The Pennsylvania State University

The Graduate School

Department of Chemistry

NITROSOALKENE ALKYLATION AND STEREOCHEMICAL STUDIES

A Thesis in

Chemistry

by

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ABSTRACT

Novel synthetic methodology involving intermolecular conjugate additions to nitrosoalkenes has been developed (Tables 2-4). The reactivity of various soft nucleophiles with both cyclic and acyclic nitrosoalkenes was explored. Both aldehyde and ketone-derived nitrosoalkenes were successful Michael acceptors. This methodology provides a means to access enolonium ion equivalents to carry out “umpolung” type chemistry.

Additionally, some of the stereochemical aspects of acyclic aldehyde-derived γ-chiral nitrosoalkenes were studied. Nitrosoalkene systems derived from several α-chloro-O-silyloximes 69, 108 and 113 were all found to undergo stereoselective attack by malonate nucleophiles to give exclusive formation of anti alkylation products 70a-d, 109, and 114. The stereochemistry of anti alkylation products 70d, 109, and 114 was determined by subjecting them to a two step [3+2] cycloaddition/derivatization sequence to give crystalline isoxazolidines 80, 111, and 116. X-ray structures of isoxazolidines 80, 111, and 116 confirmed the anti configuration of alkylation products 70d, 109, and 114 (Figures 2-4). The stereoselectivity of conjugate additions to these nitrosoalkene systems is rationalized through a modified Felkin-Anh model 102. Possible reversal of this anti stereoselectivity was explored though chelation control and was unsuccessful. Finally, a nitrogen nucleophile underwent successful conjugate addition to to give anti product 121.

Stereochemical aspects of 4-t-butyl nitrosocyclohexene 132 were also studied. Exploratory studies of conjugate addition of diethyl malonate anion with nitrosocyclohexene 132 generated from α-chlorooxime 130 (Method A) and α-chloro-O-silyloxime 131 (Method B) resulted in exclusive formation of trans alkylation product
The conjugate additions of the potassium anion of diethyl malonate to 3- and 4-substituted nitrosocyclohexenes 136 and 139 were explored and exclusive formation of alkylation products 137 and 140 (exclusive axial attack). The stereoselectivity of these conjugate additions can be rationalized by exclusive axial attack on the half-chair nitrosocyclohexene conformations 132, 136, and 139.

After difficulties with existing deoximation procedures, our group developed a novel procedure to convert ketoximes to the corresponding ketones. Oxime pivalates 157 treated with iron powder, a catalytic amount of TMSCl and a catalytic amount of glacial acetic acid in THF at room temperature gave the corresponding ketones 158 in good yields.
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Chapter 1. Chemistry of Nitrosoalkenes

Vinyl nitroso compounds 1 have been postulated as reactive intermediates in a variety of reactions since the late 1800’s. However, the first time a compound of this type was spectroscopically detected was in the 1960’s. These transient intermediates can often be detected in solution by a characteristic fleeting blue color. A few nitrosoalkenes have been isolated, but these compounds generally have bulky or electron withdrawing substituents at the β-position which stabilize this system (vide infra).

\[
\begin{align*}
1 & : \quad \begin{array}{c}
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\end{align*}
\]

1.1 Methods for Generation of Nitrosoalkenes

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

There have been a number of methods developed for the generation of nitrosoalkenes from various synthetic precursors. However, one of the most frequently used methods (Method A) for generation of nitrosoalkenes 1 is base promoted 1,4-elimination of α-functionalized oximes such as 2 where X is a leaving group (Scheme 1). The leaving group can be essentially any heteroatom functional group that can stabilize a negative charge, but most commonly a halogen has been used. Other rarer examples of such X groups previously utilized include, sulfonates, phenylsulfonates, nitrite, sulfoxides, and oxirane oxygens.47a, 28, 29, 30, 31

Scheme 1
A variety of bases can be used to induce the 1,4-elimination, but the type of base utilized can have an impact on the reaction outcome. Low solubility bases such as metal carbonates and hydroxides allow slow generation of the nitrosoalkene which helps to minimize side reactions like polymerization.\textsuperscript{1,32,33} When soluble bases like amines or alkoxides are used, they can generate the corresponding nitrosoalkene very rapidly.\textsuperscript{1,34,35}

1.1.2 Fluoride Promoted 1,4-Elimination from α-Halo-O-silyl Oximes

A useful variation of the 1,4-elimination method (Method B), developed by Denmark and coworkers, involves elimination of α-chloro-O-silyloximes 3 promoted by a fluoride source (Scheme 2).\textsuperscript{2} It was found that nitrosoalkenes generated in this way are highly reactive and have half-lives 3-5 times shorter than those generated from the corresponding α-chlorooximes using triethylamine.\textsuperscript{2} The Denmark group also discovered that the stereochemical orientation of the chlorine and/or the oxime geometry have little effect on the generation of the nitrosoalkene.

Scheme 2

1.2.3 Miscellaneous Addition and Elimination Methods

Even though most nitrosoalkenes utilized in synthesis have been generated by 1,4-elimination of α-chlorooximes and α-chloro-O-silyloximes, there are several other methods that have been occasionally used. Once such method is the combination of nitric oxide with vinyl radicals. Griffin and coworkers used this method by treating 1,1,2-trifluoriodoethylene (4) with nitric oxide to generate trifluoronitrosoethylene (5)
This route is worth noting because trifluoronitrosoethylene (5) was actually the first nitrosoalkene compound to be isolated.

**Scheme 3**

![Scheme 3](image)

Another method that has been used to prepare \(\alpha\)-chlorooximes, the most common nitrosoalkene precursors, involves treatment of an alkene 6 with nitrosyl chloride to generate nitroso-\(\alpha\)-chboroalkane 7, which then tautomerizes to afford the \(\alpha\)-chlorooxime 8 (Scheme 4).

**Scheme 4**

![Scheme 4](image)

Silyl nitronates have also been shown to be useful precursors to nitrosoalkenes. Thus, silyl nitronates such as compound 9 can be converted to the corresponding nitrosoalkene 10 by treatment with an alkyllithium (Scheme 5). In most cases, excess alkyllithium reagent undergoes conjugate addition with the product nitrosoalkene 10 to afford alkylated oxime compound 11. It has recently been found that \(\beta\)-nitroesters like compound 12 can be transformed into silyl nitronates 13 upon treatment with \(N,O\)-bis(trimethylsilyl)acetamide (BSA). These silyl nitronates 13 readily undergo elimination to generate nitrosoalkenes such as 14.
It has been reported that treatment of aryl nitrile oxides such as 16 with sulfoxonium ylide 15 can generate nitrosoalkene intermediates 17 via release of DMSO (Scheme 6). Nitrosoalkene 17 can then react with excess ylide 15 to ultimately give compounds such as 19 and 20.\textsuperscript{40}

Ring fragmentations have also been reported to generate nitrosoalkene compounds.\textsuperscript{41,42} One example of this process is treatment of $\alpha$-bromo-oxazinones 21 with sodium hydroxide to generate nitrosoalkene intermediate 22, which then tautomerizes to give conjugated oxime 23 (Scheme 7).\textsuperscript{43}
1.3 Reactions of Nitrosoalkenes

1.3.1 Tautomerization

Other than polymerization, one of the most common decomposition pathways for nitrosoalkenes that contain allylic hydrogens is tautomerization.\textsuperscript{44} For example, Kisan and coworkers reported that treatment of $\alpha$-hetero substituted-oximes 24 with TEA generates a blue colored solution indicating the formation of nitrosoalkene 25 (Scheme 8). If no nucleophile is present, the solution becomes colorless in 15-30 minutes due to conversion of the nitrosoalkene to tautomers 26 and 27.\textsuperscript{44a} On the other hand, nitrosoalkene compounds that do not contain allylic hydrogens are usually more stable since they cannot tautomerize. For instance, nitrosoalkene 28 can be isolated as a blue solid with a melting point of 38 °C (Figure 1).\textsuperscript{29}

\textbf{Scheme 8}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_8.png}
\end{center}

\textbf{Figure 1}

\includegraphics[width=0.2\textwidth]{Figure_1.png}

\textbf{Nitrosoalkene 28}

1.3.2 Cycloadditions of Nitrosoalkenes

Nitrosoalkenes 1 have been utilized as heterodienes in Diels-Alder reactions and as 1,3-dipoles in [3+2]-cycloadditions (Scheme 9).\textsuperscript{1} Much of the work with
nitrosoalkenes has focused on such compounds acting as the $4\pi$-heterodiene component in $[4+2]$-cycloadditions.

**Scheme 9**

![Scheme 9](image)

**1.3.3 Conjugate Additions of Nitrosoalkenes**

Conjugate additions to nitrosoalkenes 1 by nucleophiles is a useful means to produce $\alpha$-functionalized aldehydes and ketones (Scheme 10). When utilized in this way, nitrosoalkenes act as enolonium ion equivalents 29 which allows for the “umpolung” generation of $\alpha$-functionalized carbonyl compounds. It should be noted that there are many examples of direct $S_N2$ displacements of $\alpha$-haloketones to generate the corresponding $\alpha$-functionalized carbonyl compounds.\textsuperscript{45, 46} However, these methods are not general since several undesired side reactions are possible. For example, many nucleophiles tend to add preferentially to the electrophilic carbonyl group of such species. Additionally, in some cases Favorskii rearrangements of $\alpha$-halo carbonyl compounds can take place.\textsuperscript{47}

**Scheme 10**

![Scheme 10](image)

It has been known for many years that both hetero- and carbon-based nucleophiles can add in a conjugate fashion to nitrosoalkenes 1. Hetero-nucleophiles that have been
reported to participate in this reaction include alcohols, acetate, amines, azide, nitrite, and thiols.\(^1,8\) Carbon nucleophiles known to react with nitrosoalkenes include ketone and ester enolates, 1,3-dicarbonyl anions, malononitrile anion, acetylides, sulfoxonium ylides and alkyl or aryl Grignard reagents.\(^1,17\)

### 1.3.3.1 Conventional Procedure for Conjugate Additions to Nitrosoalkenes

In most of the literature examples of conjugate addition of nucleophiles to nitrosoalkenes at least two equivalents of the nucleophile is added to a free \(\alpha\)-halooxime, with the first equivalent acting as a base to generate the nitrosoalkene. Therefore, Ohno and coworkers found that treatment of \(\alpha\)-chlorooxime 30 with various nucleophiles gave good yields of \(\alpha\)-functionalized oximes 31 (Scheme 11).\(^17\)

**Scheme 11**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>morpholine, EtOH, rt</td>
<td>(N)-morpholino</td>
<td>71%</td>
</tr>
<tr>
<td>NaN(_3), MeCN, reflux</td>
<td>(N_3)</td>
<td>80%</td>
</tr>
<tr>
<td>AgNO(_2), ether, rt</td>
<td>NO(_2)</td>
<td>80%</td>
</tr>
<tr>
<td>NaHC((\text{CO}_2\text{Et})_2), ether</td>
<td>(\text{EtO}_2\text{C})_2\text{CH}</td>
<td>96%</td>
</tr>
<tr>
<td>PhC(\equiv\text{CMgBr},\text{THF, rt} )</td>
<td>PhC(\equiv\text{C} )</td>
<td>60%</td>
</tr>
</tbody>
</table>

### 1.3.3.2 Conjugate Additions to Nitrosoalkenes Generated via the Denmark Protocol

Even though it has been demonstrated that nitrosoalkenes readily take part in conjugate additions with a large array of nucleophiles, this methodology has not been widely utilized in organic synthesis. One reason for this may be that the typical procedure for nitrosoalkene generation requires two or more equivalents of nucleophile, making it especially wasteful if the nucleophile is expensive and not readily available.
This issue can, in principle, be addressed using the Denmark procedure which only requires one equivalent of nucleophile to generate the corresponding nitrosoalkene. Nitrosoalkenes generated in this manner have been reported to be successful Michael acceptors by several groups.\(^1\) For example, Barrett et al. have found that a single equivalent of sugar-derived hemiacetal 32 adds to one equivalent of the nitrosoalkene generated from \(\alpha\)-chloro-\(O\)-TBS-oxime 33 to afford glycoside 34 (Scheme 12).\(^{48}\) Another recent example reported by Hassner and coworkers showed that the sodium enolate of dimethyl malonate 35 adds to the nitrosoalkene generated from \(\alpha\)-bromo-\(O\)-silyloxime 36 to give conjugate addition product 37.\(^{18e}\)

Scheme 12

1.4 Previous Weinreb Group Studies on Intramolecular Conjugate Addition of Nucleophiles to Nitrosoalkenes

The Weinreb group has recently been systematically studying conjugate additions of nucleophiles to nitrosoalkenes in order to further evaluate their potential as enolonium ion equivalents. The initial investigations focused on developing intramolecular
conjugate additions of nucleophiles to nitrosoalkenes to a generate a wide variety of fused and bridged ring systems.\(^3\) Thus, \(\alpha\)-chloro-\(O\)-TBS-oxime 38 was converted into the sodium malonate anion by treatment of NaHMDS, followed by addition of TBAF to reveal the nitrosoalkene intermediate which on conjugate addition gave [2.2.2]-bicylic product 39 in good yield (Scheme 13). Heterocyclic rings were successfully generated as well. Thus, \(\alpha\)-chloro-\(O\)-TBS-oxime 40, upon addition of two equivalents of TBAF as a base at 0 °C underwent intramolecular conjugate addition to afford nitrogen heterocycle 41. Additionally, oxygen heterocycle 43 was generated in 95% yield from the corresponding \(\alpha\)-chloro-\(O\)-silyloxime 42. Other non-malonate soft nucleophiles also underwent successful intramolecular nitrosoalkene cyclization. Bridged dicyano compound 45 was formed in 82% yield from the corresponding \(\alpha\)-chloro-\(O\)-silyloxime 44. Finally, sulfone-containing \(\alpha\)-chloro-\(O\)-silyloxime 46 underwent successful intramolecular cyclization to afford bridged oxime 47 in 83% yield. Interestingly, during these studies it was found that both \(\text{Na}^+\) and \(\text{K}^+\) counterions gave much higher yields of the cyclization products compared to \(\text{Li}^+\).\(^3\)

**Scheme 13**
1.5 Previous Weinreb Group Studies on Preparation of α-Aryl Nitriles from α-Chloroaldoximes via Organocuprate Additions to Transient Nitrosoalkenes

Continuing Weinreb group studies on the use of nitrosoalkenes as enolium ion equivalents have resulted in the development of a novel method for preparing α-aryl nitriles.\(^\text{23}\) It was found that α-chloroaldoximes 48 could be treated with aryl cyanocuprates to generate transient nitrosoalkenes 49 that undergo conjugate addition with a second equivalent of the aryl cyanocuprate to give α-aryl oximes 50 (Scheme 14). The α-aryl oximes 50 are then readily dehydrated to give α-aryl nitriles 51 in good overall yields. This methodology is successful with aryl cyanocuprates containing both electron withdrawing and electron donating groups (entries 2 and 1) and with α-chloro oximes having various substitution patterns (entries 1-4) (Table 1).
Scheme 14

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Chloroaldoxime</th>
<th>Aryl cuprate</th>
<th>α-Aryl nitrile</th>
<th>Overall yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="chemical_structure_1" alt="" /></td>
<td>4-MeOC₆H₄CuCNLi</td>
<td><img src="chemical_structure_2" alt="" /></td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td><img src="chemical_structure_3" alt="" /></td>
<td>4-ClC₆H₄CuCNLi</td>
<td><img src="chemical_structure_4" alt="" /></td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td><img src="chemical_structure_5" alt="" /></td>
<td>PhCuCNLi</td>
<td><img src="chemical_structure_6" alt="" /></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="chemical_structure_7" alt="" /></td>
<td>PhCuCNLi</td>
<td><img src="chemical_structure_8" alt="" /></td>
<td>62</td>
</tr>
</tbody>
</table>
Chapter 2
Results and Discussion

Studies on Nitrosoalkene Alkylations

2.1 Intermolecular Nitrosoalkene Alkylations via the Denmark Protocol

Nitrosoalkenes formed via method A (i.e. generated from free α-chlorooximes, Scheme 1) are known to undergo intermolecular alkylation with a variety of carbon and hetero nucleophiles (vide supra). However, at the outset of this work there were only a few examples in the literature of alkylations of nitrosoalkenes generated utilizing the Denmark conditions (Method B, Scheme 2) with carbon nucleophiles. Our group decided to further explore the potential of such alkylations using these α-chloro-O-silyloxime-generated nitrosoalkenes. In addition, before the beginning of this project, there were very few reported examples of cyclic nitrosoalkenes acting as Michael acceptors and therefore we decided to explore the area in some detail as well.

Thus, former group member Max Majireck conducted our initial optimization experiments using the cyclic nitrosoalkene derived from α-chloro-O-silyloxime 53 and the enolate of methyl phenylacetate (52) as the nucleophile (Scheme 15). Deprotonation of methyl phenylacetate (52) (1.2 eq.) with KHMDS (1.2 eq.) at -78 °C was followed by addition of α-chloro-O-silyloxime 53 (1.0 eq.) and then TBAF (1.2 eq.) and warming the reaction mixture to 0 °C, followed by aqueous quench gave Michael adduct 54 in 79% yield. It was found that if the reaction mixture was allowed to warm to room temperature before an aqueous quench, formation of oxazanone 55, along with decomposition by-products, were observed.
With these optimized conditions developed, we explored the scope of this conjugate addition reaction using various ester-containing nucleophiles and nitrosoalkene precursors. This work was carried out by Max Majireck, Puhui Li and myself. It was found that both 5- and 6-membered ring nitrosoalkene derivatives were successful Michael acceptors (Table 2). Malonate derivatives gave the conjugate addition products in good to excellent yield (entries 1-3). Additionally, enolates from an α-nitroester, a β-ketoester, an α-sulfonylester, and an α-phenylester were compatible nucleophiles with nitrosocyclohexene (entries 4-7). Nitrosocyclopentene was also found to be a fairly good conjugate acceptor under these conditions (entries 8-12). Interestingly, in some cases it was found that the type of base used to generate the carbanion influences the yield of the reaction, while in other cases the counterion has no noticeable effect. This is different from the intramolecular cases previously explored by our group in which Na+ and K+ counterions generally gave better yields than Li+(vide supra).³

Scheme 15
In addition to exploring the reactivity of ketoxime-derived nitrosoalkenes, we explored reactions of aldoxime-derived nitrosoalkenes. We hoped to expand our methodology to these substrates since direct alkylation of aldehydes through enolate chemistry is normally difficult and conjugate additions to such nitrosoalkenes has not been very well explored. Malonate derivatives were found to react efficiently with the hydrocinnamaldehyde-derived nitrosoalkene (Table 3, entries 1-5). Additionally, both malonate derivatives and methyl phenylacetate underwent successful conjugate addition to cyclohexanecarboxaldehyde-derived nitrosoalkenes (entries 6-9). When the exocyclic vinylnitroso compounds were subjected to the reaction conditions along with α-
substituted malonate derivatives, conjugate addition products containing vicinal quaternary centers were obtained in good yields (entries 7-8).

Table 3. Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes Derived from Aldoxime Derivatives

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO₂C₂CO₂Et</td>
<td>PhCl/HNCl</td>
<td>PhCl/HN</td>
<td>51%f</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C₂CO₂Et</td>
<td>PhMe/HNMe</td>
<td>PhMe/HN</td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td>EtO₂C₂CO₂Et</td>
<td>EtCl/HNCl</td>
<td>EtCl/HN</td>
<td>68%d,g</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂C₂Ph</td>
<td>PhCl/HNCl</td>
<td>PhCl/HN</td>
<td>75%d,d</td>
</tr>
<tr>
<td>5</td>
<td>EtO₂C₂CO₂Et</td>
<td>PhCl/HNCl</td>
<td>PhCl/HN</td>
<td>67%d</td>
</tr>
<tr>
<td>6</td>
<td>EtO₂C₂CO₂Et</td>
<td>ClOH/EtOH</td>
<td>ClOH/Et</td>
<td>64%g,6,6</td>
</tr>
<tr>
<td>7</td>
<td>EtO₂C₂CO₂Et</td>
<td>ClOEt/MeOH</td>
<td>ClOEt/Me</td>
<td>74%</td>
</tr>
<tr>
<td>8</td>
<td>EtO₂C₂CO₂Et</td>
<td>ClEt/PhOH</td>
<td>ClEt/Ph</td>
<td>69%d</td>
</tr>
<tr>
<td>9</td>
<td>MeO₂C₂Ph</td>
<td>ClOH/EtOH</td>
<td>ClOH/Et</td>
<td>63%</td>
</tr>
</tbody>
</table>

*a*Use of LiHMDS and NaHMDS gave yields of 91% and 94% respectively. *b*No desired product was formed when using LiHMDS or NaHMDS. *c*An accurate stereochemical assignment could not be made since the products exist as a complex mixture of E/Z-isomers and/or diastereomers which were not separable by column chromatography. *d*2 eq. of KHMDS and 2 eq. of ester derivative were used. *e*The deprotonation step was performed at 0 °C to prevent freezing of the reaction mixture. *f*Use of LiHMDS and NaHMDS 34% and 51% respectively. *g*E/Z ratio could not be determined.

We also probed the reactivity of a terminal nitrosoalkene in conjugate addition reactions (Table 4). Similar to the other nitrosoalkene systems, a methyl ketone-derived nitrosoalkene reacted cleanly with malonate derivatives and methyl phenylacetate to give the conjugate addition products in good yields.
Surprisingly, we were not able to successfully extend our methodology to harder monoester or ketone enolate nucleophiles such as those derived from $t$-butyl acetate and acetophenone, respectively, although there some is literature precedent for reaction of hard nucleophiles with vinyl nitroso compounds generated through classical conditions (Method A).\(^1\) It should also be noted that the majority of Michael adducts were isolated as single oxime isomers and were assumed to be the more stable \((E)\)-geometry.

Table 4. Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes Derived from a Ketoxime Derivative

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{EtO}_2\text{C}_2\text{CO}_2\text{Et}$</td>
<td>$\text{Me}$</td>
<td>$\text{Cl}$</td>
<td>$\text{N}$</td>
</tr>
<tr>
<td>2</td>
<td>$\text{EtO}_2\text{C}_2\text{CO}_2\text{Et}$</td>
<td>$\text{Et}$</td>
<td>$\text{Cl}$</td>
<td>$\text{N}$</td>
</tr>
<tr>
<td>3</td>
<td>$\text{MeO}_2\text{C}_2\text{Ph}$</td>
<td>$\text{Ph}$</td>
<td>$\text{Cl}$</td>
<td>$\text{N}$</td>
</tr>
</tbody>
</table>
Chapter 3. Stereochemical Aspects of Nitrosoalkene Alkylation

3.1 Conjugate Addition of Carbon Nucleophiles to Acyclic Nitrosoalkenes

Background

During the course of our studies on intermolecular conjugate additions we noted that several groups have reported stereochemical studies on conjugate additions of nucleophiles to \( \gamma \)-chiral-\( \alpha,\beta \)-unsaturated esters 56 which would be analogous to \( \gamma \)-chiral nitrosoalkenes 57.\(^5,6,10\)

**Figure 2**

\[
\begin{align*}
\text{56} & \quad \approx \quad \text{57}
\end{align*}
\]

**\( \gamma \)-Chiral-\( \alpha,\beta \)-unsaturated Esters 56**

The studies reported in the literature on conjugate additions of nucleophiles to \( \gamma \)-chiral-\( \alpha,\beta \)-unsaturated esters 56 have some conflicting results about the stereoselectivity of the additions as well as the type of mechanistic stereochemical model used to rationalize the stereoselectivity.\(^5,6,10\) Four models have shown the most consistency for stereochemical prediction in these systems. A modified Felkin-Anh model 58 seems to be the most general of the four models and best predicts the stereoselectivity for conjugate addition of organocuprates, alkyl copper reagents and Grignard reagents to (\(E\))-chiral-\( \alpha,\beta \)-unsaturated esters 56 which give *anti*-59 systems preferentially (Scheme 16).\(^5a,b,6a-d\)
The stereoselectivity of conjugate additions to (Z)-γ-chiral-α,β-unsaturated esters 60 can also be predicted in most cases using a A\textsuperscript{1,3} minimized model 61 (Scheme 17). This model successfully predicts the preference for conjugate addition of Grignards and dialkylolithium cuprates to generate \textit{syn}-products 62.\textsuperscript{7} Interestingly, the diastereoselectivity of (Z)-chiral-α,β-unsaturated esters 60 is not as high as the diastereoselectivity seen for (E)-chiral-α,β-unsaturated esters 56. Additionally, alkylcopper reagents do not follow the selectivity predicted by this model but rather preferentially form \textit{anti}-products 59.\textsuperscript{5a}

Similar additions to unsaturated systems containing γ-alkoxy groups have also been reported in the literature. The stereoselectivity of nucleophilic addition of organolithium reagents and alkoxide nucleophiles to \textit{(E)}-α,β-unsaturated esters 63 are in accord with a modified polar Felkin-Anh model 64 to preferentially give \textit{syn}-products 65 (Scheme 18).\textsuperscript{9,10}
The opposite stereoselectivity was reported for the addition of organocuprates and alkyl copper reagents to (Z)-γ-alkoxy-α,β-unsaturated esters \( \text{66} \) (Scheme 19).\(^\text{10}\) It was postulated that in these additions the cuprate and alkyl copper reagents chelate with the alkoxy group to give a chelation model structure \( \text{67} \) resulting in preferential formation of \textit{anti-}\( \text{68} \).\(^\text{10}\)

**Results and Discussion**

We were interested in systematically exploring how conjugate additions of nucleophiles to γ-chiral nitrosoalkenes \( \text{57} \) would compare to the selectivity reported for the various γ-chiral-α,β-unsaturated esters. Therefore, known compound α-chloro-γ-methyldihydrocinnamaldehyde (racemic mixture of diastereomers) was converted to \( \text{O-TBS-oxime} \) \( \text{69} \) upon treatment with commercially available \( \text{O-TBS-hydroxylamine} \).\(^\text{2}\) This nitrosoalkene precursor \( \text{69} \) was subjected to the alkylation conditions previously used for achiral systems (Method \textbf{B}) with various malonate derivatives to afford
exclusively *anti* alkylation products 70a-d in yields ranging from 63-74% (Scheme 20). Syn alkylation products 71a-d were not detected in any of these alkylations.

**Scheme 20**

Initially, we had difficulties in determining the stereochemistry of these alkylation products. It was decided to attempt to derivatize products 70a-d to convert them into either more rigid or crystalline derivatives in hopes of gaining stereochemical information through NMR analysis or X-ray crystallography.

It has been reported that aldoximes can be readily converted into nitrile oxides which then can undergo intermolecular [3+2]-dipolar cycloadditions with norbornene to give bicyclic compounds. 49 Unfortunately, attempted cyclization of the nitrile oxide derived from alkylation product 70a with norbornene (72) was unsuccessful and only gave a complex mixture of products rather than the desired adduct 73 (Scheme 21).

**Scheme 21**

Intramolecular variants of nitrile oxide cycloadditions have also been reported the and therefore we decided to carry out a cycloaddition of the nitrile oxide from alkylation
product 70d to give isoxazolidine 74 (Scheme 22).\textsuperscript{50} This cycloaddition was successful but unfortunately, the product 74 was not crystalline nor did it provide sufficient stereochemical information through \textsuperscript{1}H NMR analysis to assign stereochemistry.

Scheme 22

\[
\begin{array}{c}
\text{Ph} \quad \text{NOH} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\hline
\text{70d}
\end{array}
\quad \begin{array}{c}
\text{NaOCl} \\
\text{THF} \\
0 \text{°C-rt}
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{EtO}_2\text{C} \quad \text{N} \\
\text{EtO}_2\text{C} \\
\hline
\text{74}
\end{array}
\]

\textit{O}-Acylation of alkylation product 70a with 2-nitrobenzoyl chloride to give \textit{O}-acyl oxime 75 was successful (Scheme 23). Once again, this derivative was not a crystalline solid and no stereochemical information could be extracted by NMR.

Scheme 23

\[
\begin{array}{c}
\text{Ph} \quad \text{NOH} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\hline
\text{70a}
\end{array}
\quad \begin{array}{c}
\text{2-nitrobenzoyl chloride} \\
\text{TEA, CH}_2\text{Cl}_2
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{O}_2\text{N} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\hline
\text{75}
\end{array}
\]

After a further search of the literature, we found that Hassner and coworkers had successfully generated isoxazolidine 77 though thermal intramolecular oxime-olefin cycloaddition from aldoxime 76 (Scheme 24). We decided to apply these conditions to adduct \textit{anti}-70d in the hope of preparing a crystalline derivative.\textsuperscript{8,18}
To our delight the stereochemistry of *anti*-70d was finally confirmed by X-ray analysis of isoxazolidine 80, which was prepared via a two step [3+2] cycloaddition/tosylation sequence on diethyl allyl malonate-derived oxime 70d (Scheme 25). Oxime 70d was first subjected to the thermal intramolecular oxime-olefin cycloaddition conditions reported by Hassner. Thus, nitrone intermediate 78 is generated *in situ* on heating through tautomerization of oxime 70d, which acts as a 1,3-dipole that then cyclizes with the tethered olefin. The stereochemistry of the hydrogens at the fusion of the resulting isoxazolidine 79 are in a *cis* relationship since other alignments do not allow favorable overlap of the 1,3-dipole and olefin (*cf.* 78). Isoxazolidine 79 was then treated with TsCl and K₂CO₃ at reflux in dichloromethane to give crystalline isoxazolidine 80. It is reasonable to assume that the other conjugate addition adducts 70a-c also have identical *anti* configurations.
Scheme 25

Figure 3

ORTEP Diagram of Isoxazolidine 80
After determining the stereochemistry of our initial malonate alkylation products we hoped to further explore the range of carbon nucleophiles that could be successfully utilized in this methodology. Interestingly, the enolate of 1,3-diketone 81 did not react as hoped under these conditions. Thus, when the potassium enolate of 81 was treated with the nitrosoalkene from α-chloro-O-silyloxime 69, the alkylation product 82 was not isolated, but rather a complex mixture of products was formed (Scheme 26).

**Scheme 26**

Since it had previously been reported that enolates of monoesters are good nucleophiles in conjugate additions to nitrosoalkenes, the enolate of t-buty1 acetate (83) was treated with the nitrosoalkene generated from α-chlorooxime 84 (Scheme 27). However, formation of alkylation product 85 was not observed and only a mixture of unidentified products was observed.

**Scheme 27**

With this unsuccessful result, coupled with our previous success using highly stabilized enolate nucleophiles, we decided that Meldrum’s acid would be an interesting nucleophile to use in this methodology. Meldrum’s acid derivatives 86 can be converted
through pyrolysis into ketenes \( \textbf{87} \) which can be trapped with various nucleophiles to give numerous carboxylic acid and carboxylic acid derivatives (Scheme 28).\(^{21}\)

**Scheme 28**

![Chemical structure of Scheme 28]

Unfortunately, exposure of Meldrum’s acid (\( \textbf{88} \)) to KHMDS, followed by addition of \( \alpha \)-chloro-\( O \)-silyloxime \( \textbf{69} \) and TBAF did not give any of the desired alkylation product \( \textbf{89} \) (Scheme 29). Rather, only the Meldrum’s acid was recovered.

**Scheme 29**

![Chemical structure of Scheme 29]

We also attempted to utilize the anion of nitromethane (\( \textbf{90} \)) as a nucleophile. However, treatment of the nitronate anion with \( \alpha \)-chloro-\( O \)-silyloxime \( \textbf{69} \) followed by TBAF did not give alkylation product \( \textbf{91} \), but instead a complex mixture of products was produced (Scheme 30).

**Scheme 30**

![Chemical structure of Scheme 30]
It has previously been reported by several groups that sp-hybridized carbon nucleophiles can successfully participate in conjugate additions with nitrosoalkenes. To probe this possibility, we generated the nitrosoalkene intermediate from α-chloro-O-silyloxime 69 and exposed it to both the lithium and magnesium anions of phenyl acetylene (92) (Scheme 31). However none of the desired conjugate addition product 93 was formed, but rather some of tautomer 94 was observed.

Scheme 31

In addition to acetylide nucleophiles, we briefly explored the use of cyanide as a nucleophile in conjugate additions to nitrosoalkenes. Thus, tetrabutylammonium cyanide (TBACN) (95) was treated with the nitrosoalkene generated from α-chloro-O-silyloxime 69 in hopes of producing α-cyanoxime 96 (Scheme 32). Interestingly, none of this desired product was formed but rather a small amount of tautomer 94 (15%) was generated along with 5-aminoisoxazole 97 (40%). 5-Aminoisoxazole 97 is believed to form via in situ cyclization of the initial α-cyanoxime 96, a type of reaction which has been reported previously by several groups. Aminoisoxazoles are present in many
medicinally important compounds and this unexpected result might warrant further exploration in the future.

Scheme 32

Finally, we treated the potassium enolate of O-silylcyanoxydrin 98 with the nitrosoalkene from α-chloro-O-silyloxime 69 to give α-keto oxime 99 (Scheme 33). However, no desired product 99 was observed but only the nitrosoalkene tautomer was isolated in this case.

Scheme 33

3.1.1 Modified Felkin-Anh Model as a Rationale for the anti Selectivity

The selectivity observed in these conjugate addition reactions can be rationalized using a modified Felkin-Anh model 102 (Scheme 34). A model similar to 102 has previously been used to rationalize conjugate additions of organocuprates and other organometallic reagents to analogous γ-chiral-α,β-unsaturated esters by the Yamamoto group and others (vide supra). The transient nature of nitrosoalkenes make it impossible for us to determine the E/Z geometry and therefore we have made the reasonable assumption that nitrosoalkene 100 probably adopts the more stable (E)-
geometry. We propose a reactive conformation shown in a modified Felkin-Anh model 102 with the large group (Ph) orthogonal to the double bond, resulting in preferential formation of Felkin product 104 through attack by the nucleophile via a Bürgi-Dunitz trajectory. Additionally, A1,3-strain minimized conformation 103 would predict the formation of anti-Felkin product 105.7 However, we believe this conformation is not favored here since the minimization of A1,3-strain for the related (E)-α,β-unsaturated carbonyl compounds is not a dominant factor since the carbonyl moiety is away from the substituents at the γ-position (cf. Scheme 103).

Scheme 34

It was previously reported that when a substituent at the γ-position of α,β-unsaturated ester 101 is an alkoxy group, varying ratios of both the syn and anti products were formed depending on the type of nucleophile and specific substrate (vide supra). The formation of the syn product 107 has been rationalized using a polar Felkin-Anh model similar to 106 (Scheme 35).9,10 In such a polar Felkin-Ahn model, the heteroatom (alkoxy) substituent is considered the “large” substituent and is favored to be orthogonal
to the double bond, allowing the $\sigma^*$ C-O orbital to mix with the $\pi^*$ C-C orbital, thereby lowering the energy of the LUMO.

To explore whether an analogous nitrosoalkene bearing a $\gamma$-alkoxy group would lead to the syn adduct, we prepared $\gamma$-methoxy-$\alpha$-chloro-$O$-silyloxime 108 by subjecting known compound 2-chloro-3-methoxy-3-phenylpropanal to our standard oximation conditions. Compound 108 was then subjected to the usual alkylation conditions with allyl diethyl malonate, followed by a cycloaddition/tosylation sequence to afford isoxazolidine 111 as a single crystalline stereoisomer (Scheme 36). X-Ray analysis of 111 showed that formation of the anti (Felkin) isomer was still preferred in this reaction. Attempted reversal of this anti selectivity through chelation control (cf. 112) using LiHMDS instead of KHMDS again resulted in exclusive formation of the anti (Felkin) product 109 but in a slightly lower 52% yield (Scheme 37).

Scheme 35
Scheme 36

Figure 4

ORTEP Diagram of Isoxazolidine 111
The affect on the stereoselectivity of the nitrosoalkene alkylation by replacing the \( \gamma \)-phenyl group with a bulky alkyl group was explored as well (Scheme 38). Thus, \( \gamma \)-neopentyl-\( \alpha \)-chloro-\( O \)-silyloxime 113 was subjected to the standard alkylation conditions resulting in formation of \( \textit{anti} \)-product 114 in 76% yield. \( \textit{Anti}-114 \) was converted to isoxazolidine 115 which was then derivatized with \( p \)-NsCl to give crystalline compound 116 in 68% yield. This derivative provided X-ray quality crystals, confirming the stereochemistry.
Finally, $\alpha$-chloro-$O$-silyloxime 113 (prepared by oximation of readily available 2-chloro-3,5,5-trimethylhexanal)\textsuperscript{57} underwent addition with the potassium salt of $N$-methyl-$p$-toluenesulfonamide to afford \textit{anti}-117 in 74\% yield (Scheme 39). Alkylation product 117 was then subjected to dehydration conditions to form nitrile 39. The \textit{anti} structure of 118 was established by comparing its NMR proton coupling data with closely related known compounds (\textit{cf.} Figure 6).\textsuperscript{15,25}

\textbf{Scheme 39
Attempted conjugate addition of the potassium salt of $N$-methyl-$p$-toluenesulfonamide to $\gamma$-phenyl nitrosoalkene 100 gave only a small amount of desired product 121 along with nitrosoalkene tautomer 94 as the major product (Scheme 40). This difference in the ease of tautomerization of nitrosoalkene 100 vs an aliphatic system (neopentyl series) may be due to the increased acidity of the $\gamma$-H of 100 compared to that of $\alpha$-chloro-$O$-silyl oxime 113 derived nitrosoalkene.

Scheme 40

Other amine nucleophiles such as methanesulfonamide (122) and TMS azide (124) did not give the addition products 123 and 125, respectively, when combined with the nitrosoalkene generated in situ from precursor 69, but rather afforded only tautomer 94.
Scheme 41

$\text{MsNH}_2 \quad 122$

1) KHMDS, THF, -78 °C
2) NOTBS, THF, TBAF -78-0 °C

$\text{Ph} \quad \text{Cl} \quad \text{H}$

$\text{69}$

$\text{Ph} \quad \text{Cl} \quad \text{H}$

$\text{H}$

$\text{MsNH}_2 \quad 123$

$\text{TMSN}_3 \quad 124$

1) KHMDS, THF, -78 °C
2) NOTBS, THF, TBAF -78-0 °C

$\text{Ph} \quad \text{Cl} \quad \text{H}$

$\text{69}$

$\text{NOH}$

$\text{N}_3$

$\text{125}$
3.2 Stereochemical Aspects of Nitrosocyclohexene Alkylations

Background

The stereoselectivity of conjugate additions of nucleophiles to 4-t-Bu cyclohexenes 126 and related systems have been studied.\(^\text{20}\) We decided to extend our nitrosoalkene methodology to analogous 4-t-butyl nitrosocyclohexene (127) and carry out a systematic stereochemical study of conjugate additions of nucleophiles to this and other nitrosocyclohexenyl systems (Figure 7).

**Figure 7**

The Abramovitch group and others have probed the stereochemistry of Michael additions to 4-t-butyl-cyclohexenes 126 bearing electron-withdrawing groups (Scheme 42).\(^\text{20}\) These cyclohexenyl systems 126 were subjected to numerous nucleophiles, solvents and reaction conditions to give varying ratios of the \textit{trans} (axial attack) and \textit{cis} (equatorial attack) conjugate adducts \textit{trans}-128 and \textit{cis}-129, respectively, with no generally favored preference for either mode of attack (Table 5).\(^\text{20}\) Abramovitch and coworkers found that in the conjugated nitrile system (EWG = CN) switching from the enolate of diethyl malonate to the smaller thiophenoxide nucleophile resulted in an almost complete reversal of stereoselectivity from a \textit{trans}:\textit{cis} ratio of 8:92 to 100:0. They reason that the smaller size of the thiophenoxide nucleophile diminishes the 1,3-diaxial interactions in the transition state and allow the principle of continuous orbital overlap to
control the mode of attack. Additionally, it was reported that changing from a polar protic solvent to a polar aprotic solvent attenuated the stereoselectivity of the addition and in some cases even reversed it. Abramovitch reasons that the nucleophilic anion will be more solvated in polar protic solvent, making it a weaker nucleophile and resulting in selectivity governed by product development control. On the other hand, he reasons that less solvated nucleophilic anions (in polar aprotic solvent) will be stronger nucleophiles and their mode of attack will be governed by steric interactions in a half-chair transition state. Switching the counterion of the nucleophile from Na\(^+\) to K\(^+\) also reversed or diminished the stereoselectivity (the authors did not provide a rationale for this).

**Scheme 42**
### Table 5

<table>
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<tr>
<th>Nucleophile</th>
<th>Michael Acceptor</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Product Ratio (trans: cis)</th>
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<td>KOEt</td>
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<td>reflux</td>
<td>1:99</td>
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<tr>
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<td></td>
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<td>reflux</td>
<td>91:9</td>
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<tr>
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<td></td>
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<td>reflux</td>
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<td>dioxane</td>
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<td>97 °C</td>
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<td>reflux</td>
<td>56:44</td>
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</table>
Conjugate Additions to 4-\(t\)-Butyl Cyclohexene Systems

Results and Discussion

As a starting point for our stereochemical studies, we chose cyclic nitrosoalkene \(132\) as the initial substrate (Scheme 43).\(^{12}\) During the exploratory stages, we generated the nitrosoalkene \(132\) using two different methods (1) treatment of known\(^2\) \(\alpha\)-chloroxime \(130\) with 3.0 eq. of the sodium salt of diethyl malonate at -78 °C in THF (Method A) and (2) the Denmark procedure\(^2\) involving treatment of known\(^2\) \(\alpha\)-chloro-\(O\)-silyloxime \(131\) with TBAF in THF along with 1.2 eq. of the potassium salt of diethyl malonate (Method B).
Thus, diethyl malonate was treated with base (according to Method A or B) to generate the malonate anion. \(\alpha\)-Chlorooxime 130 or \(\alpha\)-chboro-\(O\)-silyloxime 131 were then added and the nitrosoalkene intermediate 132 was generated via Method A or Method B. This intermediate was found to undergo exclusive axial attack by the enolate to afford trans alkylation product 133. These alkylation products were isolated as a single oxime geometric isomer, assumed to have the more stable (E)-configuration. The product stereochemistry was determined by extensive 2D NMR experiments. The cis alkylation product 134 was not detected. \(\textit{Cis}\)-134 would be generated from equatorial attack of the nucleophile on half-chair nitrosoalkene 132, which would proceed though a high energy twist-boat-like transition state. This analysis is based on the assumption that alkylations of vinylnitroso intermediate 132 occur through an early (reactant-like) transition state.
After these initial exploratory studies were carried out, another group member carried out more extensive studies on the 4-t-Bu system using various malonate, amine and cuprate nucleophiles. In all cases trans products are favored to varying degrees.

Additionally, the stereochemistry of the addition of diethyl malonate to nitrosocyclohexenes with other substitution patterns was briefly explored (Scheme 44). Thus, 5-methyl-α-chlorosilyloxime 135 (mixture of stereoisomers), prepared from the corresponding known α-chloroketone, was added to diethyl malonate potassium enolate. The nitrosocyclohexene 136 which presumably exists in the half chair conformation was then generated with TBAF and underwent exclusive axial attack by the enolate to give cis-137 in 45% yield. The nitrosocyclohexene 139 from known 3-ethyl-2-chlorosilyloxime 138 (mixture of stereoisomers) also underwent exclusive axial attack to give trans-140 in 34% yield. In the half-chair intermediate 139 the ethyl group is probably axial to minimize $\text{A}^{1,2}$ strain. Unfortunately, these cyclic nitrosoalkene systems did not undergo successful conjugate addition with the potassium salt of $N$-methyl-$p$-toluenesulfonamide, but only gave nitrosoalkene tautomerization products.

**Scheme 44**
Conclusion

We have systematically studied conjugate additions of an array of carbon and hetero-nucleophiles to various acyclic and cyclic nitrosoalkenes derived from both ketones and aldehydes. Additionally, we have examined some of the stereochemical aspects of the reactions of both acyclic and cyclic nitrosoalkenes with carbon and hetero-nucleophiles. All reactions were found to be highly stereoselective. The *anti* stereoselectivity of conjugate additions to acyclic nitrosoalkenes can be predicted using a modified Felkin-Anh model while the *trans* stereoselectivity of cyclic nitrosoalkenes can be rationalized via axial attack of the nucleophile on the half chair conformer of the nitrosocyclohexene. The methodology described here can be used as means to access the “umpolong” reactivity of enolonium ion equivalents.
Chapter 4. Method for Conversion of Ketoximes

During work by a group member, Max Majireck, on a natural product total synthesis it became necessary to convert an oxime generated through our nitrosalkene methodology to the corresponding ketone. However, attempts at applying various known reductive, oxidative and acidic deoximation conditions on oxime 141 failed or gave only low yields of the desired ketone 142 (Scheme 45).\textsuperscript{52}

Scheme 45

Thus we decided to develop a new mild, general deoximation procedure that would use inexpensive, stable, commercially available reagents. Additionally, we chose to focus on developing reductive conditions since hydrolytic methods to effect such a transformation are usually harsh and oxidative conditions are often incompatible with amines and indoles.

Previously, Burke and coworkers reported a method for preparation of N-acetyl enamines by heating ketoximes in toluene/acetic anhydride in the presence of iron powder.\textsuperscript{53} For instance, when propiophenone oxime (143) was heated at 75 °C with iron,
acetic anhydride and glacial acetic acid in toluene a E/Z mixture of enamide 144 was isolated (no yield reported) (Scheme 46).

**Scheme 46**

Our group had expanded the scope of this methodology to include the use of acid chlorides and chloroformates rather than acetic anhydride to give enamides and enecarbamates. For example, α-tetralone oxime 145 could be exposed to iron powder and benzoyl chloride or ethyl chloroformate to give enamide 146a and enecarbamate 146b respectively, in good yields (Scheme 47).

**Scheme 47**

We hoped that we could develop a variation of this methodology for converting oximes to the corresponding carbonyl compounds. It was envisioned that oximes 147 subjected to the Fe and a catalytic amount of TMSCl could be further reduced to generate imine anion 149 via radical 148 that upon exposure to water would give simple NH imine 150 (Scheme 48). Hydrolysis of imine 150 was expected to occur readily to afford carbonyl compounds 151.
Initial exploratory experiments were carried out by Max Majireck on oxime (mixture of E/Z isomers) (Scheme 49). It was found that exposure of this oxime to iron powder and a catalytic amount of TMSCl in THF, MeOH, or toluene at either rt or reflux gave none of desired ketone product but rather only E/Z oxime isomerization was observed.

However, it was discovered that oxime acetate underwent successful deoximation when exposed to iron powder in THF containing a catalytic amount of TMSCl at rt, followed by stirring with water to give ketone (Scheme 50). Unfortunately, this initial result was highly irreproducible and some runs gave the product cleanly while others resulted only in starting oxime acetate being recovered. After some detective work, we found that the successful reactions had been run in round-bottom flasks that were cleaned in a nitric acid bath prior to use, followed by washing with water several times and then dried. The reactions that were run in flasks not cleaned in this way gave only recovered starting material. We reasoned that trace amount of acid in the nitric acid washed flasks was catalyzing the reductive cleavage of the oxime.
acetate. It was subsequently found that adding a catalytic amount of nitric acid, $p$-toluenesulfonic acid or trifluoroacetic acid along with Fe and a catalytic amount of TMSCl gave the desired ketone product reproducibly. However, it was ultimately determined that the use of a catalytic amount of glacial acetic acid gave the best results.

**Scheme 50**

![Scheme 50](image)

It was also found during these preliminary studies that some deacetylation of oxime acetate 153 was occurring. As a result of this observation, we decided to screen the reductive cleavage of some different $O$-acyl oxime derivatives. These studies were preformed on acyl derivatives 155a-d prepared from the oxime of 4-phenylcyclohexanone (Scheme 51). It was discovered that the pivalate derivative 155d gave the best results and after additional optimization we found that the cleavage works best if the reduction step is carried out at rt for 30 min, followed by stirring the mixture with water for 15 min. If the reduction step was allowed to run for a longer time lower yields of ketone resulted and the formation of some by-products was observed. We also briefly explored the use of DMF as a solvent, but this medium gave lower yields of ketones 156a-d compared to the corresponding reaction run in THF.
Using this information, we have developed a novel method for the reductive deoximation of ketoximes using Fe powder, a catalytic amount of TMSCl and a catalytic amount of glacial AcOH in THF (Scheme 52). Various ketoxime pivalates were successful cleaved to their corresponding ketones as shown in Table 6. Using this procedure, reductive cleavage of aldoxime pivalates was also attempted. However, mixtures of the corresponding aldehyde and nitrile were isolated in these cases.

Table 6
Thus, we have developed a novel method for the mild reductive cleavage of ketoximes using Fe, a catalytic amount of TMSCl and a catalytic amount of glacial acetic acid. These conditions use inexpensive, commercially available reagents and can be run at room temperature. This method can offer a useful alternative to other reported conditions for oxime cleavage.\textsuperscript{52}
Chapter 5. Experimental

Experimental Section

**General Methods.** All non-aqueous reactions were carried out under a positive atmosphere of argon in flame-dried glassware unless otherwise noted. Anhydrous THF and CH$_2$Cl$_2$ were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification. $^1$H and $^{13}$C NMR spectra were recorded on 300, 360 or 400 MHz spectrometers. Flash column chromatography was performed using silica gel 60 (230-400 mesh).

**General Procedure for Conversion of $\alpha$-Chloroketones to $\alpha$-Chloro-$O$-TBS-oximes.** To a stirred solution of the $\alpha$-chloroketone (1.0 equiv) in CH$_2$Cl$_2$ (ca. 0.5 M) was added PPTS (0.05 equiv.) and 4Å powdered molecular sieves (~15 mg per mmol of $\alpha$-chloroketone), followed by $O$-TBS-hydroxylamine (1.1-2.0 equiv.). The resulting mixture was stirred until complete consumption of the starting $\alpha$-chloroketone was observed (typically 1-2 days) and then filtered through a Celite pad washing with CH$_2$Cl$_2$. 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 $\alpha$-chloro-$O$-TBS-oxime.

*2-Chlorocyclohexanone $O$-(tert-Butyldimethylsilyl) Oxime (53).* $\alpha$-Chloro-$O$-TBS-oxime 53 was obtained using the above general experimental procedure with the following quantities: $\alpha$-chlorocyclohexanone (1.0 mL, 8.19 mmol), CH$_2$Cl$_2$ (15 mL), PPTS (105 mg, 0.41 mmol), 4Å powdered molecular sieves (~100 mg), and $O$-TBS-
hydroxylamine (2.54 g, 16.4 mmol); 2.18 g, 100%, ~2:1 mixture of oxime isomers. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.69 (s, 0.33H), 4.77 (s, 0.67H), 3.27 (d, $J = 14.6$ Hz, 0.67H), 2.56 (td, $J = 13.9$, 4.7 Hz, 0.33H), 2.35 (d, $J = 14.2$ Hz, 0.33H) 2.22-1.81 (m, 4.67H), 1.66-1.63 (m, 1H), 1.43-1.32 (m, 1H), 1.09-0.95 (m, 9H), 0.18 (s, 6H).

2-Chloro-3-phenylpropanol $O$-(tert-Butyldimethylsilyl) Oxime (Table 3, entry 1). The title compound was obtained using the above general experimental procedure with the following quantities: 2-chloro-3-phenylpropanal$^{xxx}$ (1.0 g, 5.93 mmol), CH$_2$Cl$_2$ (10 mL), PPTS (76 mg, 0.30 mmol), 4Å powdered molecular sieves (~70 mg), and $O$-TBS-hydroxylamine (1.0 g, 6.52 mmol); 1.2 g, 70%, ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.20-7.08 (m, 6H), 5.30 (m, 0.33H), 4.59 (q, $J = 7.2$ Hz, 0.67H), 3.12-3.02 (m, 2H), 0.77-0.75 (m, 9H), 0.05-0.00 (m, 6H).

**General Procedure for Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes.** To a -78 °C solution of ester derivative (0.46 mmol) in THF (1 mL) was added KHMDS (917 µL, 0.5 M in PhMe, 0.46 mmol). The resulting solution was then stirred for 45 min at that temperature. The $O$-TBS-oxime dissolved in THF (0.38 mmol in 0.3 mL of THF) was added slowly over 1 min, followed by the dropwise addition of TBAF (458 µL, 1.0 M in THF, 0.46 mmol) over 3 min. The resulting solution was immediately transferred to a 0 °C ice bath and stirred for an additional 2 h. The reaction mixture was diluted with conc. aqueous NH$_4$Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo* to give a
residue, which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes. Isolated yields of conjugate addition products are shown in Tables 2-4.

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)acetate (Table 1, entry 1). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (br s, 1H), 4.22-4.11 (m, 4H), 3.69 (d, $J$ = 10.2 Hz, 1H), 3.20-3.16 (m, 1H), 3.01 (td, $J$ = 10.6, 4.0 Hz, 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$_3$) δ 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)-Diethyl 2-(1-(Hydroxyimino)-3-phenylpropan-2-yl)malonate (Table 3, entry 1). $^1$H NMR (300 MHz, CDCl$_3$) 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); $^{13}$C NMR (90 MHz, CDCl$_3$) 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-(Hydroxyimino)-3-phenylpropan-2-yl)-2-ethylmalonate (Table 3, entry 3). $^1$H NMR (300 MHz, CDCl$_3$) δ 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).

$^{(E)}$-Diethyl 2-Allyl-2-(1-(hydroxyimino)-3-phenylpropan-2-yl)malonate (Table 3, entry 5). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.81 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.30-7.17 (m, 5H), 5.86-5.77 (m, 1H), 5.17-5.12 (m, 2H), 4.31-4.24 (m, 4H), 3.23-3.12 (m, 2H), 2.81-2.63 (m, 3H), 1.36-1.22 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.4, 170.3, 151.0, 139.6, 132.7, 129.7, 128.8, 126.8, 119.6, 62.0, 60.8, 46.0, 39.0, 14.6.

**General Procedure for the Synthesis of α-Chloro-O-silylaldoximes.** To a stirred solution of the aldehyde (1 mmol) in CHCl$_3$ at 0 °C was added a catalytic amount of proline (0.05 mmol) and NCS (1.2 mmol). The resulting solution was warmed to rt and stirred for 12 h. The reaction mixture was diluted with pentane, filtered and washed with water. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes to provide the α-chloroaldehyde.

To a stirred solution of the α-chloroaldehyde (1 mmol) in CH$_2$Cl$_2$ (2 mL) and a spatula of 4 Å molecular sieves was added H$_2$NOTBS (147 mg, 1 mmol) and PPTS (13 mg, 0.05 mmol). The reaction mixture was stirred at rt for 12 h and then filtered through a pad of Celite. The solution was concentrated in vacuo and the residue was purified by
flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes to provide the α-chloro-O-silylaldoxime.

![Chemical Structure](image)

**2-Chloro-3,5,5-trimethylhexanal.** The product was obtained as a clear oil (5.36 g, 86%) as an inseparable mixture of diastereomers in a ~1:1 ratio. Isomer A: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 2.4$ Hz, 1H), 4.15 (dd, $J = 4.4$, 2.5 Hz, 1H), 2.35-2.26 (m, 1H), 1.54-1.51 (m, 2H), 1.18 (d, $J = 11.9$ Hz, 3H), 0.94 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 197.0, 71.8, 47.6, 33.3, 31.4, 30.2, 19.9: Isomer B: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 2.9$ Hz, 1H), 4.06 (dd, $J = 4.9$, 2.9 Hz, 1H), 2.26-2.23 (m, 1H), 1.50-1.46 (m, 2H), 1.03 (d, $J = 12.7$ Hz, 3H), 0.94 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 196.6, 71.3, 46.5, 32.6, 31.3, 30.1, 18.3

![Chemical Structure](image)

**2-Chloro-3-phenylbutanal O-TBS-oxime (69).** The product was obtained as a clear oil (485 mg, 64%) as an inseparable mixture of isomers. Data for major isomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.8$ Hz, 1H), 7.38-7.20 (m, 5H), 4.64 (dd, $J = 16.2$, 8.1 Hz, 1H), 3.22 (m, 1H), 1.51, (d, $J = 7.0$ Hz, 3H), 0.95 (s, 9H), 0.84 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 153.1, 141.6, 128.7, 128.0, 127.3, 63.0, 55.8, 45.6, 44.5, 26.0, 18.2; HRMS-ES+ ($C_{16}H_{27}NO$SiCl) calcd 312.1550 (MH$^+$), found 312.1550.
2-Chloro-3-methoxy-3-phenylpropanal O-TBS-oxime (108). The product was obtained as a clear oil (667 mg, 19%) as an inseparable ~1:1 mixture of isomers. Isomer A: $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J$ = 8.6 Hz, 1H), 7.41-7.34 (m, 5H), 4.68 (dd, $J$ = 8.6, 6.6 Hz, 1H), 4.45 (d, $J$ = 6.6 Hz, 1H), 3.38 (d, $J$ = 6.5 Hz, 3H), 0.84 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 151.4, 137.1, 128.5, 127.6, 127.4, 85.1, 60.8, 57.4, 54.0, 25.7, 18.2. Isomer B: $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J$ = 8.6 Hz, 1H), 7.41-7.34 (m, 5H), 4.64 (dd, $J$ = 8.6, 5.2 Hz, 1H), 4.51 (d, $J$ = 5.2 Hz, 1H), 3.35 (d, $J$ = 3.9 Hz, 3H), 0.84 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 151.4, 136.9, 128.6, 127.6, 127.4, 85.7, 60.0, 57.6, 52.4, 26.0, 18.2; HRMS-ES$^+$ (C$_{16}$H$_{27}$NO$_2$ClSi) calcd 328.1500 (MH$^+$), found 328.1509.

2-Chloro-3,5,5-trimethylhexanal O-TBS-oxime (113). The product was obtained as a clear oil (2.72 g, 86%) as an inseparable mixture of isomers. Data for major isomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J$ = 6.1 Hz, 1H), 4.40 (m, 1H), 2.03 (m, 1H), 1.56 (m, 2H), 1.52 (d, $J$ = 2.8 Hz, 2H), 0.95 (s, 9H), 0.97 (s, 9H), 0.20 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.8, 64.8, 59.1, 47.7, 47.3, 31.3, 30.3, 26.5, 19.5, 18.6; HRMS-ES$^+$ (C$_{15}$H$_{33}$NOClSi) calcd 306.2020 (MH$^+$), found 306.2020.

**General Procedure for the Conjugate Additions to Nitrosoalkenes.** To a stirred solution of the malonate or sulfonamide (2 mmol) in THF (2.2 mL) was added KHMDS (4 mL, 0.5 M in PhMe, 2 mmol) at -78 °C. The resulting solution was then...
stirred for 45 min at that temperature. The O-TBS oxime (1 mmol) dissolved in THF (600 uL) was added slowly over 1 min, followed by dropwise addition of TBAF (2 mL, 1.0 M in THF, 2 mmol) over 3 min. The resulting solution was immediately transferred to an ice bath and stirred for an additional 2 h. The reaction mixture was diluted with concentrated aqueous NH₄Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes.

**Diethyl 2-allyl-2-(1-(hydroxyimino)-3-phenylbutan-2-yl)malonate (70d).** The product was obtained as a clear oil (43 mg, 74%) as a ~9:1 mixture of E/Z oxime isomers. 

* (E)-Oxime isomer: 

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 7.95 \text{ (br s, 1H), 7.66 (d, } J = 9.6 \text{ Hz, 1H), 7.34-20 (m, 5H), 5.78-5.64 (m, 1H), 5.05 \text{ (br s, 1H), 5.00 (br d, } J = 5.6 \text{ Hz, 1H), 4.28-4.01 (m, 4H), 3.39-3.32 (m, 1H), 3.25 \text{ (dd, } J = 9.6, 4.6 \text{ Hz, 1H), 2.57 (d, } J = 7.2 \text{ Hz, 2H), 1.32 \text{ (t, } J = 3.6 \text{ Hz, 3H), 1.26 (t, } J = 3.6 \text{ Hz, 3H), 1.18 (d, } J = 7.1 \text{ Hz, 3H);} \]

\[ \text{C NMR (75 MHz, CDCl}_3 \text{)} \delta 170.4, 170.3, 151.0, 146.8, 132.8, 128.7, 128.0, 126.9, 119.7, 62.0, 61.8, 60.9, 49.7, 40.0, 39.4, 19.5, 14.5, 14.4; \]

HRMS-ES⁺ (C₂₀H₂₈NO₅) calcd 362.1967 (MH⁺), found 362.1971.
Diethyl 2-Ethyl-2-(1-(hydroxyimino)-3-phenylbutan-2-yl)malonate (70c). The product was obtained as a clear oil (93 mg, 72%) as a ~ 10:1 mixture of E/Z oxime isomers. (E)-oxime isomer: $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.46 (br s, 1H), 7.65 (d, $J$ = 9.7 Hz, 1H), 7.33-7.19 (m, 5H), 4.31-4.04 (m, 4H), 3.35-3.32 (m, 1H), 3.24 (dd, $J$ = 9.7, 4.3 Hz, 1H), 1.91-1.84 (m, 2H), 1.34 (t, $J$ = 1.8 Hz, 3H), 1.25 (t, $J$ = 1.8 Hz, 3H), 1.17 (d, $J$ = 7.7 Hz, 3H), 0.84 (t, $J$ = 3.7 Hz, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 170.5, 170.4, 150.5, 146.7, 128.3, 127.6, 126.4, 61.4, 61.3, 60.7, 48.9, 39.1, 28.4, 18.9, 14.1, 14.0, 8.8; HRMS-ES$^+$ (C$_{19}$H$_{28}$NO$_5$) calcd 350.1967 (MH$^+$), found 350.1963.

Diethyl 2-(1-(Hydroxyimino)-3-phenylbutan-2-yl)-2-methylmalonate (70b). The product was obtained as a clear oil (37 mg, 63%). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J$ = 9.1 Hz, 1H), 7.49 (br s, 1H), 7.33-7.19 (m, 5H), 4.13-4.00 (m, 4H), 3.30 (m, 2H), 1.43 (s, 3H), 1.36-1.15 (m, 9H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 170.8, 151.4, 146.2, 128.3, 127.8, 126.5, 61.5, 56.9, 50.3, 39.4, 20.9, 20.0, 13.9; HRMS-ES$^+$ (C$_{18}$H$_{26}$NO$_5$) calcd 336.1811 (MH$^+$), found 336.1810.
Diethyl 2-(1-(Hydroxyimino)-3-phenylbutan-2-yl)malonate (70a). The product was obtained as a clear oil (35 mg, 68%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (br s, 1H), 7.67 (d, $J$ = 7.5 Hz, 1H), 7.38-7.19 (m, 5H) 4.19 (m, 4H), 3.41 (d, $J$ = 5.7 Hz, 1H), 3.22-3.08 (m, 2H), 1.30-1.23 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.8, 168.3, 151.4, 144.0, 129.2, 127.9, 127.4, 62.2, 62.0, 53.7, 47.1, 40.3, 19.6, 14.5; HRMS-ES$^+$ (C$_{17}$H$_{23}$NO$_5$Na) calcd 344.1474 (M+Na), found 344.1478.

Diethyl 2-Allyl-2-(1-(hydroxyimino)-3,5,5-trimethylhexan-2-yl)malonate (114). The product was obtained as a clear oil (89 mg, 76%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.51 (br s, 1H), 7.58 (d, $J$ = 9.4 Hz, 1H), 5.78-5.69 (m, 1H), 5.10 (d, $J$ = 8.3 Hz, 1H), 5.05 (s, 1H), 4.25-4.11 (m, 4H), 2.88 (dd, $J$ = 9.3, 2.0 Hz, 1H), 2.80 (q, $J$ = 2.1 Hz, 1H), 2.60 (q, $J$ = 2.1 Hz, 1H), 2.1 (m, 1H), 1.36 (dd, $J$ = 11.8, 2.3 Hz, 1H), 1.33 (t, $J$ = 3.6 Hz, 3H), 1.24 (t, $J$ = 3.6 Hz, 3H), 1.10 (dd, $J$ = 14.1, 7.7 Hz, 1H), 0.90 (br s, 9H), 0.83, (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.8, 170.6, 150.8, 132.7, 119.6, 61.9, 61.8, 60.5, 51.9, 49.7, 39.5, 31.7, 30.9, 29.3, 17.9, 14.6, 14.4; HRMS-ES$^+$ (C$_{19}$H$_{33}$NO$_5$) calcd 356.2437 (MH$^+$), found 356.2428.
**N-(1-(Hydroxyimino)-3,5,5-trimethylhexan-2-yl)-N,4-dimethylbenzenesulfonamide** (117). The product was obtained as a clear oil (41 mg, 74%). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.71 (d, \(J = 8.2\) Hz, 1H), 7.31 (d, \(J = 9.1\) Hz, 2H), 7.16 (d, \(J = 7.6\) Hz, 2H), 6.91 (s, 1H), 4.23 (dd, \(J = 10.4, 7.8\) Hz, 1H), 2.75 (s, 3H), 2.45 (s, 3H), 1.86 (m, 1H), 1.07 (dd, \(J = 11.5, 7.8\) Hz, 2H), 0.98 (d, \(J = 6.6\) Hz, 3H) 0.95 (s, 9H); \(^13\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 147.8, 143.4, 135.9, 129.5, 127.6, 76.7, 61.9, 46.3, 30.8, 30.0, 29.8, 21.5, 19.7; HRMS-ES\(^+\) (C\(_{17}\)H\(_{29}\)N\(_2\)O\(_3\)S) calcd 341.1899 (MH\(^+\)), found 341.1894.

![Chemical Structure](image)

**Synthesis of Diethyl 2-Allyl-2-(3-(Hydroxyimino)-1-methoxy-1-phenylpropan-2-yl)malonate** (109). To a stirred solution of diethyl allyl malonate (1.2 mmol) in THF (2.2 mL) was added KHMDS (2.4 mL, 0.5 M in PhMe, 1.2 mmol) at -78 °C. The resulting solution was then stirred for 45 min at that temperature. TBAF was added (1.2 mL, 1.0 M in THF, 1.2 mmol) followed by dropwise addition of a solution of the O-TBS oxime 108 (1 mmol) dissolved in THF (600 uL). The resulting solution was immediately transferred to a 0 °C bath and stirred for an additional 1 h. The reaction mixture was diluted with concentrated aqueous NH\(_4\)Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\), concentrated *in vacuo* and purified by flash column
chromatography (25-50% EtOAc/hexanes). The product was obtained as a clear oil (39 mg) in 68% yield: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.78 (br s, 1H), 7.62 (d, $J = 9.6$ Hz, 1H), 7.37-7.24 (m, 5H), 5.68-5.54 (m, 1H), 5.11-5.05 (m, 2H), 4.81 (s, 1H), 4.38-4.16 (m, 4H), 3.12 (s, 3H), 3.06 (d, $J = 9.6$ Hz, 1H), 2.72-2.70 (m, 2H) 1.36 (t, $J = 3.6$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.0, 170.6, 148.6, 140.4, 131.5, 128.6, 127.9, 127.1, 120.2, 82.3, 61.9, 59.2, 57.2, 50.3, 38.9, 14.6, 14.5; HRMS-ES$^+$ (C$_{20}$H$_{28}$NO$_6$) calcd 378.1917 (MH$^+$), found 1378.1920.

**General Procedure for the Synthesis of Isoxazolidines.** A solution of $\alpha$-alkyl aldoxime (0.1 mmol) in toluene (4 mL) was heated and stirred in a sealed tube at 190 °C for 5 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes.

Diethyl 6-(1-Phenylethyl)tetrahydro-1H-cyclopenta[c]isoxazole-5,5(3H)-dicarboxylate (79). The product was obtained as a clear oil (49 mg, 57%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.31-7.22 (m, 4H), 7.16-7.11 (m, 1H), 5.20 (br s, 1H), 4.26 (q, $J = 2.4$ Hz, 2H), 4.04 (t, $J = 4.4$ Hz, 1H), 3.91 (br d, $J = 8.5$ Hz, 1H), 3.67-3.56 (m, 2H), 3.54-3.45 (m, 1H), 3.40-3.28 (m, 1H), 3.06-2.95 (m, 1H), 2.67 (t, $J = 4.5$ Hz, 1H), 2.57 (dd, $J = 12.7$, 8.0 Hz, 1H), 2.07-1.98 (m, 1H), 1.34 (d, $J = 5.2$ Hz, 3H), 1.31 (t, $J = 2.6$ Hz, 3H), 1.00 (t, $J = 3.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 170.8, 146.7, 128.5, 128.3, 126.4, 77.5, 69.6, 63.8, 61.5, 61.4, 58.2, 46.6, 41.8, 39.7, 22.5, 14.5, 14.0; HRMS-ES$^+$ (C$_{20}$H$_{28}$NO$_5$) calcd 362.1967 (MH$^+$), found 362.1970.
Diethyl 6-(Methoxy(phenyl)methyl)tetrahydro-1H-cyclopenta[c]isoxazole-5,5(3H)-dicarboxylate (110). The product was obtained as a clear oil (26 mg, 66%). $^1$H NMR (360 MHz, CDCl$_3$) δ 7.37-7.27 (m, 5H), 4.86 (d, $J$ = 1.8 Hz, 1H), 4.42-4.35 (m, 2H), 4.33-4.09 (m, 4H), 3.73 (d, $J$ = 8.4 Hz, 1H), 3.49-3.35 (m, 2H), 3.20 (s, 3H), 2.76 (dd, $J$ = 8.0, 1.9 Hz, 1H), 2.66 (dd, $J$ = 13.0, 8.2 Hz, 1H), 1.63 (dd, $J$ = 13.0, 9.3 Hz, 1H), 1.36 (t, $J$ = 3.6 Hz, 3H), 1.30 (t, $J$ = 3.6 Hz, 3H); $^{13}$C NMR (90 MHZ, CDCl$_3$) δ 171.6, 171.3, 140.4, 128.3, 127.3, 126.4, 79.9, 76.7, 63.9, 62.7, 61.3, 59.1, 56.8, 47.7, 39.9, 14.1, 14.0; HRMS-ES$^+$ (C$_{20}$H$_{28}$N$_{3}$O$_6$) calcd 378.1917 (MH$^+$), found 378.1927.

General Procedure for Synthesis of N-Tosyl Isoxazolidines. To a stirred solution of isoxazolidine (0.1 mmol) was added TsCl (19 mg, 0.1 mmol) and K$_2$CO$_3$ (28 mg, 0.2 mmol). The reaction mixture was heated at reflux for 60 h and then diluted with H$_2$O and CH$_2$Cl$_2$. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes.

Diethyl 6-(1-Phenylethyl)-1-(4-methylbenzenesulfonyl)tetrahydro-1H-cyclopenta[c]isoxazole-5,5(3H)-dicarboxylate (80). The product was obtained as a white solid (38 mg, 75%): X-ray quality crystals were prepared via slow evaporation
from isopropanol/dichloromethane. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 (d, \(J = 7.5\) Hz, 2H), 7.42 (d, \(J = 7.1\) Hz, 2H), 7.33-7.26 (m, 4H), 7.19-7.18 (m, 1H), 5.05 (t, \(J = 4.4\) Hz, 1H), 4.51 (t, \(J = 3.6\) Hz, 1H), 4.29 (q, \(J = 2.3\) Hz, 2H), 3.84-3.78 (m, 1H), 3.72-3.63 (m, 2H), 3.41 (t, \(J = 3.9\) 1H), 2.84 (t, \(J = 3.3\) Hz, 1H), 2.68 (dd, \(J = 12.3, 8.7\) Hz, 1H), 2.45 (s, 3H), 1.88 (t, \(J = 5.2\) Hz, 1H), 1.48 (d, \(J = 6.7\) Hz, 3H), 1.34 (t, \(J = 3.4\) Hz, 3H), 1.11 (t, \(J = 3.4\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.0, 170.6, 146.8, 145.3, 134.0, 130.0, 129.3, 128.6, 128.3, 126.3, 65.9, 64.1, 62.0, 61.8, 57.4, 45.9, 41.8, 38.5, 22.1, 19.1, 14.5, 14.2; HRMS-ES\(^+\) (C\(_{27}\)H\(_{34}\)N\(_{8}\)O\(_7\)) calcd 516.2056 (MH\(^+\)), found 516.2053.

Diethyl 6-(Methoxy(phenyl)methyl)-1-(4-methylbenzenesulfonyl)tetrahydro-1H-cyclopenta[c]isoxazole-5,5(3H)-dicarboxylate (111). The product was obtained as a white solid (22 mg, 68%); X-ray quality crystals were prepared via slow evaporation from isopropanol/dichloromethane; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.61 (d, \(J = 7.1\) Hz, 2H), 7.43 (t, \(J = 3.5\) Hz, 2H), 7.34-7.25 (m, 3H), 7.16 (d, \(J = 8.1\) Hz, 2H), 5.45 (t, \(J = 4.5\) Hz, 1H), 4.90 (s, 1H), 4.47 (t, \(J = 3.7\) Hz, 1H), 4.41-4.32 (m, 1H), 4.31-4.17 (m, 4H), 3.64 (t, \(J = 4.3\) Hz, 1H), 3.54 (d, \(J = 8.2\) Hz, 1H), 3.30 (s, 3H), 2.93 (d, \(J = 8.9\) Hz, 1H), 2.78 (dd, \(J = 13.3, 8.7\) Hz, 1H), 2.39 (s, 1H), 1.69-1.61 (m, 2H), 1.41 (t, \(J = 3.6\) Hz, 3H), 1.33 (t, \(J = 3.6\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.4, 171.3, 144.7, 140.5, 134.1, 129.5, 129.3, 128.5, 127.4, 127.0, 79.1, 77.5, 63.3, 62.1, 62.0, 58.7, 57.7, 46.8, 40.6, 30.1, 22.0, 14.5; HRMS-ES\(^+\) (C\(_{27}\)H\(_{34}\)N\(_{8}\)O\(_7\)) calcd 532.2005 (MH\(^+\)), found 532.1996.
Synthesis of Diethyl 6-(4,4-Dimethylpentan-2-yl)-1-(4-nitrobenzenesulfonyl)tetrahydro-1H-cyclopenta[c]isoxazole-5,5(3H)-dicarboxylate (116). A solution of diethyl 2-allyl-2-(1-(hydroxyimino)-3,5,5-trimethylhexan-2-yl)malonate (114, 0.04 mmol) in toluene (4 mL) was heated and stirred in a sealed tube at 190 °C for 5 h. The solution was concentrated in vacuo. The crude residue was dissolved in CH₂Cl₂ (430 uL) and to this solution was added NsCl (11 mg, 0.05 mmol) and TEA (7 uL, 0.05 mmol). The reaction mixture was stirred for 7 h at rt and then diluted with CH₂Cl₂. The combined organic layers were washed with water, dried over Na₂SO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting with 10-50% EtOAc/hexanes. The product was obtained as a white solid (16 mg, 68%): X-ray quality crystals were prepared via slow evaporation from isopropanol/dichloromethane: ¹H NMR (360 MHz, CDCl₃) δ 8.42 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H), 5.02 (t, J = 3.6 Hz, 1H), 4.46 (t, J = 3.9 Hz, 1H), 4.32-4.12 (m, 4H), 3.73 (d, J = 8.1 Hz, 1H), 3.66-3.58 (m, 1H), 2.73 (t, J = 6.5 Hz, 2H), 2.33 (br s, 1H), 1.73 (dd, J = 13.4, 9.1 Hz, 1H), 1.65 (d, J = 3.5 Hz, 1H), 1.61 (s, 1H), 1.45 (dd, J = 13.9, 7.4 Hz, 1H), 1.32 (t, J = 3.6 Hz, 3H), 1.27 (t, J = 3.6 Hz, 3H), 1.00 (m, 11H); ¹³C NMR (90 MHz, CDCl₃) δ 171.0, 170.4, 150.7, 142.9, 130.1, 124.1, 76.7, 63.8, 63.5, 61.7, 61.4, 57.4, 52.4, 46.3, 40.3, 31.3, 30.0, 27.9, 17.6, 14.1, 13.9; HRMS-ES⁺ (C₂₅H₃₇N₂O₉S) calcd 541.2220 (MH⁺), found 541.2206.

General Procedure for the Conversion of Aldoximes to Nitriles. A solution of α-alkyl aldoxime in pyridine (710 uL) was added MsCl (55 uL, 0.7 mmol) at 0 °C and the
mixture was stirred for 12 h. The solution was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with water, dried over Na$_2$SO$_4$ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting with 5-25% EtOAc/hexanes.

![Diethyl 2-(1-Cyano-2-phenylpropyl)-2-ethylmalonate](image)

**Diethyl 2-(1-Cyano-2-phenylpropyl)-2-ethylmalonate.** The product was obtained as a clear oil (17 mg, 73%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40-7.27 (m, 5H), 4.32-4.19 (m, 4H), 3.59 (d, $J = 3.1$ Hz, 1H), 3.25-3.16 (m, 1H), 2.25-2.14 (m, 2H), 1.43 (d, $J = 7.1$ Hz, 3H), 1.36-1.29 (m, 6H), 0.94 (t, $J = 3.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.6, 169.3, 145.0, 129.3, 127.7, 127.4, 118.5, 62.5, 59.8, 42.9, 37.3, 27.2, 18.8, 14.4, 9.1; HRMS-ES+ (C$_{19}$H$_{26}$NO$_4$) calcd 332.1862 (MH$^+$), found 332.1860.

![N-(1-Cyano-2,4,4-trimethylpentyl)-N,4-dimethylbenzenesulfonamide](image)

**N-(1-Cyano-2,4,4-trimethylpentyl)-N,4-dimethylbenzenesulfonamide** (118). The product was obtained as a clear oil (17 mg, 60%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.2$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H), 4.43 (d, $J = 10.3$ Hz, 1H), 2.83 (s, 3H), 2.48 (s, 3H), 1.92-1.86 (m, 1H), 1.75 (d, $J = 13.9$ Hz, 2H), 1.22 (d, $J = 6.6$ Hz, 3H), 0.97 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.0, 133.8, 130.5, 128.0, 115.7, 56.5, 46.1, 32.2, 31.7, 30.6, 30.1, 22.1, 20.1; HRMS-ES$^+$ (C$_{17}$H$_{27}$N$_2$O$_2$S) calcd 323.1793 (MH$^+$), found 323.1797.
Diethyl 2-((2-Nitrobenzoyl)oxy)iminoo)-3-phenylbutan-2-yl)malonate (75). To a stirred solution of aldoxime 70a (62 mg, 0.193 mmol) in CH$_2$Cl$_2$ was added triethylamine (35 µL, 0.251 mmol) and 2-nitrobenzoyl chloride (37 µL, 0.251 mmol). The reaction mixture was stirred at rt for 4 hr, washed with 1N HCl and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated in vacuo and the resulting residue was purified by column chromatography (30-50% ethyl acetate/hexanes) to give a clear oil (63 mg, 69%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 (d, $J = 8.4$ Hz, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 7.75-7.65 (m, 3H), 7.36-7.32 (m, 2H), 7.28-7.25 (m, 1H), 7.18-7.12 (m, 2H), 4.20-4.10 (m, 4H), 3.41 (d, $J = 5.4$ Hz, 1H), 3.34-3.28 (m, 1H), 1.33-0.94 (m, 9H). LRMS-ES$^+$ m/z (relative intensity) 471 (MH$^+$, 10).

Diethyl 6-(1-Phenylethyl)-3a,4-dihydro-3H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (74). To a stirred solution of oxime 70d (86 mg, 0.237 mg) in CH$_2$Cl$_2$ was added NaOCl (698 µL, 5% solution) at 0 °C. The reaction mixture was warmed to rt, stirred for 24 h, diluted with H$_2$O, and extracted with CH$_2$Cl$_2$. The organic layer was concentrated in vacuo and purified by column chromatography (40% ethyl acetate/hexanes) to give a clear oil (49 mg, 57% yield). $^1$H NMR (4360 MHz, CDCl$_3$) δ 7.53-7.41 (m, 1H), 7.33-7.28 (m, 3H), 7.24-7.19 (m, 1H), 4.63 (dd, $J = 10.9, 9.0$ Hz, 1H),
4.24-4.09 (m, 4H), 3.81 (dd, J = 12.2, 8.1 Hz, 1H), 3.41-3.35 (m, 1H), 3.14-3.10 (m, 1H), 2.90 (dd, J = 13.7, 9.2 Hz, 1H), 2.49 (dd, J = 9.3, 3.1 Hz, 1H), 1.95 (dd, J = 13.7, 8.8 Hz, 1H), 1.28 (d, J = 7.0 Hz, 2H), 1.21 (t, J = 2.5 Hz, 3H), 1.01 (t, J = 3.6 Hz, 3H). LRMS-ES$^+$ m/z (relative intensity) 360 (MH$^+$, 75).

(1$E$,2$E$)-3-Phenylbut-2-enal oxime (94). Isolated as a side product in several attempted nitrosoalkene alkylations. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.28 (d, J = 10.4 Hz, 1H), 7.82 (br s, 1H), 7.65-7.50 (m, 2H), 7.43-7.35 (m, 3H), 6.58-6.54 (m, 1H), 2.28 (s, 3H). LRMS-ES$^+$ m/z (relative intensity) 162 (MH$^+$, 25)

4-(1-Phenylethyl)isoxazol-5-amine (97). To a stirred solution of TBACN (129 mg, 0.455 mmol) in THF (989 $\mu$L) at 0 °C was added $\alpha$-chloro-O-silyloxime 69 (29 mg, 0.091 mmol) in THF (72 $\mu$L) followed by slow addition of TBAF (182 $\mu$L, 1M in THF). The reaction mixture was stirred for 1 h 45 min and diluted with H$_2$O. After extraction with ethyl acetate, the organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The resulting residue was purified by preparatory TLC (3:2:1 hexanes/dichloromethane/ethyl acetates) to give isoxazole 97 as a white solid (7.0 mg, 40%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.04 (s, 1H), 7.40-7.34 (m, 2H), 7.30-7.25 (m, 3H), 3.93 (br s, 2H), 3.84 (q, J = 7.1 Hz, 1 H), 1.59 (d, J = 7.2 Hz, 3H). LRMS-ES$^+$ m/z (relative intensity) 189 (MH$^+$, 30)
trans-(E)-Diethyl-5-(tert-Butyl)-2-(hydroxyimino)cyclohexyl)malonate (133).

**Method A:** To a stirred suspension of NaH (50 mg, 1.25 mmol) in THF (5.0 mL) at 0 °C was added diethyl malonate (190 µL, 1.25 mmol). The reaction mixture was stirred at that temperature for 30 min followed by addition of 4-(tert-butyl)-2-chlorocyclohexan-1-one oxime 130 (85 mg, 0.417 mmol) in THF (1.0 mL). After 1 h and 30 min the mixture was diluted with H₂O, extracted with ether and the organic layers were dried over Na₂SO₄. After concentration of the organic layers in vacuo the resulting residue was purified by column chromatography (30% ethyl acetate/hexanes) to give a clear oil (85 mg, 63%). **Method B:** To a stirred solution of diethyl malonate (138 µL, 0.906 mmol) in THF (2.0 mL) was added KHMDS (1.8 mL, 0.5 M in PhMe, 0.906 mmol) at -78 °C. The resulting solution was then stirred for 45 min at that temperature. The O-TBS oxime 131 (240 mg, 0.755 mmol) dissolved in THF (120 µL) was added slowly over 1 min, followed by dropwise addition of TBAF (906 µL, 1.0 M in THF, 0.906 mmol) over 3 min. The resulting solution was immediately transferred to an ice bath and stirred for an additional 2 h. The reaction mixture was diluted with concentrated aqueous NH₄Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate in hexanes (15-30%) to afford a clear oil (56 mg, 23%). ¹H NMR (400 MHz, CDCl₃) δ 8.61-8.40 (br s, 1H), 4.26-4.09 (m, 4H), 3.76 (d, J = 11.5 Hz, 1H), 3.29-3.24 (m, 1H), 3.17 (br d, J = 13.8 Hz, 1H), 2.03-1.95 (m, 2H), 1.91-
1.80 (m, 2H), 1.50 (dt, \( J = 11.9, 5.4 \) Hz, 1H), 1.42-1.36 (m, 1H), 1.30 (t, \( J = 3.6 \) Hz, 3H), 1.24 (t, \( J = 4.0 \) Hz, 3H), 0.85 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 168.3, 168.2, 159.9, 62.0, 61.9, 53.7, 42.6, 40.4, 32.8, 30.1, 27.8, 25.5, 22.5, 14.5, 14.4.

2-Chloro-5-methylcyclohexanone \( O\)-(tert-Butyldimethylsilyl) Oxime (135). To a stirred solution of the \( \alpha\)-chloroketone (3.41 mmol) in CH\(_2\)Cl\(_2\) (7 mL) and a spatula of 4 Å molecular sieves was added H\(_2\)NOTBS (529 mg, 3.41 mmol) and PPTS (spatula tip full). The reaction mixture was stirred at rt for 12 h and then filtered through a pad of Celite. The solution was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate in hexanes (5-30%) to provide the product as a clear oil (632 mg, 67%) as a mixture of (E/Z)-isomers and diastereomers: \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 5.64 (br s, 0.4H), 5.50 (br s, 0.1H), 4.72 (br s, 0.4H), 4.57 (br s, 0.1H), 3.31 (t, \( J = 5.7 \) Hz, 1H), 2.40-2.30 (m, 1H), 2.23-2.18 (m, 1H), 2.10-2.05 (m, 1H), 1.94-1.76 (m, 3H), 1.69-1.45 (m, 5H), 1.11-1.04 (m, 6H), 0.96-0.94 (m, 18H), 0.22-0.19 (m, 12H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \( \delta \) 162.7, 161.9, 160.7, 159.3, 66.3, 59.1, 54.5, 49.3, 47.4, 47.0, 38.7, 37.1, 35.4, 34.9, 33.6, 33.5, 32.4, 31.4, 31.3, 31.2, 29.7, 29.0, 28.4, 28.2, 27.6, 27.5, 26.6, 26.1, 25.8, 24.5, 23.5, 22.4, 22.1, 21.9, 21.2, 19.9, 18.9, 18.8, 18.2, 16.8; IR (thin film) 2955, 2858, 1744, 1461, 1252, 945 cm\(^{-1}\); LRMS-ES\(^+\) \( m/z \) (relative intensity) 276 (MH\(^+\), 10).

**General Procedure for Conjugate Additions to Ring-Substituted Nitrosoalkenes 136 and 139.** To a stirred solution of diethyl malonate (3 mmol, 481
mg) in THF (6.5 mL) was added KHMDS (6 mL, 0.5 M in PhMe, 3 mmol) at -78 °C. The resulting solution was then stirred for 45 min at that temperature. The O-TBS oxime (135 or 138, 1 mmol) dissolved in THF (600 µL) was added slowly over 1 min, followed by dropwise addition of TBAF (2 mL, 1.0 M in THF, 2 mmol) over 3 min. The resulting solution was immediately transferred to an ice bath and stirred for an additional 2 h. The reaction mixture was diluted with concentrated aqueous NH₄Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate in hexanes (25-40%).

**Diethyl 2-(2-(Hydroxyimino)-4-methylcyclohexyl)malonate (137).** The product was obtained as a clear oil (18 mg, 34%) as a 5:1 mixture of (E/Z) oxime isomers. \(^1\)H NMR (360 MHz, CDCl₃) δ 8.00-7.50 (br s, 1H), 4.23-4.10 (m, 4H), 3.79 (d, J = 10.0 Hz, 0.2H), 3.71 (d, J = 10.9 Hz), 3.20-3.13 (m, 0.3H), 3.11-3.04 (m, 1H), 2.86-2.72 (m, 0.3H), 2.56 (dd, J = 14.1, 4.7 Hz, 1H), 2.33 (dd, J = 14.0, 7.8 Hz, 1H), 1.93-1.74 (m, 2H), 1.72-1.61 (m, 4H), 1.44-1.37 (m, 2H), 1.30-1.19 (m, 6H), 1.01 (d, J = 7.5 Hz, 1H), 0.96 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (90 MHz, CDCl₃) δ 168.7, 168.6, 159.3, 158.8, 61.9, 60.8, 53.8, 53.5, 41.4, 33.9, 32.0, 31.4, 30.7, 29.5, 27.7, 23.1, 23.0, 21.5, 20.6, 14.6, 14.5, 14.4, 11.8; IR (thin film) 3279, 2931, 2871, 1732, 1455, 1292, 1178, 1033, 947 cm⁻¹; LRMS-ES⁺ m/z (relative intensity) 286 (MH⁺, 36).
Diethyl 2-(2-Ethyl-6-(hydroxyimino)cyclohexyl)malonate (140). The product was obtained as a clear oil (18 mg, 34%) as a ~ 11:1 mixture of (E/Z) oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.31 (s, 1H), 8.10 (s, 0.1H), 4.27-4.05 (m, 4H), 3.83 (d, $J$ = 8.5 Hz, 1H), 3.72 (d, $J$ = 8.1 Hz, 0.09H), 3.13 (d, $J$ = 10.6 Hz, 1H), 3.01 (d, $J$ = 8.5 Hz, 1H), 2.01-1.92 (m, 1H), 1.81-1.74 (m, 1H), 1.73-1.61 (m, 3H), 1.60-1.49 (m, 2H), 1.48-1.39 (m, 1H), 1.36-1.21 (m, 8H), 0.92 (t, $J$ = 5.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.3, 159.0, 158.6, 62.0, 61.9, 54.0, 53.5, 45.4, 39.7, 25.4, 25.3, 21.8, 20.5, 14.4, 12.1, 12.0, 11.7; IR (thin film) 3278, 2960, 2874, 1732, 1456, 1262, 1034, 951 cm$^{-1}$; LRMS-ES$^+$ m/z (relative intensity) 300 (MH$^+$, 26).

**General Procedure for the Conversion of Ketoxime Pivalates to Ketones.** To a solution of oxime pivalate 157 (0.10 mmol) in THF (1 mL) was added iron powder (55.8 mg, 1.0 mmol) followed by glacial AcOH (1 drop, cat.) and TMSCl (1 drop, cat.). After stirring at rt for 30 min, the reaction mixture was diluted with H$_2$O (1 mL) and stirred for an additional 15 min. The liquid phase was separated from the remaining Fe powder using a pipette and transferred to a separatory funnel. The Fe powder was then washed with EtOAc (3 x 2 mL) and the washings were added to the separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc. The
combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes. Known ketones 158 were characterized by comparison to their reported $^1$H NMR spectra (cf. Table 6).
References


50. Modified procedure of unpublished work.


57. Prepared from the corresponding commercially available aldehyde (see Experimental).