ethynylation of β-ketoesters. Thus, conjugate addition of β-ketoester 139 to EBX (138), generated from TMS-EBX (137) in the presence of the fluoride source TBAF, provides intermediate 141, which spontaneously eliminates to yield carbene 142 (Scheme 37). Subsequent 1,2-hydride shift then provides the adduct 140 in 88% yield.
We therefore sought to apply this alkylation method to the formation of α-alkynyl-β-diesters. However, subjecting keto diester 129 to the Waser conditions failed to provide any of desired alkyne 143 (Scheme 38). In addition, treatment of keto diester 129 with 137 and bases such as KO’Bu, NaH, or LiHMDS, followed by TBAF, produced none of the desired alkyne 143.
Since keto diester 129 failed to undergo the desired ethynylation with TMS-EBX (137), our focus shifted instead to the alkoxy carbonylation of previously synthesized alkyne 140 (Scheme 139). Thus, treatment of a mixture of dimethyl carbonate and alkyne 140 with NaH in a variety of solvents at different temperatures led only to the recovery of starting material (Table 5.5, entries 1 and 2). Acylations with ethyl cyanofomate or methyl chloroformate were also attempted with various bases (entries 3-8). However, none of these conditions produced any of the desired product 143. Indeed, ketone 140 was unreactive even with a large excess of methyl chloroformate using NaH at several temperatures (entries 9-11).

Scheme 139

![Scheme 139](image)

Table 5.5 Attempted Alkoxy carbonylation of Alkyne 140

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Carbonylation Agent</th>
<th>Additive</th>
<th>Temperature</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>0 °C</td>
<td>THF</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>rt</td>
<td>DMF</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>ethyl cyanofomate</td>
<td>HMPA</td>
<td>-78 °C - 0 °C</td>
<td>THF</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>ethyl cyanofomate</td>
<td>-</td>
<td>-78 °C - 0 °C</td>
<td>THF</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>methyl chloroformate</td>
<td>-</td>
<td>rt</td>
<td>DMF</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>methyl chloroformate</td>
<td>-</td>
<td>-78 °C - 0 °C</td>
<td>THF</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>methyl chloroformate</td>
<td>-</td>
<td>0 °C - rt</td>
<td>THF</td>
</tr>
<tr>
<td>8</td>
<td>nBuLi</td>
<td>methyl chloroformate</td>
<td>-</td>
<td>0 °C - rt</td>
<td>THF</td>
</tr>
<tr>
<td>9</td>
<td>NaH (15 eq)</td>
<td>methyl chloroformate (30 eq)</td>
<td>-</td>
<td>rt</td>
<td>DMF</td>
</tr>
<tr>
<td>10</td>
<td>NaH (15 eq)</td>
<td>methyl chloroformate (30 eq)</td>
<td>-</td>
<td>0 °C - rt</td>
<td>DMF</td>
</tr>
<tr>
<td>11</td>
<td>NaH (15 eq)</td>
<td>methyl chloroformate (30 eq)</td>
<td>-</td>
<td>-78 °C - rt</td>
<td>DMF</td>
</tr>
</tbody>
</table>
Since we felt that the alkyne proton might be causing a problem in these acylation reactions, we sought to prepare TMS-protected alkyne 144 via silylation of alkyne 140. However, reaction of terminal alkyne 140 with TMSCl under various reaction conditions failed to provide any of the desired TMS derivative 144 but rather led to only decomposition (Scheme 140). Given the difficulty in preparing α-alkynyl-β-keto diester 143, we decided to explore the feasibility of the Pd-catalyzed annulation strategy toward tronocarpine (1) with α-alkynyl-β-keto ester 140 as a model.

Scheme 140

At the outset our studies, we planned to access the indole moiety in tronocarpine (1) using a Larock indole synthesis (Scheme 141). Thus, commercially available 2-iodoaniline (105) and alkyne 140 were combined in DMF with Pd(OAc)$_2$, various bases and additives at several temperatures (Table 5.6). When the phase transfer catalyst $^t$Bu$_3$NCl was employed, decomposition resulted regardless of the base used (entry 1-2). When LiCl was used, similar disappointing results were observed (entry 3-10). The use of a soluble base such as LDA also failed to give any appreciable product (entries 11 and 12). When PPh$_3$ and $^t$Bu$_3$NCl were used as additives, various bases were employed at several temperatures. The use of K$_2$CO$_3$ (entries 13-16) and Na$_2$CO$_3$ (entry 17) provided only decomposition products. Interestingly, when KOAc was employed as base, on one occasion the reaction provided the desired indole 145 at 90 °C (entry
18). However, this reaction was not reproducible under seemingly identical conditions. When a lower temperature (80 °C) was employed, the reaction did not proceed at all (entry 19), while higher temperature (100 °C) gave undesired decomposition products (entry 20).

Scheme 141

Table 5.6 Attempted Larock Indole Synthesis of 2-Iodoaniline (105) and Alkyne 140

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>$n$Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>90 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>$n$Bu$_4$NCl</td>
<td>KOAc</td>
<td>90 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>K$_2$CO$_3$</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>K$_2$CO$_3$</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>K$_2$CO$_3$</td>
<td>90 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>K$_2$CO$_3$</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>KOAc</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>KOAc</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>KOAc</td>
<td>90 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>LiCl</td>
<td>KOAc</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>LDA</td>
<td>65 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>LDA</td>
<td>85 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>90 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>16</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>17</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>Na$_2$CO$_3$</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>18</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>KOAc</td>
<td>90 °C</td>
<td>XX</td>
</tr>
<tr>
<td>19</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>KOAc</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>20</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, $n$Bu$_4$NCl</td>
<td>KOAc</td>
<td>100 °C</td>
<td>decomp</td>
</tr>
</tbody>
</table>
We reasoned that the free amino group of 2-iodoaniline (105) might somehow be impeding the coupling process and thus prepared sulfonamide 146 to attempt the annulations (Scheme 142). A N-tosyl group was chosen based upon literature precedent for its use in tandem Sonogashira/heteroannular reactions to form indoles.51 A variety of reaction conditions were screened, using catalytic Pd(OAc)$_2$, various additives, and bases including soluble (Table 5.7, entries 1-4) and insoluble ones (entries 5-15). However, none of the desired N-Ts indole 147 could be isolated under any of these conditions.

Scheme 142

![Scheme 142](image)

Table 5.7 Attempted Larock Indole Synthesis of Iodoaniline 146 and Alkyne 140

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>LDA</td>
<td>DMF</td>
<td>65 °C</td>
<td>comp</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>LDA</td>
<td>DMF</td>
<td>85 °C</td>
<td>comp</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>NEt$_3$</td>
<td>DMF</td>
<td>65 °C</td>
<td>comp</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, Cul</td>
<td>NEt$_3$</td>
<td>DMF</td>
<td>85 °C</td>
<td>comp</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>70 °C</td>
<td>comp</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>90 °C</td>
<td>comp</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>50 °C</td>
<td>comp</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>60 °C</td>
<td>comp</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>65 °C</td>
<td>comp</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>70 °C</td>
<td>comp</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>80 °C</td>
<td>comp</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>90 °C</td>
<td>comp</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)$_2$</td>
<td>n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>70 °C</td>
<td>comp</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)$_2$</td>
<td>n-Bu$_4$NCl</td>
<td>KOAc</td>
<td>DMF</td>
<td>80 °C</td>
<td>comp</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)$_2$</td>
<td>-</td>
<td>n-Bu$_4$NOAc</td>
<td>MeCN</td>
<td>30 °C</td>
<td>comp</td>
</tr>
</tbody>
</table>
Given our failure to effect the annulations using the Larock indole synthesis, we instead turned to tandem Sonogashira/heteroannulation methodology (Scheme 143). Using the cocatalysts Pd(PPh₃)₂Cl₂ and CuI with NEt₃ as base, 2-iodoaniline (105) and alkyne 140 were reacted at a variety temperatures, leading only to recovery of starting material or decomposition (Table 5.8, entries 1-4). The use of Pd(PPh₃)₄ as catalyst also failed to provide the desired product (entry 5).

![Scheme 143](image)

Table 5.8 Attempted Tandem Sonogashira Coupling/Cyclization of 2-Iodoaniline (105) and Alkyne 140

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>CuI</td>
<td>NEt₃</td>
<td>60 °C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>CuI</td>
<td>NEt₃</td>
<td>80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>CuI</td>
<td>NEt₃</td>
<td>100 °C</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>CuI</td>
<td>NEt₃</td>
<td>120 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh₃)₄</td>
<td>CuI</td>
<td>NEt₃</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
</tbody>
</table>

We presumed that the free amine in 2-iodoaniline (105) was again interfering with the reaction, and thus attempted a similar reaction with N-Ts-protected iodoaniline 146. When sulfonamide 146 was combined with alkyne 140 under the tandem Sonogashira coupling conditions using cocatalytic Pd(PPh₃)₂Cl₂ and CuI, NEt₃ as base at 60 °C, the desired indole 147 was isolated in 75% yield. Increasing the reaction temperature to 80 °C provided no improvement in yield, with increasing amounts of decomposition being observed.
With an efficient route to indole 147 now in hand, we next turned our attention to alkoxy carbonylation in order to prepare the key substrate for lactamization (Scheme 145). However, treatment of keto ester 147 with a variety acylating agents including dimethyl carbonate (Table 5.9, entries 1-4) and alkyl cyanoformates (entries 5-9) failed to provide the corresponding keto diester 148. When we examined acylation of indole 147 with methyl chloroformate (entries 11-14), no reaction occurred at room temperature or upon warming of the reaction mixture. The use of the bases LDA or LiHMDS led to exclusive formation of a compound with the correct molecular weight as determined by mass spectrometry (entries 12-14). However, after careful examination of the product via NMR, it was determined that the undesired \( O\)-acylation compound 149 had instead been produced.

### Scheme 145

\[
\begin{align*}
\text{147} & \xrightarrow{\text{DMF}} \text{148, 149}
\end{align*}
\]

### Table 5.9 Attempted Alkoxy carbonylation of Keto Ester 147

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Ester Derivative</th>
<th>Additive</th>
<th>Temperature</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>-78 °C</td>
<td>THF</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>rt</td>
<td>DMF</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>40 °C</td>
<td>DMF</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>dimethyl carbonate</td>
<td>-</td>
<td>rt</td>
<td>THF</td>
</tr>
</tbody>
</table>
We next attempted to utilize the mild alkoxy carbonylation method recently demonstrated by Hale and coworkers,\textsuperscript{70} to prepare C-acylation compounds using an alkyl pentafluorophenylcarbonate (150) as the reactive acylating agent. However, when substrates 147 and 140 were treated with methyl pentafluorophenylcarbonate (150) in the presence of MgBr\textsubscript{2}Et\textsubscript{2}O, DMAP and \textit{i}-Pr\textsubscript{2}NEt, only starting material was observed at various temperatures in both cases (Scheme 146).

\textbf{Scheme 146}
We next decided to attempt the analogous alkoxycarbonylation sequence on the \( N\)-H indole 145. However, strongly basic and reducing detosylation conditions on 147 were problematic due to the presence of the ketone functionality. When \( N\)-tosyl cleavage was attempted using Mg, with or without \( \text{NH}_4\text{Cl} \),\textsuperscript{71} decomposition or polymerization of starting material was observed (Scheme 147). When reductive cleavage of N-S bond was attempted using sodium naphthalenide\textsuperscript{72} the starting material was recovered. Moreover, the use of mild bases\textsuperscript{73} such as \( \text{Cs}_2\text{CO}_3 \), \( \text{Na}_2\text{CO}_3 \), and \( \text{K}_2\text{CO}_3 \) failed to remove the tosyl group, leading to an unidentified side product.

Scheme 147

**Deprotection Conditions:**
1. SMEAH, o-xylene
2. Mg, \( \text{CH}_3\text{OH} \)
3. Mg, \( \text{NH}_4\text{Cl}, \text{CH}_3\text{OH}:\text{THF} \ (1:1) \)
4. Mg, \( \text{NH}_4\text{Cl}, \text{CH}_3\text{OH} \)
5. NaH, cyclohexanol, THF
6. Na, naphthalene, THF, \(-78 \text{ °C} \) - rt
7. \( \text{NaOCH}_3, \text{CH}_3\text{OH} \)
8. TBAF, THF, rt - 70 °C
9. Na(Hg), \( \text{Na}_2\text{HPO}_4 \), \( \text{CH}_3\text{OH} \), \(-78 \text{ °C} \) - 40 °C
10. SmI\(_2\), DMPU, THF, 70 °C
11. \( \text{Cs}_2\text{CO}_3 \), \( \text{CH}_3\text{OH}:\text{THF} \ (1:2) \)
12. \( \text{Na}_2\text{CO}_3 \), \( \text{CH}_3\text{OH}:\text{THF} \ (1:2) \)
13. \( \text{K}_2\text{CO}_3 \), \( \text{CH}_3\text{OH}:\text{THF} \ (1:2) \)
5.2.2.3 Attempted Indole Synthesis Using a Carbamate Protecting Group

Since detosylation of the indole nitrogen in 147 appeared problematic, we next investigated the use of electron withdrawing N-protecting groups on the 2-iodoaniline that would be easier to remove. Thus, benzyl 2-iodophenylcarbamate (150)\textsuperscript{74} and \textit{tert}-butyl 2-iodophenylcarbamate (114)\textsuperscript{75} were prepared according to literature procedures (Scheme 148).

\textbf{Scheme 148}

![Scheme 148](image)

When \textit{N}-Cbz-protected iodoaniline 150 and alkyne 140 were subjected to the reaction conditions optimized for \textit{N}-Ts-\textit{o}-iodoaniline (146) (Cf Scheme 147), none of the desired indole 151 was produced (Scheme 149), with only a trace of Sonogashira coupling product 153 isolated instead (Table 5.10, entry 1). Although some of the Sonogashira product was isolated if the reaction was run at 40 °C, the reaction was very sluggish (entry 2). Optimal conditions for the formation of indole 153 were found to occur at 50 °C (entry 3). However, none of the desired heteroannulation indole product 151 could be detected. When \textit{N}-Cbz 2-iodoaniline (150) was subjected to the Larock indole synthesis conditions optimized for \textit{N}-H iodoaniline 105 (Cf. Table 5.6, entry 18), the result was decomposition of the starting material regardless of temperature used (entries 4 and 5).

Similarly, when \textit{N}-Boc-2-iodoaniline (114) and alkyne 140 were subjected to the reaction conditions optimized for \textit{N}-Ts iodoaniline, none of the desired product 152 was produced, but rather only resulted in the decomposition of starting material (entries 6 and 7). When \textit{N}-Boc-\textit{o}-iodoaniline (114) was subjected to the Larock indole synthesis conditions optimized for \textit{N}-H iodoaniline 105, a trace of the Sonogashira coupling product 154 was isolated (entry 8). Optimal
conditions for the formation of 154 were found to occur at 40 °C (entry 9). Similar to N-Cbz protected iodoaniline 150, none of the desired heteroannulation product 152 could be detected.

Scheme 149

Table 5.10 Attempted Tandem Sonogashira Coupling of Carbamate Protected Iodoanilines and Alkyne 140

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R = Cbz</td>
<td>Pd(PPh3)2Cl2</td>
<td>Cul</td>
<td>NEt3</td>
<td>60 °C</td>
<td>153+decomp</td>
</tr>
<tr>
<td>2 R = Cbz</td>
<td>Pd(PPh3)2Cl2</td>
<td>Cul</td>
<td>NEt3</td>
<td>40 °C</td>
<td>Sm + 153</td>
</tr>
<tr>
<td>3 R = Cbz</td>
<td>Pd(PPh3)2Cl2</td>
<td>Cul</td>
<td>NEt3</td>
<td>50 °C</td>
<td>153 (64%)</td>
</tr>
<tr>
<td>4 R = Cbz</td>
<td>Pd(OAc)2</td>
<td>PPh3, n-Bu4NCl</td>
<td>KOAc</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>5 R = Cbz</td>
<td>Pd(OAc)2</td>
<td>PPh3, n-Bu4NCl</td>
<td>KOAc</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>6 R = Boc</td>
<td>Pd(PPh3)2Cl2</td>
<td>Cul</td>
<td>NEt3</td>
<td>60 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>7 R = Boc</td>
<td>Pd(PPh3)2Cl2</td>
<td>Cul</td>
<td>NEt3</td>
<td>80 °C</td>
<td>decomp</td>
</tr>
<tr>
<td>8 R = Boc</td>
<td>Pd(OAc)2</td>
<td>PPh3, n-Bu4NCl</td>
<td>KOAc</td>
<td>60 °C</td>
<td>154+decomp</td>
</tr>
<tr>
<td>9 R = Boc</td>
<td>Pd(OAc)2</td>
<td>PPh3, n-Bu4NCl</td>
<td>KOAc</td>
<td>40 °C</td>
<td>154 (36%)</td>
</tr>
</tbody>
</table>

Since we were unable to effect the desired tandem Sonogashira/heteroannulation sequence with carbamate derivatives, the two-step sequence was instead attempted. Thus, carbamate-protected Sonogashira alkynes 153 and 154 were treated with mild bases such as TBAF and a palladium catalyst since the ketone functionality prohibited the use of strong bases (Scheme 150). Despite attempting the reaction under a host of mild cyclization conditions, the desired indole keto esters 151 and 152 could not be isolated.
We attributed the failure of Sonogashira products 153 and 154 to cyclize in part to the bulky protecting group on the amine nitrogen. Thus, to resolve this issue, we attempted the heteroannulation sequence on the NH Sonogashira-type product 155. After some experimentation, conditions for removal of the Boc protecting group in 154 were found using TFA in CH₂Cl₂ at room temperature (Scheme 151). However, the attempted cyclization of alkyne amine 155 under various conditions failed to provide any of the desired indole product 145, with only decomposition being observed. Thus, we concluded that carbamate protection of the amino nitrogen would not be serviceable and shifted our attention to other electron withdrawing groups.
5.2.2.4 Attempted Indole Synthesis Using an Acetamide Protecting Group

Since Sakamoto et al. reported the successful tandem Sonogashira/heteroannulation of (2-iodophenyl)acetamide (156) to produce free indole 158 in one step (Scheme 152),76 we decided to utilize an acetate protecting group for the tronocarpine system. In this reaction, TBAF serves as both the base for the formation of indole as well as the subsequent protecting group cleavage to the free NH indole.

Thus, we prepared N-(2-iodophenyl)acetamide (156) from the corresponding 2-iodoaniline (105),77 and subjected it and alkyne 140 to Sakamoto’s conditions. However, all attempts to effect the desired cyclization met with failure, regardless of the combination of Pd catalysts, additives, bases, and temperature employed (Scheme 153).
5.2.2.5 Attempted Indole Synthesis via Other Sulfonamide Protecting Groups

We reasoned that the strongly electron withdrawing nature of an $N$-sulfonyl group provided the ideal reactivity for the Pd-catalyzed cross coupling/heteroannulation reactions.\textsuperscript{62} Thus, given our previous success with the $N$-Ts protecting group (vide supra) and the corresponding failures of $N$-Boc, Cbz, and Ac, we attempted the tandem coupling/heteroannulation on substrates bearing potentially more easily cleavable $N$-sulfonyl protecting groups. Thus, we prepared sulfonamides 160-163 from 2-iodoaniline (105) via conventional methods and subjected these substrates to the coupling with alkynyl ketoester 140.\textsuperscript{78}
The reaction of \(N\)-(2-iodophenyl)methanesulfonamide (160) with alkyne 140 catalyzed by Pd failed to provide any measurable quantity of the indole 165, regardless of additives, solvents, and temperature employed (Scheme 155).

**Scheme 155**

\[
\begin{align*}
\text{160} & \quad \text{140} \\
\text{ArI} & \quad \text{CO}_{2}\text{CH}_3 \\
\text{N} & \quad \text{C} \\
\text{H}_2\text{CO} & \quad \text{O} \\
\text{M} & \quad \text{N} \\
\end{align*}
\]

Pd Catalyst: \(\text{Pd(OAc)}_2\), \(\text{Pd(PPh}_3)_2\text{Cl}_2\),
Additive: \(\text{PPh}_3\), \(\text{Bu}_3\text{NOCl}\), \(\text{CuI}\), \(\text{LiCl}\),
Base: \(\text{KOA}\), \(\text{NEt}_3\), \(\text{TBAF}\), \(\text{KOAc}\), \(\text{Bu}_3\text{NOAc}\), \(\text{TMG}\),
Solvent: \(\text{DMF}\), \(\text{CH}_3\text{CN}\),
Temperature: \(\text{rt}, 40^\circ\text{C}, 60^\circ\text{C}, 70^\circ\text{C}, 80^\circ\text{C}, 100^\circ\text{C}\)

However, we were pleased to discover that treatment of \(N,N\)-dimethylsulfamoyl amide-protected iodoaniline 161 and alkyne 140 with a combination of \(\text{Pd(PPh}_3)_2\text{Cl}_2\) and \(\text{CuI}\) as catalyst at 80 °C afforded a trace of the desired indole 166 (Scheme 156). When the reaction temperature was lowered to 70 °C, the yield of indole 166 was improved to 30%. However, further decreasing the reaction temperature afforded no improvement in yield. We next sought to find appropriate deprotection conditions for indole 166 and thus screened a variety of methods. However, attempted deprotection of indole 166 with TBAF, \(\text{SmI}_2\)-DMPU, and various acidic reagents all led to decomposition.
We next attempted the cross-coupling/heteroannulation of 2,4-dinitrobenzenesulfonamide iodoaniline 162 and alkyne 140, but under no conditions we were able to effect the desired reaction to form indole 167 (Scheme 157).

However, we were pleased to discover that cross coupling/heteroannulation with 4-nitrobenzenesulfonamide iodoaniline 162 and alkyne 140 cleanly afforded the desired protected indole 168 in excellent yield (Scheme 158). Moreover, we were able to effect a mild deprotection of 168 with PhSH in the presence of carbonate $K_2CO_3$ and $Cs_2CO_3$ to furnish the free indole 145. We later
found that by raising the Sonogashira/heteroannulation reaction temperature to 80 °C, the deprotected NH indole 145 could be isolated directly in acceptable yield, thus performing three transformations in a single synthetic operation. We hypothesize that the NEt₃ base functions as both the cyclization and deprotection reagent.

Our success was short lived, however, since the attempted alkoxy carbonylation of 168 with LiHMDS and methyl chloroformate led to the exclusive formation of undesired O-acylate compound 169. Similar, deprotection of the O-acylate compound 169 provided the corresponding indole 170.

**Scheme 158**

---

163 + 140 → 145

**Pd(PPh₃)₂Cl₂, Cul**

NEt₃, DMF, 80 °C

80%

168

**LiHMDS**

methyl chloroformate

THF, -78 °C, 90%

169 R=nosyl

PhSH, K₂CO₃, CH₃CN

170 R=H
5.3 Studies on the Formation of the Lactam Ring

5.3.1. Attempted Direct Installation of a C-3 Nitroethylene Unit onto Indoles 145 and 147

In order to move forward with testing same step of the total synthesis, we decided to attempt the C3-functionalization of indole 145 with a nitroethylene synthetic equivalent in order to install the caprolactam moiety with of tronocarpine (1). To this end, the free indole 145 was treated with commercially available 1-dimethylamino-2-nitroethylene (10) in the presence of TFA at a variety of temperatures (Scheme 159). However, the desired 3-functionlized indole 171 could not be detected. Similarly, transformation with the N-tosyl indole 147 led only to the recovery of the starting material.

We next decided to attempt a one-pot reductive alkylation of indole using the N-protected aminoethyl acetal 174 in the presence of TFA and triethylsilane as reported by Piersanti et al. to install the desired functionality at C3 (Scheme 160). However, despite the reported tolerance of an array of sterically demanding C2-functionalities on 175, we were unable to prepare the desired C3-alkylated indole 176 as either N-H or N-Ts derivatives.
With an efficacious direct route to a C3-nitroethylene indole eluding us, we next decided to explore a more indirect route involving one carbon homologation of 3-formyl indole 177. To this end, Vilsmeier-Haack formylation of indole 145 furnished the requisite aldehyde 177 in excellent yield (Scheme 161). Subjection of aldehyde 177 to Henry reaction conditions using CH$_3$NO$_2$ was attempted using a variety of soluble bases, such as TBAF (entry 1),$^{85}$ NEt$_3$ (entry 2), TMG (entry 3), and TMEDA (entry 4) and insoluble bases such as NH$_4$OAc (entries 5-11),$^{86}$ KOAc (entry 12),$^{87}$ K$_2$CO$_3$ (entry 13), Al$_2$CO$_3$ (entries 14 and 15),$^{88,89}$ K$_3$PO$_4$ (entry 16), imidazole (entry 17), and Amberlyst A21.$^{90}$ However, all attempts to produce 171 or 178 met with failure. In addition, attempted reactions with ethylenediamine diacetate resulted in decomposition.$^{91}$
Table 5.11 Attempted Henry Reaction of Aldehyde 177

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Drying Agent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF</td>
<td>-</td>
<td>THF</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>NEt₃</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>unknown</td>
</tr>
<tr>
<td>3</td>
<td>TMG</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>4</td>
<td>TMEDA</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>SM+decomp</td>
</tr>
<tr>
<td>5</td>
<td>NH₄OAc</td>
<td>-</td>
<td>CH₃OH</td>
<td>rt</td>
<td>unknown</td>
</tr>
<tr>
<td>6</td>
<td>NH₄OAc</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>unknown</td>
</tr>
<tr>
<td>7</td>
<td>NH₄OAc</td>
<td>-</td>
<td>-</td>
<td>90 °C</td>
<td>unknown</td>
</tr>
<tr>
<td>8</td>
<td>NH₄OAc</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>unknown</td>
</tr>
<tr>
<td>9</td>
<td>NH₄OAc</td>
<td>Na₂SO₄</td>
<td>-</td>
<td>75 °C</td>
<td>unknown</td>
</tr>
<tr>
<td>10</td>
<td>NH₄OAc</td>
<td>4ÅMS</td>
<td>-</td>
<td>75 °C</td>
<td>unknown</td>
</tr>
<tr>
<td>11</td>
<td>NH₄OAc/acetic acid</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>unknown</td>
</tr>
<tr>
<td>12</td>
<td>KOAc</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>13</td>
<td>K₂CO₃</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>14</td>
<td>Al₂O₃ (neutral)</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>15</td>
<td>Al₂O₃ (basic)</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>16</td>
<td>K₃PO₄</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>17</td>
<td>imidazole</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>18</td>
<td>Amberlyst A21</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>decomp</td>
</tr>
</tbody>
</table>
Since the Henry reaction of 3-formyl indole 177 was problematic, an observation we have attributed, in part, to competitive deprotonation of the indole NH, we attempted to explore the sequence with an $N$-protected indole-3-carboxaldehyde 179. Thus, we attempted the protection of NH indole aldehyde 177 (Scheme 162), followed by a Henry reaction. To this end, the free indole-3-carboxaldehyde 177 was treated with a variety of reagents such as CbzCl, MeI and TsCl under mildly basic conditions in order to avoid competitive reaction with the labile keto ester moiety. However, none of the attempted reactions led to any desired $N$-protected product.

**Scheme 162**

Since the indole nitrogen could not be easily reprotected at this stage, we decided to explore an alternative formylation procedure, this time employing the $N$-Ts indole ketoester 147. Thus, indole 147 was treated with TiCl$_4$ and dichloromethyl methyl ether according to the procedures of Schlueter and Spin (Scheme 163). However, these reactions resulted in decomposition along with the recovery of a small amount of starting material.
We next decided to attempt a one-pot indirect nitroaldol reaction reported by Williams and coworkers that involved iridium as the catalyst to install the requisite nitroethylene moiety at C3 (Scheme 164). The reaction proceeds via the transfer of a “borrowed hydrogen.” The treatment of alcohol 182 with combination of a catalytic amount of [Ir(COD)Cl]2 and dppp in the presence of Cs₂CO₃ generates intermediate 184 via temporary removal of a “borrowed hydrogen.” This intermediate is then converted into nitrostyrene 185 via a nitroaldol reaction. The “borrowed hydrogen” is then returned to the alkene to form the corresponding saturated nitro compound 183 in 44% yield, along with 7% of aldehyde 184 and 22% of nitrostyrene 185.
Despite having been used little in total synthesis, we hoped that we could apply this novel catalytic reaction to the preparation of nitro compound 188 (Scheme 165). To this end, attempted selective reduction of the aldehyde moiety of indole 177 using one equivalent of NaBH₄ at -78 °C failed to give the desired alcohol 187 but rather only unidentified by-products were produced. We reasoned that the failure may be due to the competitive reduction of the ketone moiety of indole 177. Thus, several attempts were made to protect the ketone, but all failed perhaps due to steric crowding with the formed quaternary center and the newly introduced acetal. Additionally, treatment of free indole 145 with formaldehyde in aqueous THF at 70 °C only led to decomposition of starting material. ⁹⁵

Scheme 165

5.3.2 Attempted Indirect Installation of a C-3 Aminoethyl Unit into Indole 147

We also attempted to install a C-3 aminoethyl moiety using a Pd-catalyzed Heck coupling of N-vinylphthalimide (190) with indole-3-bromide 189 to afford the α,β-unsaturated phthalimide 191, according to the method of Nájera and coworkers. ⁹⁶ Subsequent hydrogenation of the corresponding Heck product 191 using Wilkinson’s catalyst and subsequent hydrazinolysis
would provide indole-3-ethylamine 192. Thus, treatment of N-Ts indole 147 with Br₂ or NBS produced the corresponding 3-bromoindole 189 in good yield. This bromoindole 189 was subjected to a Heck coupling with N-vinylphthalimide (190) under a variety of conditions. However, none of the desired coupling product 191 was detected.

Scheme 166

5.3.3 Attempted Installation of a C-3 Acetonitrile Unit onto Indole 177

Since the installation of a C-3 nitroethylene or aminoethyl unit onto our indole system appeared problematic, we shifted our focus to the conversion of 3-formyl NH indole 177 to the corresponding indole-3-acetonitrile 194. Bergman and coworkers have shown that exposure of 3-formyl indoles in CH₃CN to TMSCN furnishes the corresponding cyanohydrin silyl ethers during their efforts to synthesize the marine alkaloids rhopaladins A, B, C and D. We hoped to employ an analogous transformation on our indole-3-carboxaldehyde 177 to provide cyanohydrin silyl ether 193, which we could subsequently transform to the corresponding indole-3-acetonitrile
or the corresponding indole-3-ethylamine 195 (Scheme 167). However, subjection of indole-3-aldehyde 177 to Bergman’s reaction conditions at room temperature, as well as at 40 °C, only led to the recovery of starting material (Table 5.12, entries 1 and 2). When the temperature was raised to 60 °C, a trace amount of cyanohydrin silyl ether 193 was detected via mass spectrometry but the product yield was too low to be of synthetic use. In fact, the reaction was irreproducible using any variations in temperature and in several runs only starting material was recovered. The use of the more polar solvent CH$_3$OH also failed to provide any of the desired cyanohydrin silyl ether 193 (entry 4).  

The use of the Lewis acid ZnI$_2$ as an additive has been shown to catalyze cyanohydrins formation. However, this modification was not effective in our system. Molecular iodine I$_2$ was also investigated as an additive, and in fact did on one occasion provide the desired cyanohydrin silyl ether 193 but only in trace amount.

**Scheme 167**

![Scheme 167](image)

**Table 5.12 Attempted Conversion of Aldehyde 177 to Cyanohydrin Silyl Ether 193**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>CH$_2$CN</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>CH$_2$CN</td>
<td>40 °C</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>CH$_2$CN</td>
<td>60 °C</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>CH$_3$OH</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>ZnI$_2$</td>
<td>CH$_2$CN</td>
<td>rt</td>
<td>decomp</td>
</tr>
<tr>
<td>6</td>
<td>I$_2$</td>
<td>CH$_2$CN</td>
<td>rt</td>
<td>trace</td>
</tr>
</tbody>
</table>
We next explored the feasibility of C3-functionalization of indole ketoester 145 and 168 with the Eschenmoser salt (196) in order to generate gramine 197. Subsequent quaternization of 197, followed by nucleophilic displacement with cyanide would then provide the nitrile homologue 198 (Scheme 168). Unfortunately, however, the Mannich reaction of the free indole 145 could not be effected despite the use of an array of temperatures and solvents (Table 5.13, entries 1-7). When indole 145 and dimethylmethylene ammonium chloride (196) were reacted in DMF at 35 °C, a complex mixture of products resulted (entry 2). Although mass spectrometric analysis of this mixture revealed a signal corresponding to the mass of the desired product 197a, the mixture could not be separated chromatographically and the reaction was irreproducible on a larger scale. All other attempts to use dimethylmethylene ammonium chloride (196) with indole 145 met with failure with either decomposition or starting material recovery being the only result. Similarly, the Mannich reaction of the N-protected indole 168 could not be effected despite the use of a variety of temperatures (entries 8-10), although mass spectrometric analysis of the mixture revealed a signal corresponding to the mass of the desired product 197b.

Scheme 168

Table 5.13 Attempted Conversion of Indoles 145 and 168 to Gramine 197

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>35 °C</td>
<td>crude mass = 329.1</td>
</tr>
</tbody>
</table>
3. DMF 40 °C  SM+decomp
4. DMF 50 °C  decom
5. CHCl₃ rt  SM
6. CHCl₃ 35 °C  SM+decomp
7. CHCl₃ 40 °C  decom
R = Ns
8. DMF 40 °C  crude mass = 513.3
9. DMF 55 °C  crude mass = 513.3
10. DMF 80 °C  decom

5.3.4 Attempted Installation of a C-3 Acrylate Ester Unit onto Indole 145

Since we were unable to effect the direct installation of an ethylamino unit at C3, we next decided to explore a more indirect method that incorporates acrylate ester at C3. A reduction of ester in 200 would provide corresponding acid 201. The acid moiety in 201 could then be converted to the amine 202 via a hydrogenation followed by a Schmidt rearrangement using diphenylphosphoryl azide (Scheme 169). Wu and coworkers have reported such a method involving treatment of indole with ethyl propiolate using PtCl₂ catalysis at high temperature, which produced indole-3-acrylate ester. Thus, we subjected indole ketoester 145 to the Wu conditions as well as an alternative method using a catalyst system of FeCl₃/AgOTf. However, neither reaction provided any of the desired indole-3-acrylate ester 200.

Scheme 169
Given the failure of the metal-catalyzed reactions shown above, we next investigated a Wittig-type homologation of indole-3-carboxaldehyde 177 which could allow access the desired C3-acrylate ester 200 (Scheme 170). However, neither the classical Wittig triphenylphosphorane 203 nor the Emmons-Horner-Wadsworth modified reagents 204 and 205 were reactive with the aldehyde moiety in 177, despite the use of a variety of bases including LiHMDS, NaH, KOAc, K₂CO₃, NEt₃, and i-Pr₂NEt. This failure may derive from the electronic nature of aldehyde 177, which is actually a vinylogous amide. This functionality could be also be deprotonated by the ylide, thus suppressing the desired Wittig reaction.

Scheme 170

5.3.5 Additional Attempts at C3-Functionalization of Simple Indoles and Applications to the Tronocarpine Model Substrates

We next decided to investigate the feasibility of using an alternative coupling of an indole at C-3 with an electron deficient alkene to generate an indole-3-acrylate ester. We first explored C3-functionalization of indole itself as a very simple model system.
To this end, we decided to use the Pd-catalyzed methods developed by Gaunt\textsuperscript{111} and Thai,\textsuperscript{112} who showed that treatment of electron deficient alkenes such as 207 and indole with Pd(OAc)$_2$ and either Cu(OAc)$_2$·H$_2$O or AgOAc resulted in indole-3-acrylate ester. Thus, we first subjected indole (206) to these conditions (Scheme 171). When Cu(OAc)$_2$·H$_2$O was used as oxidant, indole-3-acrylate ester (208) was produced in reasonable yield. Similarly, use of the oxidant AgOAc provided 208 in only 15% yield. Thus, we reacted both NH indole ketoester 145 and $N$-Ts-protected indole ketoester 147 under the optimized condition with acrylate 207. However, in both cases only starting material recovery was observed.

**Scheme 171**

![Scheme 171](image)

We next decided to investigate the feasibility of using a Heck coupling of a 3-halo indole like 211 with an electron deficient alkene to achieve the desired C3-functionalization. Preliminary studies were first conducted with simple $N$-Ts 3-bromoindole (211a) and 3-iodoindole (211b).\textsuperscript{113}
The Heck coupling of $N$-Ts-3-bromoindole (211a) with commercially available ethyl acrylate (207) using the catalytic system of Pd(OAc)$_2$ and P(o-tol)$_3$, along with NEt$_3$ in DMF successfully furnished indole-3-acrylate ester 212 in acceptable yield (Scheme 172). The optimal reaction temperature was determined to be 80 °C, leading to an inseparable mixture of undesired indole 213 and starting indole 211a in >50% overall yield. Further increasing the reaction temperature and time resulted in increasing amounts of undesired $N$-Ts indole 213, thus decreasing the overall yield. We next replaced the P(o-tol)$_3$ with PPh$_3$ in hopes that this less sterically demanding additive would promote formation of the desired cross-coupled indole. However, this modification was not effective in increasing the reaction yield. We were pleased to find that cross coupling of $N$-Ts 3-iodoindole 211b with ethyl acrylate (207) under virtually identical conditions afforded the requisite coupling product 212 in much better yield (~50%). However, subjection of the 3-bromoindole tronocarpine model system 189 (Cf Scheme 166) to the Heck conditions led to no appreciable amount of the desired product 210.

Scheme 172
Given the success of the iodoindole Heck reaction, we attempted to prepare N-Ts 3-iodoindole ketoester 214. However a variety of I⁻ sources were investigated but all failed to give 214.

Scheme 173

Given the failure of the Heck coupling reaction, alternative Pd-catalyzed cross coupling routes to 3-functionalized indole were explored. One such method to potentially access 216 was the Suzuki coupling of N-Ts-3-bromoindole with boronic acid 215, which was prepared from methyl propiolate according to the literature procedure. Unfortunately, subjection of 211a and 215 to a catalytic system of Pd(OAc)₂ and P(o-tol)₃ in DMF:H₂O (1:1) at 80 °C resulted only in an intractable mixture of products that contained compounds that had the correct molecular weight for indole 216 as determined by mass spectrometry, but comprised less than 10% of the mass balance.

Scheme 174
Similarly, Stille coupling\textsuperscript{115} of simple \(N\)-Ts-3-bromoindole (211a) with alkyltin coupling partner 217, prepared from ethyl propiolate,\textsuperscript{116} was also attempted, with the desired indole-3-acrylate ester 212 being isolated in acceptable yield (Scheme 175). However, extension of the optimized conditions to the tronocarpine model system 189 resulted only in either the recovery of starting material or decomposition, depending the reaction temperature.

Scheme 175

\[
\begin{align*}
\text{Br} & \quad \text{Ts} \\
\text{Br} & \quad \text{H}_3\text{CO} \\
\text{Ts} & \quad \text{Ts} \\
\text{Ts} & \quad \text{Ts} \\
\text{Ts} & \quad \text{Ts} \\
\text{Ts} & \quad \text{Ts} \\
\end{align*}
\]

5.4 Studies on Synthesis of a More Substituted Alkyne Precursor for Tronocarpine

As a part of our ongoing studies towards a total synthesis of tronocarpine (1), we decided to prepare an alkylnyl ketodiester coupling partner to evaluate the tandem Sonogashira/heteroannelation reaction with more appropriate functionality than 140. The plan was that the C4-methyl ester on ketone would eventually become part of the aminal moiety of the tronocarpine molecule (Cf. Scheme 7).\textsuperscript{117} To this end, silyl ether 222 was prepared from commercially available ketoester 218 in four steps following the literature procedure.\textsuperscript{118,119} Although this method allowed ready access to compound 222, the high price of the starting ketoester 218 made this method impractical for large scale exploratory operations.
Thus, we have used an inexpensive method to generate the known β-ketoester \( \text{224} \) via a tandem double Michael addition/intramolecular Claisen condensation of ethyl acetate and methyl acrylate using LDA (Scheme 177). Subsequent alkynylation of \( \text{224} \) with TMS-EBX (137) in the presence of TBAF at \(-40^\circ\text{C}\) indeed furnished the desired α-alkynyl-β-ketodiester \( \text{225} \) as predominately one stereoisomer of unknown configuration in 71% yield.

With alkynyl ketodiester \( \text{225} \) in hand, we attempted the tandem Sonogashira coupling/heteroannulation with \( N \)-Ns 2-idoaniline \( \text{163} \) to access indole ketodiester \( \text{226} \) using the previously optimized conditions (Cf Scheme 144). However, reaction at \( 60^\circ\text{C} \) failed to produce
any of the N-Ns or N-H indole 226 or 227, resulting instead only in decomposition. On the other hand, by lowering the temperature to room temperature, the N-Ns indole 226 was formed in moderate yield. Increasing the temperature did not provide the NH indole 227, instead resulting in increased amounts of decomposition products.

Scheme 178

Due to the presence of two ester groups on the indole 226, there was a potential regioselectivity issue on the future installation of lactam ring (Cf Scheme 7). Thus, alkynyl keto diester 225 was deemed not the ideal substrate to use in our total synthesis of tronocarpine (1).

As an alternative system, we have prepared the alkynyl ketoester ketal 231 as a coupling partner for N-Ns 2-iodoaniline in the tandem coupling/annulation reaction (Scheme 179). To this end, commercially available 1,4-cyclohexanedione (228) was mono-protected with one equivalent of ethylene glycol to provide monoketal 229 in low (unoptimized) yield. Alkoxy carbonylation of ketone 229 with ethyl cyanoformate upon deprotonation by LDA yielded ketal β-ketoester 230. Subsequent treatment of 230 with TMS-EBX (137) provided the desired alkynyl ketoester 231.
Scheme 179

When N-Ns iodoaniline 163 and alkynyl ketoester ketal 231 were reacted under the optimized tandem Sonogashira/heteroannulation conditions at room temperature, the N-protected indole 232 was formed in 62% yield. Raising the reaction temperature to 60 °C, provided the desired NH indole 233 but in low yield.

Scheme 180

232: R=nosyl, 62%, rt
233: R=H, 19%, 60 °C
5.5 Conclusion and Future Strategy for the Synthesis of Tronocarpine

Various synthetic approaches towards the total synthesis of tronocarpine (1) have been examined. A route to the natural product involving a tandem Sonogashira/heteroannulation was investigated. However, C-3 functionalizations of the indole products have been unsuccessful to date using several strategies.

Since the difficulties associated with converting indole $\beta$-ketoester into the requisite lactam precursor may due to the presence of the ketone moiety and/or bulky substituent on C2 of indole 145, future work will attempt to determine if an appropriately $O$-acylated indole such as 234 would be compatible with the chemistry described in Scheme 159-166 to afford 235, thereby providing a viable route for a synthesis of the tronocarpine core 35 (Scheme 181). An alternative route would involve the use of prefunctionalized alkyne 236 to give 2,3-disubstituted indole 237 via a regioselective Larock indole synthesis, eventually leading to a total synthesis of tronocarpine (1).

Scheme 181
Chapter 6 Experimental Section

General Methods. All non-aqueous reactions were carried out under an inert atmosphere of argon in flame-dried glassware using standard Schlenk techniques unless otherwise indicated. Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, dimethylformamide, and toluene were obtained from a solvent dispensing system equipped with alumina drying columns. Additional solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). Analytical and preparative thin layer chromatography (TLC) were performed using 0.5 or 1.0 mm EM Science silica gel 60 PF<sub>254</sub> plates. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker CDPX-300, DPX-300, AMX-360, or DRX-400 MHz spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR. Nominal mass spectral data (MS) were obtained on an Applied Biosystems 150EX instrument. High resolution mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.
Dimethyl 3-Phenylcyclohex-1-ene-1,3-dicarboxylate (67). A solution of bromobenzene (44 mg, 0.277 mmol) in toluene (3 mL) was treated with ester 65 (50 mg, 0.253 mmol), P(Bu)_3 (3 mg, 0.014 mmol), Pd(db)_(2) (8 mg, 0.014 mmol), and LiHMDS (1 M in THF, 0.63 mL, 0.630 mmol). The resulting mixture was heated at 60 °C for 24 h and then cooled to rt. The mixture was washed with NH$_4$Cl, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:12 EtOAc:hexanes) to afford the title compound 67 as a light yellow solid (48 mg, 70%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.29-7.15 (m, 5H), 3.69 (s, 3H), 3.67 (s, 3H), 2.48-2.27 (m, 1H), 2.27-2.21 (m, 2H), 1.78-1.71 (m, 1H), 1.57-1.51 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.3, 168.0, 143.3, 139.4, 133.3, 129.1, 127.6, 127.0, 53.2, 53.1, 52.3, 34.1, 24.7, 19.6.

N-(2-Bromophenethyl)cyclohex-1-ene-1-carboxamide (81). To a solution of 1-cyclohexene-1-carboxylic acid (565 mg, 6.701 mmol) in benzene (10 mL) was added 2 drops of DMF and oxalyl chloride (850 mg, 0.58 mL). When gas evolution had ceased, the reaction mixture was evaporated under reduced pressure to afford the crude acyl chloride 80. The compound was used for the next step without purification.

To a solution of primary amine 75 (889 mg, 4.467 mmol) in CH$_2$Cl$_2$ (10 mL) was added NEt$_3$ (1.87 mL, 13.401 mmol), and the crude acyl chloride 80 in CH$_2$Cl$_2$ (10 mL) was added to this mixture. The mixture was stirred at rt for 1 h, and washed with saturated NH$_4$Cl. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organics
were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound **81** as a clear oil (1.183 g, 87%). ^1^H NMR (300 MHz, CDCl₃) δ 7.46 (J = 8.3 Hz, d, 1H), 7.29-7.14 (m, 2H), 7.06-7.02 (m, 1H), 6.53-6.51 (m, 1H), 5.75 (br s, 1H), 3.50 (J = 6.1 Hz, q, 2H), 2.93 (J = 6.9 Hz, t, 2H), 2.08-2.05 (m, 4H), 1.61-1.46 (m, 4H); ^1^C NMR (75 MHz, CDCl₃) δ 169.1, 138.9, 134.0, 133.5, 133.3, 131.5, 128.7, 128.0, 125.0, 39.8, 36.2, 25.8, 24.6, 22.5, 22.0.

![Image](image-url)

**1,2,3,4,7,8-Hexahydrodibenzo[c,e]azocin-5(6H)-one (83).** A solution of amide **81** (44 mg, 0.143 mmol) in toluene (4 mL) was treated with P(‘Bu)₃ (2 mg, 0.007 mmol), K₂CO₃ (50 mg, 0.358 mmol) and Pd(dba)₂ (4 mg, 0.007 mmol). The resulting mixture was heated at 80 ºC for 24 h and then cooled to rt. The mixture was washed with NH₄Cl, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound **83** as a clear oil (12 mg, 35%). ^1^H NMR (300 MHz, CDCl₃) δ 7.72 (br s, 1H), 7.13 (J = 8.1 Hz, t, 2H), 6.93 (J = 8.3 Hz, t, 2H), 5.99-5.91 (m, 1H), 4.04 (J = 4.8 Hz, t, 2H), 2.91 (J = 8.2 Hz, t, 2H), 2.44-2.07 (m, 4H), 1.70-1.59 (m, 4H); LRMS-ES+ m/z (relative intensity) 228 (MH⁺, 50).
Methyl 1-Ethynyl-2-oxocyclohexanecarboxylate (140). To a solution of ketoester 139 (874 mg, 5.60 mmol) in THF (35 mL) was added hypervalent iodine reagent 137 (1.376 g, 4.0 mmol) at –78 ºC, followed by TBAF solution (1 M in THF, 4 mL, 4.0 mmol). The reaction mixture was then stirred at –40 ºC for 5 h. The reaction was quenched by slow addition of saturated NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 140 as a white solid (636 mg, 88%).

¹H NMR (300 MHz, CDCl₃) δ 3.65 (s, 3H), 2.86-2.67 (m, 1H), 2.44 (s, 1H), 2.32-2.18 (m, 2H), 2.01-1.97 (m, 1H), 1.87-1.80 (m, 2H), 1.65-1.58 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 202.9, 169.0, 80.0, 76.5, 58.7, 53.6, 38.8, 37.6, 27.7, 21.7; HRMS-EI [M+H]+ calcd for C₁₀H₁₃O₃, 181.0865; found, 181.1851.

Methyl 1-(1H-Indol-2-yl)-2-oxocyclohexanecarboxylate (145). Method A: A solution of iodoaniline 163 (180 mg, 0.445 mmol) in DMF (12 mL) was treated with alkyne 140 (180 mg, 0.999 mmol), CuI (18 mg, 0.090 mmol), NEt₃ (5 mL) and PdCl₂(PPh₃)₂ (34 mg, 0.048 mmol). The resulting mixture was heated at 80 ºC for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5
EtOAc:hexanes) to afford the title compound 145 as a dark yellow solid (63 mg, 53%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.81 (br s, 1H), 7.54 ($J = 8.8$ Hz, d, 1H), 7.29 ($J = 8.1$ Hz, d, 1H), 7.11 ($J = 6.0$, 1.1 Hz, td, 1H), 7.04 ($J = 7.0$, 0.9 Hz, td, 1H), 6.38 (s, 1H), 3.67 (s, 3H), 2.93-2.88 (m, 1H), 2.47-2.42 (m, 2H), 2.27-2.18 (m, 1H), 1.98-1.73 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 205.2, 168.8, 135.0, 133.0, 126.2, 120.9, 119.1, 118.5, 109.8, 100.0, 60.0, 51.8, 39.4, 33.7, 25.4, 20.8; HRMS-EI [M+H]$^+$ calecd for C$_{16}$H$_{18}$NO$_3$, 272.1287; found, 272.1275.

Method B: To a solution of indole 168 (40 mg, 0.088 mmol) in CH$_3$CN (4 mL) was added PhSH (0.01 mL, 0.105 mmol) and Cs$_2$CO$_3$ (87 mg, 0.264 mmol). The mixture was stirred at rt overnight. 2 M HCl was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 145 as a dark yellow solid (18 mg, 75%).

Method C: To a solution of indole 168 (10 mg, 0.022 mmol) in CH$_3$OH (1 mL) was added PhSH (8 drops) and K$_2$CO$_3$ (30 mg, 0.217 mmol). The mixture was stirred at rt overnight. 2 M HCl was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 145 as a dark yellow solid (6 mg, 99%).

Methyl 2-Oxo-1-(1-tosyl-1H-indol-2-yl)cyclohexanecarboxylate (147).$^{123}$ A solution of iodoaniline 146 (70 mg, 0.187 mmol) in DMF (7 mL) was treated with alkyne 140 (70 mg, 0.389 mmol), CuI (6 mg, 0.032 mmol), PdCl$_2$(PPh$_3$)$_2$ (12 mg, 0.017 mmol), and NEt$_3$ (3.5 mL). The
resulting mixture was heated at 60 °C for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the indole 147 as a light yellow solid (60 mg, 75%). ¹H NMR (300 MHz, CDCl₃) δ 7.68 (J = 8.3 Hz, d, 2H), 7.39-7.28 (m, 2H), 7.00-6.93 (m, 3H), 6.44 (s, 1H), 3.62 (s, 3H), 3.15 (br s, 1H), 2.57-2.45 (m, 4H), 2.08 (s, 3H), 1.88-1.63 (4H); ¹³C NMR (75 MHz, CDCl₃) δ 206.2, 170.6, 145.2, 140.6, 137.4, 136.8, 130.0, 128.8, 128.0, 125.0, 123.6, 121.4, 114.6, 111.8, 65.1, 60.8, 53.3, 40.8, 38.3, 21.9, 14.6; HRMS-EI [M+H]+ calcd for C₂₃H₂₄NO₅S, 426.1375; found, 426.1368.

6-(Methoxycarbonyl)-6-(1-tosyl-1H-indol-2-yl)cyclohex-1-enyl Methyl Carbonate (149). To a solution of ketoester 147 (460 mg, 1.08 mmol) in THF (200 mL) was added LiHMDS (1 M in toluene, 2.16 mL, 2.16 mmol). The reaction mixture was then stirred at rt for 1 h. Methyl chloroformate (612 mg, 6.48 mmol) was added at rt. The resulting mixture was stirred at rt overnight, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the enol carbonate 149 as a white solid (355 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.40 (m, 4H), 7.15-7.04 (m, 4H), 6.87 (s, 1H), 5.96-5.93 (m, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 2.83-2.65 (m, 2H), 2.32 (s, 3H), 2.23-2.12 (m, 2H), 1.67-1.64 (m, 1H), 1.30-1.19 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 154.4, 145.5, 144.8, 141.6, 137.8, 137.1, 130.0, 128.6, 127.3, 124.9, 123.7, 122.0, 121.4, 114.8,
Benzyl 2-(2-(1-(Methoxycarbonyl)-2-oxocyclohexyl)ethyl)phenylcarbamate (151).

A solution of iodoaniline 150 (70 mg, 0.198 mmol) in DMF (7 mL) was treated with alkyne 140 (71 mg, 0.397 mmol), CuI (7 mg, 0.039 mmol), PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.020 mmol), and NEt$_3$ (3.5 mL). The resulting mixture was heated at 50 °C for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:8 EtOAc:hexanes) to afford the title compound 151 as a yellow solid (51 mg, 64%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.15 ($J = 8.3$ Hz, d, 1H), 7.87 (s, 1H), 7.38-7.23 (m, 7H), 6.91 ($J = 4.1$ Hz, t, 1H), 5.17 (s, 2H), 3.58 (s, 3H), 2.86-2.78 (m, 1H), 2.48-2.40 (m, 2H), 2.16-2.15 (m, 1H), 1.98-1.92 (m, 2H), 1.82-1.76 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.6, 169.1, 153.6, 140.6, 136.4, 131.5, 130.5, 129.0, 128.7, 128.6, 128.3, 122.7, 118.1, 110.7, 92.3, 83.7, 67.5, 59.6, 53.8, 39.2, 37.5, 30.1, 27.6, 22.0; HRMS-EI [M+H]$^+$ calcd for C$_{25}$H$_{25}$NO$_5$S, 406.1654; found, 406.1648.
tert-Butyl 2-(2-(1-(Methoxycarbonyl)-2-oxocyclohexyl)ethynyl) Phenylcarbamate (152). A solution of iodoaniline 114\textsuperscript{125} (1.408 g, 4.411 mmol) in DMF (140 mL) was treated with alkyne 140 (1.590 g, 8.832 mmol), PPh\textsubscript{3} (231 mg, 0.882 mmol), Bu\textsubscript{4}NCl (1.560 mg, 4.851 mmol) Pd(OAc)\textsubscript{2} (198 mg, 0.882 mmol), and KOAc (2.160 mg, 22.050 mmol). The resulting mixture was heated at 40 °C for 24 h and then cooled to rt. The mixture was filtered through a pad of Celite which was washed with CH\textsubscript{2}Cl\textsubscript{2}. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 152 as a yellow oil (824 mg, 51%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 8.09 (J = 8.4 Hz, d, 1H), 7.61 (br s, 1H), 7.37-7.18 (m, 2 H), 6.87 (J = 7.66 Hz, t, 1H), 3.84 (s, 3H), 2.86-2.79 (m, 1H), 2.49-2.38 (m, 2H), 2.21-2.15 (m, 1H), 2.04-1.79 (m, 4H), 1.56 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 202.6, 169.2, 153.0, 141.0, 131.7, 130.4, 122.2, 118.0, 110.5, 92.1, 83.9, 81.2, 59.7, 53.8, 39.2, 37.6, 28.8, 27.7, 22.1; HRMS-ESI [M+H]\textsuperscript{+} calcd for C\textsubscript{21}H\textsubscript{26}NO\textsubscript{5}, 372.1811; found, 372.1801.

Methyl 1-(2-(2-Aminophenyl)ethynyl)-2-oxocyclohexanecarboxylate (155). To a solution of Sonogashira product 154 (10 mg, 0.027 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added trifluoroacetic acid (0.2 mL). The mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 155 as clear oil (5 mg, 68%). \textsuperscript{1}H
NMR (300 MHz, CDCl₃) δ 7.20-7.17 (m, 1H), 7.08-7.03 (m, 1H), 6.63-6.56 (m, 2H), 4.40 (br s, 1H), 3.77 (s, 3H), 2.90-2.80 (m, 1H), 2.54-2.34 (m, 2H), 2.19-1.77 (m, 6H); LRMS-ES+ m/z (relative intensity) 272 (MH⁺, 100).

N-(2-Iodophenyl)-N,N-dimethylsulfamoyl Amide (161). To a solution of 2-iodoaniline (105, 1.00 g, 4.56 mmol) in pyridine (13.7 mL, 13.70 mmol) was added dimethylsulfamoyl chloride (1.5 mL, 13.70 mmol) at rt. The reaction mixture was stirred at rt for 48 h. The reaction mixture was extracted with 2 M HCl solution and with EtOAc. The organic layer was washed with saturated NaHCO₃ solution, then dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 161 as a brown solid (521 mg, 44%) along with 200 mg of iodoaniline 105 which was recovered. ¹H NMR (300 MHz, CDCl₃) δ 7.68 (J = 7.9, 1.3 Hz, dd, 1H), 7.63 (J = 9.9, 1.2 Hz, dd, 1H), 7.26 (J = 8.0, 1.3 Hz, td, 1H), 6.77 (J = 7.8, 1.4 Hz, td, 1H), 6.57 (s, 1H), 2.76 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 138.2, 137.3, 128.5, 124.9, 119.4, 89.1, 37.3; HRMS-EI [M+H]⁺ calcd for C₈H₁₂INO₂S, 326.9664; found, 326.9662.
**N-(2-Iodophenyl)-2,4-dinitrobenzenesulfonamide (162).** To a solution of 2-iodoaniline (105, 1.00 g, 4.56 mmol) in pyridine (0.41 mL, 5.02 mmol) was added 2,4-dinitrobenzenesulfonyl chloride (1.338 g, 5.02 mmol) at rt. The reaction mixture was stirred at rt overnight. The reaction mixture was extracted with 2 M HCl solution and with EtOAc. The organic layer was washed with saturated NaHCO₃ solution, then dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:10 EtOAc:hexanes) to afford the title compound 162 as a brown solid (1.00 g, 48%).

**1H NMR (300 MHz, CDCl₃) δ 9.07 (J = 2.4 Hz, t, 1H), 8.29 (J = 9.0, 2.4 Hz, dd, 1H), 7.71-7.63 (m, 2H), 7.18 – 7.13 (m, 1H), 6.99-6.96 (m, 1H), 6. 67-6.71 (m, 1H); **

**13C NMR (75 MHz, CDCl₃) δ 150.4, 143.8, 142.3, 141.1, 138.0, 128.5, 126.4, 124.3, 122.0, 120.1, 112,4, 85.1.**

**Methyl 1-(1-(N,N-Dimethylsulfamoyl)-1H-indol-2-yl)-2-((methoxycarbonyl)oxy)cyclohexanecarboxylate (166).** A solution of alkyne 140 (50 mg, 0.153 mmol) in DMF (5 mL) was treated with iodoaniline 161 (55 mg, 0.307 mmol), CuI (6 mg, 0.031 mmol), PdCl₂(PPh₃)₂ (10 mg, 0.015 mmol), and NEt₃ (2.5 mL). The resulting mixture was heated at 70 °C for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were
dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 166 as a light yellow solid (17 mg, 30%). ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.45 (m, 2H), 7.26-7.21 (m, 2H), 6.43 (s, 1H), 3.69 (s, 3H), 2.84 (s, 6H), 2.52-2.48 (m, 4H), 2.11-1.49 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 206.2, 170.5, 140.9, 137.1, 128.6, 124.2, 123.3, 121.3, 113.9, 109.8, 64.7, 51.3, 38.4, 38.4, 38.1, 30.1, 22.0; HRMS-EI [M+H]⁺ calcd for C₁₈H₂₃N₂O₅S, 379.1328; found, 379.1313.

**Methyl 1-(1-((4-Nitrophenyl)sulfonyl)-1H-indol-2-yl)-2-oxocyclohexane Carboxylate** (168). A solution of iodoaniline 163 (100 mg, 0.247 mmol) in DMF (10 mL) was treated with alkyne 140 (89 mg, 0.495 mmol), CuI (9 mg, 0.049 mmol), PdCl₂(PPh₃)₂ (17 mg, 0.025 mmol), and NEt₃ (5 mL). The resulting mixture was heated at 60 °C for 24 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 168 as a dark yellow solid (87 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.17-8.14 (m, 2H), 8.01 (J = 8.9 Hz, t, 2H), 7.51-7.41 (m, 2H), 7.18-7.06 (m, 2H), 6.56 (br s, 1H), 3.74 (s, 3H), 2.64-2.49 (m, 4H), 1.78-1.31 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 168.4, 148.7, 143.0, 138.6, 135.4, 127.3126.9, 123.6,
Methyl 2-(Methoxycarbonyloxy)-1-(1-(4-nitrophenylsulfonyl)-1H-indol-2-yl)cyclohex-2-enecarboxylate (169). To a solution of indole 168 (27 mg, 0.059 mmol) in THF (3 mL) was added LiHMDS (1 M in toluene, 0.12 mL, 0.120 mmol). The reaction mixture was then stirred at -78 °C for 1 h. Methyl chloroformate (33 mg, 0.05 mL, 0.708 mmol) was added at -78 °C. The resulting mixture was stirred at rt overnight. The reaction was quenched by slow addition of saturated NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 169 as a light yellow solid (27 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 8.24 (J = 8.9 Hz, d, 2H), 8.12-8.09 (m, 2H), 7.58-7.50 (m, 2H), 7.21-7.14 (m, 2H), 7.00 (s, 1H), 6.01 (J = 3 Hz, d, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.88-2.68 (m, 2H), 2.42-2.30 (m, 2H), 1.76-1.73 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 154.5, 150.6, 145.1, 141.8, 137.6, 128.9, 128.8, 125.6, 124.6, 124.5, 122.3, 122.0, 116.2, 114.6, 55.8, 55.3, 53.6, 53.2, 33.4, 30.1, 24.28, 17.9; LRMS-ES+ m/z (relative intensity) 515 (MH⁺, 70).
Methyl 1-(1H-Indol-2-yl)-2-(methoxycarbonyloxy)cyclohex-2-enecarboxylate (170).

To a solution of indole 169 (10 mg, 0.022 mmol) in CH$_3$CN (1 mL) was added PhSH (8 drops) and K$_2$CO$_3$ (30 mg, 0.217 mmol). The mixture was stirred at rt overnight. 2 M HCl was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 170 as a dark yellow solid (6 mg, 99%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.89 (br s, 1H), 7.53 (J = 9.2 Hz, d, 1H), 7.38 - 7.10 (m, 4H), 6.47 (s, 1H), 3.76 (s, 6H), 3.03 - 2.97 (m, 2H), 2.48 - 2.28 (m, 4H); LRMS-ES+ m/z (relative intensity) 330 (MH$^+$, 75).

Methyl 1-(3-Formyl-1H-indol-2-yl)-2-oxocyclohexanecarboxylate (177). To a solution of DMF (0.6 mL) in CH$_2$Cl$_2$ (4 mL) at 0 °C was added POCl$_3$ (0.2 mL). The reaction mixture was slowly warmed to rt and stirred for 1.5 h. The solution was then cooled to 0 °C and indole 145 (40 mg, 0.147 mmol) in CH$_2$Cl$_2$ was added slowly. The resulting mixture was slowly warmed to rt and stirred for 1.5 h. The solution was cooled to 0 °C again. Saturated NaHCO$_3$ was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to afford the title compound 177 as a light yellow solid (42 mg, 95% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.52 (br s, 1H), 10.14 (s,
1H), 8.11-8.02 (m, 1H), 7.38-7.33 (m, 1H), 7.23-7.12 (m, 2H), 3.76 (s, 3H), 2.77-2.28 (m, 3H), 2.28-2.18 (m, 1H), 2.10-2.01 (m, 2H), 1.90-1.57 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 204.8, 184.8, 171.1, 143.6, 134.2, 127.8, 127.0, 125.4, 120.6, 117.0, 66.8, 53.9, 53.4, 41.4, 38.5, 27.3, 22.1, 21.9; HRMS-EI [M+H]^+ calcd for C\(_{17}\)H\(_{18}\)NO\(_4\), 300.1236; found, 300.1222.

![Diagram](image)

**Methyl 1-(3-Bromo-1-tosyl-1H-indol-2-yl)-2-oxocyclohexanecarboxylate** (189).

Method A: To a solution of indole 147 (10 mg, 0.024 mmol) in CH\(_2\)Cl\(_2\) (1 mL) at 0 °C was added NBS (16 mg, 0.089 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Saturated Na\(_2\)S\(_2\)O\(_3\) was added and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 189 as a yellow solid (11 mg, 92% yield).

Method B: To a solution of indole 147 (10 mg, 0.024 mmol) in CH\(_2\)Cl\(_2\) (1 mL) at 0 °C was added Br\(_2\) (0.001 mL, 0.026 mmol). The reaction mixture stirred at 0 °C for 5 min. Saturated Na\(_2\)S\(_2\)O\(_3\) was added and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 189 as a yellow solid (10 mg, 83% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.72 \((J = 7.6\) Hz, d, 1H), 7.47 \((J = 8.3\) Hz, d, 2H), 7.28-7.09 (m, 3H), 6.97 \((J = 8.2\) Hz, d, 2H), 3.80 (s, 3H), 3.37 (s, 1H), 2.67 (m, 3H), 1.97 (s, 3H), 1.95-1.48 (m, 4H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 205.6, 170.3, 145.2, 138.2, 136.3, 133.9, 131.3, 129.6, 127.8, 127.0, 125.4, 120.6, 117.0, 66.8, 53.9, 53.4, 41.4, 38.5, 27.3, 22.1, 21.9; HRMS-EI
[M+H]+ calcd for C_{23}H_{23}BrNO_5S, 504.0480; found, 504.0463.

(E)-Ethyl 3-(1H-Indol-3-yl)acrylate (208). Method A: A solution of indole 206 (30 mg, 0.256 mmol) in DMF:DMSO (9:1) (1 mL) was treated with ethyl acrylate (207, 0.05 mL), Pd(OAc)$_2$ (5 mg, 0.022 mmol), and Cu(OAc)$_2$·H$_2$O (90 mg, 0.452 mmol). The resulting mixture was heated at 70 °C for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 208 as a light yellow solid (24 mg, 44%).

Method B: A solution of indole 206 (30 mg, 0.256 mmol) in DMF:DMSO (9:1) (1 mL) was treated with ethyl acrylate (207, 0.05 mL), Pd(OAc)$_2$ (5 mg, 0.022 mmol), and AgOAc (80 mg, 0.479 mmol). The resulting mixture was heated at 80 °C for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 208 as a light yellow solid (8 mg, 15%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.53 (br s, 1H), 7.95-7.83 (m, 2H), 7.57-7.33 (m, 2H), 7.23-7.02 (m, 2H), 6.48 ($J$ = 17.8 Hz, d, 1H), 4.15 ($J$ = 7.2 Hz, q, 2H), 1.26 ($J$ = 7.1 Hz, t, 3H). Spectral data were consistent with literature values.
(E)-Ethyl 3-(1-Tosyl-1H-indol-3-yl)acrylate (212). Method A: A solution of 3-bromoindole 211a (30 mg, 0.086 mmol) in DMF (1 mL) was treated with ethyl acrylate (207, 0.1 mL), Pd(OAc)$_2$ (2.5 mg, 0.011 mmol), P(o-tol)$_3$ (5 mg, 0.016 mmol), and NEt$_3$ (0.1 mL). The resulting mixture was heated at 80 °C for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 212 as a yellow solid (12 mg, 38%).

Method B: A solution of 3-iodoindole 211b (30 mg, 0.075 mmol) in DMF (1 mL) was treated with ethyl acrylate (207, 0.05 mL), Pd(OAc)$_2$ (2.5 mg, 0.011 mmol), P(o-tol)$_3$ (5 mg, 0.016 mmol), and NEt$_3$ (0.05 mL). The resulting mixture was heated at 80 °C for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 212 as a yellow solid (24 mg, 86%).

Method C: A solution of 3-bromoindole 217 (30 mg, 0.086 mmol) in DMF (1 mL) was treated with tin reagent 217$^{116}$ (100 mg, 0.256 mmol), Pd(dba)$_2$ (5 mg, 0.008 mmol), and PPh$_3$ (5 mg, 0.019 mmol). The resulting mixture was heated at 80 °C for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:8 EtOAc:hexanes) to afford the title compound 212 as a yellow solid (21 mg, 68%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.93 ($J = 6.4$ Hz, d, 1H), 7.77-7.68 (m, 5H), 7.34-7.24 (m, 3H), 7.22 (s, 1H), 6.45 ($J = 16$ Hz, d, 1H), 4.20 ($J = 7.1$ Hz, q, 2H), 2.28 (s, 3H), 1.27 ($J = 7.8$ Hz, t, 3H). Spectral data were consistent with literature values.$^{128}$
(E)-Methyl 3-(1-Tosyl-1H-indol-3-yl)acrylate (216). A solution of indole 211a (30 mg, 0.086 mmol) in DMF:H₂O (2:1) (1 mL) was treated with boronic acid 215 (30 mg, 0.230 mmol), Pd(OAc)₂ (5 mg, 0.022 mmol), P(o-tol)₃ (5 mg, 0.016 mmol), and NEt₃ (0.05 mL). The resulting mixture was heated at 80 ºC for 18 h and then cooled to rt. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:5 EtOAc:hexanes) to afford the title compound 216 as a light yellow solid (<10% mass recovered). ¹H NMR (300 MHz, CDCl₃) δ 8.01 (J = 7.8 Hz, d, 1H), 7.86-7.74 (m, 5H), 7.45-7.25 (m, 3H), 7.09 (s, 1H), 6.52 (J = 18 Hz, d, 1H), 3.76 (s, 3H), 2.36 (s, 3H); HRMS-EI [M+H]⁺ calcd for C₁₉H₁₈NO₅S, 356.0957; found, 356.0968.

Dimethyl 1-Ethynyl-6-oxocyclohexane-1,3-dicarboxylate (225). To a solution of dimethyl 4-hydroxycyclohexene-3-ene-1,3-dicarboxylate (224, 27 mg, 0.13 mmol) in THF (10 mL) at -78 ºC was added hypervalent iodine reagent 137 (50 mg, 0.15 mmol), followed by TBAF solution (1 M in THF, 0.15 mL, 0.15 mmol). The reaction mixture was then stirred at -40 ºC for 2 h. The reaction was quenched by slow addition of saturated NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (4:4:1 hexanes:CH₂Cl₂:EtOAc) to afford the title compound 225 as a white solid (21 mg, 71%). ¹H NMR (300 MHz, CDCl₃) δ 3.82
(s, 3H), 3.70 (s, 3H), 3.23 (m, 1H), 3.06 (m, 1H), 2.69 (s, 1H), 2.54-2.33 (m, 4H), 1.90 (m, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.4, 174.1, 168.4, 79.2, 57.6, 53.8, 52.6, 38.6, 36.8, 29.7;
HRMS-EI [M+H]$^+$ calcd for C$_{12}$H$_{15}$O$_5$, 239.0919; found, 239.0911.

Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1H-indol-2-yl)-6-oxocyclohex-ane-1,3-dicarboxylate (226). A solution of alkyne 225 (100 mg, 0.42 mmol) in DMF (11.5 mL) was treated with iodoaniline 163 (150 mg, 0.37 mmol), CuI (20 mg, 0.11 mmol), PdCl$_2$(PPh$_3$)$_2$ (20 mg, 0.03 mmol), and NEt$_3$ (5 mL). The resulting mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1.5 EtOAc:hexanes) to afford the title compound 226 as a light yellow solid (70 mg, 31%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.16 (d, $J = 8.8$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 7.66 (m, 1H), 7.44 (m, 1H), 7.20 (m, 2H), 6.59 (s, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.46 (m, 1H), 3.04-2.81 (m, 3H), 2.51 (s, 1H), 2.14 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 204.5, 174.5, 170.1, 150.7, 144.0, 138.7, 138.1, 129.1, 126.4, 125.2, 124.4, 122.0, 115.5, 64.7, 53.9, 53.6, 52.6, 38.2, 37.4, 37.3; HRMS(EI) [M+H]$^+$ calcd for C$_{24}$H$_{23}$N$_2$O$_9$S, 515.1124; found, 515.1133.
Ethyl 7-Ethynyl-8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (231). To a solution of keto ester 230 (10 mg, 0.0438 mmol) in THF (10 mL) at -40 °C was added hypervalent iodine reagent 137 (15 mg, 0.0437 mmol), followed by TBAF solution (1 M in THF, 0.1 mL, 0.1 mmol). The reaction mixture was then stirred at –40 ºC for 2 h. The reaction was quenched by slow addition of saturated NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford a residue which was purified by flash column chromatography on silica gel (1:4 EtOAc:hexanes) to afford the title compound 231 as colorless liquid (4.8 mg, 44%).

Ethyl 7-(1-(4-Nitrophenylsulfonyl)-1H-indol-2-yl)-8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (232). A solution of iodoaniline 163 (100 mg, 0.247 mmol) in DMF (8 mL) was treated with alkyne 231 (50 mg, 0.200 mmol), CuI (10 mg, 0.060 mmol), PdCl₂(PPh₃)₂ (10 mg, 0.020 mmol), and NEt₃ (1 mL). The resulting mixture was heated at rt for 5 days. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 ether:hexanes) to afford the title compound 232 as a yellow oil (65 mg, 62%). ¹H NMR (300 MHz, CDCl₃) δ 8.19 (d, J = 8.96 Hz, 2H), 8.01 (d, J
= 8.5 Hz, 2H), 7.58 (m, 1H), 7.43 (m, 1H), 7.16 (m, 2H), 6.58 (s, 1H), 4.32 (m, 2H), 3.98 (m, 4H), 3.14 (d, J = 13.8 Hz, 1H), 2.92 (m, 2H), 2.72 (m, 1H), 2.53 (m, 1H), 1.97 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 204.3, 170.4, 150.8, 144.4, 139.9, 137.6, 129.2, 129.1, 125.9, 124.8, 124.5, 121.9, 115.7, 115.0, 107.1, 65.4, 64.6, 64.1, 63.4, 53.9, 42.6, 38.1, 32.2, 14.3; LRMS-ES+ m/z (relative intensity) 529 (MH+, 50).

Ethyl 7-(1H-Indol-2-yl)-8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (233). A solution of alkyne 231 (50.0 mg, 0.10 mmol) in DMF (8 mL) was treated with iodoaniline 163 (50 mg, 0.10 mmol), CuI (10 mg, 0.06 mmol), PdCl2(PPh3)2 (10 mg, 0.02 mmol), and NEt3 (1 mL). The resulting mixture was stirred at 60 °C for 20 h. The solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to afford the title compound 233 as a light yellow solid (12.6 mg, 19%). 1H NMR (300 MHz, CDCl3) δ 7.91 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 3.9 Hz, 2H), 7.58 (m, 1H), 5.93 (s, 1H), 4.29 (m, 2H), 4.09 (m, 4H), 3.28 (dd, J = 14.3, 3.44 Hz, 1H), 3.15 (dd, J = 14.0, 6.9 Hz, 1H), 2.69 (m, 1H), 2.32 (d, J = 14.2, 1H), 2.12 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 203.7, 170.8, 166.8, 147.3, 140.1, 134.9, 130.8, 125.8, 124.3, 120.8, 106.8, 104.4, 65.4, 64.9, 62.7, 59.8, 42.1, 37.9, 35.3, 30.1, 14.3.
6.1 References and Notes


(114) Berrée, F.; Debache, A.; Marsac, Y.; Collet, B.; Girard-Le Bleiz, P.; Carboni, B. 


(117) This work was performed in collaboration with Guanqun Zhang of our group.


VITA

Puhui Li

Puhui Li was born in 1984 and raised in Sichuan, China. After graduating from Chengdu No. 7 High School in 2002, she attended the University of Leeds in the United Kingdom. While enrolled at the University of Leeds, Puhui also did summer research internship at Peking University with Dr. Xinshan Ye developing new chemical methodology and improving her laboratory skills. In August of 2004, she attended the Pennsylvania State University Park, where she did undergraduate research with Dr. Steven M. Weinreb synthesizing a model system related to a total synthesis of an anticancer compound of marine origin. After finishing an exchange program at the Pennsylvania State University, she attended Texas Tech University in 2005 where she received her bachelor’s degree in chemistry in 2007. While at Texas Tech, she did undergraduate research with Dr. Guigen Li focused on large scale synthesis to develop fundamental laboratory skills. In summer 2006, Puhui worked as an internship at Texas Tech University Health Science Center with Dr. Kendra Runbaugh, where she synthesized isomers of 3OC_{12}-homoserine lactone and applied them in mammalian assays and bacterial assays. In August 2007, she began graduate education at the Pennsylvania State University in Professor Steven M. Weinreb’s group in the area of synthetic organic chemistry.