New Methods for the Synthesis of All-Carbon Quaternary Centers via the Reactions of *N*-Vinyl Nitrones and Phenyl Hydrazines with Ketenes

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B.S., Chemistry, University of Central Florida, 2007

A thesis submitted to the

Faculty of the Graduate School of the

University of Colorado in partial fulfillment

of the requirement for the degree of

Doctor of Philosophy

Department of Chemistry and Biochemistry

2013

This thesis entitled:

New Methods for the Synthesis of All-Carbon Quaternary Centers via the Reactions of *N*-Vinyl Nitrones and Phenyl Hydrazines with Ketenes

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Had been approved for the Department of Chemistry and Biochemistry

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

Michael, Ryan Edward (Ph.D., Chemistry)

New Methods for the Synthesis of All-Carbon Quaternary Centers via the Reactions of *N*-Vinyl Nitrones and Phenyl Hydrazines with Ketenes

Thesis directed by Professor Tarek Sammakia

This dissertation describes the development of new cascade reactions for the synthesis of quaternary carbons bearing additional proximal hindrance. The general reaction design principles are described which include the *in-situ* generation of a vicinal di-π system capable of undergoing a charge-accelerated [3,3]-sigmatropic rearrangement facilitated by the cleavage of a weak heteroatom-heteroatom bond. Also described is a practical route for the synthesis of *N*-vinyl nitrones that utilizes a 1,4-conjugate elimination as the key step. The reaction of an *N*-vinyl nitrone and a disubstituted ketene to form all-carbon quaternary centers is also detailed. Mechanistic studies provide evidence that the reaction proceeds by a pericyclic cascade reaction involving an initial [3 + 2] dipolar cycloaddition followed by two consecutive [3,3]-sigmatropic rearrangements. An asymmetric version of this reaction based on a chiral auxiliary approach is also described. Finally, a new method for the synthesis of oxindoles containing a quaternary carbon at the 3-position is described. This novel method proceeds via the copper triflate-mediated reaction of a phenyl-hydrazine and a ketene.

Acknowledgements

I would like to start by thanking the people who made the Sammakia lab such a wondrous place to work these last few years. Carolynn, I will always miss your nail biting stories. Will, you always know how to cheer someone up. Jeffrey, you've shown me how to lead by example. Mai, you just made things happen. Katelyn, you rekindled my interest in Disney movies. And honorary member Price, I will always regret that Thanksgiving I missed out on. In all seriousness though, I could not have made it without you. Thanks.

I would also like to thank Professor Tarek Sammakia, who without his support none of this would have ever happened. Tarek has taught me not only chemistry, but also how to think about problems, and most importantly, how to communicate. Thank you Tarek.

Most of all I would like to thank my beautiful wife Maureen. Maureen's patience and support have made all this possible. And lastly, my little Lily, who brings more joy into my life than I thought possible.

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The Claisen and Related Rearrangements

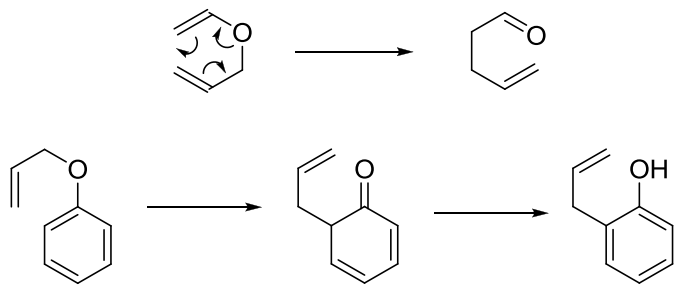
1.1 Introduction

The stereoselective synthesis of all-carbon quaternary centers continues to be a challenge in contemporary organic chemistry.[1] Especially difficult is the synthesis of quaternary carbons that bear additional proximal steric hindrance or are otherwise strained. Historically, there have been several approaches to the synthesis of compounds bearing all-carbon quaternary centers including biomimetic cation-π-cyclizations,[2] cycloadditions,[3] enolate alkylations,[4] metal catalyzed cross-coupling and related processes,[5] Michael additions,[6] radical reactions,[7] and sigmatropic rearrangements.[8] Much of the impetus within the chemical community for developing these methods is derived from an interest in the synthesis of biologically active natural products that bear this motif,[9] and many of the solutions that have been developed are specific to certain classes of natural products. What is lacking in these methods is a generalized approach for the synthesis of small fragments containing an all-carbon quaternary center that contains additional functional handles that allow for further manipulation. This thesis describes the development of a general strategy as well as specific technologies based upon [3,3]-sigmatropic rearrangements to achieve these goals.

1.2 The Claisen Rearrangement

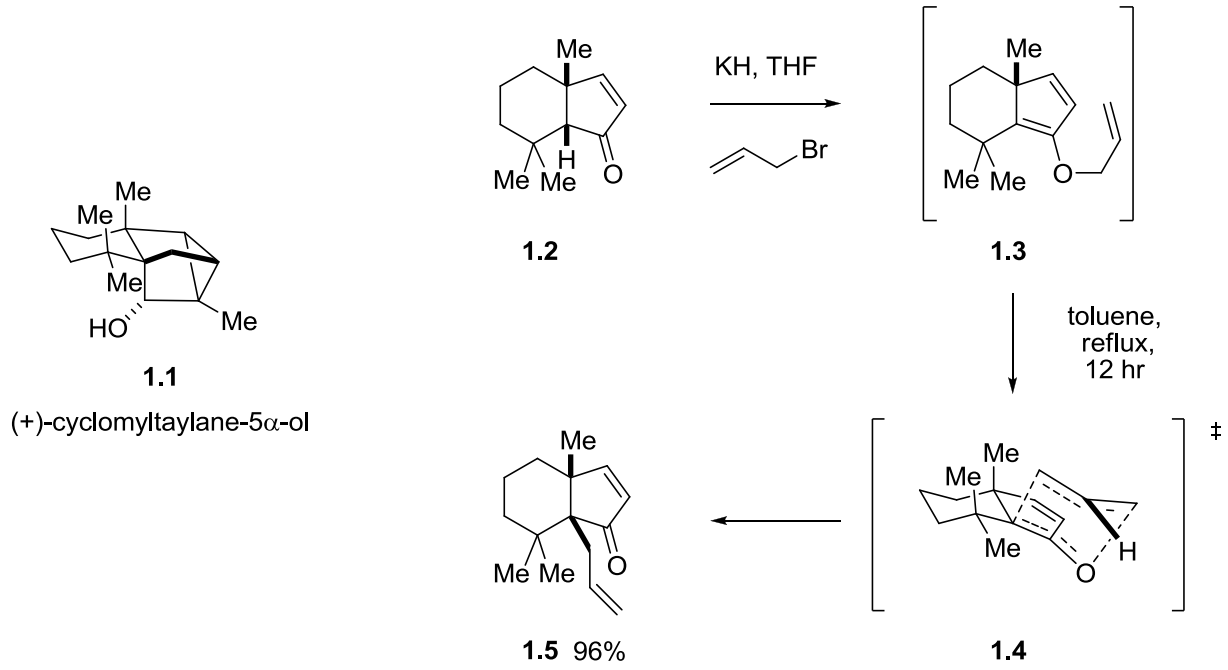
The first recorded example of a [3,3]-sigmatropic rearrangement was reported in 1912, by Rainer Ludwig Claisen, who described the thermal rearrangement of aromatic and aliphatic allyl

Figure 1.1 The Claisen-Rearrangement



vinyl ethers (Figure 1.1).[10] Since this report, the Claisen rearrangement and closely related variants have become widely recognized as a powerful stereoselective carbon-carbon bond forming reaction and have been frequently applied to complex molecule synthesis.[11] This potential has prompted the intense study and development of several variations that are also of synthetic utility. Formally, the Claisen rearrangement is an intramolecular S_N2' reaction of an enol displacing an allylic alcohol, generating a carbon-carbon σ-bond with concomitant double bond migration. The reaction can be described as a system comprised of vicinal π-bonds linked by a carbon heteroatom σ-bond that upon heating undergoes rearrangement by a suprafacial, concerted, asynchronous process to give a γ,δ- unsaturated carbonyl. The process is exothermic by *ca.* 16 kcal/mol[12] in the parent aliphatic system due to the formation of a C-O π-bond at the expense of a C-C π-bond. The favorable energetics of the Claisen rearrangement allow for the facile construction of hindered bonds. During the total synthesis of (+)-cyclamyltaylane-5α-ol **1.1**,[13] Hagiwara and colleagues exploited this fact with an impressive application of the Claisen rearrangement to the synthesis of vicinal all-carbon quaternary centers (Scheme 1.1).

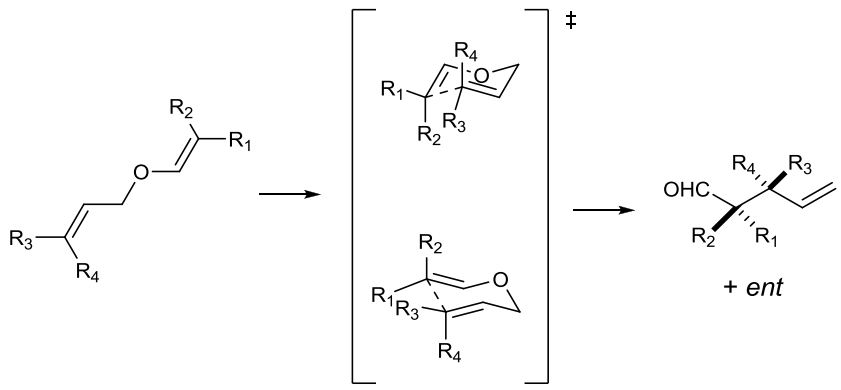
Scheme 1.1 Hagiwara's Total Synthesis of (+)-cyclamyltaylane-5α-ol



Treatment of **1.2** with base followed by allylbromide generated allyl-vinyl ether **1.3** which in refluxing toluene underwent [3,3]-sigmatropic rearrangement to afford the α-allylated bicyclic ketone **1.5** in a 96% yield. To rationalize the stereoselectivity, the authors proposed that the cyclopentadiene portion of allyl-vinyl ether **1.3** forces the molecule into a bowl-like shape resulting in the approach of the π-system from the convex face.

The Claisen rearrangement can also allow for the efficient and controlled installation of two vicinal stereocenters. This is a consequence of the tendency for acyclic systems to proceed through a highly ordered, six-member, chair-like transition state (Figure 1.2).[14] This organization allows for the reliable synthesis of either diastereomer of the product provided that the geometry of the olefins in the stating material can be controlled. In the transition state, the system will adopt a conformation that minimizes 1,3-diaxial interactions resulting in a highly selective reaction.

Figure 1.2 The Claisen Rearrangement Chair-Like Transition State



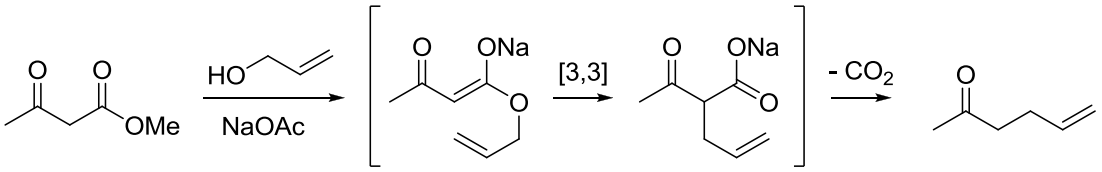
One disadvantage of the Claisen rearrangement remains the limited accessibility of the requisite starting allyl-vinyl ethers. Traditionally these compounds were obtained by either mercuric salt, or acid-catalyzed ether exchange with allylic alcohols, or acid-catalyzed vinylation of allylic alcohols with acetals.[15] In addition to low yields, the stereochemistry in these reactions is difficult to control and the use of toxic mercury is undesirable. Many of the efforts directed toward the study of the Claisen rearrangement involve simplifying access to the required vicinal di-π systems in addition to variations of the functionality present in the product (*vide infra*).

1.3 Variations of the Claisen Rearrangement

The highly stereoselective formation of a carbon-carbon bond possible in the Claisen rearrangement prompted the exploration for simplified reaction conditions. A major advancement came with several variations of the Claisen rearrangement that allow in-situ generation of the necessary vicinal di-π system, thereby eliminating the cumbersome synthesis of the requisite starting materials. The first of these modifications was published by Carroll in 1940.[16] The Carroll reaction is a thermal rearrangement of an allylic *β*-ketoester followed by

decarboxylation of the resulting β-keto carboxylate salt (Scheme. 1.2). The allylic β-ketoesters could be generated in-situ from the ketoester and an allylic alcohol followed by enolization, [3,3]-sigmatropic rearrangement, and decarboxylation to yield the γ,δ-usaturated ketones in one pot.

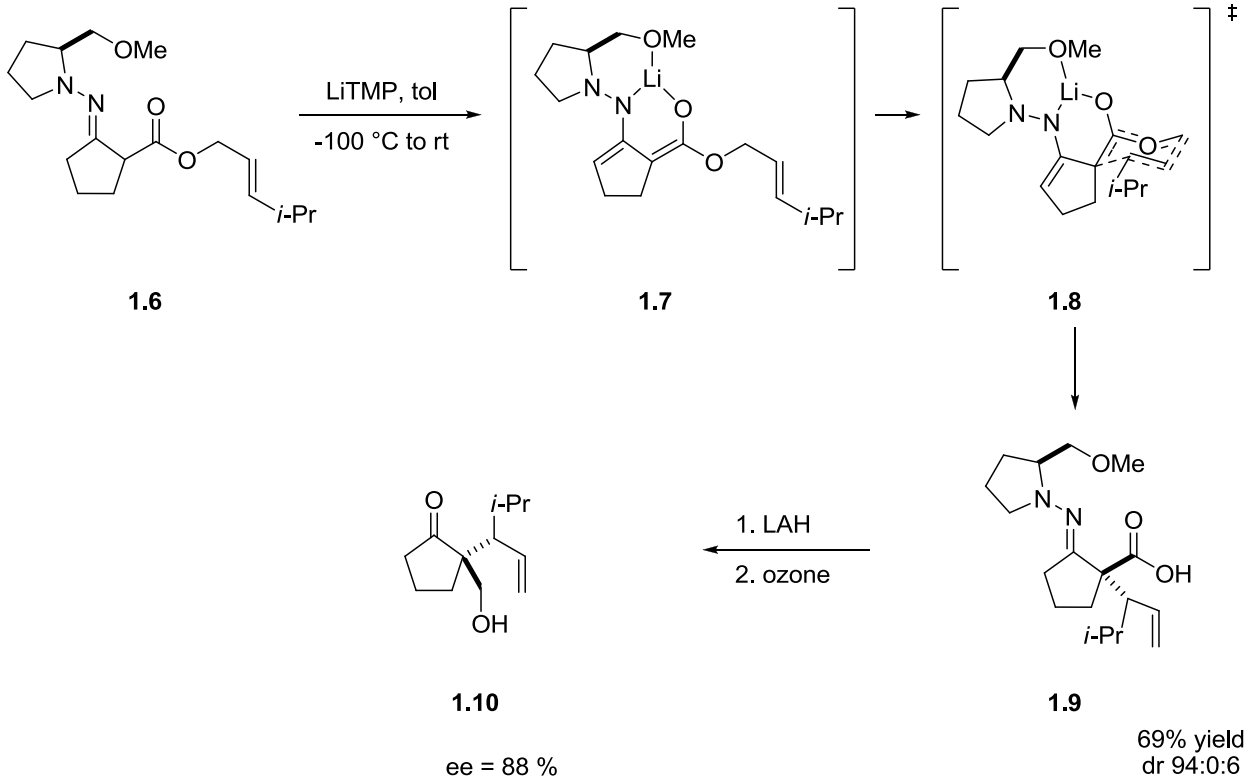
Scheme 1.2 The Carroll Rearrangement



The Carroll rearrangement requires high temperatures, typically 130 – 220 °C. Milder conditions could be achieved by treatment of the allylic acetoacetates with 2 equivalents of LDA thereby generating the dianion. The dianion, upon gentle heating, undergoes [3,3]-sigmatropic rearrangement and decarboxylation allowing the isolation of the γ,δ-usaturated ketone.

Enders and colleagues demonstrated the versatility of the Carroll rearrangement by the development of an enantio and diastereoselective reaction that provided highly congested, functionalized ketones based on a chiral auxiliary approach (Scheme 1.3).[17] Treatment of SAMP derived hydrazone **1.6** with LiTMP at – 100 °C, followed by warming to room temperature, resulted in the stereoselective formation of vicinal quaternary/tertiary stereocenters in a 96 % yield and a diastereomeric ration of 94:6. Reduction of the carboxylic acid with LAH followed by oxidative removal of the auxiliary furnished the functionalized ketone with the highly congested bond.

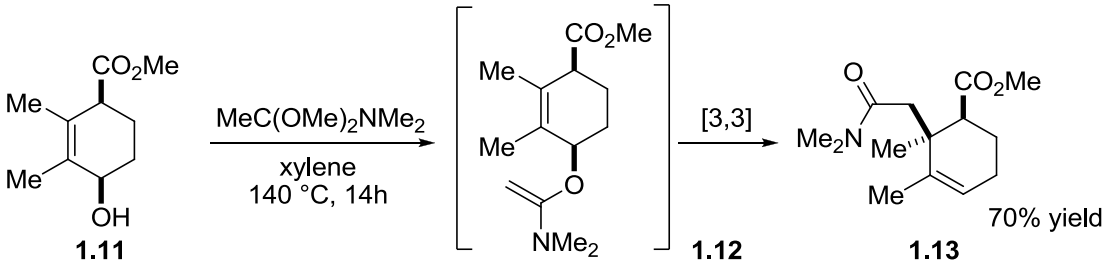
Scheme 1.3 Enders' Asymmetric Carroll Rearrangement



A variation of the Claisen rearrangement that generates the vicinal di-π system *in situ* while providing an unsaturated amide as the product was originally reported by Meerwein in 1961,[18] and revisited by Eschenmoser and colleagues in 1964.[19] In the Meerwein-Eschenmoser-Claisen variant, an allylic alcohol is combined with an amide acetal leading to alcohol exchange and the elimination of methanol to generate the vicinal di-π system in the form of an *N,O*-ketene acetal (Scheme 1.4). The presence of an electron donating amino substituent on the ketene acetal substantially increases the rate of the [3,3]-sigmatropic rearrangement (*vide infra*). The high temperatures usually applied were required to facilitate the elimination steps; the pericyclic reaction itself proceeds at comparatively low temperature. The essentially neutral conditions are tolerant of a variety of functional groups, and apart from the operational simplicity and the

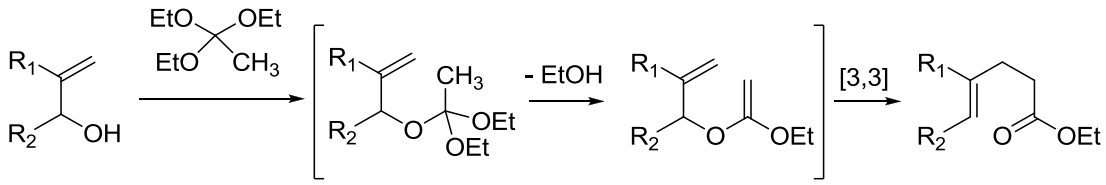
capacity to form alkenes stereoselectively, the real value in the Meerwein-Eschenmoser-Claisen reaction is the ability to form all carbon quaternary centers stereoselectively. For instance, treatment of *cis*-allylic alcohol **1.11** with dimethylacetamide dimethyl acetal in refluxing xylenes gave *cis* amide **1.13** in 70 % yield; the corresponding *trans*-allylic alcohol furnishes the analogous *trans*-amide in a comparable yield. The suprafacial nature of the sigmatropic rearrangement results in a high level of chirality transfer from *N,O*-ketene acetal **1.12** to the product.

Scheme 1.4 The Meerwein-Eschenmoser-Claisen



A related modification was developed by Johnson and colleagues and elegantly applied during their work on the total synthesis of squalene.[20] In this manifestation, an allylic alcohol is combined with ethyl orthoacetate and catalytic acid resulting in the formation of the mixed ortho ester. The mixed ortho ester proceeds to lose a molecule of ethanol generating a ketene-acetal which rapidly undergoes a [3,3]-sigmatropic rearrangement resulting in a γ,δ-unsaturated ester (Scheme 1.5).

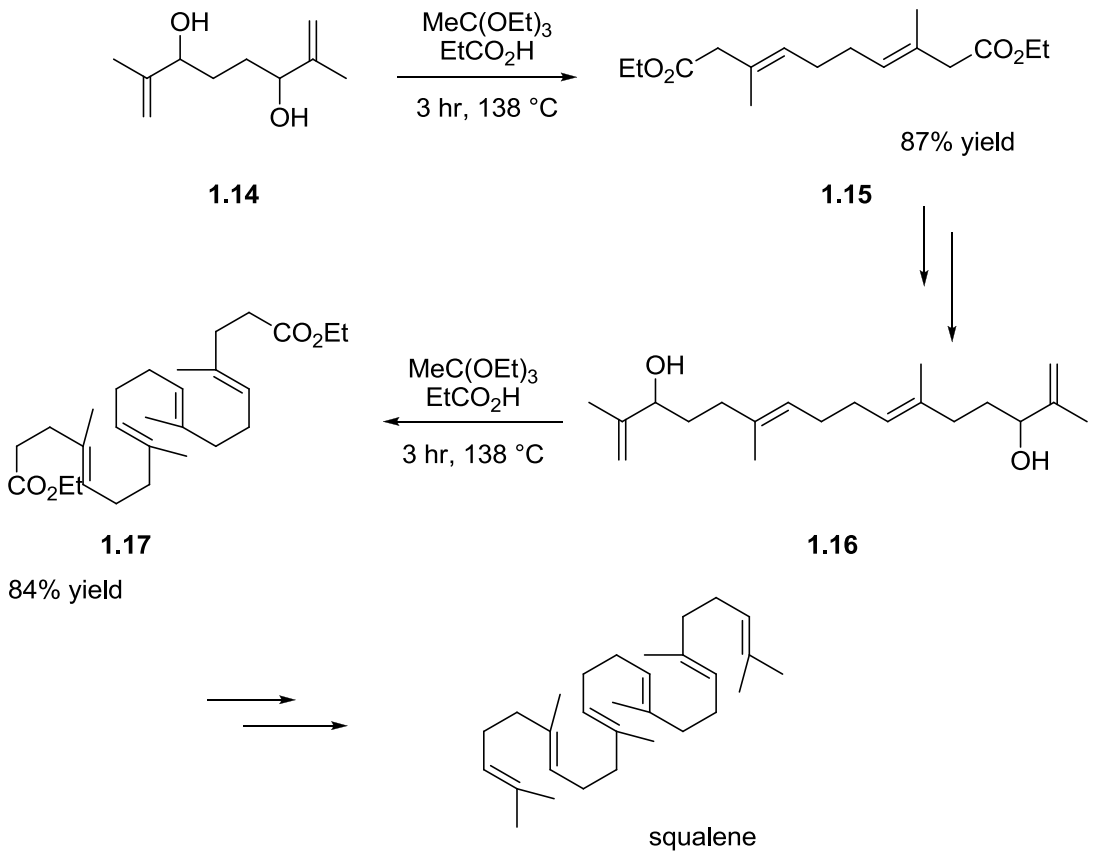
Scheme 1.5 The Johnson-Claisen Rearrangement



During the total synthesis of squalene, Johnson and co-workers utilized a double Johnson-Claisen reaction twice thereby providing a concise synthesis of the desired target (Scheme 1.6). Key steps involved the treatment of bis-allylic alcohol **1.14** with triethylorthoformate under acidic conditions and heating to 138 ° C for 3 hours which afforded the double chain extended diester **1.15** in an 87 % yield. Similar treatment of intermediate **1.16** resulted in an 84 % yield of **1.17**. It should be noted that the Johnson-Claisen rearrangement is highly selective for *E*-trisubstituted olefins when the starting allylic alcohols contains a 1,1-disubstited alkene.

A drawback of the Johnson-Claisen rearrangement is the inability to access stereochemically defined ketene-acetals. Unlike the Meerwein-Eschenmoser-Claisen rearrangement that proceeds through the *E*-amino ketene acetal, the Johnson variant gives E/Z mixtures, it is therefore more appropriately applied to orthoacetate systems, or systems with an α-stereocenter that may be eliminated in the following steps.

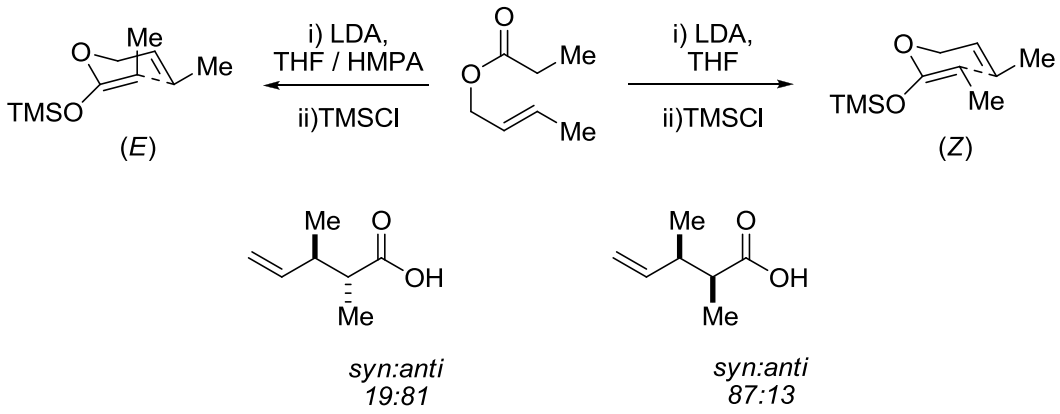
Scheme 1.6 Johnson's Total Synthesis of Squalene



In a seminal publication by Ireland and coworkers in 1972,[21] a major advancement was reported that addressed the lack of control of the olefin geometry with *in-situ* generated vicinal di-π systems. In the Ireland-Claisen rearrangement, a trimethylsilyl ketene acetal, prepared by treating an allylic ester with base at low temperature followed by trapping with TMSCl, when allowed to warm to room temperature undergoes a [3,3]-sigmatropic rearrangement to afford a γ,δ-unsaturated carboxylic acid in high yield and moderate to good selectivity (Scheme 1.7). By trapping the ester enolate at low temperature as the silyl ketene acetal, side reactions proceeding through ketene formation via enolate elimination are thus avoided. The reaction is facile and takes place at or below room temperature with a rate acceleration of *ca* 10^6 relative to the parent

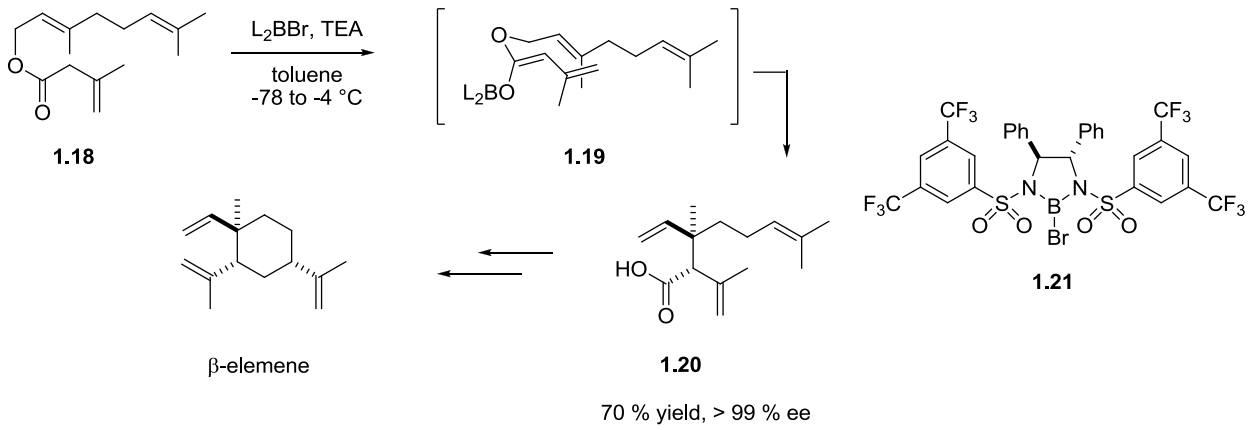
ally vinyl ether. As noted above, the [3,3]-sigmatropic event goes through a rigid chair-like transition state. By judicious selection of the enolization conditions, either isomer of the silyl ketene acetal is accessible, allowing for the selective formation of either diastereomer of the product. The reaction also takes place under mild conditions rendering this protocol the most functional group tolerant of the reactions considered thus far.

Scheme 1.7 The Ireland-Claisen



The Ireland-Claisen rearrangement has been utilized in the construction of numerous natural products.[22] Corey et al. made use of Johnson's discovery during the synthesis of *β*-elemene (Scheme 1.8).[23] The soft enolization of trienic ester **1.18** with chiral boron Lewis acid **1.21** and triethylamine at low temperature provided the boron enolate that upon warming underwent a [3,3]-sigmatropic rearrangement via the characteristic chair-like transition state. This resulted in trienic acid **1.20**, which contains a vicinal quaternary-tertiary center, in high yield and excellent enantioselectivity.

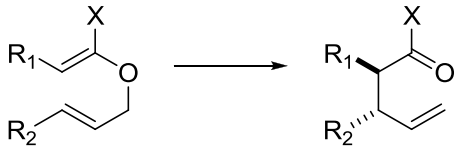
Scheme 1.8 Corey's Total Synthesis of β-elemene



1.3 Charge Accelerated Variants

Substituents present in the vicinal di-π system have a remarkable effect on the facility of the reaction. Pioneering studies by Evans demonstrated the profound rate enhancements achievable by appropriately placed charge within the vicinal di-π systems.[24] Subsequently Denmark made the empirical observation that increasing the π-donor ability of a substituent at the 2 position results in a substantial increase in the rate of the reaction.[25] On progressing towards better π-donors in the series of H/alkyl, OR, NR_2, and finally to OM, a continuous drop in the reaction temperature was noted (Figure 1.3)

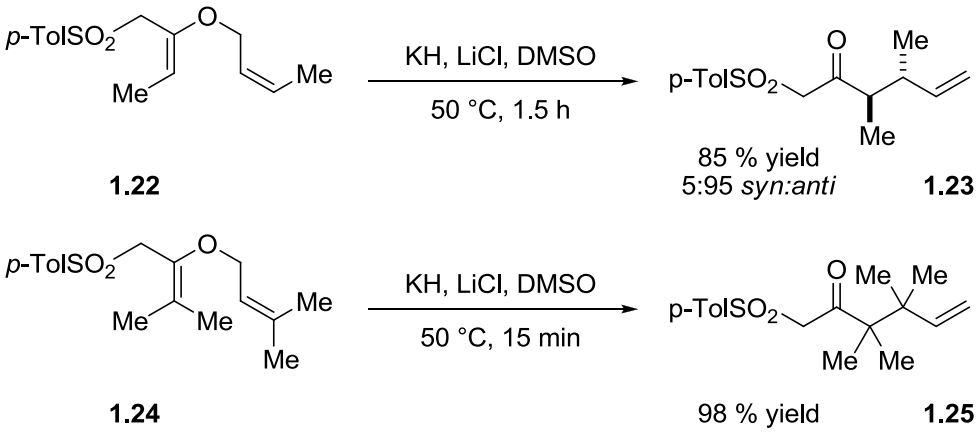
Figure 1.3 Influence of Substitution on the Claisen Rearrangement



X	T °C
H, Alkyl	160-200
OR	135
NR_2	110-140
OLi, OTMS	25-67

While in the case of the Ireland-Claisen rearrangement this was manifest as an anionic oxygen atom, Denmark and Harmata have shown that a carbanion at this position also markedly speeds up the reaction (Scheme 1.9). Amazingly, Denmark has also shown that the carbanion accelerated Claisen rearrangement is tolerant of extreme steric hindrance in the form of vicinal all-carbon quaternary centers.[26] The remarkable facility of this reaction is attributed to the rate enhancement afforded by the charge acceleration as well as a significant thermodynamic driving force apparent from the *ca.* 10 pKa unit difference between the starting monosubstituted allylic aryl sulphone and the ketone product. Rearrangement of the disubstituted allylic aryl sulphone **1.24** was even more facile requiring only 15 minutes to reach completion whereas the monosubstituted sulphone **1.22** required 1.5 hours at the same temperature. The authors conclude that the increase in acidity of **1.25** relative to **1.23** results in an enthalpic advantage that more than compensates for the strain energy associated with the formation of vicinal quaternary centers. Another contributing factor could be the increased reactivity due to the higher energy anion derived from the less basic sulphone **1.24**

Scheme 1.9 Carbanion-accelerated Claisen rearrangements



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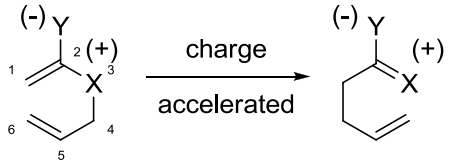
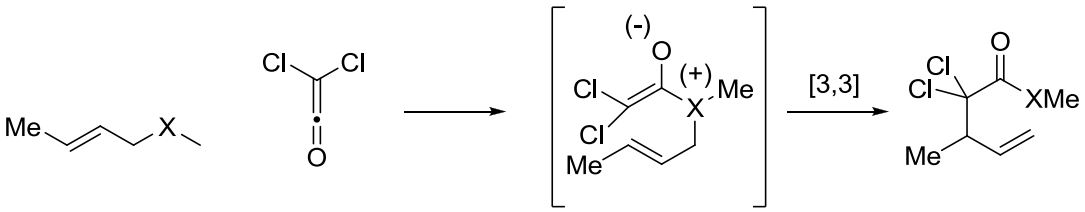
The distribution of charge in other positions within the vicinal di-π system also has a remarkable effect on the reaction. It has been demonstrated that a positive charge on a heteroatom in the 3 position leads to a beneficial effect (Figure 1.4).

Figure 1.4 Charge Acceleration of the Claisen Rearrangement



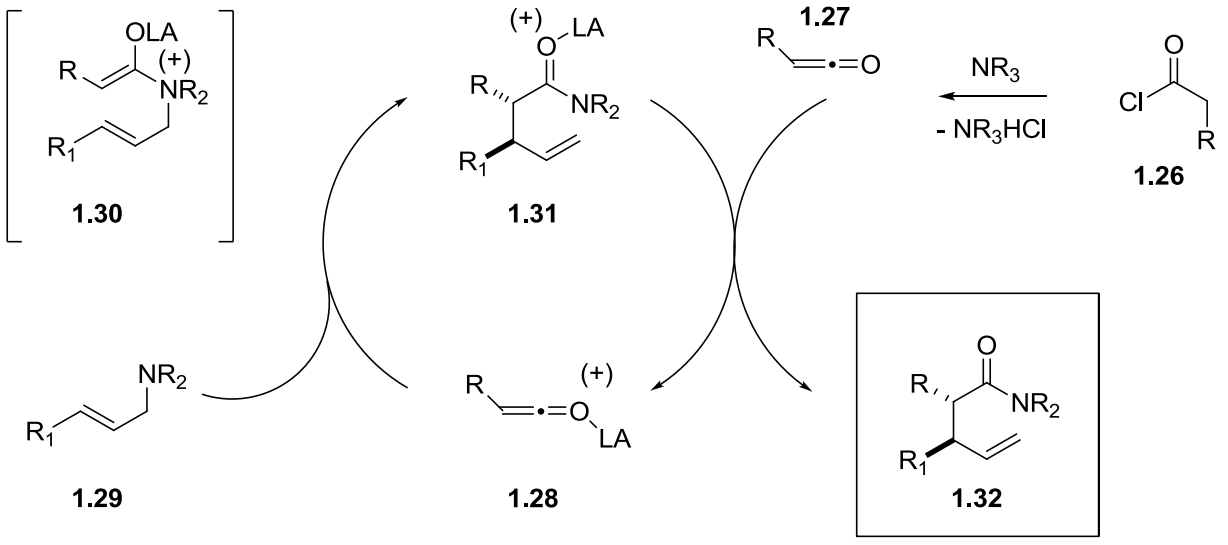
In a reaction first described in 1978[27] and further explored in 1983[28], Bellus and Malhberbe reported a variation of the Claisen reaction that takes advantage of charge acceleration in the form of zwitterionic oxyanion at the 2a position and a cationic hetero-atom at the 3-postion. This intermediate is produce by the reaction of dichloroketene with an ally amine, ether, or sulfide, and it rapidly undergoes a [3,3]-sigmatropic rearrangement (Scheme 1.10). The facility of this reaction can be ascribed to two contributing factors: a marked rate enhancement due to the presence of charged substituents, as well as a significant thermodynamic effect brought about by the charge neutralization in going from the zwitterionic intermediate to the product.

Scheme 1.10 The Bellus-Malhberbe-Claisen



The Bellus-Malhberbe-Claisen reaction was revisited by MacMillan and Yoon in 1999 who demonstrate the reaction is amenable to Lewis acid catalysis (Scheme 1.11).[29] The first step in the catalytic cycle is the dehydrohalogenation of acid chloride **1.26**, generating monosubstituted ketene **1.27**. The Lewis acid then binds to the carbonyl of ketene **1.27** forming the activated complex **1.28** which undergoes nucleophilic attack by ally amine **1.29** providing zwitterionic vicinal di-π complex **1.30.** Intermediate **1.30** is highly activated by a strong π-donating substituent at position 2a in the form of O-LA, as well as positively charged nitrogen substituent at the 3 position. A rapid [3,3]-sigmatropic rearrangement ensues accompanied by charge neutralization forming the key carbon-carbon bond. De-complexation regenerates the Lewis acid which reenters the catalytic cycle and provides the γ,δ-unsaturated amide **1.32**

Scheme 1.11 MacMillan and Yoon's Catalytic Acyl Claisen

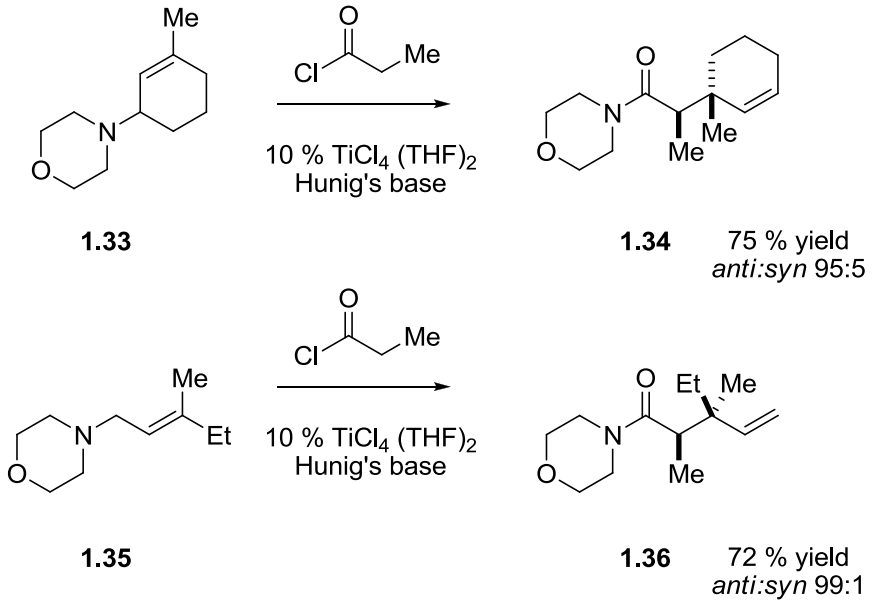


MacMillan and Yoon's catalytic acyl Claisen rearrangement is a remarkable reaction that proceeds in high yields and diastereoselectivities while also allowing the construction off all-

carbon quaternary stereocenter in the presence of additional proximal steric hindrance (Scheme 1.12).

When trisubstituted ally amine **1.33** was treated with propionyl chloride in the presence of 10 mol % catalyst and base, the addition-rearrangement sequence described above ensued providing unsaturated amide **1.34**, which contains 2 adjacent all-carbon quaternary centers, in a 75 % yield and 95:5 *anti:syn* selectivity. Furthermore, in the acyclic system generated by the reaction of ally amine **1.35** with methyl ketene, the yield of amide **1.36** was 72 % with a selectivity of 99:1. This demonstrates the potential of the system to form highly congested bonds in a stereoselective manner.

Scheme 1.12 Construction of All-Carbon Quaternary Centers via MacMillan and Yoon's Acyl Claisen Rearrangement

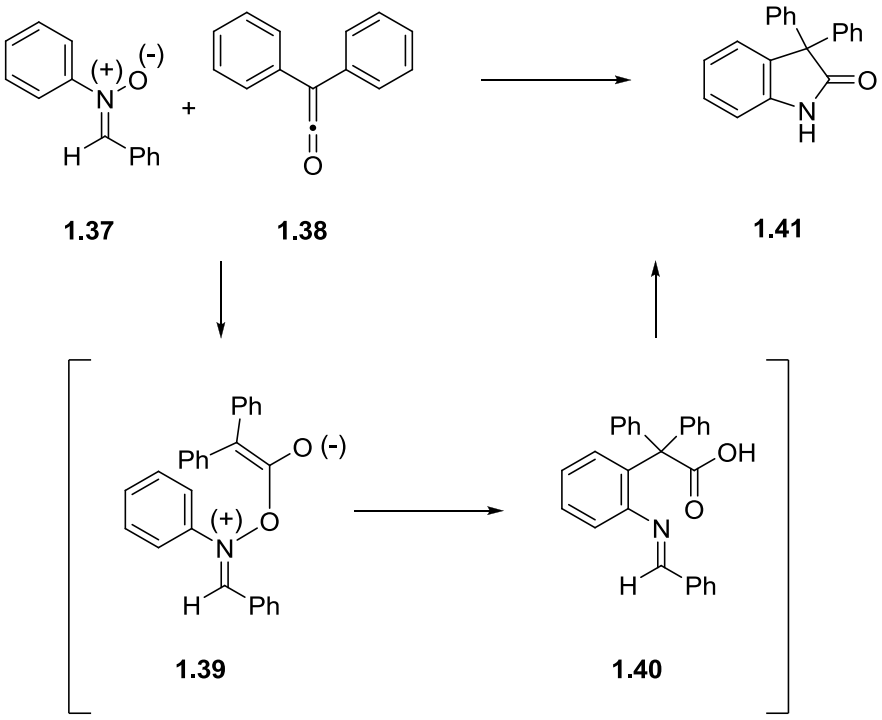


A fascinating reaction that was until recently thought to undergo a charge accelerated [3,3]-sigmatropic rearrangement was originally described by Staudinger in 1919,[30] although the

correct structure of the product was not deduced until 1953 by Hassal and Lipman (Scheme 1.13).[31]

In this adaptation, diphenylketene **1.38** was treated with *N*-phenyl nitrone **1.37** to produce zwitterionic enolate **1.39** resulting from nucleophilic addition of the nitrone oxygen onto the carbonyl of the ketene. Intermediate **1.39** was thought to then undergo a charge accelerated [3,3]-sigmatropic rearrangement followed by tautomerization/rearomatization.[32] It was possible to isolate the imino acid **1.40**, but an aqueous acidic workup promoted the hydrolysis of the imine moiety and lactam formation which provided the 3,3-disubstituted oxindole **1.41.**

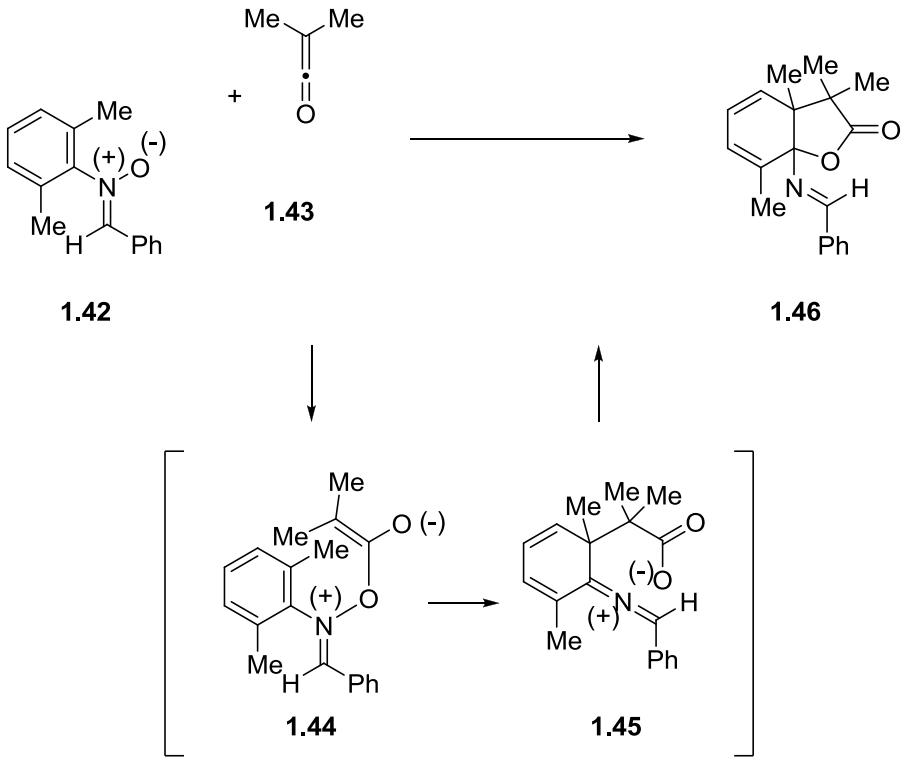
Scheme 1.13 Staudinger's Synthesis of Oxindoles



In 1971, Taylor described a single variant of this reaction using *N*-2,6-xylyl nitrone **1.42**,[33] wherein the product bears vicinal all-carbon quaternary centers and no longer contains the

aromatic benzene ring (Scheme 1.14). This latter reaction proceeds in 55% yield after crystallization and is truly remarkable given the steric hindrance and loss of aromaticity in the product. The capacity for the creation of such a hindered bond accompanied by the energy penalty due to the loss of aromaticity is due to two main factors: the charge acceleration provided by a π-donor at the 2a-position in addition to the positive charge on the nitrogen at the 4-position, and the major contribution manifest in the breaking of the inherently weak *N-O* bond, with a bond strength *ca.* of 50 kcal/mol.[34]

Scheme 1.14 Taylor's Application of the Staudinger Oxindole Synthesis



More recently in 2009,[35] Smith reported an asymmetric version of this reaction utilizing a chiral auxiliary based upon a Garner's aldehyde derived aryl nitrone (Scheme 1.15). The reaction was believed at the time to follow a similar path to the Staudinger reaction described

above. Upon hydrolysis and cyclization of imino acid **1.61,** Garner's aldehyde **1.53** could be reclaimed and recycled. Further, at the time of publication the mechanism by which the stereochemical information was transferred from the chiral auxiliary to the new stereocenter was unknown.

Scheme 1.15 Smith's Asymmetric Staudinger Oxindole Synthesis

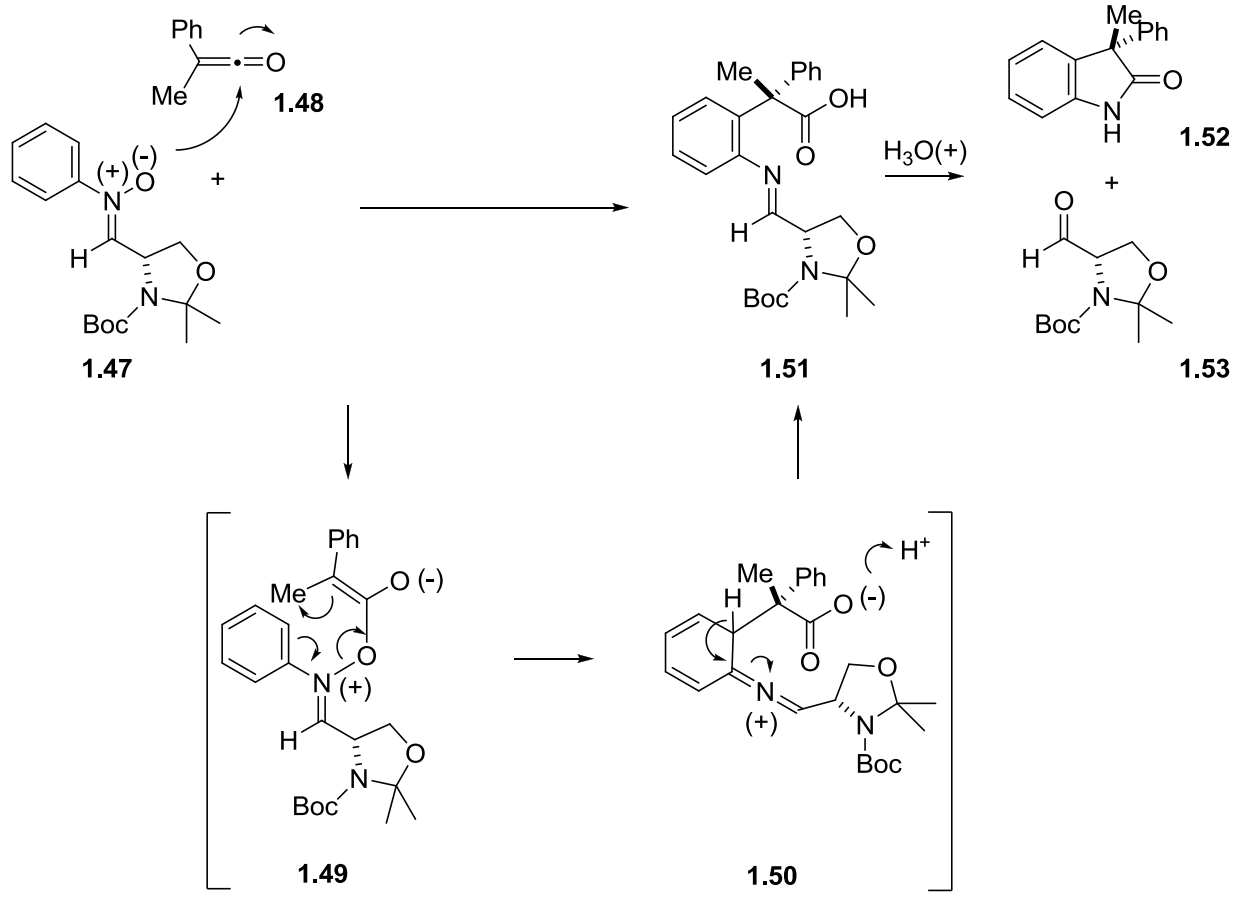
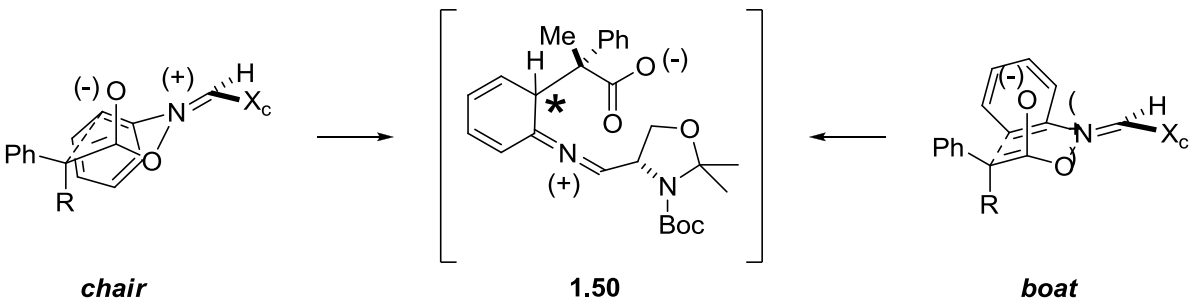


Figure 1.5 Possible Stereochemical Pathways in Smith's Staudinger Oxindole Synthesis



chair **1.50** ***boat***

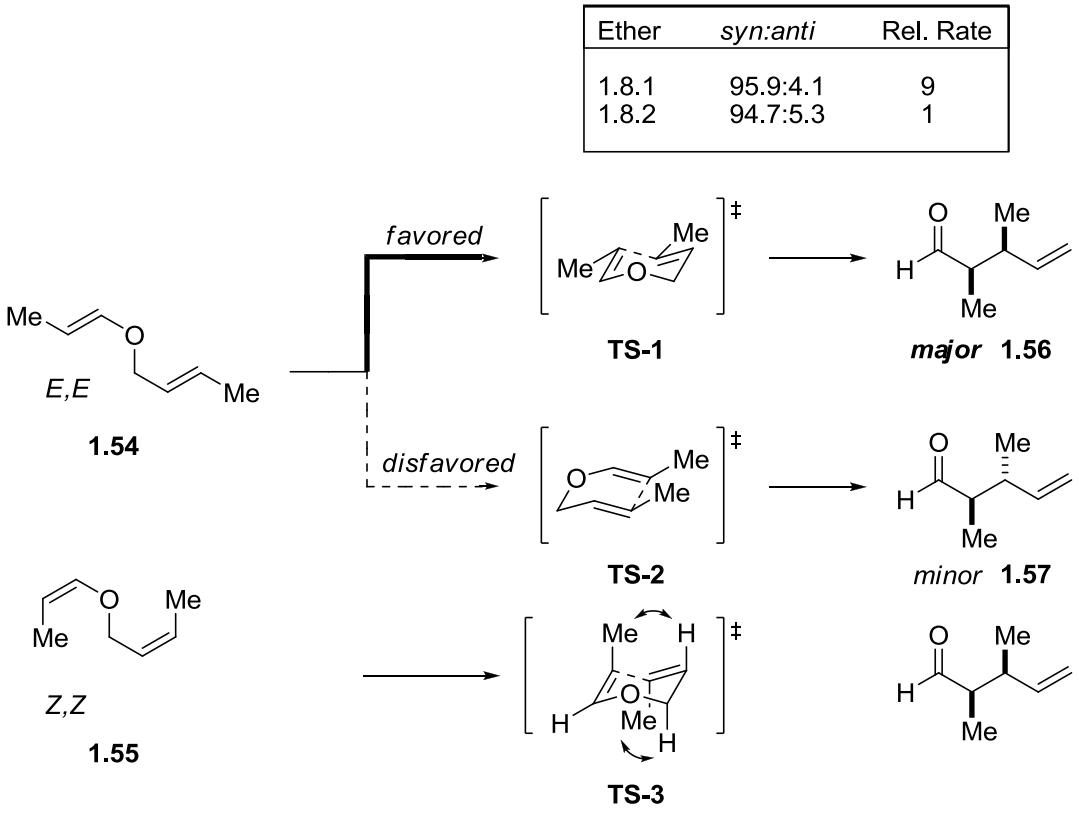
The absolute stereochemistry of the 3 position of oxindole **1.52** was proven by analogy with known compounds. Assuming a [3,3]-sigmatropic rearrangement, a transition state adopting the boat or chair configuration could not be determined at the time due to the loss of stereochemical information during the rearomatization of intermediate **1.50**. Both the chair and boat conformations in the transition state would lead to the observed product, the only difference being the stereochemistry at the stereocenter in the ring which is destroyed upon rearomatization. It was also unclear at this time how the stereochemical information possessed in intermediate **1.49** was conveyed through what appears to be a significant physical distance between the newly formed stereocenter and the stereochemical information provided by the chiral auxiliary.

1.5 Stereochemical Considerations

As noted above, the high stereoselectivity in the Claisen rearrangement is a direct consequence of acyclic vicinal di-π systems to adopt a highly ordered, 6-memebered chair-like conformation in the transition state. A classic example that confirms the preference for a chair-like transition state provided by Hansen and co-workers in 1968 (Scheme 1.16).[36] Hansen's group studied the Claisen rearrangement of *E,E*-allyl-vinyl ether **1.54** and *Z,Z*-allyl-vinyl ether **1.55** in the gas phase at 160 °C (Figure 1.8). Both the *E,E*- and *Z,Z*-isomers rearrange to provide

syn-unsaturated aldehyde **1.56** as the major product with a high degree of selectivity. *E,E*-isomer **1.54** was slightly more selective, but intriguingly reacted 9 times as fast at *Z,Z*-isomer **1.55**. The stereochemistry of the major product for both isomers is readily explained by invoking a chair-like transition state. *E,E*-isomer **1.54** proceeds through **TS-1** to yield the *syn* aldehyde **1.8.3** as the major product.

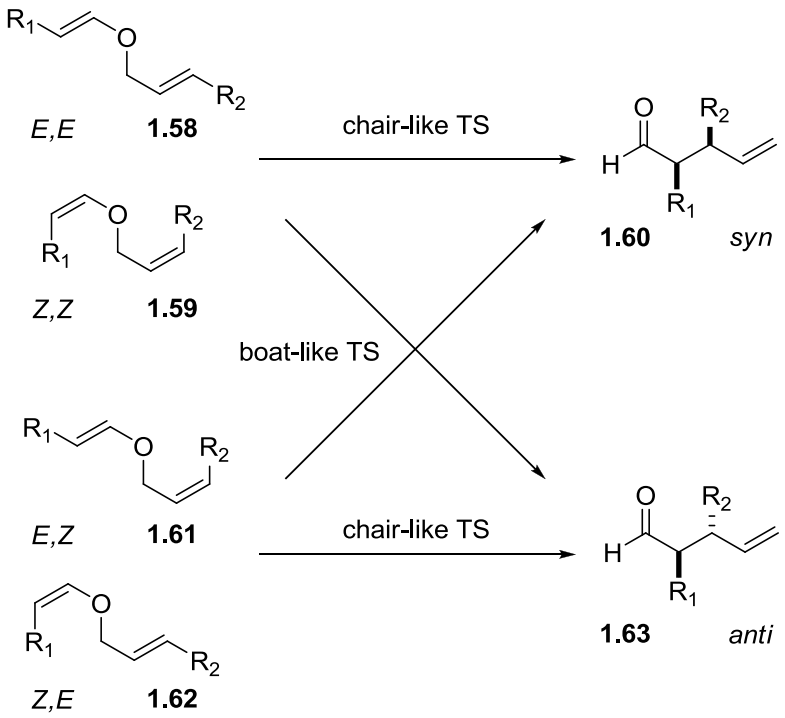
Scheme 1.16 Stereochemistry of the Acyclic Claisen-Rearrangement



The sluggish rate for the rearrangement of isomer **1.55** can be rationalized by examining the transition state **TS-3,** which unlike **TS-1**, places the methyl substituents in axially positions causing considerable 1,3-diaxially interactions at the transition state thereby raising the energy of **TS-3** relative to **TS-1**.

Figure 1.6 summarizes the relationship between the olefin geometry in the starting material, the transition state geometry, and the product stereochemistry. Both *E,E*-isomer **1.58** and *Z,Z*-isomer **1.59** produce product **1.60** with syn-stereochemistry when they proceed through a chair-like transition state and give product **1.63** with anti-stereochemistry in the case of a boat like transition state. The *E,Z* and *Z,E*-isomers **1.61** and **1.62** show the exact opposite behavior.

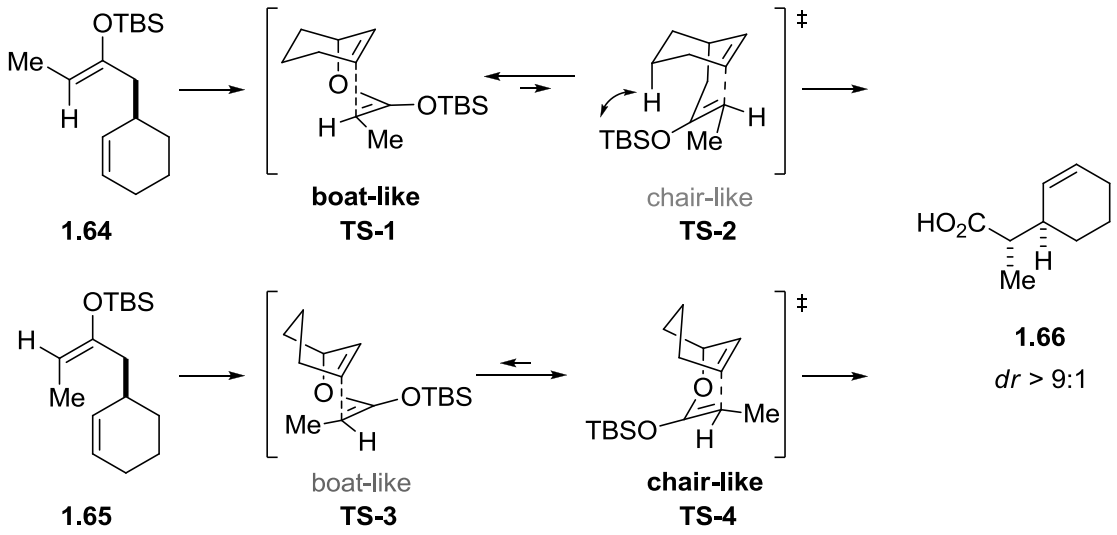
Figure 1.6 Effect of Olefin/Transition State Geometry on Product Stereochemistry



In the case of cyclic systems, the situation is not as straightforward.[37] For example, both *E* and *Z*-cyclohexenyl ketene acetals **1.64** and **1.65** undergo the Claisen rearrangement to give predominantly product **1.66** (Scheme 1.17). In the case of *E*-ketene acetal **1.64**, the chair-like transition state **TS-2** is destabilized by a steric interaction between the OTBS and the axial hydrogen on the adjacent ring resulting in the reaction proceeding through the lower energy boat-like transition state **TS-1.** The rearrangement *Z*-ketene acetal **1.65** provides the same

stereoisomer **1.66** but proceeds through the chair-like transition state **TS-4** which no longer suffers from the unfavorable interaction present in **TS-2**.

Scheme 1.17 Stereochemistry of the Cyclic Claisen-Rearrangement



1.6 General Considerations in Reaction Design

At the outset of this project our main goal was to design new reactive systems for the formation of all-carbon quaternary centers, with or without additional proximal steric hindrance, under mild conditions that would be a general solution applicable to variety of complex systems and substitution patterns. The Claisen rearrangement and variants thereof were used as a template to achieve these goals. The mechanistic principles outlined above that form the basis of these new systems are summarized below.

The stereoselective formation of carbon-carbon bonds as a result of the highly organized 6-member transition state of [3,3]-sigmatropic rearrangements provides the underlying reactivity for carbon-carbon bond formation that we wished to exploit. We also sought to form the desired vicinal di-π system *in situ* via the coupling of two π-systems thereby removing the need for

cumbersome starting material synthesis. Additionally, we desired systems that could take advantage of charge acceleration in the sigmatropic rearrangement step. And finally, we wished to provide a thermodynamic driving force by cleaving a weak heteroatom-heteroatom bond during the sigmatropic rearrangement.

Figure 1.7 General Mechanistic Principles

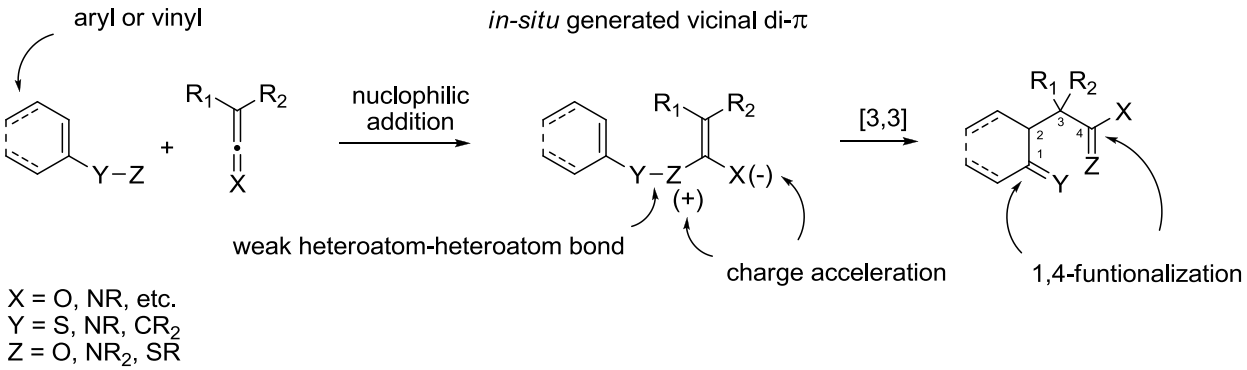
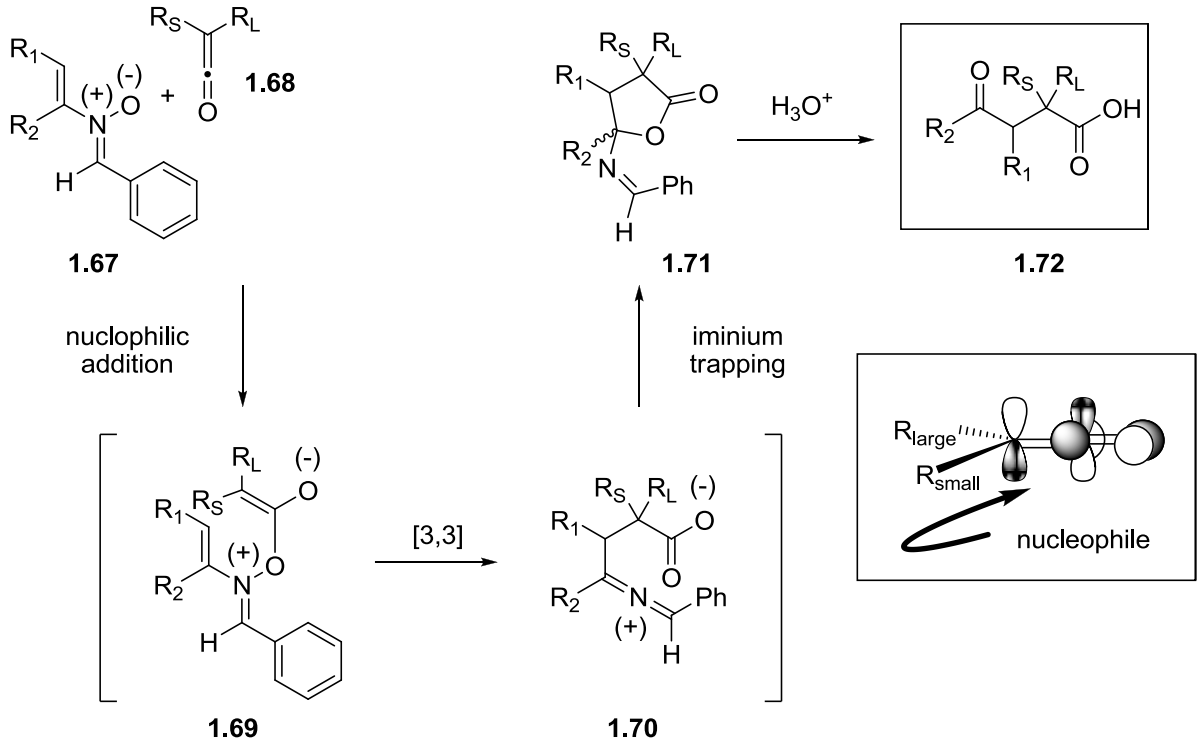


Figure 1.7 provides a generic description of the designed reactive system containing the mechanistic principles outlined above. An aryl or vinyl heteroatom substituted component would undergoe nucleophilic addition to a cumulene (or activated alkyne not shown) generating the vicinal di-π intermediate that is poised to undergo a charged-accelerated [3,3]-sigmatropic rearrangement. Various combinations of heteroatoms within the nucleophilic component, as well as the cumulene, will allow a large number of permutations that benefit from the described mechanistic principles allowing access to diverse functionality in the products containing the hindered bond.

The first system we wished to study was an extension of the reaction described by Staudinger (Scheme 1.13). It was envisioned that utilizing an *N*-vinyl nitrone as the nucleophilic component, and a ketene as the electrophile, the requisite zwitterionic vicinal di-π intermediate

could be prepared (Scheme 1.18). We believed the orthogonal nature of the ketene π-orbitals would allow for the stereoselective formation of the zwitterionic enolate **1.69** arising from nucleophilic addition in the plane of the sterically least hindered substituent on the ketene.

Scheme 1.18 *N*-vinyl Nitrone/Ketene Cascade



This intermediate would then undergo [3,3]-sigmatropic rearrangement facilitated by charge acceleration. Here the reaction deviates from the reaction described by Staudinger as the iminium carboxylate product **1.70** lacks the ability to re-aromatize. It was envisioned that carboxylate **1.70** would cyclize onto the resulting iminium yielding imino-lactam **1.71** that upon hydrolysis of the imine moiety would result in a 1,4-keto acid containing an all-carbon quaternary center flanked by a tertiary or quaternary center. Our efforts towards realizing these goals are described in the following chapters.

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Chapter 2

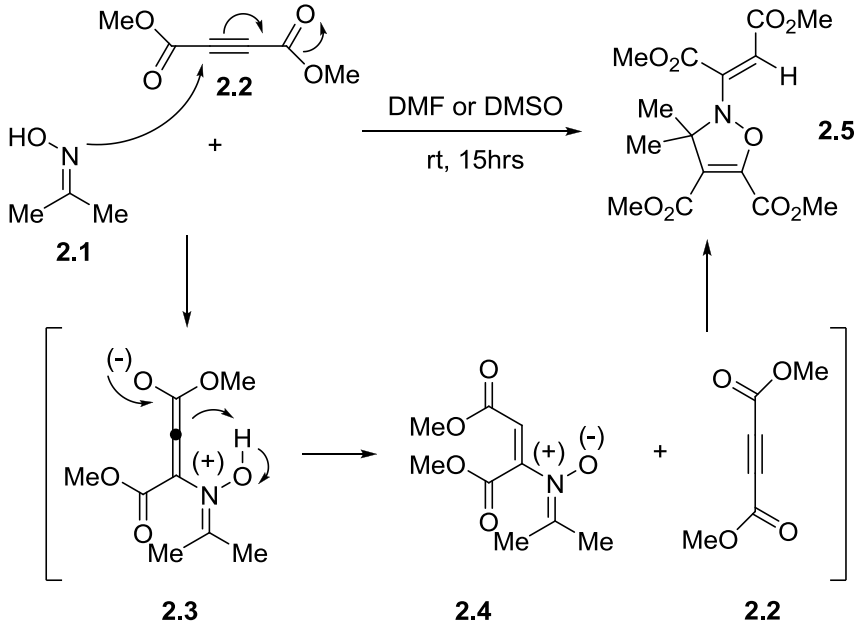
The Synthesis of *N*-Vinyl Nitrones

2.1 Previous Syntheses of *N*-Vinyl Nitrones

As detailed in the introductory chapter, we wished to explore the reactivity of *N*-vinyl nitrones as coupling partners for the generation of systems capable of undergoing a [3,3]-sigmatropic rearrangement resulting in the formation of hindered all-carbon quaternary centers. To achieve this goal we first required a short, succinct route to this class of compounds. A review of the literature revealed that *N*-vinyl nitrones have appeared in only a limited number of studies,[1] often as hypothetical reaction intermediates or as unexpected products, though they had been isolated in a couple of instances. Examples of vinyl nitrones in the literature are provided below.

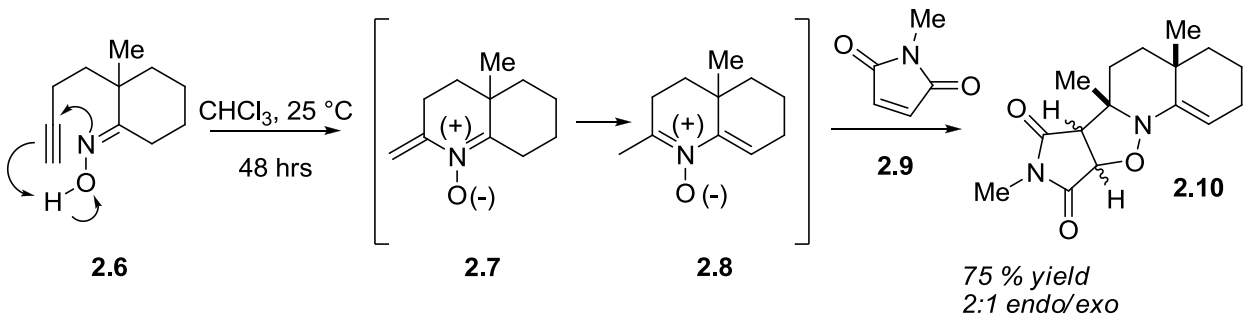
During the study of the cycloaddition of oximes with activated alkynes,[2] Winterfeldt and Krohn proposed an *N*-vinyl nitrone as a reaction intermediate (Scheme 2.1). Treatment of oxime **2.1** with dimethylacetylenedicarboxylate **(2.2)** in DMF or DMSO at room temperature resulted in the isolation of adduct **2.5**. To rationalize the formation of the observed product, the authors propose nucleophilic addition of oxime **2.1** onto the activated alkyne **2.2** producing intermediate **2.3**, a proton transfer would then result in fully conjugated *N*-vinyl nitrone **2.4**. *In situ* trapping of nitrone **2.4** by means of a [3+2]-dipolar cycloaddition of with another equivalent of activated alkyne **2.2** would account for the observed product **2.5**.

Scheme 2.1 Winterfeldt and Krohn's Cycloaddition of Ketoximes



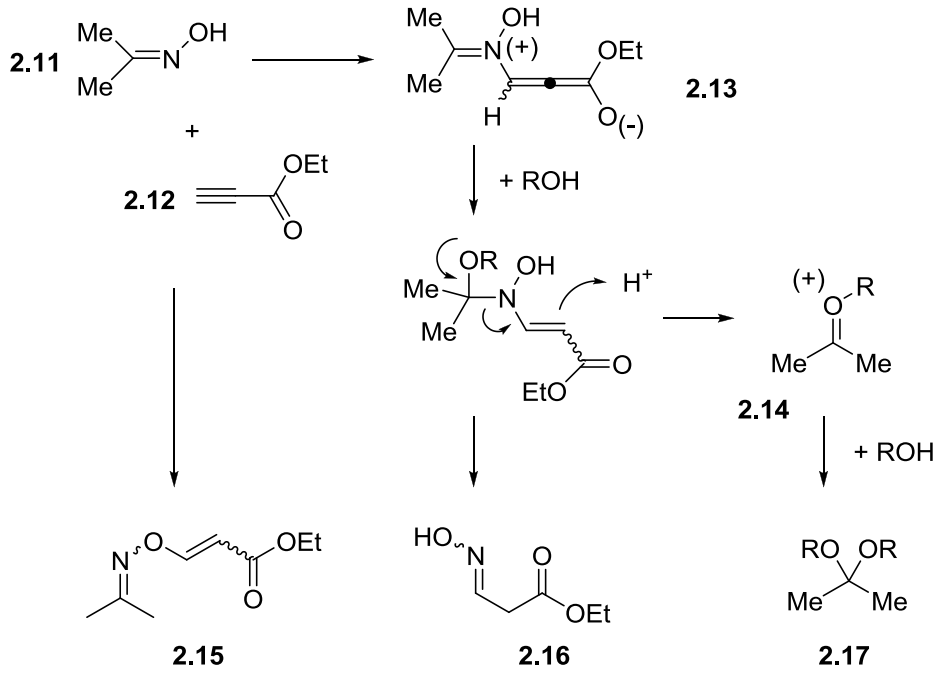
An intramolecular version of this reaction that proceeds without the need for electronic activation of the alkyne was reported by Grigg and co-workers in 1993 (Scheme 2.2).[3] The authors demonstrated that an oxime containing a suitably positioned terminal alkyne can react via a 6-exo-dig or 5-exo-dig cyclization to provide an *N*-vinyl nitrone that can then be trapped with maleimide (**2.9**) to generate two new rings. *N*-vinyl nitrone **2.7** was proposed to result from a 1,3-azaprotio cyclotransfer of δ-alkynyl oxime **2.6**. Tautomerization to nitrone **2.8**, followed by dipolar cycloaddition, occurs on addition of *N*-methyl maleimide (**2.9**) providing tetracycle **2.10** in 75 % yield as a 2:1 mixture of the *endo/exo* diastereomers. Semiempirical calculations support the concerted, asynchronous nature of the cyclotransfer with substantially more C-N bond formation than C-H bond formation at the transition state.

Scheme 2.2 Grigg's Intramolecular 1,3-Azaprotio Cyclotransfer Synthesis of *N*-Vinyl Nitrones



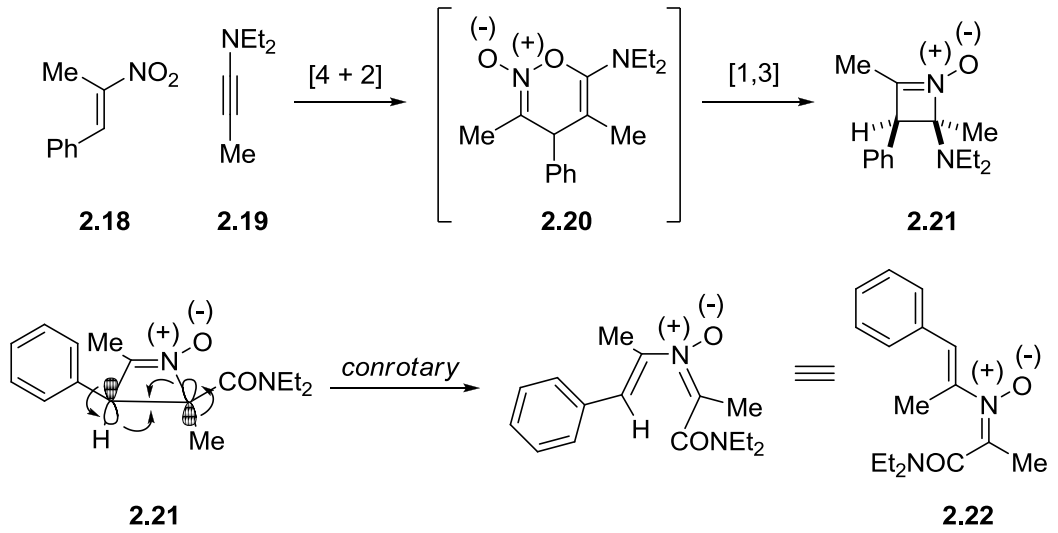
The first report of a study directed toward the synthesis and isolation of an *N*-vinyl nitrone was published in 1999 by Heaney who wished to exploit the intermolecular 1,3-azaprotio cyclotranfer described above. The strategy was to omit the addition of a trapping reagent that would then allow for the isolation of the *N*-vinyl nitrone (**2.13**) (Scheme 2.3).[4] Unfortunately, treatment of oxime **2.11** with alkynoate **2.12** resulted in complex mixtures containing both *E/Z* isomers of products arising from *O*-alkylation (**2.15**) in addition to oximes (**2.16)** resulting from C-N bond fragmentation.

Scheme 2.3 Heaney's Attempted Isolation of *N*-Vinyl Nitrones via an Intermolecular 1,3-Azaprotio Cyclotranfer



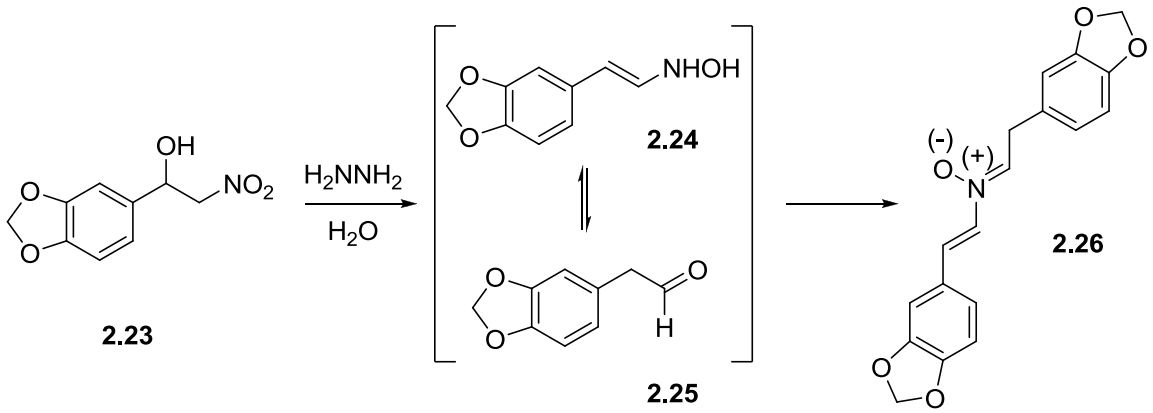
A small number of *N*-vinyl nitrones have by synthesized by Reinhoudt and co-workers via a pericyclic rearrangement process (Figure 2.4).[5] Nitroalkene **2.18** and alkyne **2.19** undergo a formal [4 + 2] (the authors propose a stepwise process) providing intermediate **2.20**. A [1,3]-sigmatropic rearrangement, driven by the cleavage of a weak N-O bond and the formation of a C=O, provides nitrone **2.21**. Upon heating, 4-member cyclic nitrone **2.21** underwent a thermally allowed, conrotatory, electrocyclic ring opening process that provided *N*-vinyl nitrone **2.22** in modest yield. A number of substrates were subjected to the reaction conditions; unfortunately, only four of which resulted in *N*-vinyl nitrone products.

Scheme 2.4 Reinhoudt's Electrocyclic Ring Opening of 4-Membered Cyclic Nitrones for the Synthesis of *N*-Vinyl Nitrones



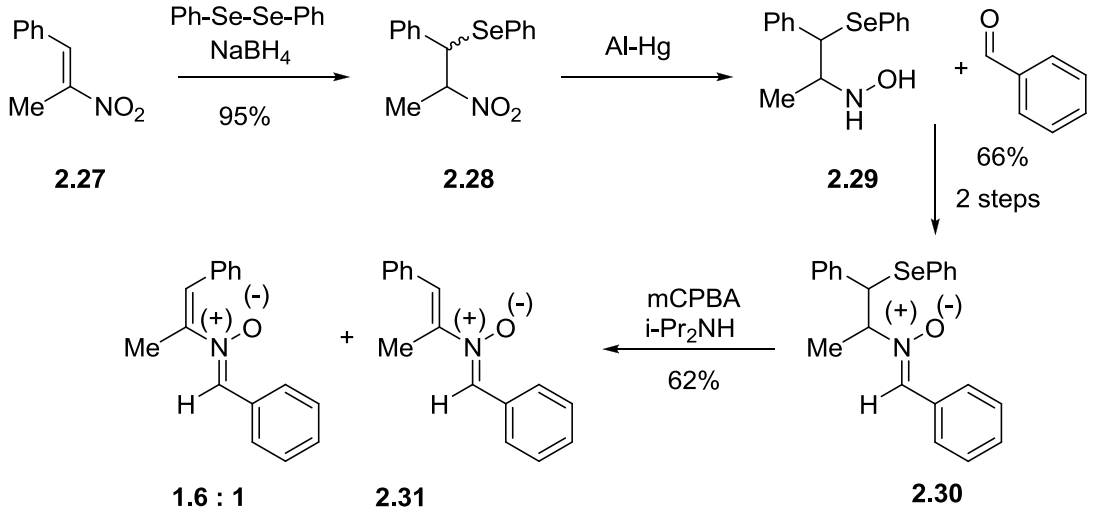
While attempting to reduce a nitro group in **2.23** with hydrazine, Singh and colleagues isolated an unexpected product that they characterized as *N*-vinyl nitrone **2.26** (Scheme 2.5).[6] The reaction presumably occurs via the reduction and dehydration of **2.23** forming **2.24**, which partially hydrolyzes under the reaction conditions to **2.25.** Condensation of **2.24** with aldehyde **2.25** would provide nitrone **2.26**. No other *N*-vinyl nitrones were synthesized via this method.

Scheme 2.5 Sings's Unexpected Isolation of an *N*-Vinyl Nitrone



In a seminal report, Denmark and Montgomery published the first general route to *N*-vinyl nitrones in 2006 (Scheme 2.6).[7] They accomplished this feat by utilizing a strategy that masks the alkene as a selenide during the synthesis of the nitrone, after which the alkene is revealed by selenoxide elimination. The sequence commenced with the conjugate addition of an *in-situ* generated selenide upon α,β-unsaturated nitroalkene **2.27**. The resultant nitro group of selenide **2.28** was subjected to reduction by the use of aluminum amalgam to provide hydroxylamine **2.29**. Hydroxylamine **2.29** was difficult to work with due to rapid decomposition at room temperature and instability to silica gel chromatography and as such, it was taken on crude. Condensation of crude hydroxylamine **2.29** with 5 equivalents of benzaldehyde provided nitrone **2.30** thereby setting the stage for the key selenide oxidation/elimination step. Treatment of nitrone **2.30** with *m*CPBA resulted in the desired oxidation of the selenide to the selenoxide, which spontaneously eliminated phenylselenic acid to provide *N*-vinyl nitrone **2.31** in 62 % yield as a 1.6:1 *Z/E* mixture of isomers.

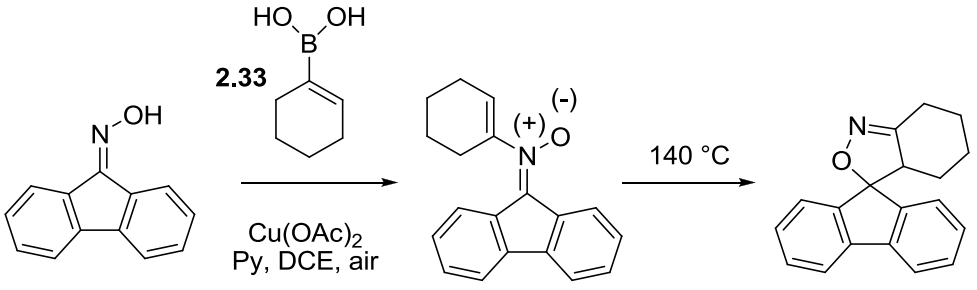
Scheme 2.6 Denmark and Montgomery's Synthesis of *N*-Vinyl Nitrones



This work provided the first general method for the synthesis of *N*-vinyl nitrones which allowed the study of this intriguing class of compounds. While a groundbreaking achievement in the field, the cumbersome approach inherent to the strategy of masking the alkene suffers from a number of drawbacks. Unfortunately, the sequence requires four steps from non-commercially available nitroalkene **2.27**. In addition, the utilization of a toxic and malodorous selenide reagent, coupled with the undesirable use of the heavy metal mercury, present significant disadvantages to the practical implementation of the described route as a general method for the study of these compounds. The lack of regioselectivity in the selenide oxidation/elimination sequence limits the scope to substrates lacking an additional α-proton, or mixtures of the desired *N*-vinyl nitrones, in addition to an *N*-allyl nitrone will result. The lack of *E/Z*- selectivity is also undesirable.

More recently and while our work was in progress, Anderson and coworkers described the synthesis and reactivity of fluorenone derived *N*-vinyl nitrones (Scheme 2.7).[8]

Scheme 2.7 Anderson's Synthesis of Fluorenone Derived *N*-Vinyl Nitrones



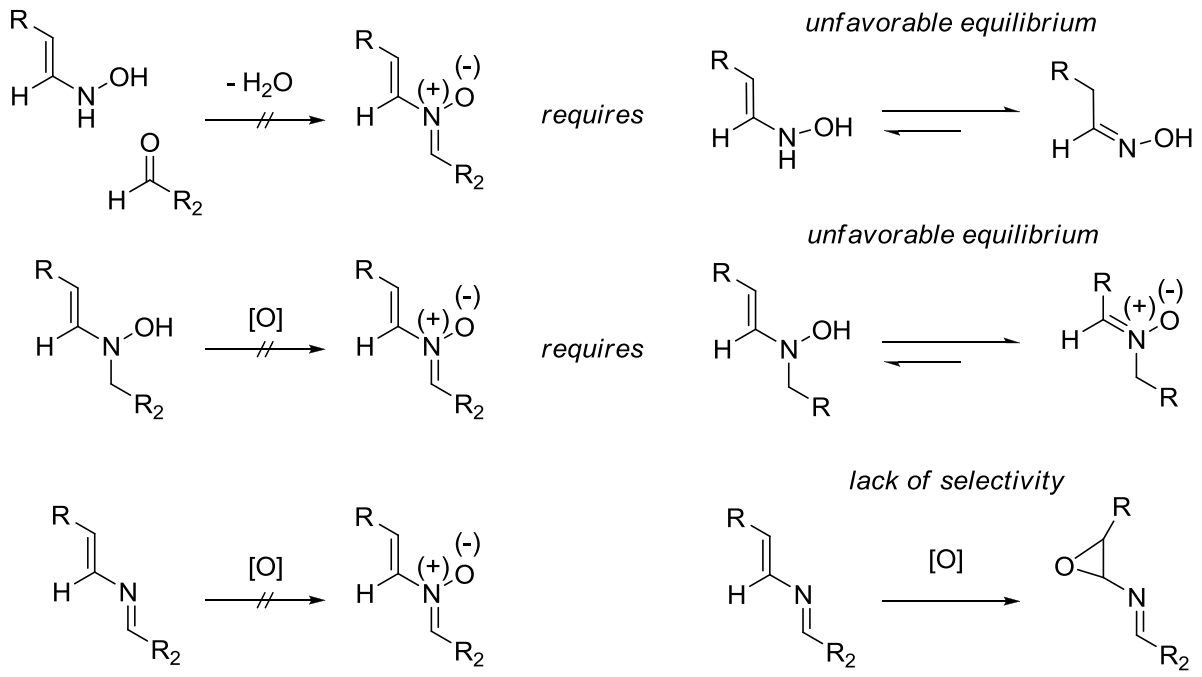
While attempting a copper (II) catalyzed *O*-vinylation of fluorenone oxime **2.32** with vinyl boronic acid **2.33**, the group unexpectedly isolated *N*-vinyl nitrone **2.34**. Upon heating to 140

°C, the nitrone underwent skeletal rearrangement resulting in spirocycle **2.35**. This method is concise and deserves further consideration as a general method for the access of *N*-vinyl nitrones. Unfortunately, this transformation might be somewhat limited in scope as only *N*-vinyl nitrones derived from fluorenone oxime are reported and the authors do not comment on the limited range of substrates reported in the study.

2.2 The Difficulties with Traditional Methods for the Synthesis of *N*-Vinyl Nitrones

The synthesis of nitrones is most commonly accomplished by the condensation of a hydroxylamine with a carbonyl derivative,[9] or by the oxidation of a hydroxylamine[10] or secondary amine.[11] While these methods have proven effective for countless numbers of nitrones, they are not applicable to the synthesis of *N*-vinyl nitrones (Figure 2.1). Unfortunately, in the case of condensation with a carbonyl derivative as well as the oxidation of a hydroxylamine, the requisite ene-hydroxylamine starting material is not accessible due to unfavorable equilibria between the ene-hydroxylamine and oxime or nitrone tautomers. While conditions could possibly be developed for the oxidation of a secondary amine, significant selectivity problems would need to be to be overcome for this to be a viable process.

Figure 2.1 Traditional Methods for the Preparation of Nitrones

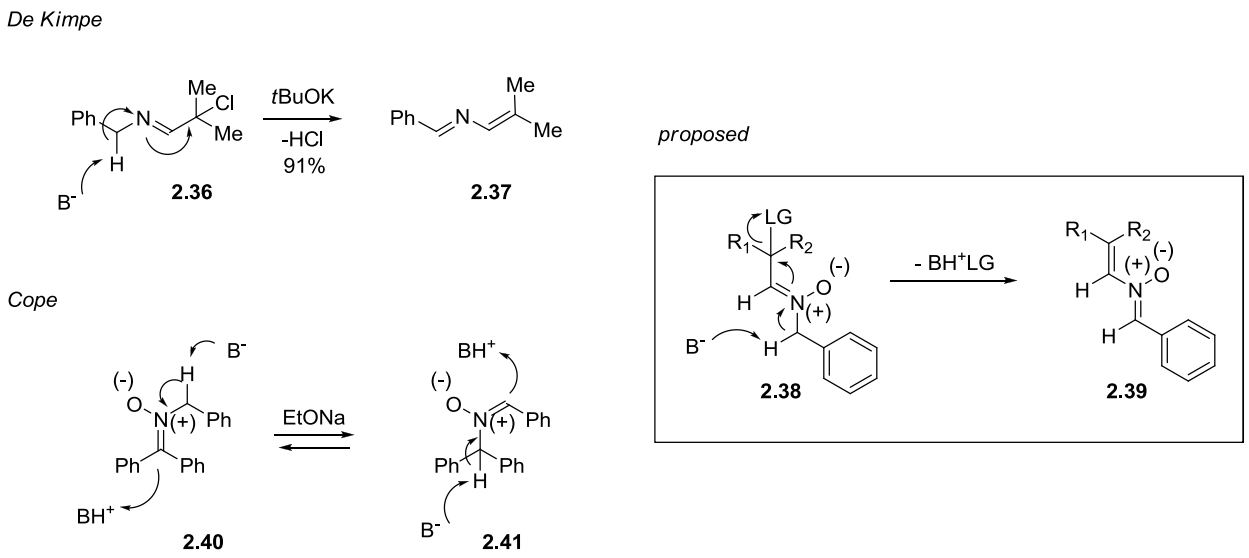


2.3 *N*-Vinyl Nitrones via 1,4-Conjugate Elimination of α-Chloro-aldehydes

The lack of existing methods coupled with our need for a general route that provides ready access to a variety of *N*-vinyl nitrones necessitated the development of a new synthesis of these compounds. A report published by De Kimp *et al.* detailing the synthesis of conjugated aza-dienes by a 1,4-conjugate elimination attracted our attention.[12] Treating α-chloro imine **2.36** with *t*-BuOK resulted in the 1,4-elimination of HCl to provide *N*-vinyl imine **2.37** (Scheme 2.8). A similar reaction could be imagined wherein α-chloro nitrone **2.38** is treated with base to induce 1,4-conjugate elimination to provide the desired *N*-vinyl nitrone **2.39** without the need for elaborate strategies to mask the sensitive vinyl moiety. The desired reactivity is predicated upon sufficient acidity of the proton in the 1-position of an appropriately substituted nitrone. Evidence that this would be the case could be found in the work of Cope who published a report detailing

the isomerization of *N*-benzyl-*C*-phenyl nitrone **2.40**.[13] This isomerization suggests that protons in the α-protons of nitrones are sufficiently acidic to be deprotonated by mild base, and that with a suitably positioned leaving group, the α-proton on nitrone **2.40** can also be deprotonated by mild base, thereby inducing the desired 1,4-conjugate elimination in analogy to the reaction described by De Kimpe.

Scheme 2.8 1,4-Conjugate Elimination for Synthesis of *N*-Vinyl Nitrones

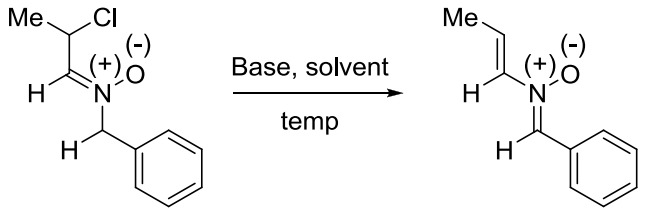


Our studies commenced with the condensation of α-chloropropionaldehyde and benzylhydroxylamine as a model system in order to explore the viability of this process. We prepared the corresponding α-chloro nitrone (**2.42**) by condensation with the commercially available benzylhydroxylamine following a slight modification of a procedure first described by Eschenmoser.[14] The procedure is straightforward: benzylhydroxylamine was added to a 1:1 mixture of DCM/ether that contained α-chloropropionaldehyde and $MgSO_4$. The flask was then flushed with nitrogen, sealed with a polyethylene cap and allowed to stir overnight at 4 °C with

the exclusion of light (there are reports of this class of compounds being light sensitive although no such sensitivity was noted in our studies).[15] This procedure afforded ample quantities of α-chloro nitrone **2.42** in high yield which allowed us to focus on the development of conditions for the 1,4-conjugate elimination (Table 2.1).

We then subjected this material to a variety of basic elimination conditions (Table 2.1). We found that triethylamine was not effective and provided no reaction (entry 1) whereas the slightly stronger amine base, DBU (2 equiv), provided the product in good yield, but required several days for the reaction to proceed to full conversion (entry 2). The stronger base, *t*-BuOK, provided the product in good yield in THF at 23 °C (75%, entry 3) and excellent yields at -78 °C (91%, entry 4). The yield was comparable, though slightly diminished in Et_2O at -78 °C (85%, entry 5), and the stronger metal-amide derived base, KHMDS, provided useful yields at -78 °C (71%, entry 6); however, this and other strong metal amide bases (LDA, KHMDS, and LiHMDS) provided complex mixtures at 23 °C (entries 7-9). As such, we deemed the conditions described in entry 4, *t*-BuOK in THF at -78 °C, to be optimal for the elimination reaction.

Table 2.1 Optimization of the Conditions for the 1,4-Conjugate Elimination of HCl



2.42 **2.43**

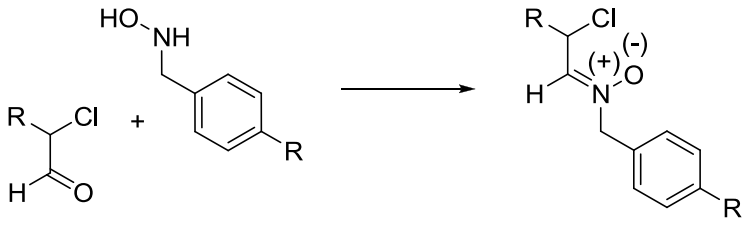
entry	base[a]	solvent	temp	time	yield[b]
1	TEA	THF	23 °C	24 h	0 %
2	DBU[c]	THF	23 °C	72 h	90 %
3	*t*-BuOK	THF	23 °C	5 min	75 %
4	***t*-BuOK**	**THF**	**-78 °C**	**5 min**	**91 %**
5	*t*-BuOK	Et_2O	-78 °C	5 min	85 %
6	KHMDS	THF	-78 °C	5 min	71 %
7	LDA	THF	23 °C	5 min	0 %[d]
8	LiHMDS	THF	23 °C	5min	0 %[d]
9	KHMDS	THF	23 °C	5 min	0 %[d]

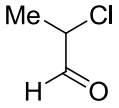
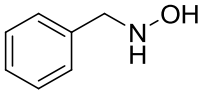
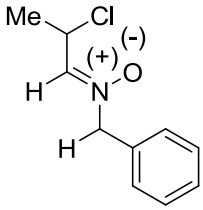
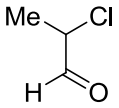
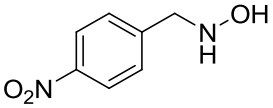
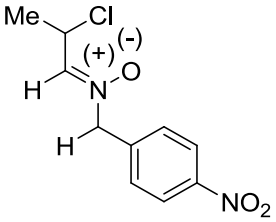
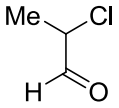
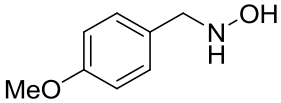
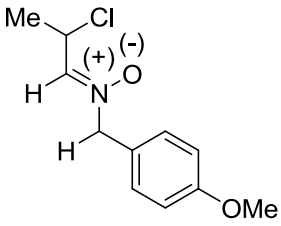
[a] 1.1 equiv base was used unless otherwise noted. [b]Isolated yield after flash chromatography. [c] 2.0 equiv base used. [d]A complex mixture was observed from which no product was isolated.

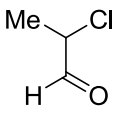
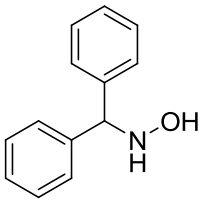
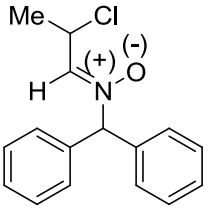
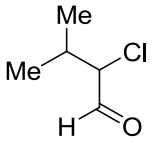
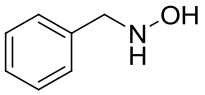
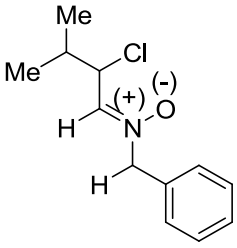
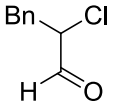
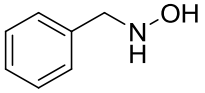
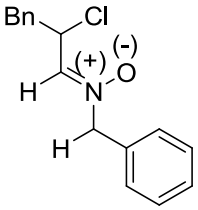
In order to explore the scope of this process, we synthesized a variety of aldehyde-derived α-chloro nitrones (Table 2.2).[16] In general, α-chloro nitrones derived from aldehydes were stable at low temperature indefinitely, although if left on the bench at room temperature overnight slight decomposition was observed. Also noteworthy, all of the α-chloro nitrones that

were utilized in this study were crystalline solids that could be purified by recrystallization or flash chromatography.

Table 2.2 The Condensation of α-Chloro Aldehydes With Hydroxylamines



[a]entry	aldehyde	hydroxylamine	product	yield[b]
1				96%
2				95%
3				90%

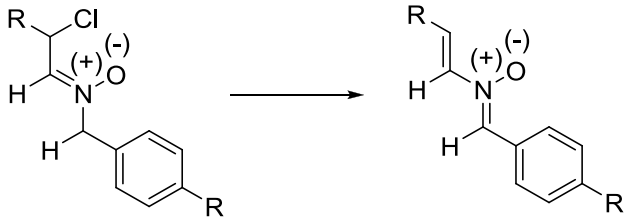
4				91%
5				93%
6				89%

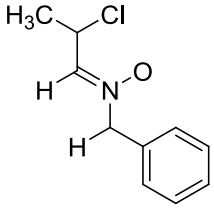
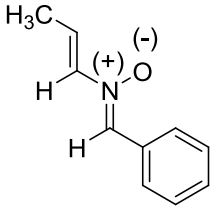
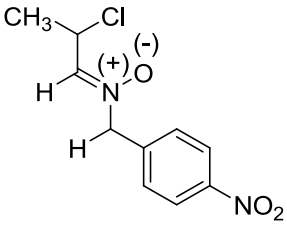
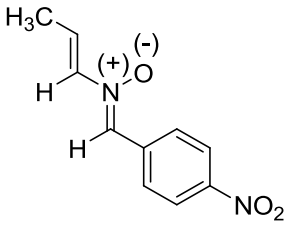
[a] Conditions: The α-chlororaldehyde (1 equiv) was treated hydroxylamine (1 equiv) and Na_2SO_4 (5 equiv) in 1:1 DCM/ether and allowed to stir 16 hrs at 4 °C. [b] Isolated yield after flash chromatography.

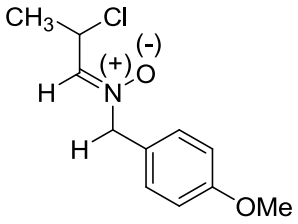
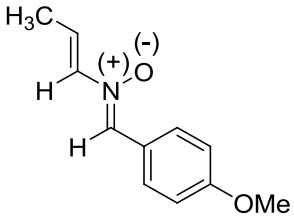
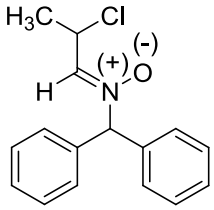
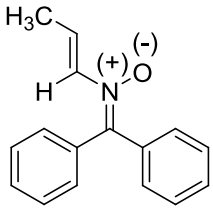
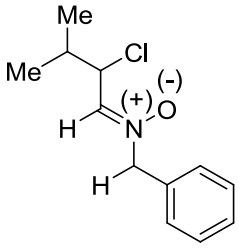
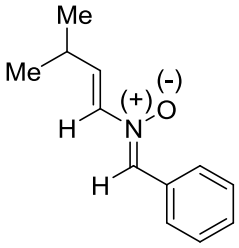
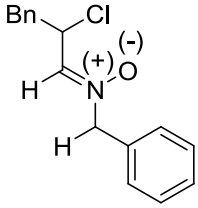
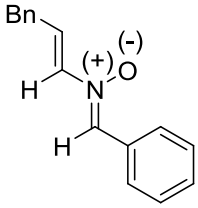
We then subjected the α-chloronitrones prepared above to the optimized 1,4-elimination conditions (Table 2.3). The reactions were stirred for 30 minutes (-78 °C), but most were complete in less than five minutes as judged by TLC. In all cases, the reaction was highly stereoselective and provided the *E*-alkene as the only isomer detected by ^{1}H NMR. Electron withdrawing groups on the arene (*p*-nitrophenyl, entry 2) facilitated the reaction such that the use of the amine base, DBU, provided the product in reaction times of about one hour at room temperature (2 equiv DBU in THF; data not shown). Electron donating groups on the phenyl group, such as *p*-methoxyphenyl, provided the product in a slightly diminished yield of 72%

(entry 3). This data suggests that an increase in acidity of the benzylic proton α-to the nitrone nitrogen facilitates the reaction (*vida infra*). The conditions are tolerant of steric hinderance at either end of the molecule (entries 4 and 5) and of a phenyl group at the α-carbon of the nitrone, thereby allowing for the synthesis of aryl-conjugated *N*-vinyl nitrones (entry 6). It is also worth noting that the *N*-vinyl nitrone products are amenable to aqueous work up, purification by flash chromatography, and are stable indefinitely at – 20 °C.

Table 2.3 Scope of *t*-BuOK Induced 1,4-Elimination of HCl from α-Chloro Nitrones



entry	Cl-nitrone	*N*-vinyl nitrone	yield
1			91%
2[b]			94%

3[c]			72%
4			86%
5			86%
6			69%

[a] Conditions: The chloro nitrone (1 equiv) was treated with *t*-BuOK (1.1 equiv) in THF at – 78 °C. [b] Yield after flash chromatography.

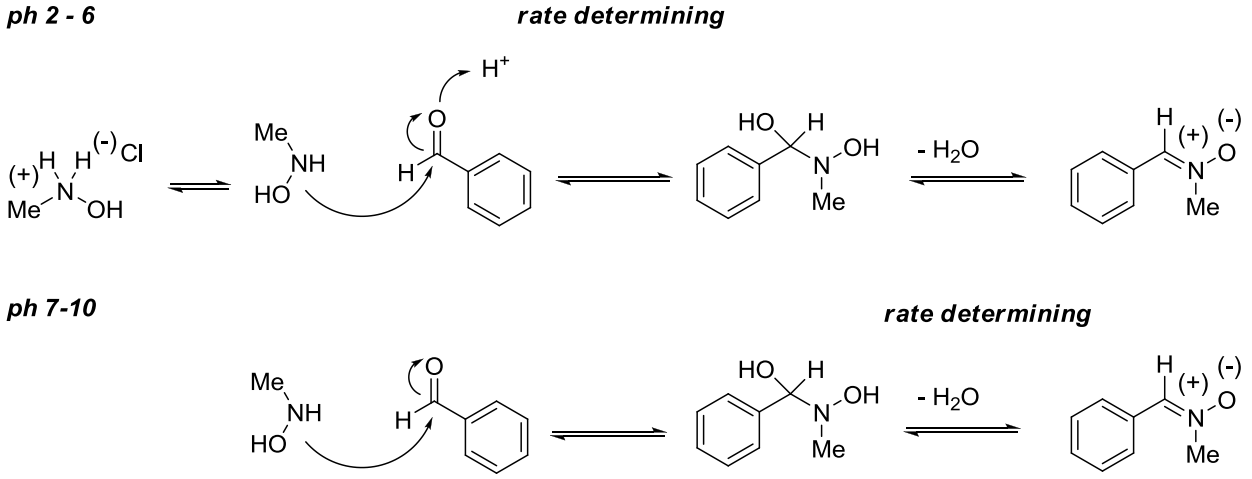
2.4 Application of a 1,4-Conjugate Elimination for the Synthesis of Ketone Derived *N*-Vinyl Nitrones

We next turned our attention to the synthesis of *N*-vinyl nitrones derived from ketones. The condensation of hydroxylamines with ketones is known to be more challenging than the analogous condensation with aldehydes,[17] and the limited general methods that have been developed typically require forcing conditions resulting in minimal functional group tolerance.[18] Our attempts to apply the conditions that were successful with aldehydes to the condensation of

benzylhydroxylamine and α-chloro ketone **2.44** provided no conversion. In a rare example of a room temperature condensation of hydroxylamines with ketones, Tejero and colleagues reported high yields for several substrates, albeit without the complication of additional functional groups, when the reaction was promoted by $ZnCl_2$.[19] Several attempts utilizing the reported conditions in addition to various modifications led to the formation of the desired α-chloro-keto nitrone in only trace amounts. Beauchemin made the observation that the thermal stability of the hydroxylamine starting material is highly solvent and substituent dependent; significant decomposition was noted with heating in several solvents, with the exception of *t*-BuOH.[20] The report noted that heating the hydroxylamine and ketone in *t*-BuOH to 110 °C in a sealed tube overnight resulted in high yields of ketonitrones. Application of Beauchemin's conditions to benzylhydroxylamine and 2-chloro-butanone (**2.44**) led to only complex mixtures and recovery of starting hydroxylamine.

The rate-determining step in the condensation of hydroxylamines with a carbonyl compounds has been shown to be pH dependent in protic solvents (Scheme 2.9).[21] At low pH, nucleophilic addition upon the carbonyl is the rate determining step until pH ~ 2, below which the limited amount of un-protonated hydroxylamine is insufficient for the reaction to occur. At neutral and higher pH, proton transfer and loss of water become rate limiting.

Scheme 2.9 The Dependence of the Rate Determining Step on pH in the Condensation of a Hydroxylamine and Carbonyl Compound

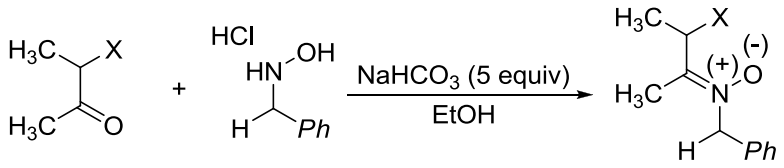


Our conditions for the condensation of α-chloroaldehydes utilized the aprotic solvents DCM and diethyl ether. These conditions unfortunately provided no reaction with the chloroketone system; however, we speculated that the use of a protic solvent in addition to catalytic Bronsted acid would facilitate addition to the carbonyl as well as the subsequent proton transfer and loss of water. We therefore explored the use of protic solvents in the presence of various Bronsted acids in hopes of achieving the desired condensation. The use of methanesulfonic acid, acetic acid, and *p*-toluenesulfonic acid all proved competent at catalyzing the desired transformation, albeit in variable yields (*vide infra*). Extensive experimentation led to the realization that while this approach allowed for the isolation of the requisite α-chloro nitrones, the yields were unfortunately variable and not reproducible on a consistent basis. A rough correlation between the isolated yield and the time spent between work-up and purification was noted which led to unsuccessful attempts toward the development of a one-pot procedure. Eventually, we realized the α-chloro nitrones are inherently unstable compounds that are too

difficult and inconvenient to work with rendering them unsuitable for our need and that an alternate approach was necessary.

The inherent instability of the ketone derived α-chloronitrones eventially prompted the study of less reactive leaving groups that would presumably still participate in the 1,4-conjugate elimination while being less prone to deleterious side reactions and decompostion pathways. Seeking to achieve a delecate balance between reactivity and stability, we ultimately studied the use of methoxy, phenoxy, and acetoxy leaving groups (Table 2.4).

Table 2.4 Synthesis of α-Substituted Nitrones



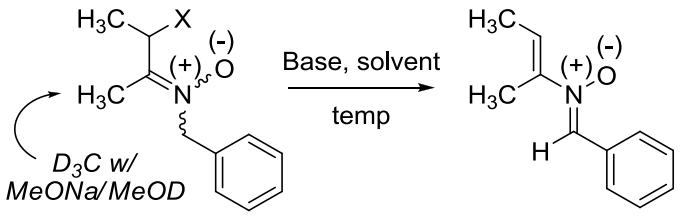
[a]entry	ketone	X	product	[b]yield, %
1	**2.44**	Cl	**2.48**	see text
2	**2.45**	OMe	**2.49**	88
3	**2.46**	OPh	**2.50**	91
4	**2.47**	OAc	**2.51**	83

[a] Conditions: The ketone (1.1 equiv) was treated with BnNHOH•HCl (1 equiv) and $NaHCO_3$ (5 equiv) in EtOH (0.5 M) and stired for 16 hrs at room temperatre. [b] Isolated yields after flash chromatography.

The corresponding nitrones derived from the parent 2-butanone with the appropriate leaving group were synthesized for each of the requisite substrates.[22] In general, high yields

were obtained by the condensation of the appropriate ketone with benzyl hydroxyl amine•HCl using modified Barton conditions (*N*-benzylhydroxylamine•HCl, $NaHCO_3$ (5 equiv), EtOH; **2.49**, 88%; **2.50**, 91%; **2.51**, 83%).[23] The nitrones were produced as *E/Z*-mixtures that were prone to partial equilibration during flash chromatography, although this has no effect on the efficacy of the overall sequence as both isomers are competent substrates for the subsequent transformations (*vide infra*). The α-methoxy and α-phenoxy nitrones are bench stable with no noticeable decomposition after 1 week at room temperature. The α-acetoxy nitrones can be stored at -20 °C without noticeable decomposition, but undergo slight to moderate decomposition upon storage at room temperature overnight.

Table 2.5 Optimization of 1,4-Conjugate Elimination Conditions for Ketone Derived Nitrones



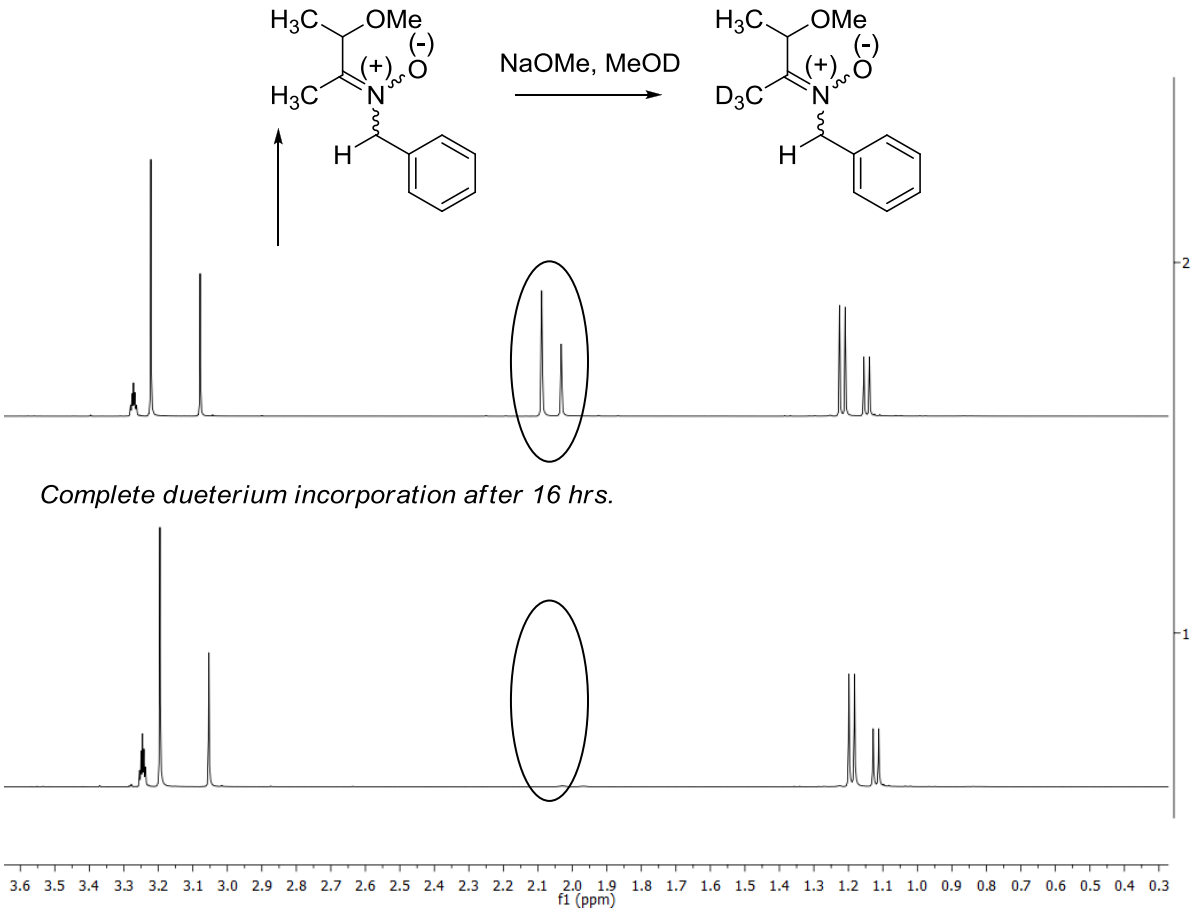
entry	X	Base	Solvent	temp	yield[a]
1	OMe	*t*-BuOK	THF	-78 °C/RT	0 %[c]
2	OMe	MeONa	MeOD	RT	0 %[d]
3	OMe	KHMDS	THF	-78 °C	0 %[c]
4	OMe	LiHMDS	THF	-78 °C	0 %[c]
5	**OPh**	***t*-BuOK**	**THF**	**-78 °C**	**85 %**
6	**OPh**	**KHMDS**	**THF**	**-78 °C**	**89 %**
7	OPh	LiHMDS	THF	-78 °C	65 %
8	OPh	KOH	EtOH	0 °C/RT	0 %[e]
9	OPh	DBU	THF	0 °C/RT	0 %[e]

10	OPh	NaH	THF	0 °C/RT	0 %[e]
11	**OAc**	***t*-BuOK**	**THF**	**-78 °C**	**79 %**

[a] Isolated yield after flash chromatography. [b] A complex mixture was observed from which no product was isolated. [c] No product was isolated, partial decomposition was observed. [d] Deuterium incorportaion was cleanly observed exclusively at the methyl group α-to the nitrone. [e] No reaction was observed.

A variety of conditions were then explored to induce the conjugate elimination of the various leaving groups (Table 2.5). The optimized conditions that were effective with the α-chloro aldehyde-derived nitrones were applied to compound **2.49**, but only partial decomposition was observed and no product was isolated (entry 1). In an attempt to obtain data that would illuminate fundamental mechanistic principals of the system under study, we conducted a series of experiments that were amenable to *in situ* observation via ^{1}H NMR. An extremely valuable observation was noted when the elimination was attempted with catalytic MeONa (10%) in MeOD; even though no conversion to the desired product was observed. After 16 hours, essentially complete exchange of the protons for deuterium occurred at the Me group adjacent to the nitrone as judged by disappearance of the Me resonance in the ^{1}H NMR (entry 2). Surprisingly, prolonged exposure to these conditions for 1 week provided no evidence of deuterium incorporation elsewhere in the molecule as judged by ^{1}H NMR (Figure 2.2).

Figure 2.2 Site of Deuterium Exchange

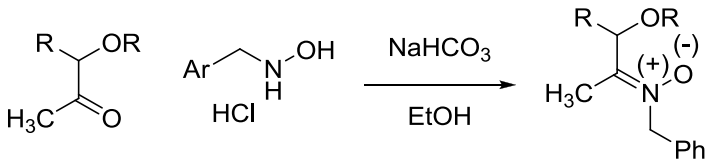


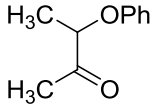
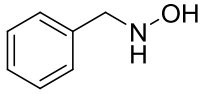
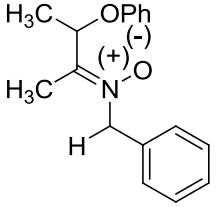
The use of the stronger bases, KHMDS and LiHMDS, was also studied but produced a complex mixture from which no desired product could be isolated (entries 3 and 4, respectively). Examining the data revealed that while replacement of the chloride for a methoxy group achieved the goal of imparting stability to the substrate, the elimination of MeOH was not possible under the reaction conditions attempted. The deuterium incorporation solely on the methyl group α-to the nitrone implies that with a strong kinetic base, deprotonation likely occurs solely at this position and that this species then acts as a base in an intra or intermolecular fashion to effect the irreversible 1,4-conjugate elimination. With the working hypothesis that

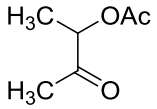
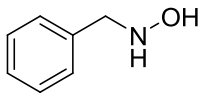
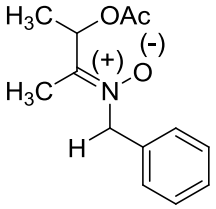
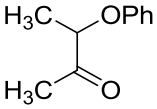
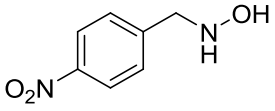
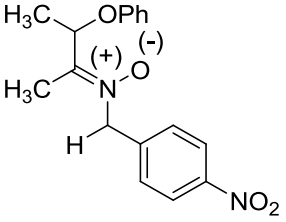
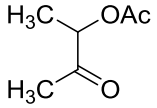
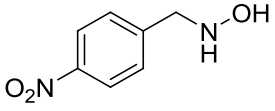
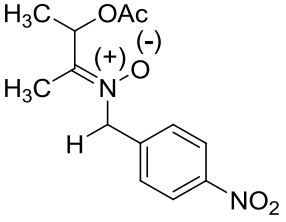
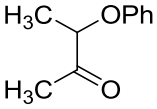
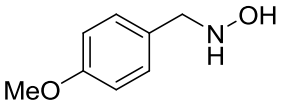
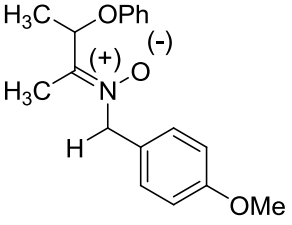
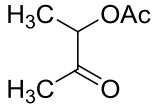
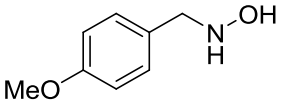
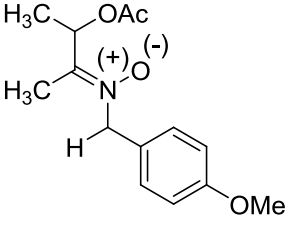
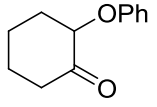
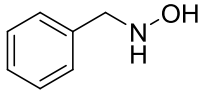
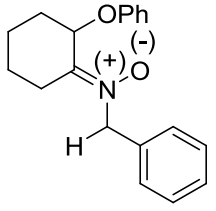
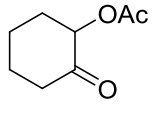
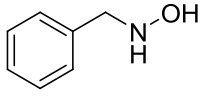
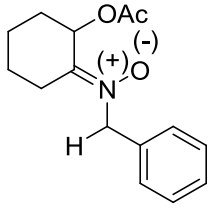
deprotonation at the benzylic position only occurs to a small extent under the reaction conditions and that ejection of the leaving group is rate limiting, we sought to find a balance between the reactivity and inherent stability of the intermediate nitrones by employing the corresponding α-phenoxy and α-acetoxy substrates. We found that the use of *t*-BuOK or KHMDS were both effective with the phenoxy substrate (85% and 89% yields, respectively, entries 5 and 6) and that *t*-BuOK at -78 °C was effective with the acetoxy substrate (entry 11). While KHMDS was not studied with acetoxy as a leaving group, comprable yields could be expected.

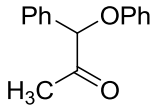
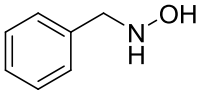
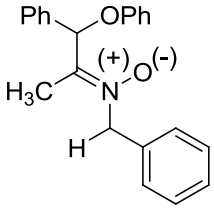
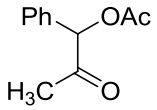
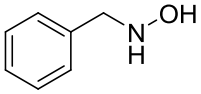
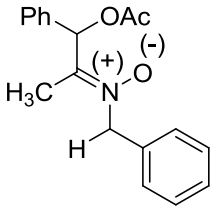
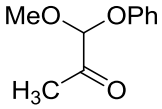
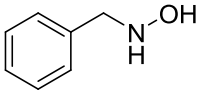
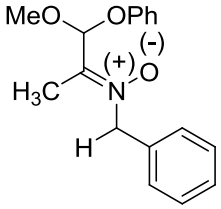
Having discovered substrates that posessed the desired stability while also proving competent participants in the desired 1,4-conjugate elemination, we next explored the scope of the optimized conditions. The condensation of the appropiate α-phenoxy or α-acetoxy ketone with a hydroxylamine hydrochloride provided the substrates listed in Table 2.6

Table 2.6 Scope of the α-Phenoxyketone/ α-acetoxyketone Hydroxylamine Condensation



entry	ketone	hydroxylamine	product	yield[a]
1				91

2				83
3				90
4				78
5				82
6				97
7				93
8				73

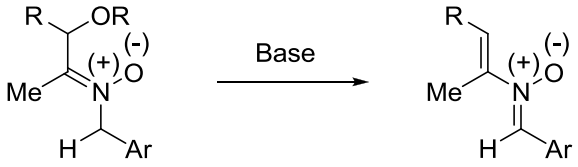
9				90
10				60
11				65

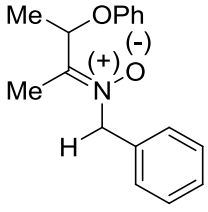
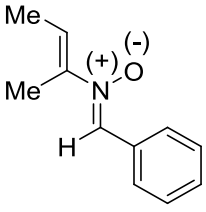
[a]Isolated yield after flash chromatography.

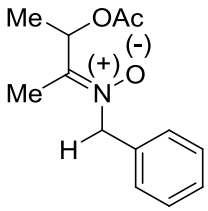
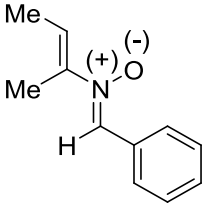
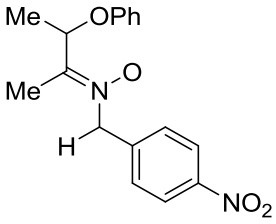
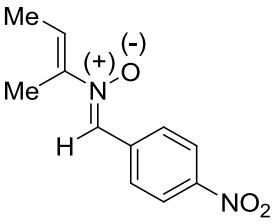
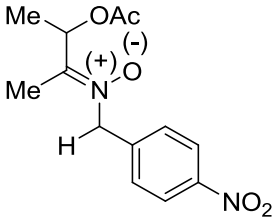
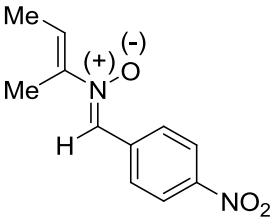
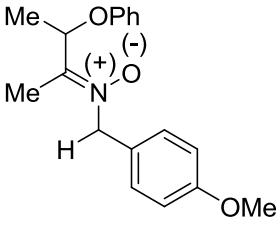
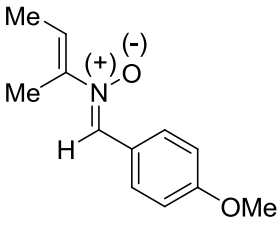
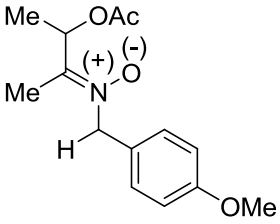
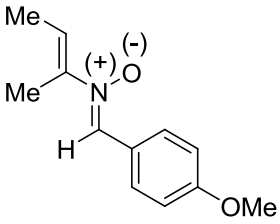
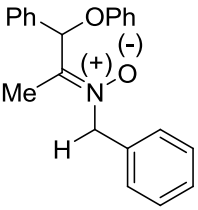
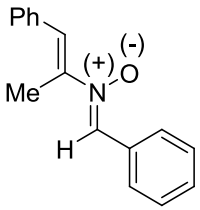
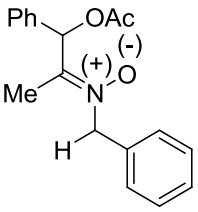
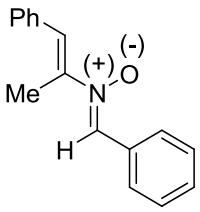
We then subjected these compounds to the optimized elimination conditons (Table 2.7). As in the case of the aldehyde-derived substrates, the reaction is stereoselective and provides the *E*-isomers of the *N*-vinyl nitrones to the limit of detection by ^{1}H NMR (assinged by analagy to known compounds). With electronically neutral substrates, both phenoxy and acetoxy leaving groups provided good yields of the product (compare entry 1 with entry 2, and entry 9 with entry 10). When the substrate contained a *p*-nitro phenyl group the reaction utilizing a phenoxy leaving group occurred; however, the product was not stable under the reaction conditions leading to low yields. Switching to an acetoxy leaving group remedied the problem and therefore suggests the byproduct phenoxide anion was responsible for the decomposition, perhaps by reacting with the product. While not attempted, a milder amine base may be sufficient to effect the transformation due to the increased acidity of the benzylic protons

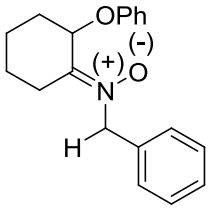
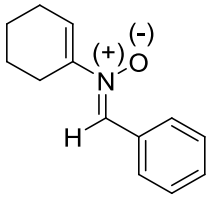
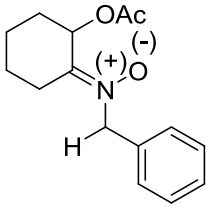
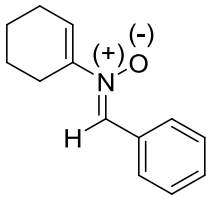
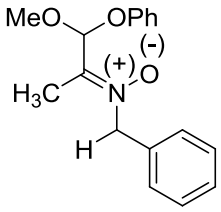
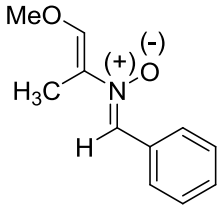
imparted by the nitro group as was observed in the analogous reaction with aldehydes (*vide supra*). The elimination of phenoxide also fails with substrates that possess decreased acidity at the benzylic position (entry 5) providing only complex mixtures in leiu of the desired product. Again, exchanging the leaving group to an acetoxy moiety allowed the reaction to procede in good yield (entry 6). This system is also ameniable to the formation of *N*-vinyl nitrones which contain a ring (entries 9 and 10). In the case of aryl substitution (entries 7 and 8) good yields were obtained only in the case of the acetoxy leaving group. It is possible that the increase in acidity imparted by the phenyl ring α-to the leaving group provided alternatve destructive pathways under the basic reaction conditions. Finally, substrates that bear both alkoxy and phenoxy subsitution at the α-carbon of the nitrone preferentially eliminate the phenoxy group thereby providing access to α-alkoxy substituted *N*-vinyl nitrones (entry 11).

Table 2.7 Scope of the 1,4-Conjugate Elimination for the Synthesis of Ketone Derived *N*-Vinyl Nitrones



[a]entry	nitrone	Base	producr	yield[b]
1		KHMDS		89

2		*t*-BuOK		80
3		KHMDS		see text
4		*t*-BuOK		79
5		KHMDS		0
6		*t*-BuOK		71
7		KHMDS		40
8		*t*-BuOK		81

9		KHMDS		74
10		*t*-BuOK		70
11		KHMDS		60

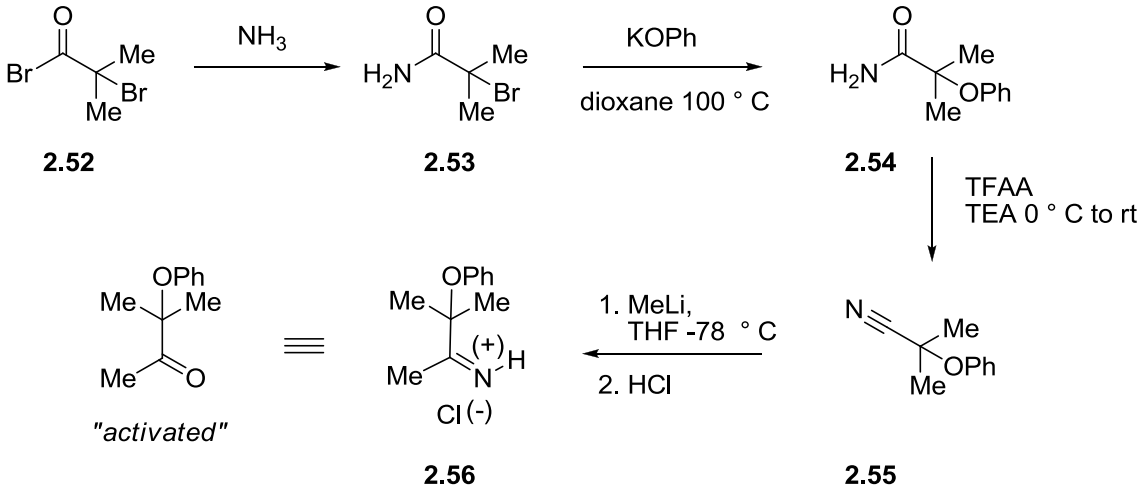
[a] Conditions: the nitrone (1 equiv) was treated with base (1.1 equiv) at -78 °C in THF.
[b]Isolated yield after flash chromatography.

2.5 The Synthesis of Tri-Substituted *N*-Vinyl Nitrones

Utilization of *N*-vinyl nitrones as coupling partners to generate a vicinal di-π system capable of producing vicinal all-carbon quaternary centers would require the use of a tri-substituted *N*-vinyl nitrone substrate. Unfortunately, formation of such a hindered system was unsuccessful when an appropriately substituted ketone was treated with benzylhydroxylamine HCl under our modified Barton conditions. We suspected the problem was a result of the decreased ability of the hindered ketone to undergo nucleophilic addition by the hydroxylamine. We therefore reasoned that using an activated ketone equivalent in the form of an iminium salt would facilitate the nucleophilic addition allowing access to this class of *N*-vinyl nitrone.[24] To explore this possibility we synthesized α-phenoxy iminium salt **2.56** (Scheme 2.10).[25] Treatment

of α-bromoisobutyryl bromide (**2.52**) with gaseous ammonia afforded amide **2.53** in quantitative yield. Displacement of the bromide by phenoxide followed by dehydration provided nitrile **2.55**. Methyl lithium addition to nitrile **2.55** gave the imine which was isolated as the hydrochloride salt **2.56**. It is noteworthy that the iminium salts (described in ref. 23) are free flowing powders that are bench stable at room temperature indefinitely.

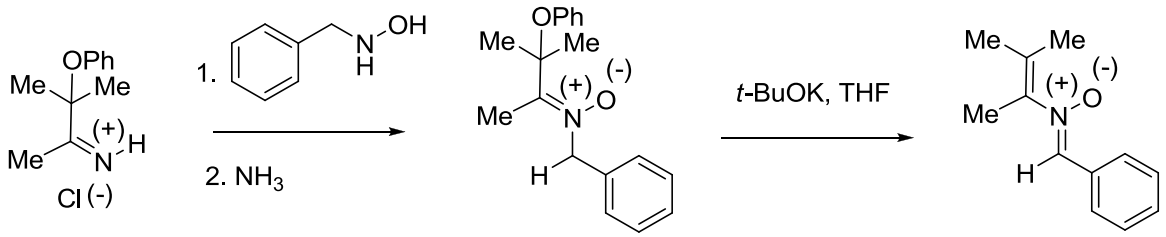
Scheme 2.10 Synthesis of Activated Ketone Equivalent



Our initial attempts for the synthesis of the α-phenoxy nitrone derived from iminium salt **2.56** were carried out in protic solvents (MeOH and EtOH) using conditions similar to our modified Barton conditions; while evidence of product formation was noted, diminished yields resulting from product decomposition in these solvents necessitated a different approach. Gratifyingly, when a THF suspension of iminium **2.56** is treated with benzylhydroxylamine (free base) and allowed to age for 30 minutes, followed by bubbling gaseous ammonia through the reaction, nitrone **2.57** was isolated in 77 % yield after flash chromatography (Scheme 2.11). The order of addition as well as the aging period are key to a successful reaction. Control

experiments that deviated from this protocol provide little or no conversion. Nitrone **2.57** was then subjected to our standard elimination conditions resulting in tri-substituted *N*-vinyl nitrone **2.58** in good yield.

Scheme 2.11 Synthesis of Trisubstituted *N*-Vinyl Nitrones



2.56 **2.57** **2.58**

This method provides a complimentary route to our other protocols for *N*-vinyl nitrone synthesis by expanding the scope to hindered substrates that are not amenable to other methods. The exploration of the scope of this process is currently being studied.

2.6 Concluding Remarks

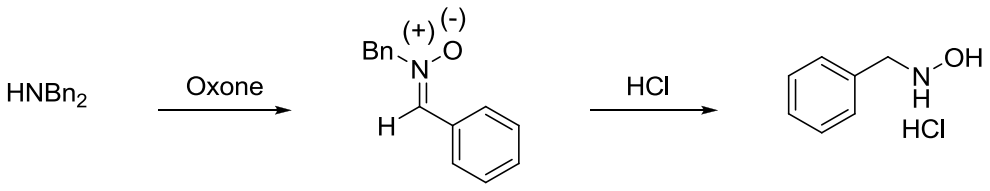
In conclusion, we have developed a two step route to *N*-vinyl nitrones that utilizes a 1,4-conjugate elimination as the key step. With minor modifications, this strategy has proven general in allowing access to a wide range of electronically and sterically differentiated *N*-vinyl nitrones. Through this process, we have also gained invaluable knowledge about the stability and reactivity of this intriguing class of compounds. In the next chapter, we detail our studies of the reactivity of *N*-vinyl nitrones.

2.7 Experimental

General Information: All reactions were performed in oven-dried or flame-dried glassware under a dry nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under nitrogen prior to use. THF and Et_2O were distilled from Na benzophenone ketyl under nitrogen prior to use. Benzylhydroxylamine HCl is commercially available or can be synthesized according to the procedure below. Unless otherwise noted, all other chemicals were used as received from the supplier. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz in $CDCl_3$ using residual $CHCl_3$ (7.24 ppm) as the internal reference. ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz in $CDCl_3$ using residual $CHCl_3$ (77.26 ppm) as the internal reference. Infrared (IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization.

Synthesis of staring materials:

The benzylhydroxylamine HCl used in this study was synthesized by a two-step procedure starting from dibenzylamine:[26]



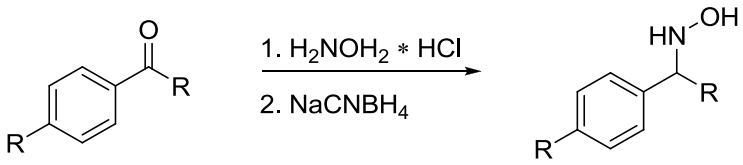
(*Z*)-*N*-Benzylidene(phenyl)methanamine oxide: To a stirred solution of dibenzylamine (8.25 mL, 42.9 mmol, 1 equiv) in a mixture of acetonitrile/THF 4:1 (63 mL:16 ml, 0.54 M) and aqueous EDTA solution (60 mL, 0.01 M, 0.014 equiv) at 0 °C was added $NaHCO_3$ (18.02 g, 215

mmol, 5 equiv). While cooling to maintain the internal temperature at ~ 5 °C (ice bath), Oxone (27.7 g, 45.1 mmol, 1.05 equiv) was added over 2 h under vigorous stirring (*caution*, gas evolution). The suspension was stirred for an additional 20 min followed by the addition of ethyl acetate (200 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude material does not need further purification but may be purified by silica gel flash column chromatography (20:1 to 1:1, hexanes/EtOAc; Rf = 0.31 1:1 hexanes/EtOAc) if desired. The yield of (*Z*)-*N*-Benzylidene(phenyl)methanamine oxide after chromatography was 9.06 g (76 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19-8.23 (m, 2H), 7.47-7.51 (m, 2H), 7.38-7.43 (m, 7H), 5.08 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.4, 133.2, 130.5, 130.3, 129.2, 129.0, 128.6, 128.5, 71.2. The data is consistent with the literature.[27]

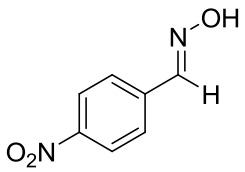
Benzylhydroxylamine HCl Approximately 200 ml of 20% aq HCl was added to the crude (*Z*)-*N*-Benzylidene(phenyl)methanamine oxide in a 500 mL round bottom flask. The flask was fitted to a rotary evaporator keeping the water bath temperature at 70 °C with slow rotation under atmospheric pressure. After 30 min, the pressure was carefully reduced to approximately 100 mmHg and benzaldehyde was distilled off with H_2O. When the total volume reached approximately 30 mL, the flask was removed from the rotary evaporator and the semi-solid mixture was washed with toluene (3 × 20 mL) and then concentrated in vacuo. 30 ml of toluene was added and the suspension sonicated for ~ 5 min followed by concentration in vacuo to give a pale yellow solid. Recrystallization from hot MeOH and ether gave a 4.9 g (93 %) of a white crystalline solid. ^{1}H NMR (500 MHz, D_2O): δ = 11.9 (br, 2 H), 11.0 (br, 1 H), 7.57– 7.37 (m, 5 H), 4.31 (s, 2 H). ^{13}C NMR (100 MHz, D_2O): δ = 131.6, 130.3, 129.1, 128.0, 62.2. The data is

consistent with the literature. The HCl salt is stable indefinitely at -20 °C. If the freebase is required, the salt can be taken up in H_2O and the pH adjusted to ~ 10 by the addition of 3 M NaOH followed by extraction with DCM, drying over $MgSO_4$, and concentration under reduced pressure to give the freebase as a white solid.

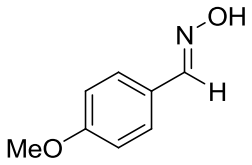
The *p*-nitrobenzylhydroxylamine, *p*-methoxybenzylhydroxylamine, and dibenzylhydroxylamine were prepared by a two-step method consisting of formation of the oxime followed by reduction similar to known chemistry.[28,29]



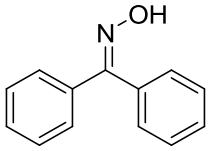
General synthesis of the oximes: A mixture of the ketone or aldehyde (0.050 mol), $NH_2OH{\cdot}HCl$ (0.074 mol, 5.13 g), CH_3COONa (0.125 mol, 10.26 g), 20 mL ethyl alcohol and 60 mL water were placed in a 250 mL round-bottomed flask with a reflux condenser. The flask was heated to reflux and allowed to stir until tlc analysis indicated the starting material had been consumed. The solution was allowed to cool to room temperature during which time the oxime precipitates from solution. The solid was collected by filtration, washed with water and recrystallized from ethyl alcohol to obtain a pure solid.



***p*-nitrobenzaldehyde oxime:** The general procedure was followed to yield 8.00 g (96%) of a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.9Hz), 7.93 (1H, br s), 8.20 (1H, s), 8.25 (2H, d, *J* = 8.9Hz). ^{13}C NMR (100 MHz, d4-MeOD) δ 133.5, 136.8, 136.9, 149.0, 156.3, 157.0. The data is consistent with the literature.[30]



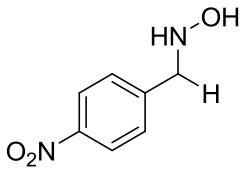
***p*-methoxybenzaldehyde oxime:** The general procedure was followed to yield 6.92 g (92%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.47, 114.39, 124.69, 128.66, 150.03, 161.21. The data is consistent with the literature.[31]



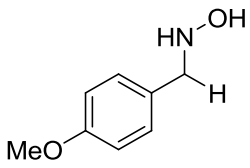
benzophenone oxime: The general procedure was followed to yield 8.23g (83%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 7.43-7.50 (m, 7 H), 7.30-7.37 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 136.1, 132.6, 129.5, 129.2, 129.1, 128.3, 128.2, 127.8. The data is consistent with the literature.[32]

General procedure for reduction of the oxime: To a solution of the oxime (~ 20 mmol, 1 equiv) in 10 mL of methanol was added one drop of methyl orange. The solution was acidified

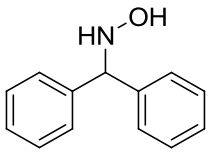
to a pink color with addition of 2 M HCl in methanol. $NaBH_3CN$ (0.75 equiv) was added in small portions while the solution was kept pink by the periodic addition of 2 M HCl. The addition continued until the pink color sustained. The mixture was allowed to stir for one additional hour before the methanol was removed under reduced pressure. The pH was adjusted to 10-11 with NaOH, and the residue was extracted three times with EtOAc, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford the desired hydroxylamines as the freebase. The HCl salts were obtained by dissolving the crude hydroxylamines in Et_2O or dioxane and bubbling dry HCl gas until the formation of crystals ceased.



***N*-(4-nitrobenzyl)hydroxylamine:** The general procedure was followed to yield a yellow solid. The data is consistent with the literature.



***N*-(4-Methoxybenzyl)hydroxylamine**: The general procedure was followed to yield a white solid (72%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.23 (m, 2 H), 6.89–6.85 (m, 2 H), 3.93 (s, 2 H), 3.79 (s, 3 H), NH and OH not observed. The data is consistent with the literature.[33]

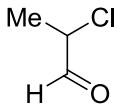


***N*-benzhydrylhydroxylamine:** The general procedure was followed to yield a white solid (69%). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.47 – 7.16 (m, 10H); 5.58 (br. s, 1H); 5.23 (s, 1H); 4.99 (br. s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): 140.7; 128.7, 127.7, 127.6 70.8. The data is consistent with the literature. [34]

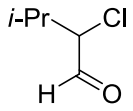
The α-chloroaldehydes were prepared by one of two general methods: treatment of the aldehyde with sulfuryl chloride, or proline catalyzed chlorination with NCS.

General procedure utilizing SO_2Cl_2: 1.1 equiv of SO_2Cl_2 was added dropwise to the aldehyde at 0°C. The bath was removed and the mixture allowed to stir for 1 hr. After 1 hr the reaction was poured into water and extracted with DCM, washed with$NaHCO_3$ (*caution, evolution of gas*), dried with $MgSO_4$ and concentrated. The crude chloro aldehydes were purified by distillation.

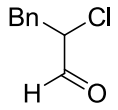
General procedure utilizing NCS with proline as the catalyst: To a solution of the aldehyde (1 equiv) in CCl_4 (1M) were added proline (15 mol %) and NCS (1.1 equiv). The mixture was stirred for 18 h at ambient temperature and the precipitate was separated by filtration. The solvent was removed and the crude chloro aldehydes were purified by distillation.



2-chloropropanal: H-NMR (500 MHz, $CDCl_3$) δ 1.61 (d, 3H, *J* = 6.8 Hz, H3), 4.28 (qd, 1H, *J* = 6.8, 1.8 Hz, H2), 9.54 (d, *J* = 1.8 Hz, H1). The data is consistent with the literature.[35]



2-chloro-3-methylbutanal: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (2d, 6H, *J* = 6.9Hz), 2.30-2.36 (m, 1H), 4.02 (dd, 1H, *J* = 2.7; 2.6 Hz), 9.49 (d, 1H, *J* = 2.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): = 17.6, 19.5, 30.8, 70.4, 196.1. The data is consistent with the literature.[36]



2-chloro-3-phenylpropanal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.57 (d, *J* = 2.1 Hz, 1H), 7.38-7.25 (m, 5H), 4.41 (ddd, *J* = 8.1 Hz, *J* = 5.7 Hz, *J* = 2.1 Hz, 1H), 3.41 (dd, *J* = 14.4 Hz, *J* = 5.7 Hz, 1H), 3.11 (dd, *J* = 4 Hz, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 135.4, 129.4, 128.7, 127.4, 63.9, 38.3; The data is consistent with the literature.[37]

Synthesis of α-methoxy and α-phenoxy ketones was accomplished by the displacement of the appropriately substituted bromo or chloro ketone by methoxide or phenoxide ion by known methods.[38]

The α-acetoxy ketones were prepared by the method of Tompkinson.[39]

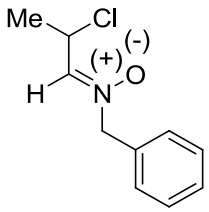
General procedure (A) for the synthesis α-chloro nitrones: Freshly distilled α-chloro aldehyde (1 equiv) was dissolved in a 1:1 mixture of dichloromethane/ether (0.1 M) and sodium sulfate (5 equiv) was added. The suspension was placed in ice bath 0°C and allowed to stir for 15 min. Solid benzylhydroxylamine (1 equiv) was added in one portion and the reaction was purged with N_2, sealed with a yellow cap and allowed to stir at 4 °C for 16 hours. The suspension was filtered through a pad of Celite, the filter cake rinsed with additional dichloromethane and concentrated at reduced pressure in a room temperature bath. The crude α-chloro nitrones were purified by flash chromatography (silica gel, MeOH:$CHCl_3$).

General procedure (B) for the synthesis of aldehyde derived *N*-vinyl nitrones by 1,4-conjugate elimination of α-chloro nitrones: The α-chloro nitrone was taken up in THF (0.15 M), cooled to -78 °C (dry ice/acetone) and allowed to stir for 15 min. at which point a *t*-BuOK solution (1 M in THF;1.1 equiv) was added via syringe. The reaction allowed to stir at -78 °C until the disappearance of starting material by tlc. The cold solution was then poured directly into a separatory funnel containing pH 7 buffer solution (potassium phosphate monobasic sodium hydroxide buffer) and the reaction flask rinsed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc x 3. The combined organic layers were washed with brine, the brine was back extracted with EtOAc, the combined organic layers dried over magnesium sulfate and concentrated at reduced pressure in a room temperature water bath. The crude *N*-vinyl nitrones were purified by flash chromatography (silica gel, hexanes:EtOAc).

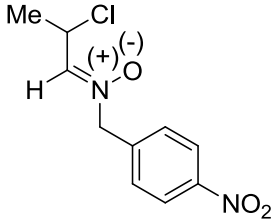
General procedure (C) for the synthesis of α-aryloxy and α-acyl nitrones: The α-aryloxy or α-acyl ketone (1.1 equiv) and benzylhydroxylamine HCl (1 equiv) were dissolved in EtOH (0.5M). $NaHCO_3$ (5 equiv) was added in one portion and the resulting suspension was allowed to stir at room temperature for 16 hours. The suspension was filtered through a pad of Celite, the filter cake rinsed with dichloromethane and concentrated at reduced pressure in room temperature bath. The crude α-aryloxy or α-acyl nitrones were purified by flash chromatography (silica gel, hexanes:EtOAc).

General procedure (D) for the synthesis of ketone derived *N*-vinyl nitrones by 1,4-conjugate elimination of α-aryloxy or α-acyl nitrones: The α-aryloxy or α-acyl nitrone (1 equiv) was dissolved in THF (0.15 M), placed in a bath at - 78°C (dry ice/acetone) and allowed to stir for 15 min. KHMDS (1 M THF; 1.1 equiv) or *t*-BuOK solution (1 M in THF;1.1 equiv) was added via syringe and the reaction allowed to stir until the starting material was no longer visible by tlc. The cold solution was then poured into a separatory funnel containing pH 7 buffer solution (potassium phosphate monobasic sodium hydroxide buffer) and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc x 3. The combined organic layers were washed with brine, the brine back extracted with EtOAc, the combined organic layers dried with magnesium sulfate, and concentrated at reduced pressure in a room temperature bath. The crude *N*-vinyl nitrones were purified by flash chromatography (silica gel, hexanes:EtOAc).

Table 2.2

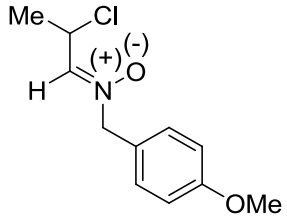


Entry 1 (*Z*)-*N*-(2-chloropropylidene)-1-phenylmethanamine oxide: Prepared by general procedure A (96 %). White solid. R*f* = 0.38 ($CHCl_3$/MeOH 97:3); mp = 91-92 °C; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.38 (s, 5H), 6.76 (d, *J* = 7.4, 1H), 5.20 (apparent p, *J* = 6.9, 1H), 4.88 (s, 2H), 1.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 132.3, 129.6, 129.5, 129.3, 69.9, 49.0, 22.5; IR (thin film): 3402, 3143, 3093, 3068, 3036, 3010, 2890, 2972, 2930, 2883, 2866, 1577, 1457, 1426, 1213, 1204, 930, 706 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{24}Cl_2N_2O_2$ $[2M + Na]^+$: 417.1108; found: 417.1071.

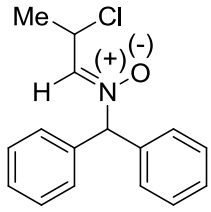


Entry 2 (*Z*)-*N*-(2-chloropropylidene 1-(4-nitrophenyl)methanamine oxide: Prepared by general procedure A (95%). Yellow solid. R*f* = 0.52 ($CHCl_3$/MeOH 97:3); mp = 97-99 °C (decomp); ^{1}H NMR (300 MHz, Chloroform-d) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.18 (apparent p, *J* = 7.2 Hz, 1H), 4.98 (s, 2H), 1.64 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 139.3, 130.0, 124.3, 100.2. 68.8, 48.7, 22.2; IR (thin

film): 3110, 3081, 2987, 2934, 2865, 1602, 1581, 1521, 1349, 1211, 914, 717 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{12}ClN_2O_3$ $[M + H]^+$: 243.0531; found: 243.0533

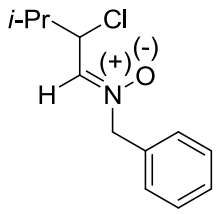


Entry 3 (*Z*)-*N*-(2-chloropropylidene)-1-(4-methoxyphenyl)methanamine oxide: Prepared by general procedure A (90%). Off white solid. R*f* = 0.39 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 7.4 Hz, 1H), 5.16 (dq, *J* = 7.4, 6.8 Hz, 1H), 4.78 (s, 2H), 3.77 (s, 3H), 1.56 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 137.9, 131.3, 124.2, 114.7, 69.3, 55.6, 49.0, 22.2; IR (thin film): 3393, 3073, 3036, 2997, 2960, 2935, 2911, 1613, 1587, 1515, 1442, 1456, 1424, 1033, 913 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{29}Cl_2N_2O_4$ $[2M + H]^+$: 455.1500; found: 455.1515

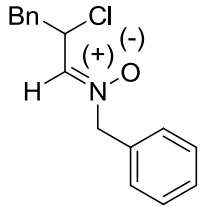


Entry 4 (Z)-*N*-(2-chloropropylidene)-1,1-diphenylmethanamine oxide: Prepared by general procedure A (91%). White solid. R*f* = 0.57 (2:1 hexanes/EtOAc); mp = 109-111°C (decomp); ^{1}H NMR (300 MHz, Chloroform-d) δ 7.42 – 7.24 (m, 10H), 6.85 (d, *J* = 7.4, 1H), 6.18 (s, 1H), 5.29 (dq, *J* = 7.4, *J* = 6.9 1H), 1.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3,

136.5, 136.5, 129.1, 129.1, 129.1, 129.0, 128.9, 128.8, 82.7, 49.21, 22.3; IR (thin film): 3067, 3033, 2992, 1561, 1496, 1457, 1449, 1278, 1128, 744, 717, 623 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{32}H_{32}Cl_2N_2O_2Na$ $[2M + Na]^+$: 569.1733; found: 569.1728



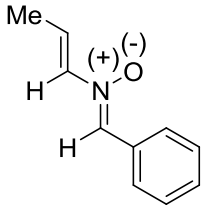
Entry 5 (*Z*)-*N*-(2-chloro-3-methylbutylidene)-1-phenylmethanamine oxide: Prepared by general procedure A (93%). White solid. R*f* = 0.25 (2:1 hexanes/EtOAc); mp = 68-69 °C; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.38 (s, 5H), 6.77 (d, *J* = 7.9, 1H), 5.04 (dd, *J* = 7.9, 5.8 Hz, 1H), 4.90 (s, 2H), 2.12 (pd, *J* = 6.7, 5.8 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 132.5, 129.5, 129.4, 129.3, 70.1, 59.6, 33.2, 19.0, 18.7; IR (thin film): 3422, 3068, 3032, 2981, 2960, 2869, 1578, 1588, 1120, 723, 697, 678 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{32}Cl_2N_2O_2Na$ $[2M + Na]^+$: 473.1739; found: 473.1741



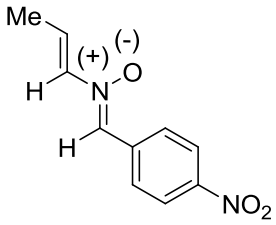
Entry 6 (Z)-*N*-(2-chloro-3-phenylpropylidene)-1-phenylmethanamine oxide: Prepared by general procedure A (89%). White solid. R*f* = 0.62 (1:1 hex/EtOAc); mp = 97-99°C; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.37 (d, *J* = 2.3 Hz, 3H), 7.29 – 7.22 (m, 5H), 7.16 – 7.10 (m, 2H), 6.73 (d, *J* = 7.4 Hz, 1H), 5.34 (td, *J* = 6.9, 7.4 Hz, 1H), 4.84 (s, 2H), 3.18 (d, *J* = 6.9 Hz, 2H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 137.1, 136.0, 132.2, 129.59, 129.51, 129.41, 129.26, 128.74, 127.44, 70.0, 53.5, 41.4; IR (thin film): 3071, 3026, 2937, 1575, 1496, 1455, 1418, 1354, 1285, 1233, 1194, 1142, 1108, 1078, 1017, 943, 914, 830, 760, 708, 696 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{17}ClNO$ $[M + H]^+$: 274.0994; found: 274.0998

Table 2.3

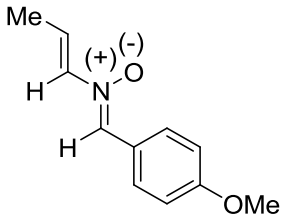


Entry 1 (*1E,NZ*)-*N*-benzylideneprop-1-en-1-amine oxide: Prepared by general procedure B (88%). White solid. R*f* = 0.35 (2:1 hexanes/EtOAc); mp = 109-111 °C decomp; ^1H NMR (300 MHz, Chloroform-d) δ 8.52 – 7.95 (m, 2H), 7.40 – 7.32 (m, 3H), 7.30 (s, 1H), 6.92 – 6.65 (m, 2H), 1.79 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.0, 130.82, 130.53, 129.39, 128.61, 124.7, 14.2; IR (thin film): 3108, 3070, 1593, 1151, 1347, 1312, 1167, 939, 921, 866 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{23}N_2O_2$ $[2M + H]^+$: 323.1755; found: 323.1765

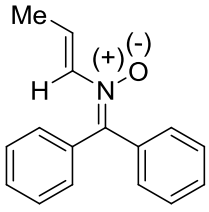


Entry 2 (*1E,NZ*)-*N*-(4-nitrobenzylidene)prop-1-en-1-amine oxide: Prepared by general procedure B (94%). Yellow solid. R*f* = 0.35 (2:1 hexanes/EtOAc); ^1H NMR (300 MHz,

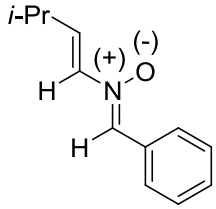
Chloroform-d) δ 8.44 (d, *J* = 9.1 Hz, 2H), 8.25 (d, *J* = 9.1 Hz, 2H), 7.46 (s, 1H), 7.12 – 6.67 (m, 2H), 1.91 (d, *J* = 5.7 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 137.23, 136.28, 132.69, 129.7, 127.3, 124.1, 14.5; IR (thin film): 3108, 3070, 2973, 2360, 1593, 1151, 1347, 1312, 1167, 939, 921, 866 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{20}N_4O_6Na$ [2M + Na]$^+$: 435.1276; found: 435.1284



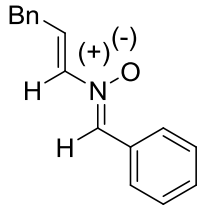
Entry 3 (*1E,NZ*)-*N*-(4-methoxybenzylidene)prop-1-en-1-amine oxide: Prepared according to the general procedure B (72%). White solid. R*f* = 0.41 (1:1 hexanes/EtOAc); mp = 103-106 °C; ^{1}H NMR (300 MHz, Chloroform-d) δ 8.29 (d, *J* = 9.1Hz, 2H), 7.25 (s, 1H), 6.94 (d, *J* = 9.1 Hz, 2H), 6.88 – 6.64 (m, 2H), 3.84 (s, 3H), 1.86 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 137.0, 134.8, 131.7, 123.90, 123.68, 114.3, 55.6, 14.4; IR (thin film): 3397, 3064, 3002, 2967, 2936, 2917, 2839, 1601, 1553, 1506, 1255, 1159, 1155, 1028, 932, 922, 847 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{26}N_2O_4Na$ [2M + Na]$^+$: 405.1785; found: 405.1792



Entry 4 (*E*)-*N*-(diphenylmethylene)prop-1-en-1-amine oxide: Prepared by general procedure B (86%). White solid. R*f* = 0.39 (1:1 hexanes/EtOAc); mp = 86-87°C; ^{1}H NMR (300 MHz, Chloroform-d) δ 8.02 – 7.85 (m, 2H), 7.57 – 7.38 (m, 3H), 7.35 – 7.25 (m, 5H), 6.90 (dq, *J* = 12.8, 7.2 Hz, 1H), 6.71 (d, *J* = 12.8, Hz, 1H), 1.73 (d, *J* = 7.2, Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 135.2, 134.9, 134.4, 131.01, 130.85, 130.08, 129.76, 129.09, 128.0, 126.0, 14.9; IR (thin film): 3443, 3091, 3056, 2966, 2939, 2914, 2875, 2851, 2360, 2342, 1492, 1444, 1437,1349,1263,1234, 954, 936 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{32}H_{30}N_2O_2Na$ $[2M + Na]^+$: 497.220; found: 497.2211

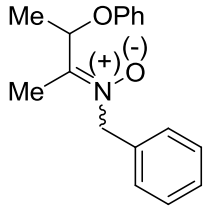


Entry 5 (*1E,NZ*)-*N*-benzylidene-3-methylbut-1-en-1-amine oxide: Prepared by general procedure B (86%). White solid. R*f* = 0.52 (2:1 hexanes:EtOAc); mp = 79-80 °C; ^{1}H NMR ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.34 – 8.24 (m, 2H), 7.46 – 7.38 (m, 3H), 7.36 (s, 1H), 6.84 (dd, *J* = 13.0, 6.9 Hz, 1H), 6.72 (d, *J* = 13.0 Hz, 1H), 2.53 (m, *J* = 6.9 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 6H).; - ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 135.5, 134.6, 131.00, 130.74, 129.54, 128.8, 28.63, 22.2; IR (thin film): 3426, 3056, 2961, 2928, 2869, 1574, 1550, 1456, 1165, 1139, 946, 755 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{30}N_2O_2Na$ $[2M + Na]^+$: 401.2200; found: 401.2210



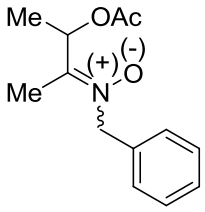
Entry 6 (*1E,NZ*)-*N*-benzylidene-3-phenylprop-1-en-1-amine oxide: Prepared by general procedure B (69%). Clear oil. R*f* = 0.54 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, Chloroform-d) δ 8.41 – 8.12 (m, 2H), 7.49 – 7.16 (m, 9H), 7.06 (dt, *J* = 12.9, 7.1 Hz, 1H), 6.69 (d, *J* = 12.9 Hz, 1H), 3.56 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.5, 135.2, 131.2, 130.6, 129.64, 129.02, 128.94, 128.85, 128.77, 126.9, 35.2; IR (thin film): 3061, 3027, 1719, 1602, 1574, 1547, 1495, 1446, 1431, 1323, 1306, 1155, 1076, 1029, 950, 921, 752, 691 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{16}NO$ $[M + H]^+$: 238.1227; found: 238.1227

Table 2.6 The compounds listed in Table 2.6 were formed as *E/Z* mixtures that partially equilibrate during chromatography. No attempt was made at separating the mixtures as both isomers yield the same product of the elimination step.

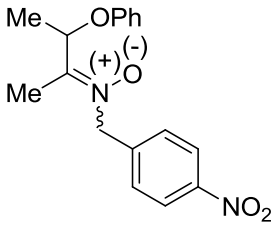


Entry 1 *N*-(3-phenoxybutan-2-ylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (91%). Clear oil. R*f* = 0.31 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, Chloroform-d) δ 7.41 – 7.27 (m, 5H), 7.22 – 7.13 (m, 2H), 6.99 – 6.85 (m, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.85 (q, *J* = 6.5 Hz, 1H), 5.02 (s, 2H), 1.91 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR

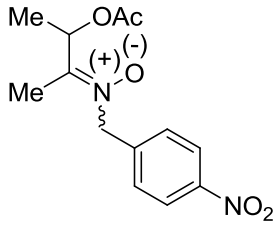
(75 MHz, $CDCl_3$) δ 157.3, 148.5, 133.3, 129.9, 129.1, 128.6, 128.0, 121.4, 114.8, 69.5, 65.2, 16.4, 12.7; IR (thin film): 3405, 3063, 3032, 2981, 2933, 2869, 1599, 1587, 1496, 1455, 1373, 1342, 1294, 1162, 1086, 1028, 755, 695 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{20}NO_2$ $[M + H]^+$: 270.1489; found: 270.1492



Entry 2 ***N*-(3-acetoxybutan-2-ylidene)-1-phenylmethanamine oxide**: Prepared by general procedure C (83%). Clear oil. R*f* = 0.52 (2% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, Chloroform-d) major: δ 7.44 – 7.26 (m, 5H), 5.82 (q, *J* = 6.7 Hz, 1H), 5.53 (d, *J* = 14.4 Hz, 1H), 5.10 (d, *J* = 14.4 Hz, 1H), 2.04 (s, *J* = 3H), 2.01 (s, 3H), 1.92 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H) minor: δ 7.44 – 7.26 (m, 5H), 6.07 (q, *J* = 6.6 Hz, 1H), , 5.05 (s, 2H), 2.05 (s, 3H), 1.92 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 134.4, 133.5, 129.2, 129.1, 128.7, 128.6, 127.9, 127.5, 68.9, 68.1, 65.6, 65.3, 21.1, 21.0, 17.9, 15.2, 13.2, 13.1; IR (thin film): 3397, 3031, 2983, 2933, 1740, 1667, 1583, 1497, 1455, 1371, 1309, 1234, 1169, 1080, 1029, 947, 733, 701 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{26}H_{35}N_2O_6$ $[2M + H]^+$: 471.2490; found: 471.2498

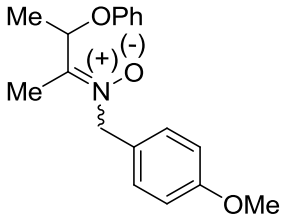


Entry 3 1-(4-nitrophenyl)-*N*-(3-phenoxybutan-2-ylidene)methanamine oxide: Prepared by general procedure C (90%). Yellow oil. R*f* = 0.29 (1:1 hexanes/EtOAc), ^{1}H NMR (300 MHz, Chloroform-*d*) Major: δ 8.18 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.29 – 7.08 (m, 2H), 6.99 – 6.85 (m, 2H), 6.78 (d, *J* = 8.8 Hz, 1H), 5.85 (q, *J* = 6.5 Hz, 1H), 5.30 – 5.04 (m, 2H), 1.93 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H). Minor: δ 8.13 (d, *J* = 8.9 Hz, 2H), 7.50 – 7.45 (d, *J* = 8.9 Hz, 2H), 7.28 – 7.06 (m, 2H), 7.00 – 6.87 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 1H), 5.33 – 5.01 (m, 3H), 2.15 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 13.9, 16.4, 19.4, 63.1, 64.0, 69.3, 73.2, 114.7, 116.5, 121.7, 122.9, 123.8, 124.1, 124.2, 124.3, 128.96, 129.00, 129.94, 130.01, 140.22, 140.46, 148.1, 149.5, 156.9, 157.1; IR (thin film): 3381, 3249, 3110, 3063, 3041, 2984, 2934, 2868, 1718, 1599, 1587, 1522, 1492, 1456, 1348, 1321, 1293, 1230, 1159, 1128, 1109, 1086, 1027, 956, 956, 937, 855, 809, 756, 734, 694 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{19}N_2O_4$ $[M + H]^+$: 315.1340; found: 315.1346

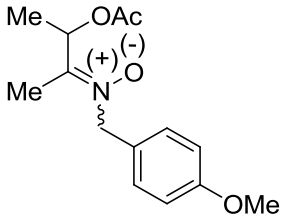


Entry 4 *N*-(3-acetoxybutan-2-ylidene)-1-(4-nitrophenyl)methanamine oxide: Prepared by general procedure C (78%). Yellow oil. R*f* = 0.67 (2% MeOH/DCM); ^{1}H NMR (300 MHz, Chloroform-*d*) Major: δ 8.21 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 0H), 6.02 (q, *J* = 6.7 Hz, 1H), 5.54 (d, *J* = 14.7 Hz, 1H), 5.20 (d, *J* = 14.7 Hz, 1H), 2.06 (s, 3H), 1.93 (s, 3H), 1.39 (d, *J* = 6.7 Hz, 3H).; Minor: δ 8.20 (d, 9.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 5.75 (q, *J* = 6.7 Hz, 1H), 5.12 (d, *J* = 4.5 Hz, 2H) 2.06 (s, 3H), 2.03 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz,

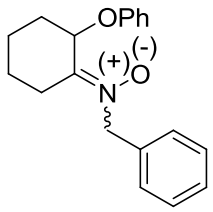
$CDCl_3$) δ 170.5, 170.28, 148.1, 147.6, 141.0, 140.5, 129.72, 129.09, 128.5, 124.39, 124.26, 123.8, 68.8, 68.0, 64.0, 63.8, 21.0, 20.9, 18.2, 15.1, 13.2, 13.2; IR (thin film): 3399, 3112, 3079, 2987, 2937, 2856, 1740, 1603, 1522, 1496, 1452, 1371, 1348, 1313, 1236, 1170, 1109, 1081, 1027, 647, 912, 859, 812, 771, 736, 704 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}N_2O_5$ $[M + H]^+$: 281.1132; found: 281.1135



Entry 5 1-(4-methoxyphenyl)-*N*-(3-phenoxybutan-2-ylidene)methanamine oxide: Prepared by general procedure C (82%). Clear oil. R*f* =0.31 (1:1 hexanes/EtOAc*;* ^{1}H NMR (300 MHz, Chloroform-d) δ 7.33 – 7.23 (m, 2H), 7.17 (dd, *J* = 8.8, 7.4 Hz, 2H), 6.86 (dd, *J* = 8.8, 6.8 Hz, 3H), 6.74 (d, *J* = 8.8Hz, 2H), 5.81 (q, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 2.9 Hz, 2H), 3.77 (s, 3H), 1.91 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 157.2, 1478.0, 129.9, 129.6, 125.4, 121.4, 114.7, 114.4, 69.5, 64.6, 55.5, 16.4, 12.6; IR (thin film): 3404, 3062, 3039, 2981, 2958, 2934, 2837, 1612, 1599, 1587, 1514, 1494, 1457, 1433, 1341, 1375, 1251, 1177, 1157, 1127, 1086, 1030, 937, 889, 821, 756, 694 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{36}H_{43}N_2O_6$ $[2M + H]^+$: 599.3116; found: 5993121.

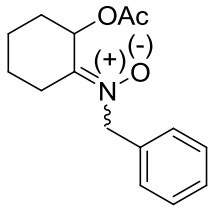


Entry 6 *N*-(3-acetoxybutan-2-ylidene)-1-(4-methoxyphenyl)methanamine oxide: Prepared by general procedure C (97%). Clear oil. R*f* =0.36 (3% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, Chloroform-*d*) Major: δ 7.29 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.05 (q, *J* = 6.6 Hz, 1H), 5.43 (d, *J* = 14.0 Hz, 1H), 5.00 (d, *J* = 14 Hz, 1H), 3.77 (s, 3H), 2.05 (s, 3H), 1.94 (s, 3H), 1.35 (d, *J* = 6.6 Hz, 3H); Minor: δ 7.35 (d, *J* = 9.0 Hz, 2H), 6.87 – 6.84 (d, *J* = 9.0 Hz,2H), 5.87 (q, *J* = 6.6 Hz, 1H), 4.95 (s, 2H), 3.77 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 159.8, 145.8, 129.5, 129.2, 126.5, 125.6, 114.5, 114.4, 68.9, 68.1, 64.9, 64.7, 55.5, 21.1, 21.0, 17.9, 15.2, 13.2, 13.0; IR (thin film): 2983, 2936, 2837, 1740, 1613, 1585, 1514, 1456, 1371, 1304, 1248, 1177, 1079, 1029, 821, 776 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{28}H_{39}N_2O_8$ $[2M + H]^+$: 531.2701; found: 531.2704

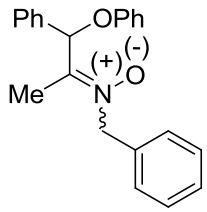


Entry 7 *N*-(2-phenoxycyclohexylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (93%). Clear oil. R*f* = 0.28 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, Chloroform-d) δ 7.39 – 7.16 (m, 6H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 2H), 5.92 (q, *J* = 2.0 Hz, 1H), 5.05 (d, *J* = 1.9 Hz, 2H), 2.68 – 1.49 (m, 6H), 1.35 – 1.09 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.9, 133.8, 129.9, 129.1, 128.6, 128.0, 121.3, 115.2, 68.1, 65.1, 32.1, 27.7, 27.5, 19.8; IR (thin film): 3386, 3061, 2940, 2863, 1726, 1596, 1495, 1455, 1360, 1294,

1231, 1152, 1126, 1072, 1028, 1000, 978, 755, 729, 696 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{38}H_{42}N_2O_4Na$ $[2M + Na]^+$: 613.3037; found: 613.3039

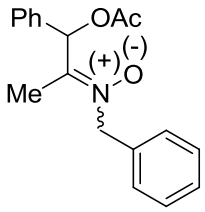


Entry 8 *N*-(2-acetoxycyclohexylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (73%). Clear oil. R*f* = 0.67 (3% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, Chloroform-d) Mixture of *E/Z* isomers: δ 7.45 – 7.29 (m, 10H), 6.47 (s, 1H), 5.89 (d, *J* = 1.4 Hz, 1H), 5.59 (d, *J* = 14.3 Hz, 1H), 5.18 – 4.97 (m, 3H), 3.64 – 3.45 (m, 2H), 2.71 (d, *J* = 15.2 Hz, 2H), 2.44 (td, *J* = 14.0, 4.9 Hz, 2H), 2.21 – 2.06 (m, 2H), 2.06 (s, 3H), 2.01 (s, 3H), 1.98 – 1.85 (m, 2H), 1.82 – 1.17 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 145.8, 134.6, 129.1, 128.5, 128.4, 127.8, 127.7, 68.0, 65.5, 31.5, 27.8, 24.6, 24.1, 21.1, 19.6; IR (thin film): 3031, 3063, 2940, 2864, 1735, 1570, 1497, 1455, 1437, 1370, 1288, 1232, 1182, 1140, 1075, 1012, 976, 933, 871, 733, 703 cm^{-1}.

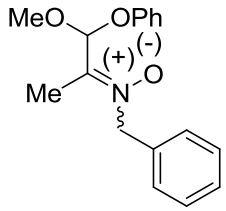


Entry 9 *N*-(1-phenoxy-1-phenylpropan-2-ylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (90%). Clear oil. R*f* = 0.52 (2% MeOH/$CHCl)_3$; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.68 – 7.61 (m, 2H), 7.42 – 7.3 (m, 7H), 7.26 – 7.18 (m, 3H), 7.00 (s, 1H), 6.98

– 6.88 (m, 3H), 5.03 (d, *J* = 5.1 Hz, 2H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.8, 146.7, 137.0, 133.2, 130.7, 129.94, 129.64, 129.55, 129.51, 129.46, 129.35, 129.24, 129.20, 129.05, 128.85, 128.81, 128.67, 128.63, 128.52, 128.46, 128.20, 128.09, 127.52, 127.08, 126.59, 126.04, 122.5, 121.7, 116.3, 115.8, 115.1, 73.3, 71.5, 65.2, 61.0, 14.9, 13.2; IR (thin film): 3062, 3033, 2958, 1715, 1598, 1587, 1495, 1454, 1384, 1294, 1231, 1150, 1079, 1031, 930, 754, 734, 700 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{22}NO_2$ $[M + H]^+$: 332.1645; found: 332.1648

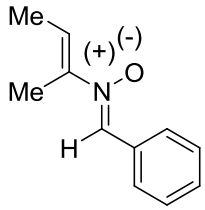


Entry 10 *N*-(1-acetoxy-1-phenylpropan-2-ylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (60%). Clear oil. R*f* = 0.37 (2% MeOH/DCM)*;* ^{1}H NMR (300 MHz, Chloroform-*d*) Mixture of *E/Z* isomers: δ 7.52 – 7.45 (m, 4H), 7.39 – 7.20 (m, 15H), 7.18 (s, 1H), 6.92 (s, 1H), 6.88 – 6.81 (m, 1H), 5.66 (d, *J* = 14.3 Hz, 1H), 5.17 (d, *J* = 14.3 Hz, 1H), 5.04 (s, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.7, 20.95, 21.1, 65.32, 65.84, 72.22, 72.29, 125.8, 126.7, 127.56, 128.27, 128.40, 128.59, 128.66, 128.69, 128.71, 128.76, 128.87, 128.94, 129.08, 129., 133.3, 134.4, 135.6, 136.1, 144.3, 169.6, 170.1; IR (thin film):3063, 3032, 2933, 1745, 1603, 1583, 1496, 1454, 1432, 1372, 1233, 1164, 1082, 1028, 1002, 978, 916, 844, 808, 754, 736, 700 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{20}NO_3$ $[M + H]^+$: 298.1438; found: 298.1441



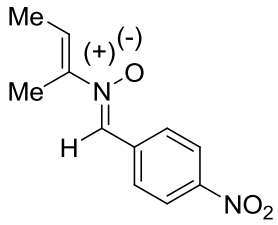
Entry 11 *N*-(1-methoxy-1-phenoxypropan-2-ylidene)-1-phenylmethanamine oxide: Prepared by general procedure C (65%). Clear oil. R*f* = .044 (2% MeOH/$CHCl)_3$; ^{1}H NMR (300 MHz, Chloroform-d) Mixture of *E/Z*: δ 7.45 – 7.30 (m, 8H), 7.30 – 7.14 (m, 6H), 7.10 – 6.89 (m, 3H), 6.81 (d, *J* = 8.7 Hz, 3H), 6.48 (s, 1H), 5.83 (s, 1H), 5.18 (s, 2H), 5.04 (s, 2H), 3.52 (s, 3H), 3.39 (s, 3H), 2.19 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 155.9, 144.4, 143.4, 133.5, 132.9, 1, 129.95, 129.90, 129.12, 129.06, 128.71, 128.69, 128.31, 128.21, 128.16, 123.51, 123.10, 122.4, 117.6, 117.1, 116.6, 102.7, 99.2, 97.3, 65.5, 65.1, 56.9, 54.6, 14.1, 13.1; IR (thin film): 3063, 3033, 3006, 2960, 2936, 2835, 1590, 1492, 1456, 1382, 1355, 1292, 1244, 1197, 1161, 1115, 1078, 1065, 1028, 1003, 969, 849, 756, 996 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M + H]^+$: 286.1438; found: 286.1437

Table 2.7

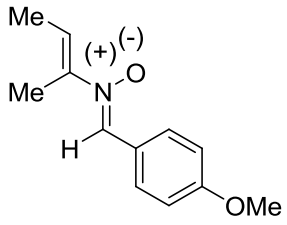


Entry 1 (*2E,NZ*)-*N*-benzylidenebut-2-en-2-amine oxide: Prepared by general procedure D (89%). White solid. R*f* = 0.33 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, Chloroform-d) δ 8.38 – 8.18 (m, 2H), 7.59 (s, 1H), 7.47 – 7.34 (m, 3H), 6.11 (q, *J* = 7.1 Hz, 1H), 2.13 (s, 3H), 1.76 (d, *J*

= 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 133.5, 131.0, 130.8, 129.2, 128.7, 120.1, 13.62, 13.1; IR (thin film): 3172, 3056, 3025, 2979, 2924, 2859, 1686, 1575, 1551, 1486, 1446, 1407, 1376, 1322, 1302, 1188, 1125, 1072, 1029, 972, 948, 932, 755, 692 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{26}N_2O_2Na$ $[2M + Na]^+$: 373.1887; found: 373.1896

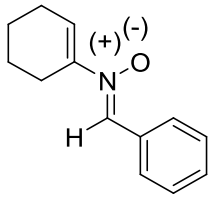


Entry 2 (*2E,NZ*)-*N*-(4-nitrobenzylidene)but-2-en-2-amine oxide: Prepared by general procedure D (77%). Yellow solid. R*f* = 0.32 (1:1 hexanes/EtOAc)*;* mp = 99-102°C; ^{1}H NMR (300 MHz, Chloroform-d) δ 8.42 (d, *J* = 9.0Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.73 (s, 1H), 6.18 (q, *J* = 7.1 Hz, 1H), 2.13 (s, 3H), 1.78 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.8, 136.6, 131.2, 129.4, 124.0, 121.4, 13.6, 13.1; IR (thin film): 3107, 1742, 1668, 1538, 1505, 1441, 1415, 1382, 1332, 1164, 1131, 1109, 1099, 1005, 952, 883, 866, 856, 807, 748, 692 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{13}N_2O_3$ $[M + H]^+$: 221.0921; found: 221.0927

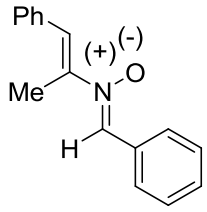


Entry 3 (*2E,NZ*)-*N*-(4-methoxybenzylidene)but-2-en-2-amine oxide: Prepared by general procedure D (71%). White solid. R*f* = 0.33 (2% MeOH/DCM); ^{1}H NMR (300 MHz,

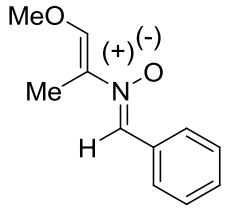
Chloroform-d) δ 8.28 (d, *J* = 9.0, Hz, 2H), 7.52 (s, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.11 (q, *J* = 7.1 1H), 3.84 (s, 3H), 2.12 (s, 3H), 1.76 (d, *J* = 7.1 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 133.2, 131.3, 124.0, 119.7, 114.1, 114.0, 55.6, 13.6, 13.1. IR (thin film):3173, 2933, 2838, 1602, 1575, 1507, 1458, 1442, 1419, 1401, 1322, 1305, 1255, 1170, 1113, 1072, 1029, 949, 842 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{31}N_2O_4$ $[2M + H]^+$: 411.2279; found: 411.2291



Entry 4 (*Z*)-*N*-benzylidenecyclohex-1-enamine oxide: Prepared by general procedure D (74%). Clear oil. R*f* = 0.62 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, Chloroform-d) δ 8.35 – 8.19 (m, 2H), 7.58 (s, 1H), 7.48 – 7.34 (m, 3H), 6.45 (m, 1H), 2.54 (m, 2H), 2.23 (m, 2H), 1.96 – 1.73 (m, 2H), 1.73 – 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 132.8, 131.0, 130.8, 129.4, 128.9, 128.7, 122.8, 25.5, 24.5, 22.6, 21.7; IR (thin film): 3417, 3052, 2936, 2860, 1550, 1445, 1408, 1170, 1147, 1079, 1056, 1035, 927, 884, 804, 754, 691 cm^{-1}.



Entry 5 (*1E,NZ*)-*N*-benzylidene-1-phenylprop-1-en-2-amine oxide:[1] Prepared by general procedure D (81%). The data is consistent with the published values.



Entry 6 (*1E,NZ*)-*N*-benzylidene-1-methoxyprop-1-en-2-amine oxide: Prepared by general procedure D (60%) Clear oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.40 – 8.18 (m, 2H), 7.44 (s, 1H), 7.43 – 7.35 (m, 3H), 3.78 (s, 3H), 2.12 (t, 3H); NMR (75 MHz, $CDCl_3$) δ 147.8, 131.8, 131.2, 130.6, 129.4, 128.7, 127.3, 61.3, 11.5; IR (thin film): 3065, 2960, 2930, 2854, 1670, 1594, 1558, 1491, 1474, 1446, 1403, 1376, 1320, 1259, 1242, 1191, 1144, 1089, 1028, 971, 887, 847, 803, 754, 691 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{14}NO_2$ $[M + H]^+$: 192.1019; found: 192.10260

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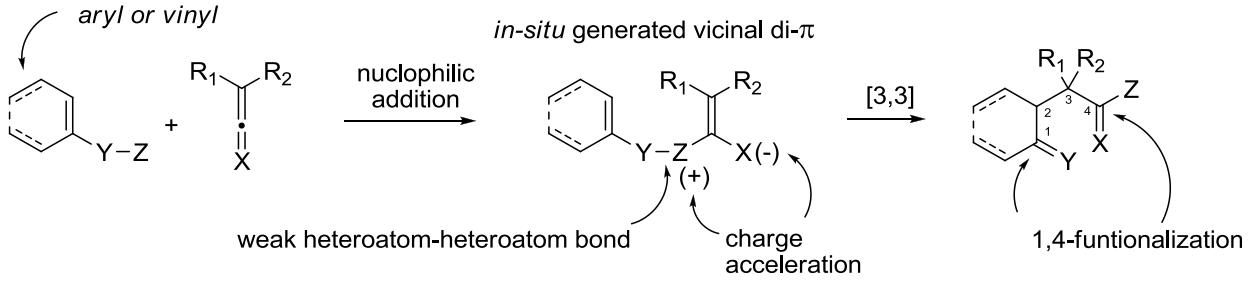
Chapter 3

The Reaction of *N*-Vinyl Nitrones and Ketenes

3.1 General Reaction Considerations

Having realized an efficient route to a variety of structurally and electronically diverse *N*-vinyl nitrones, we next directed our attention toward the development of methods for the synthesis of all-carbon quaternary centers. The general theme of this approach involves the attack of a heteroatom onto a cumulene or heterocumulene to generate an enolate or related structure wherein the enolate is part of a vicinal di-π-system capable of undergoing a charge accelerated [3,3]-sigmatropic rearrangement. The end result would be a small molecule that contains an all-carbon quaternary center with an adjacent tertiary or quaternary center with residual 1,4-oxygenation allowing for further manipulation (Figure 3.1).

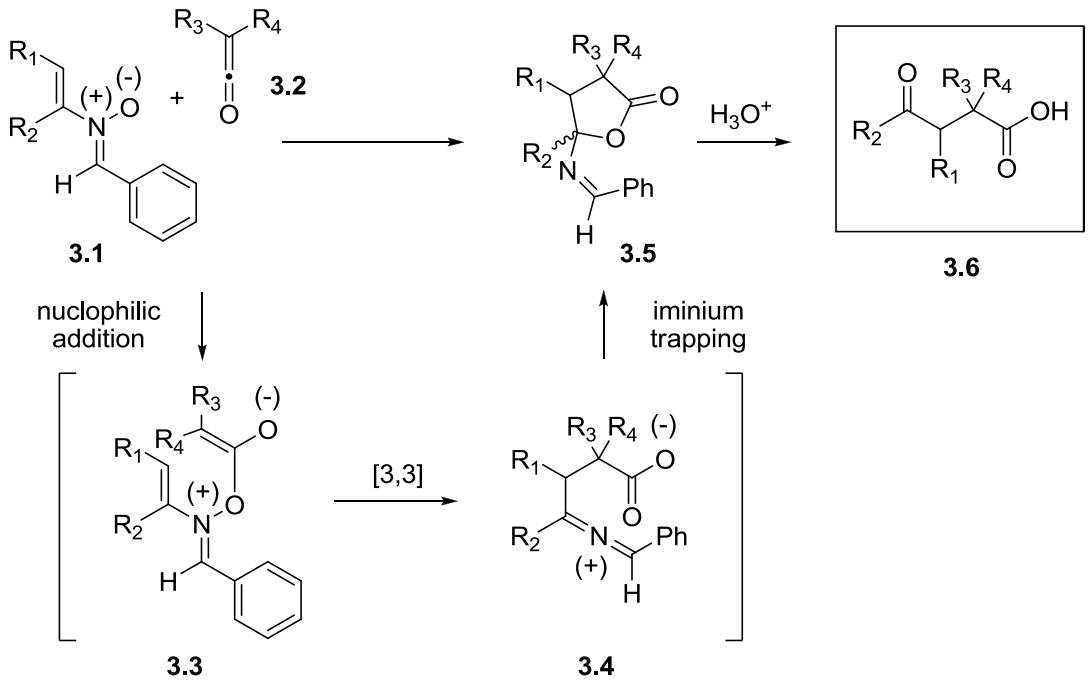
Figure 3.1 General Reaction Design



3.2 Initial Studies of the Reaction of *N*-Vinyl Nitrones and Ketenes

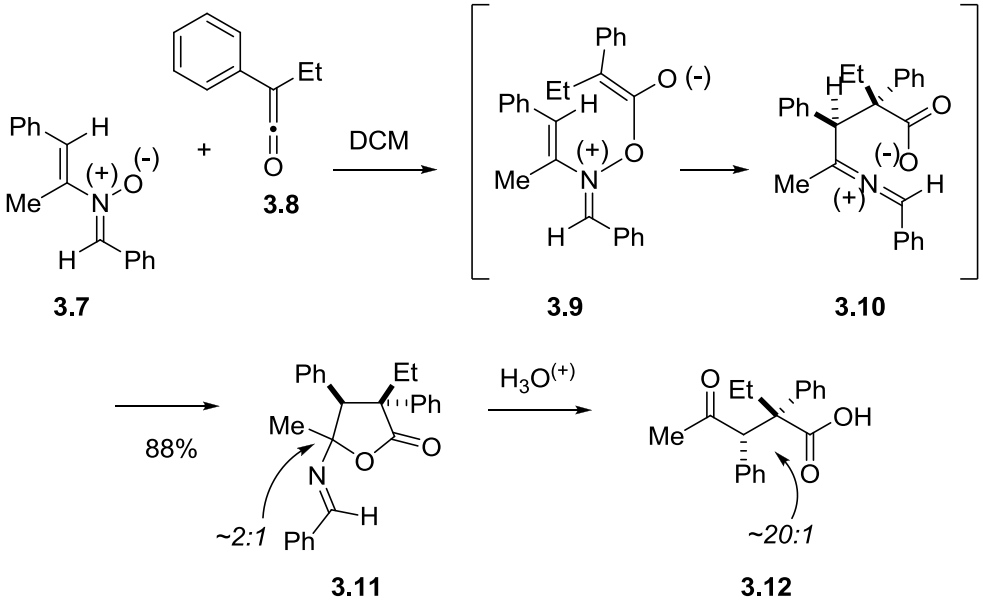
The first reaction we wished to study was that of an *N*-vinyl nitrone with a ketene (Scheme 3.1). We chose to use a disubstituted ketene as these compounds can be purified by distillation and are stable for extended periods at - 20 °C rendering their handling convenient. In addition, the products of reactions with disubstituted ketenes would contain a quaternary carbon center, a structural motif of interest to our research group. We envisioned a reaction wherein the attack of an *N*-vinyl nitrone, such as **3.1**, onto a disubstituted ketene **3.2** would result in the stereoselective formation of intermediate enolate **3.3** via nucleophilic addition of the nitrone oxygen onto the ketene with approach from the less hindered face of the ketene. Intermediate **3.3** is poised to undergo a charge-accelerated [3,3]-sigmatropic rearrangement facilitated by the cleavage of the weak N-O bond.[1] Cyclization of **3.4** to form lactone **3.5,** followed by hydrolysis, would then provide the desired product (**3.6)**.

Scheme 3.1 General Reaction for the Synthesis of All-Carbon Quaternary Centers



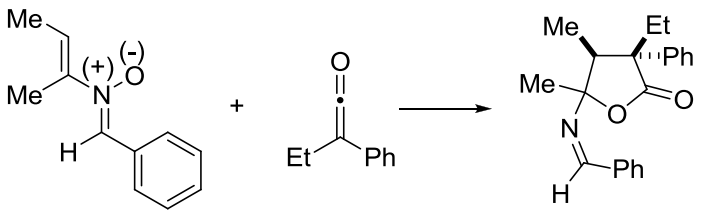
To explore the feasibility of this system we first studied the reaction of *N*-vinyl nitrone **3.7** with phenyl ethyl ketene (**3.8**, Scheme 3.2). The initial conditions consisted of adding a solution of freshly distilled ketene **3.8** to a solution of nitrone **3.7** in DCM at room temperature. Monitoring the reaction by TLC immediately following the addition of the ketene showed complete consumption of the starting nitrone and the presence of two new products of lower polarity. Upon work-up and purification by flash chromatography, lactone **3.11** was isolated in 88% yield as a 2:1 mixture of diastereomers at the aminal carbon, with greater than 20:1 stereoselectivity for the newly form C-C bond. This mixture, upon hydrolysis with THF/HCl(aq), gave **3.12** as a single isomer within the limits of detection of ^{1}H NMR.

Sheme 3.2 Initial Proof of Concept



A brief optimization of the reaction was then undertaken (Table 3.1). The reaction provided high yields in all solvents tested; acetonitrile and THF both provided a yield of 90 %, slightly outperforming DCM (85%), toluene (83%), and diethyl ether (81%) (compare entries 1 and 2 with entries 3, 4, and 5). The reaction proceeds rapidly at room temperature, reaching completion once all of the ketene has been added. No reaction takes place at -78 °C, while at -40 °C, the reaction occurs over the course of several hours. No catalyst or promoter is necessary; however, the lack of reactivity at low temperatures holds promise for the development of a catalytic asymmetric reaction without the complication of a non-catalyzed racemic background reaction.

Table 3.1 Optimization of the Conditions for the Ketene/*N*-Vinyl Nitrone Reaction



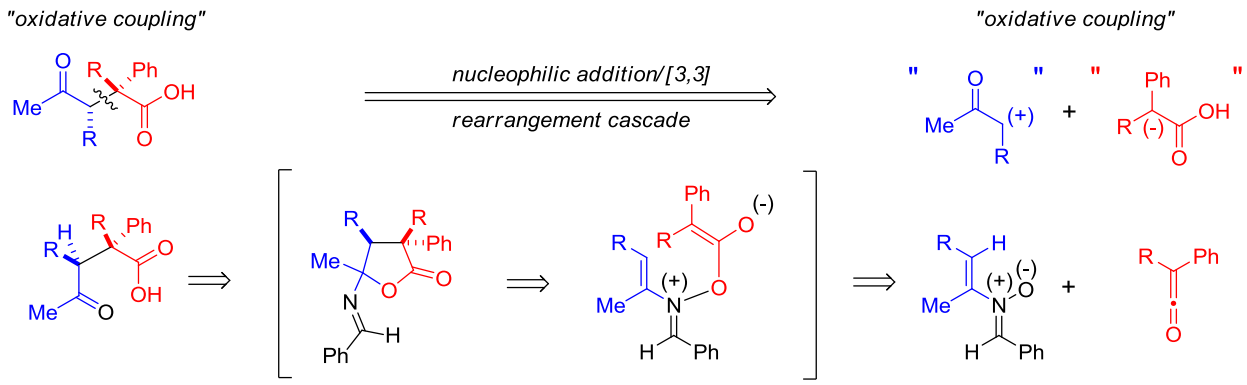
3.13 **3.11** **3.14**

[a]entry	solvent	temp °C	[b]yield, %
1	acetonitrile	23	90
2	THF	23	90
3	DCM	23	85
4	toluene	23	83
5	Et_2O	23	81
6	THF	-78	0
7	THF	-40	91[c]

[a] Conditions:A solution of the ketene (1.2 eq) in the indicated solvent was added to a solution of the nitrone at the stated temperature. [b] Isolated yields after flash chromatography. [c] Reaction time of 10 hrs.

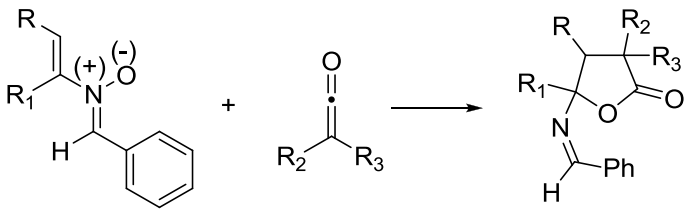
This reaction sequence can be viewed as the synthetic equivalent of an oxidative coupling of two enolates via an enolate equivalent and an oxyallyl cation equivalent wherein the ketene acts as an enolate equivalent precursor and the vinyl nitrone acts as a formal "oxyallyl cation" precursor (Figure 3.2)[2]. The overall transformation can be viewed as an umpolung bond construction as the α-carbon of one of the two carbonyls must act as an electrophile. This reaction also achieves the elusive goal of the diastereoselective formation of an all-carbon quaternary center adjacent to an all carbon tertiary center in an acyclic system. Viewing this complex reaction in these ways can simplify synthetic planning.

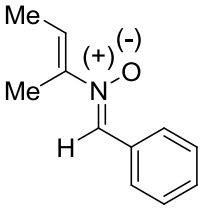
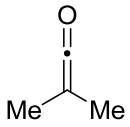
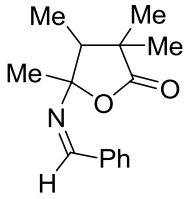
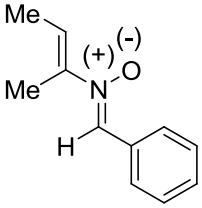
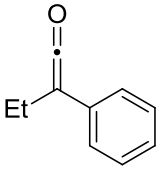
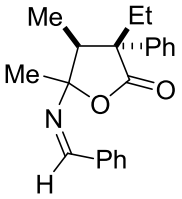
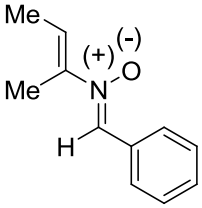
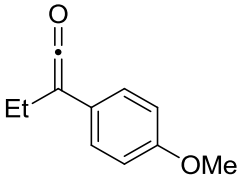
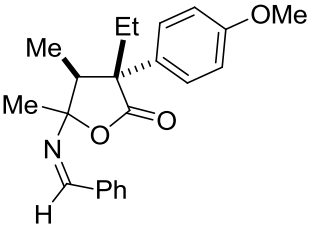
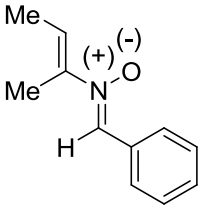
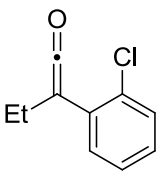
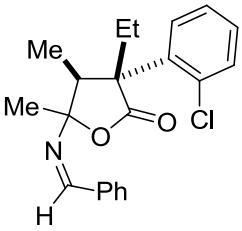
Figure 3.2 The Reaction is the Equivalent of an Overall Oxidative Coupling

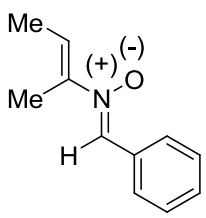
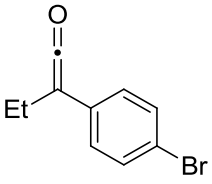
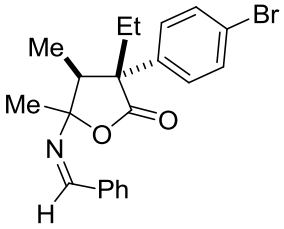
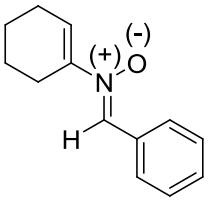
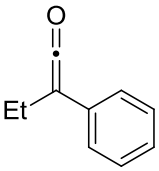
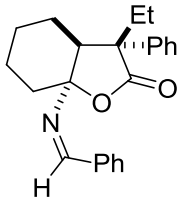
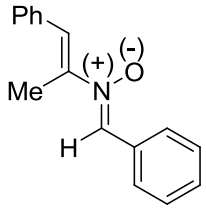
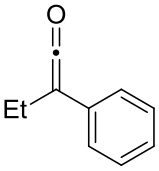
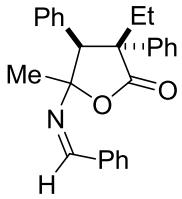


The high yield and facility with which the model reaction occurred prompted the study of the various nitrones depicted in Table 2. As noted above, the reaction provides high yields in all the solvents tested, with THF providing the highest yield. Therefore, we chose THF as the solvent for this study. In all cases, good yields and high diastereoselectivity were noted. The reaction is capable of creating dialkyl (entry 1), diarly (entry 2), and alky aryl (entries 3-8) all carbon quaternary centers. Ketenes that possess electron donating groups (entry 4), sterically demanding *o*- chloro substitution (entry 5), as well as bromo substitution (entry 6), were all good reaction partners. Cyclic *N*-vinyl nitrones can be used (entry 8) to form products that contain rings. Further, substrates that possess aryl substitution (entry 9) on the nitrone, provide diastereoselective formation of α-aryl ketones in high yields (after hydrolysis), a challenging feat with current technology.

Table 3.2 Scope of the *N*-vinyl Nitrone/Ketene Reaction



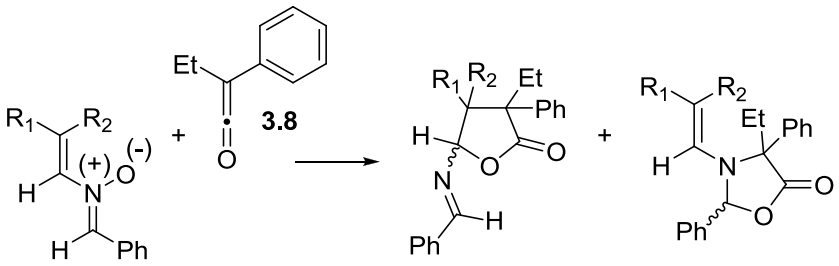
entry[a]	nitrone	ketene	product	yield,[b] %
1	 **3.13**	 **3.16**	 **3.20**	92
2	 **3.13**	 **3.8**	 **3.14**	85
3	 **3.13**	 **3.17**	 **3.21**	89
4	 **3.13**	 **3.18**	 **3.22**	73

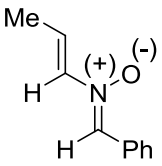
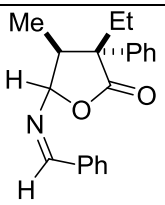
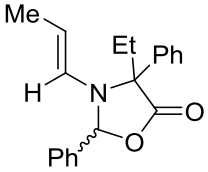
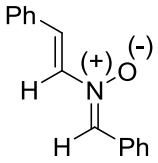
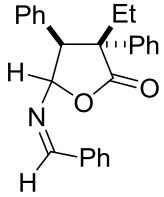
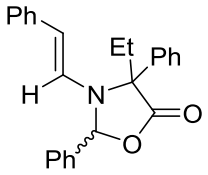
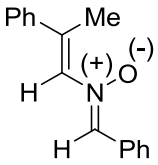
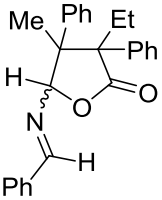
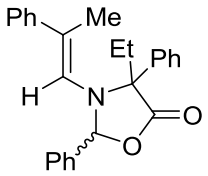
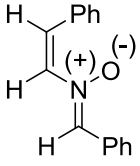
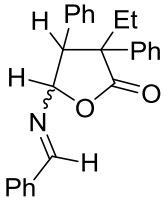
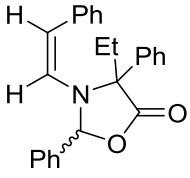
5				77
	3.13	**3.19**	**3.23**	
6				86
	3.15	**3.8**	**3.24**	
7				90
	3.7	**3.8**	**3.11**	

[a]Conditions: A solution of ketene (1.1 equiv, 1.0M in THF) was added to a solution of the nitrone (1 equiv, 0.2M in THF) at rt. [b] Isolated yields after column chromatography.

We next sought to extend the reaction to *N*-vinyl nitrones derived from aldehyde substrates (Table 3.3). However, when *N*-vinyl nitrone **3.25** was treated with phenyl ethyl ketene (**3.8**), a mixture of 4 compounds comprised of two sets of diastereomers was isolated. The desired lactone **3.26** was isolated in 54 % yield as well as compound **3.27** in a 32 % yield (entry 1). Nitrone **3.28** also provided a mixture of **3.29** in 31 % yield and in 23% yield (entry 2). The more highly substituted *N*-vinyl nitrone **3.31** provided none of the desired product, only undesired product **3.33** (entry 3). Interestingly, the *Z* isomer of nitrone **3.7**, provided exclusively product **3.35** with none of **3.34** being observed.

Table 3.3 Reaction of Aldehyde Derived *N*-Vinyl Nitrones with Ketenes

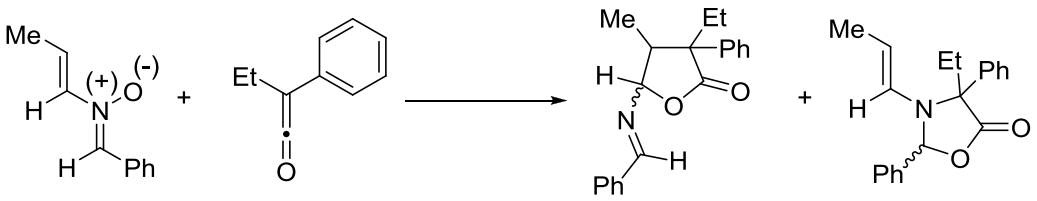


entry	nitrone		yield %		yield %
1			54		32
	3.25	**3.26**		**3.27**	
2			31		23
	3.28	**3.29**		**3.30**	
3			0		*n.d.*
	3.31	**3.32**		**3.33**	
4			0		*n.d.*
	***Z*-3.7**	**3.34**		**3.35**	

[a] Conditions: A solution of the ketene (1.2 eq) in THF was added to a solution of the nitrone in THF at room temperature. [b] Isolated yields after flash chromatography. *n.d.* = not determined.

These perplexing results prompted us to undertake a short survey of the reaction conditions in order to examine the extent of solvent and temperature effects upon the product distribution (Table 3.4). *N*-vinyl nitrone **3.25**, which provided a mixture under the initial reaction conditions, was chosen as a model substrate. The identity of the solvent or the temperature of the reaction did not significantly influence the product distribution.

Table 3.4 Solvent and Temperature Effect on Product Distribution



3.25 **3.8** **3.26** **3.27**

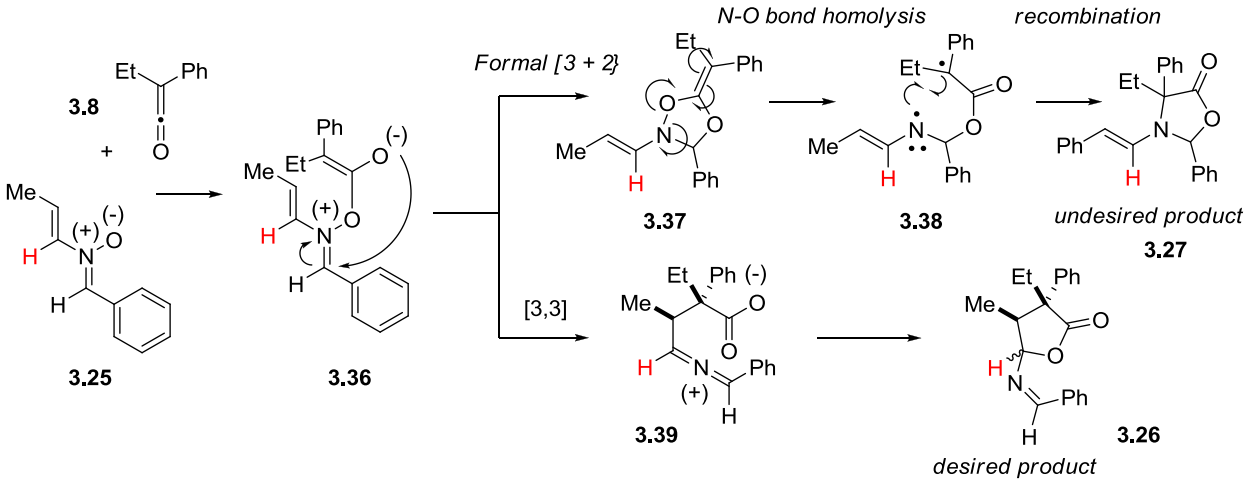
entry	solvent	temp °C	[b]ratio **3.26**:**3.27**
1	acetonitrile	23	0.9
2	THF	23	1.1
3	DCM	23	1
4	toluene	23	1.3
5	Et_2O	23	1
6	THF	-40	1.1

[a]Ratio determined by ^{1}H NMR of the crude reaction mixture.

To account for the formation of the undesired product, we formulated a working mechanistic hypothesis (Scheme 3.3). Our mechanism assumes initial nucleophilic attack of the nitrone oxygen onto the ketene to produce intermediate **3.36**. This intermediate can then

undergo the desired [3,3]-sigmatropic rearrangement to produce compound **3.39**. Alternatively, the oxygen atom of intermediate enolate **3.36** can attack the iminium carbon to provide the formal [3+2] dipolar cycloaddition product **3.37**. Homolysis of the weak N-O bond in **3.37** would generate a stabilized benzylic oxy-allyl di-radical **3.38**, which could undergo radical recombination to provide the undesired product **3.27**. N-O bond homolysis has been observed in similar heterocyclic systems and is often initiated by visible light. With this in mind, we conducted a series of experiments with the rigorous exclusion of light; however, this had no effect on the product distribution. We also note that homolysis can occur in the initially formed intermediate, **3.36**, however, this was deemed less likely as we felt that the charge acceleration of the [3,3] rearrangement would tend to favor this pathway over the homolysis. Finally, we also note that a concerted [3+2] cycloaddition is viable and could lead to intermediate **3.37** directly (*vide infra*).

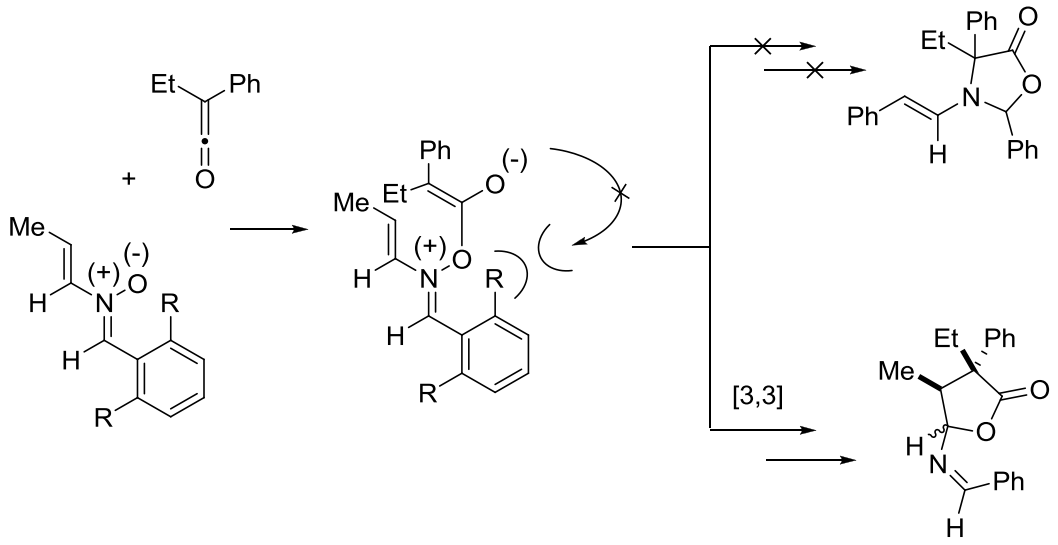
Scheme 3.3 Mechanism of Byproduct Formation



With the working hypothesis that *O*-alkylation of zwitterionic enolate **3.36** was leading to the undesired product, we reasoned that increasing the steric bulk in the proximity of the

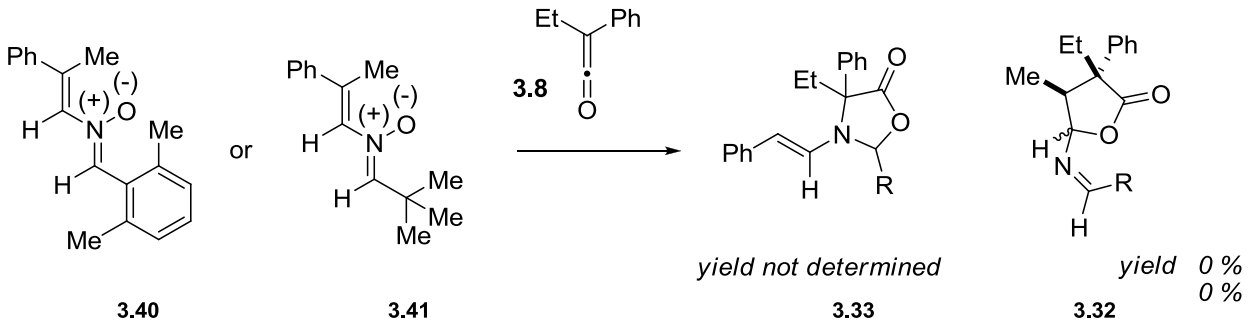
iminium ion might slow the *O*-alkylation of enolate **3.36** enough that the desired [3,3]-sigmatropic rearrangement would become the dominant pathway (Scheme 3.4). This could be achieved without compromising the generality of the reaction by increasing the steric bulk of the aryl portion of an *N*-vinyl nitrone such that attack on the carbon is slowed. We also note that this moiety is cleaved during the hydrolysis of the product lactam and as such, it is not incorporated into the product.

Scheme 3.4 Idea to Sterically Block the Iminium



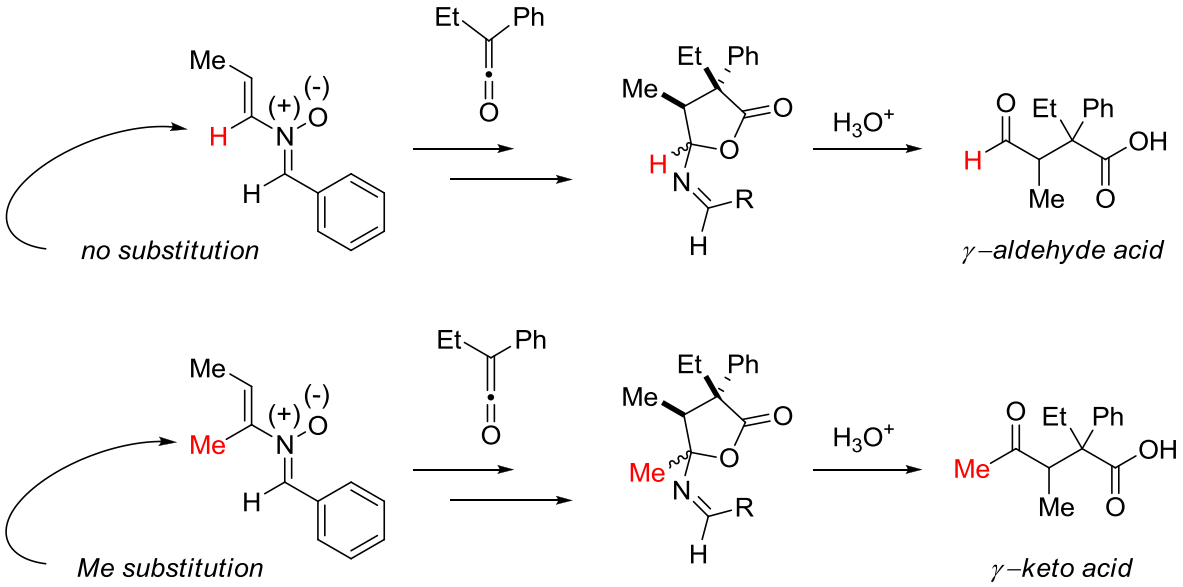
In order to explore this hypothesis, we synthesized *N*-vinyl nitrones **3.40** and 3**.41**, incorporating a 2,6-xylyl or *t*-butyl group, respectively, to provide the necessary bulk. We then studied the reaction of these compounds with phenyl ethyl ketene under our standard reaction condition (Scheme 3.5) and found that the increase in steric bulk failed to alter the course of the reaction and that both compounds provided undesired compound **3.33** presumably derived from the homolysis of the N-O bond from an intermediate similar to **3.37**.

Scheme 3.5 Sterically Hindered Nitrone Has No Effect On the Reaction Outcome



Reflecting on the data collected thus far led to the observation that the reaction of *N*-vinyl nitrones derived from aldehydes with ketenes typically provided mixtures that slightly favored the desired imino-lactone (**3.26** ~ 60 %, Table 3.4) over the undesired oxazolidinone (**3.27** ~ 40% Table 3.4), with the exception of *N*-vinyl nitrones derived from aldehydes that contain disubstitution on the vinyl moiety, which lead exclusively to the undesired oxazolidinone (**3.33,** Table 3.3 entry 3). This is in contrast to the reaction of *N*-vinyl nitrones derived from ketones, which provide high yields of the desired imino-lactone, without a trace of the undesired oxazolidinone. In terms of synthetic utility, the difference between utilizing a ketone-derived *N*-vinyl nitrone and an aldehyde-derived *N*-vinyl nitrone in this reaction resides in the functionality present in the product following hydrolysis of the imino-lactone: ketone-derived nitrones produce γ-keto acids whereas aldehyde-derived nitrones produce γ-aldehyde acids (Scheme 3.6). While the designed reaction is capable of the formation of a γ-aldehyde acid that contains a hindered all-carbon quaternary center with high stereoselectivity, the modest yields (~ 60 %) are a current limitation of this technology.

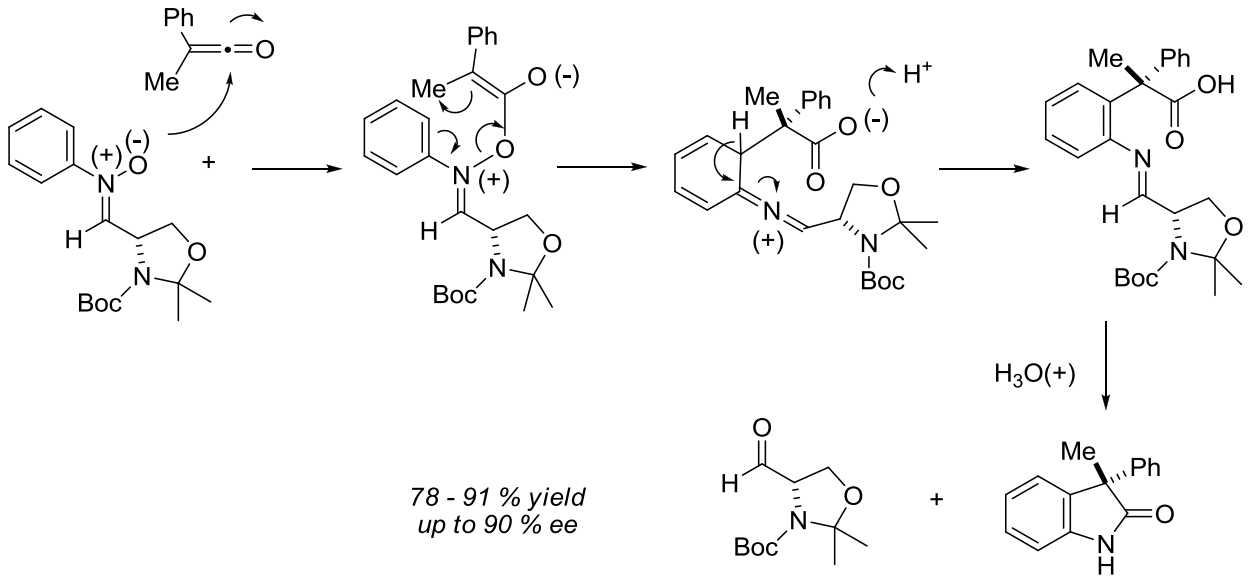
Scheme 3.6 The Different Products that Arise From the *N*-Vinyl Nitrone Substitution



3.3 Mechanistic Studies

Having demonstrated the limits and generality of this new reaction, we next turned our attention towards gaining a more detailed mechanistic understanding of this reaction. An asymmetric iteration of the Staudinger oxindole synthesis was described by Smith and co-workers in 2009, using a chiral auxiliary based approach (Scheme3.7).[3] Replacing the *C*-phenyl group in the Staudinger reaction with a Garner's aldehyde-derived chiral auxiliary, provides oxindole products in good *ee*'s (typically in the mid 80's) and high yields.

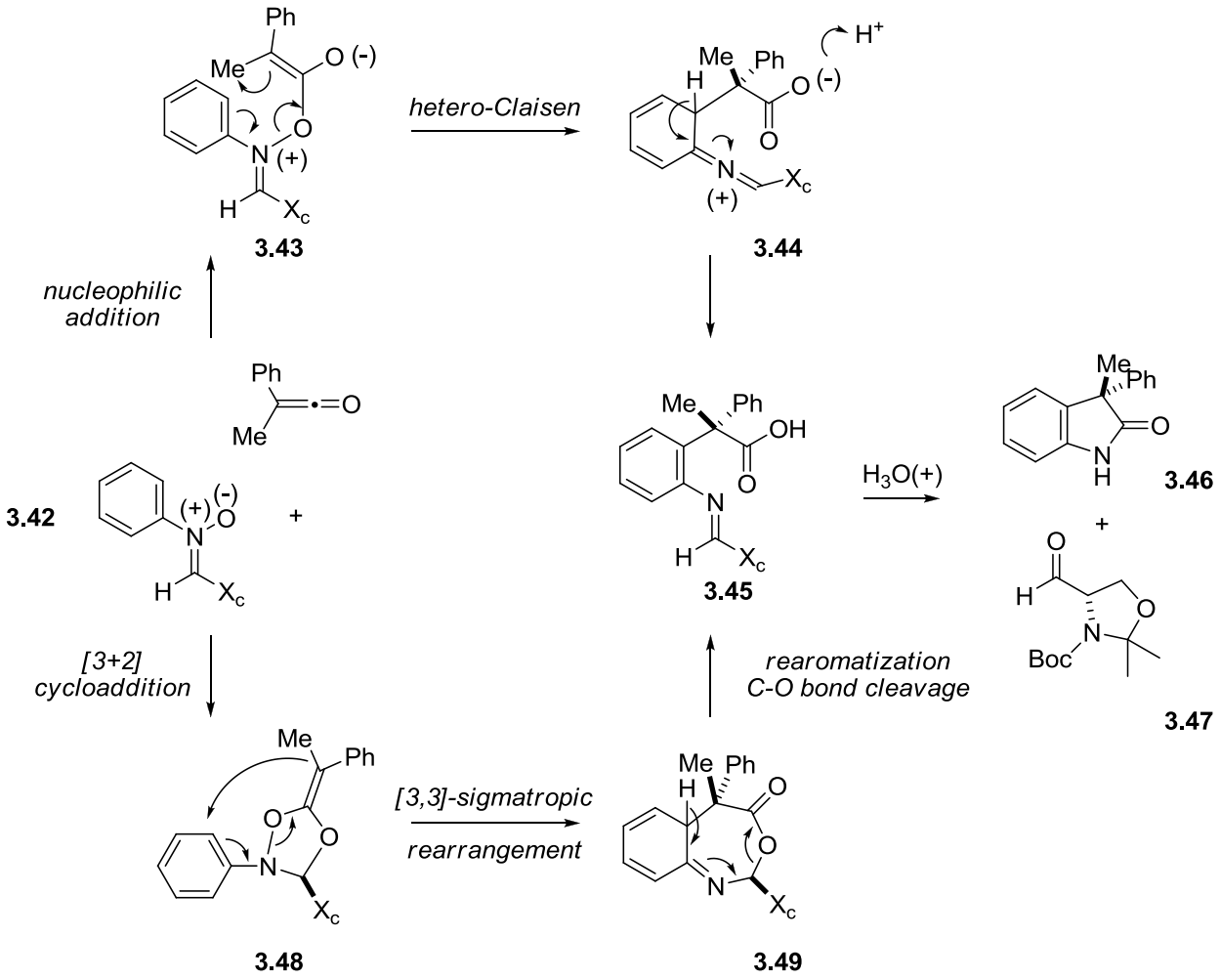
Scheme 3.7 Smith's Asymmetric Oxindole Synthesis and Initial Mechanistic Hypothesis



During the course of this work, Smith, in collaboration with Houk, reported mechanistic studies of this reaction by *ab initio* calculations at B3LYP/6-31G(d) level of theory in an effort to understand the origin of asymmetric induction, as well as the gross mechanistic features (Scheme 3.8).[4] Surprisingly, all attempts by Houk and coworkers to locate the transition structure for the sigmatropic rearrangement step in the "nucleophilic addition" pathway (**3.43** to **3.44**) failed. Instead, the lowest energy path to the product involved an initial 1,3-dipolar cycloaddition between the C=O of the ketene and the nitrone (the corresponding cycloaddition between the C=C of the ketene and the nitrone was calculated to be over 10 kcal/mol higher in energy) to provide1,4,2-dioxazolidine (**3.48**). This heterocycle bears an exocyclic alkylidene, and is capable of undergoing a [3,3]-sigmatropic rearrangement with the phenyl group of the nitrone to provide a 7-membered ring intermediate (**3.49**) that can undergo rearomatization with concomitant hemiaminal C-O bond cleavage and eventual hydrolysis to the observed product (**3.45**). This mechanistic insight is counterintuitive, and at first glance, the distance between the

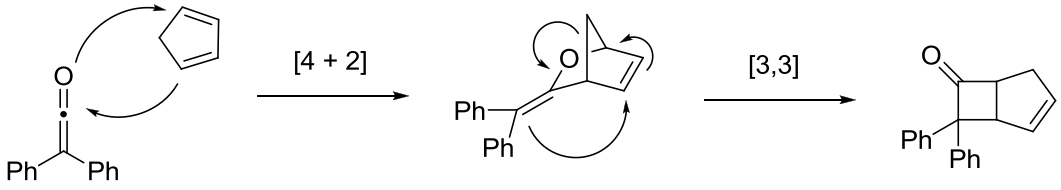
alkylidene and the phenyl group in the cycloaddition adduct (**3,48**) appears prohibitive for a subsequent [3,3]-sigmatropic rearrangement. Indeed, the calculated bond length at the forming C-C bond in the transition structure of the [3,3] rearrangement is very long at 3.47 Å. As such, there is little C-C bond-making in the transition state and N-O bond-breaking dominates. The intrinsically weak N-O bond, typically ~50 kcal/mol,[1] contributes to the remarkable facility of this reaction, which proceeds rapidly at -78 °C, indicating that both the 1,3-dipolar cycloaddition and [3,3]-sigmatropic rearrangement are facile.

Scheme 3.8 Houk and Smith's Pericyclic Cascade Mechanism



While not widely appreciated, a similar pathway is thought to be operative in another classical ketene reaction, the formal [2 + 2] cycloaddition of a ketene with a diene (Scheme 3.9).[5] Machiguchi has shown that the reaction of diphenyl ketene with cyclopentadiene proceeds by an initial [4 + 2] cycloaddition with the ketene carbonyl assuming the role of dienophile. The resulting alkylidiene **3.50** then undergoes a [3,3]-sigmatropic rearrangement to provide the observed formal [2 + 2] addition product. It should be noted, however, that the system contains additional complexities. Even though alkylidene **3.50** was fully characterized experimentally by low temperature NMR spectroscopy, Singleton has published compelling reports indicating the reaction produces both the [4 + 2] and [2 + 2] product simultaneously due to a bifurcation in the surface of the minimum energy pathway.[6]

Scheme 3.9 Ketene Olefin Formal [2 + 2] Mechanism

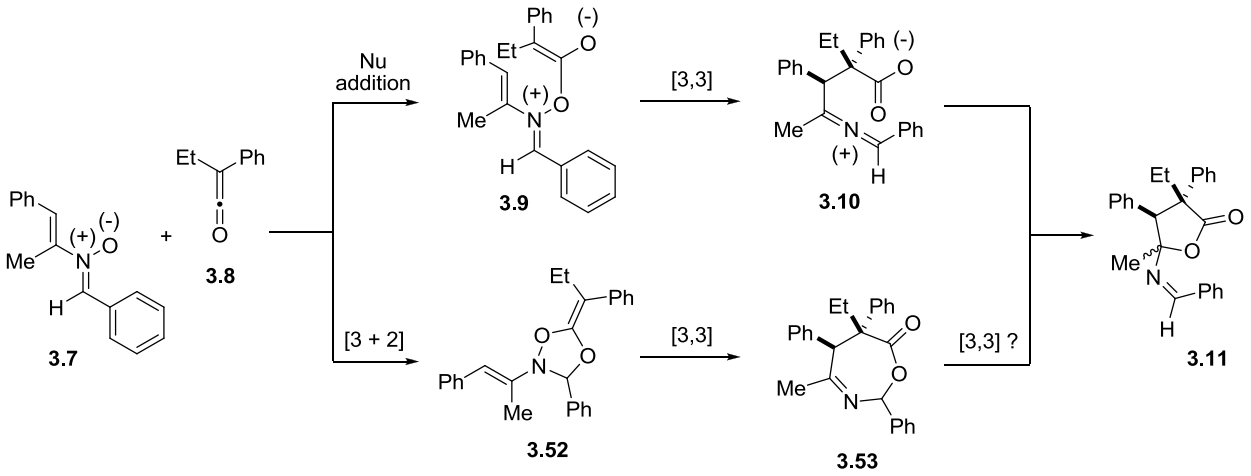


3.50 **3.51**

In analogy to the reaction of *N*-phenyl nitrones with ketenes, there are two plausible mechanisms for the reaction of *N*-vinyl nitrones and ketenes: a direct nucleophilic attack of the nitrone oxygen to the ketene to provide a zwitterionic enolate (**3.9**, Scheme 3.10), or a 1,3-dipolar cycloaddition between the carbonyl of the ketene and the *N*-phenyl nitrone (**3.7**). We had originally designed this reaction with the zwitterionic enolate mechanism in mind; however. given that the *N*-phenyl nitrone / ketene reaction was calculated by Houk and Smith to proceed by the 1,3- dipolar cycloaddition mechanism, our sense was that the corresponding reaction with

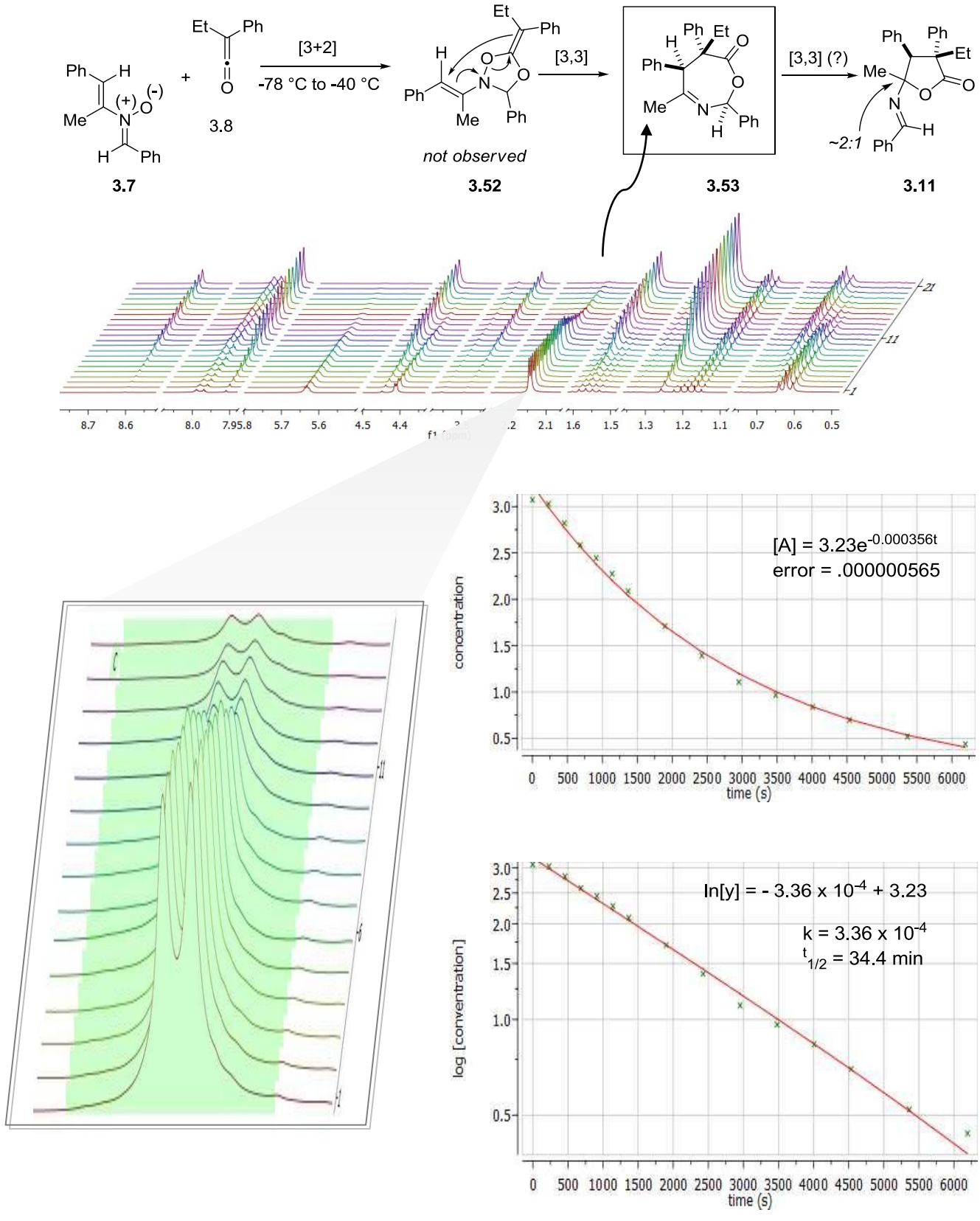
N-vinyl nitrones could similarly proceed by this mechanism. In order to elucidate the operative mechanism, we reasoned that intermediate **3.52** and/or **3.53**, might be observable spectroscopically at low temperature.

Scheme 3.10 Mechanistic Possibilities for the *N*-Vinyl Nitrone/Ketene Reaction



Towards this end, we studied the reaction of nitrone **3.7** and ketene **3.8** by ^{1}H NMR in CD_2Cl_2 at -80°C (Figure 3.3). No reaction was observed at this temperature, so the solution was warmed to -50 °C wherein an intermediate (**3.53**) was slowly observed to grow in. The sample was further warmed to -35 °C, whereupon the reaction had cleanly proceeded almost entirely to intermediate **3.53**. Holding the probe at this temperature allowed us to observe the transformation of **3.53,** to the product (**3.11**), which occurred in a first order process with a half-life of 34.4 minutes; no other intermediates were observed.

Figure 3.3 Kinetics of Product Formation



This protocol was repeated, but after intermediate **3.53** was formed at -30 °C, the probe was cooled back down to -50 °C where **3.53** was stable for hours which allowed characterization by ^{1}H and ^{13}C NMR, COSY, and HMBC in order to elucidate its structure. Figure 3.4 shows the 400 MHz ^{1}H NMR of compound **3.53,** with normal (Lorentz-transformed) processing on the top; on the bottom the resolution has been enhanced with a TRAF (Transform of Reverse Added FIDs")[7] function. In the enhanced spectra the protons attached to C-2 and C-8 clearly show up as doublets and the proton attached to C-6 is a pentet.

Figure 3.4 Resolution Enhanced ^{1}H NMR of Intermediate Oxazapinone

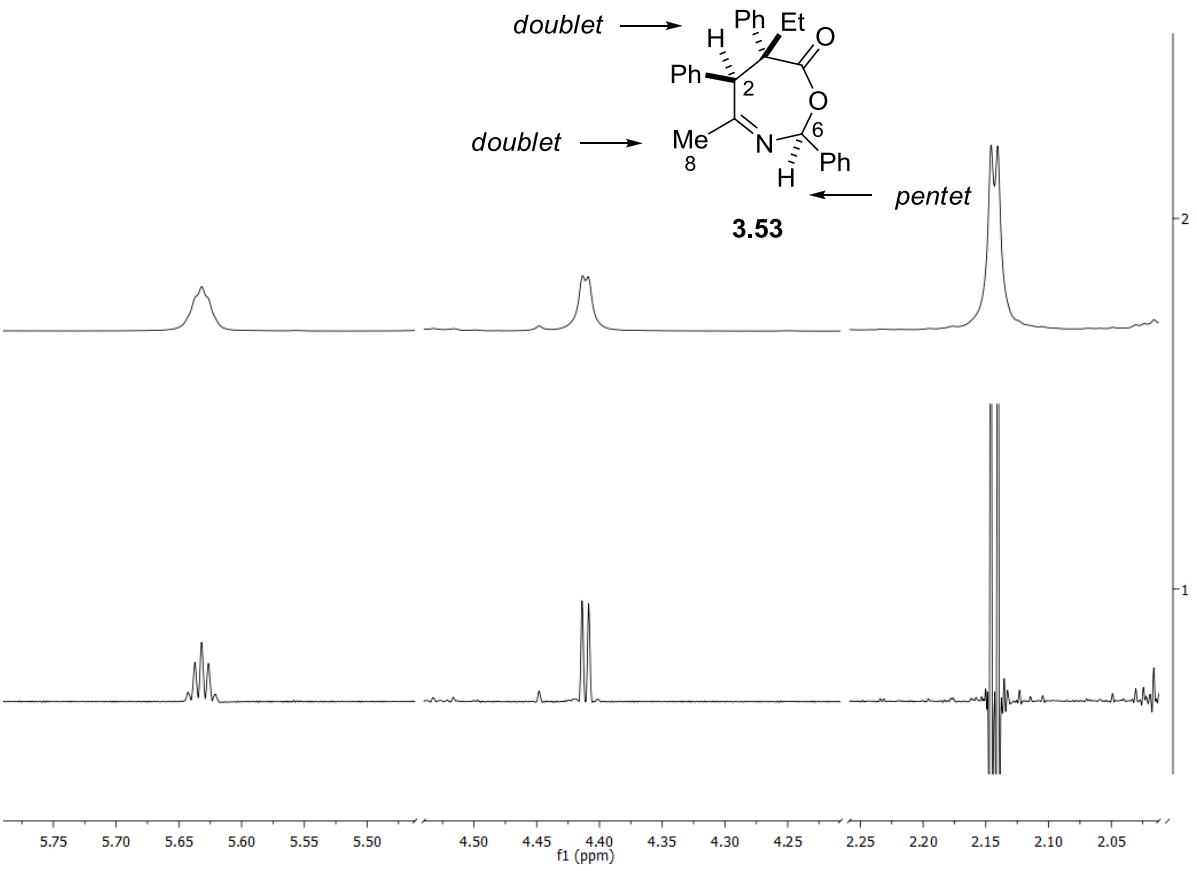
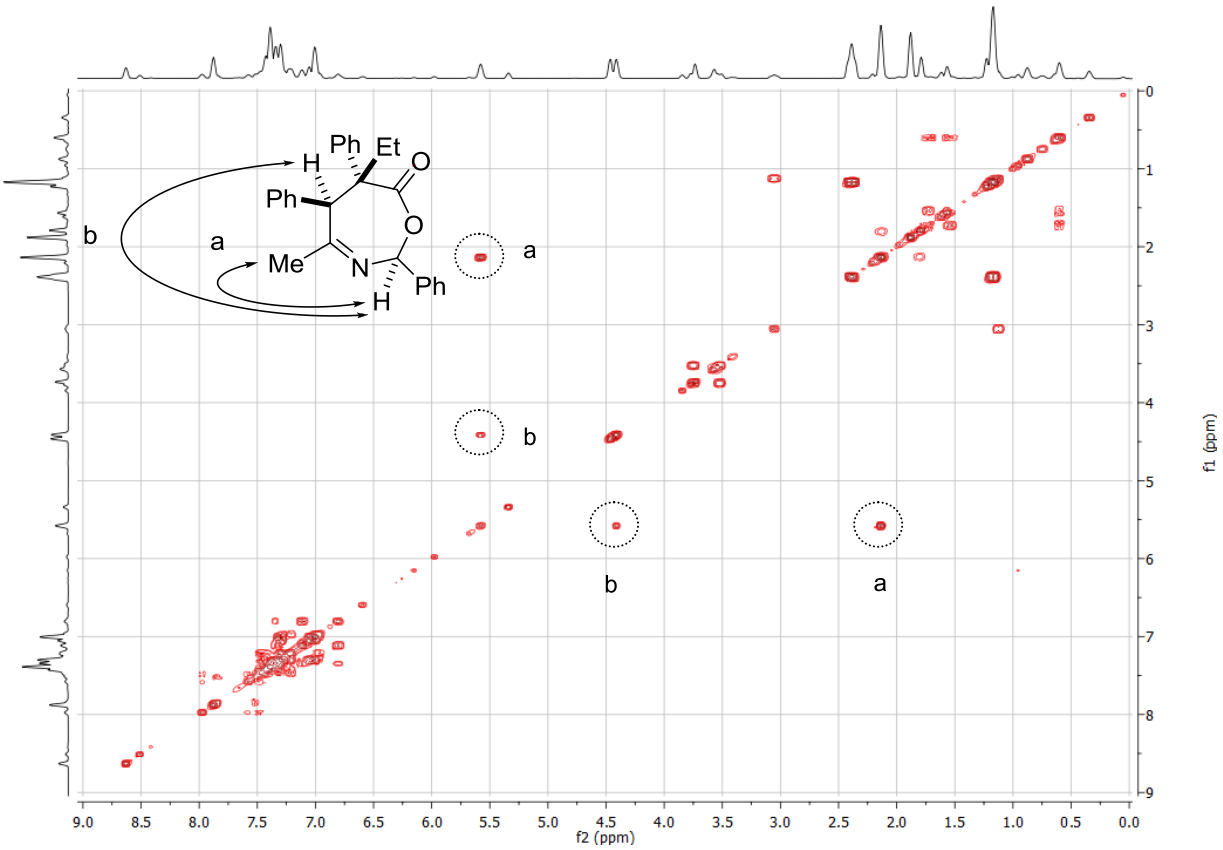


Figure 3.5 displays the long-range COSY spectrum of the same sample.[8] This data clearly depicts the long-range coupling between the protons attached to C-2 and C-6, in addition to C-2 and C-8, which allowed us to unambiguously assign the structure to compound **3,53 (**Figure 3.5**).** Such long-range coupling has been observed in related heterocycles and is not consistent with any other potential structure for this intermediate.[9] .

Figure 3.5 Long Range Coupling in the Intermediate Oxazapinone

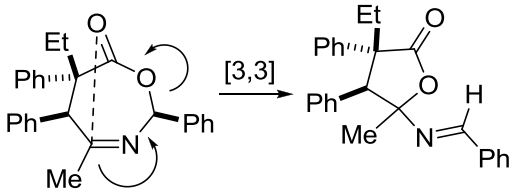


This provides strong experimental evidence in support of the proposed [3 + 2] dipolar cycloaddition followed by a [3,3]-sigmatropic rearrangement mechanism for this process. Compound **3.53** was the only reactive intermediate observed by NMR. No evidence for the

initial cycloadduct, **3.52**, was obtained; even when both starting materials **3.7** and **3.8** were still visible in the spectrum, and no other intermediates were observed. This indicates that under these conditions this substrate combination undergoes the [3,3]-sigmatropic rearrangement faster than the [3+2] cycloaddition. We note that this is the first experimental evidence for the mechanism of this process, and that it indirectly supports the Houk and Smith mechanism for the corresponding reaction on *N*-phenyl nitrones.

In the case of the *N*-aryl nitrone/ketene reaction, the 7-membered ring intermediate rearomatization with concomitant C-O bond cleavage. This is not possible for the 7-membered ring intermediate in *N*-vinyl nitrone/ketene rearrangement as there is no aromatic group to undergo rearomatization. We hypothesize that the 5-member ring lactone product arises via an additional [3,3]-sigmatropic rearrangement of 7-membered ring intermediate **3.53** driven by the formation of the energetically favorable 5-member ring at the expense of the 7-member ring (Scheme 3.11). Studies are underway to elucidate this possibility (*vide infra*).

Scheme 3.11 Possible [3,3]-Sigmatropic Rearrangement as the Last Step

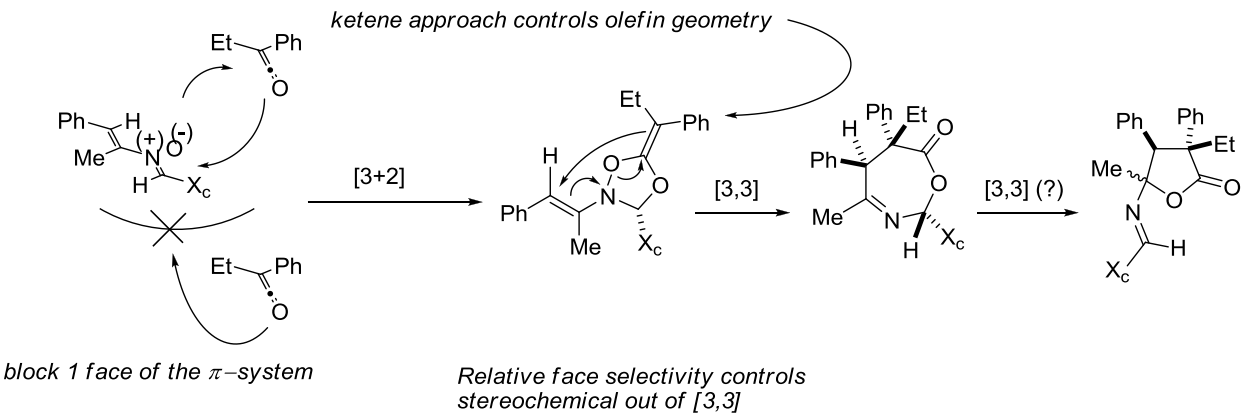


3.4 The Development of an Asymmetric *N*-Vinyl Nitrone/Ketene Pericyclic Reaction Cascade

With an enhanced mechanistic understanding of the *N*-vinyl nitrone/ketene pericyclic cascade, we sought to exploit this information in the development of an asymmetric reaction to

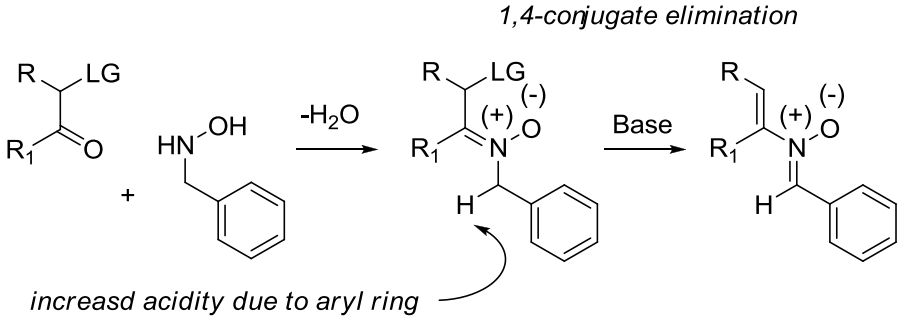
control the absolute stereochemistry of the product. In order to accomplish this goal, we wished to first study a chiral auxiliary-based approach wherein we attached a chiral group to the *N*-vinyl nitrone component of the reaction. This renders the faces of the nitrone diastereotopic, the role of the chiral auxiliary then being to provide high levels of diastereotopic face selectivity in the [3+2] cycloaddition reaction. In addition, the cycloaddition has to occur with high levels of diastereotopic face selectivity in the ketene component with a preference to approach the ketene from the less hindered substituent to provide the resulting exocyclic alkene with high levels of stereoselectivity. Finally, the reaction must proceed with high levels of relative face selectivity in the [3,3] sigmatropic rearrangement step. Results to date with achiral *N*-vinyl nitrones indicated that the products could be formed with high levels of stereocontrol between the two stereocenters in the product. This suggests that the approach of the nitrone to the ketene occurs selectively from the less hindered face and that the [3,3] sigmatropic rearrangement step proceeds with high levels of relative face selectivity. As such, the remaining challenge is control of the diastereotopic face selectivity in cycloaddition reactions with a chiral *N*-vinyl nitrone. We noted in the related *N*-aryl nitrone/ketene cascade, Smith has shown that diastereotopic face selectivity in the nitrone component of the [3 + 2] dipolar cycloaddition is feasible with good levels of asymmetric induction emanating from a chiral auxiliary derived from Garner's aldehyde on the nitrone. This coupled with the fact that the nitrone appendage is readily hydrolyzed, which would facilitate recycling of the auxiliary, led us to pursue a similar strategy.

Scheme 3.12 Factors that Control the Stereochemistry In the Pericyclic Cascade



A Garner's aldehyde-derived nitrone is not compatible with our synthesis of *N*-vinyl nitrones which requires increased acidity at the α-carbon, usually in the form of a simple aryl ring, to facilitate the deprotonation that initiates the 1,4-conjugate elimination (Scheme 3.13). This necessitated the development of an alternative chiral auxiliary bearing an aryl group.

Scheme 3.13 Increased Acidity Needed for the 1,4-Elimination

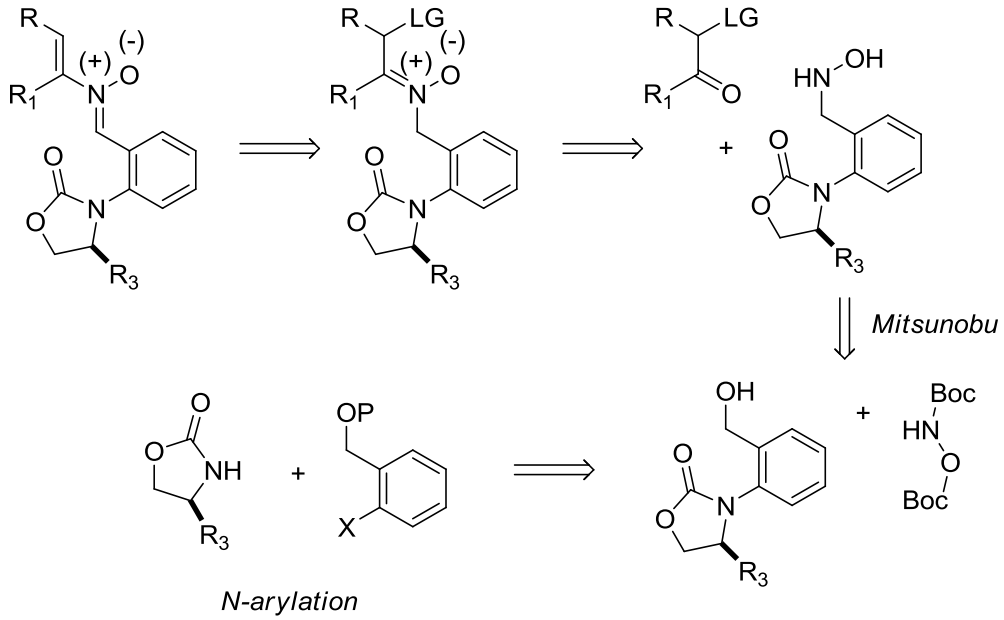


Oxazolidinone chiral auxiliaries, initially developed by Evans, are a privileged class of chiral auxiliaries that have been effectively utilized for asymmetric induction in a number of systems.[10] Due to their proven utility, commercial availability, as well as ease of access from the corresponding amino acid, we focused on this class of compounds as the source of chiral

information in the design of a suitable chiral auxiliary. We reasoned that a chiral oxazolidinone substituent within the aromatic ring of an *N*-vinyl nitrone would enable the [3 + 2] dipolar cycloaddition to proceed with the necessary π-facial selectivity. We therefore required a method for the synthesis of an *N*-vinyl nitrone with the appropriately positioned oxazolidinone auxiliary.

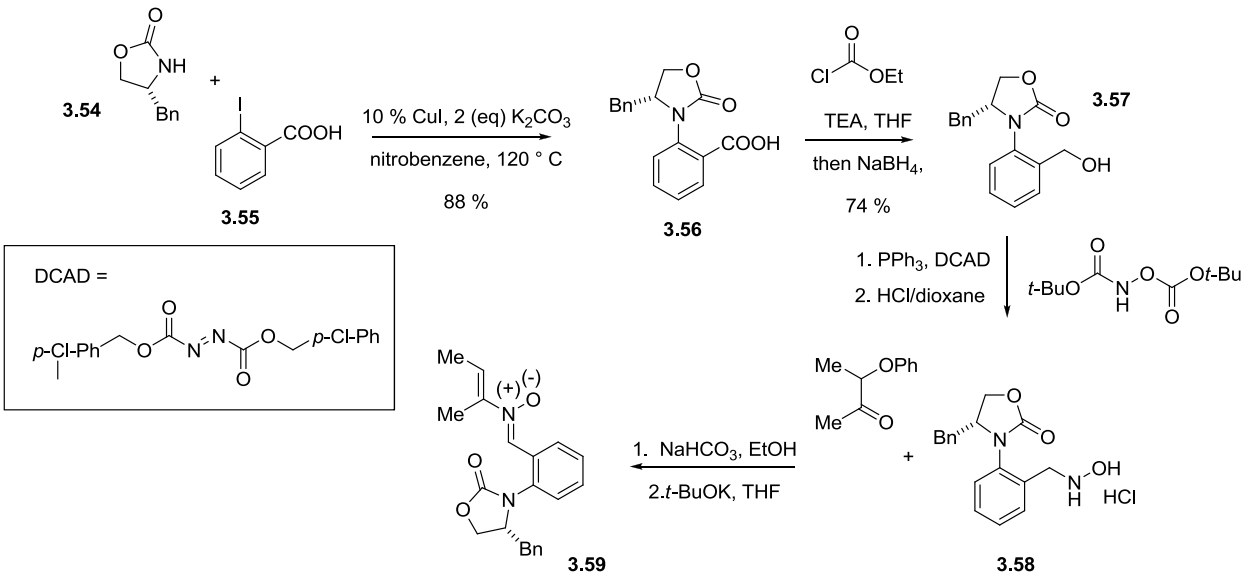
Our retrosynthetic plan is outlined in Scheme 3.14 We anticipated that an *N*-aryl coupling of an oxazolidinone and *o*-iodobenzylic alcohol (or equivalent) via a copper catalyzed or promoted Goldberg reaction could install the oxazolidinone onto the aromatic ring.[11] A Mitsunobu reaction utilizing *N*,*O*-bis-Boc protected hydroxylamine as the nucleophile could then displace the benzylic alcohol and provide the required substituted benzylhydroxylamine.[12] Deprotection under acidic conditions would result in an *ortho*-substituted benzylhydroxylamine salt which could be subjected to our two step *N*-vinyl nitrone synthesis.

Scheme 3.14 Retrosynthesis for the Chiral Auxiliary



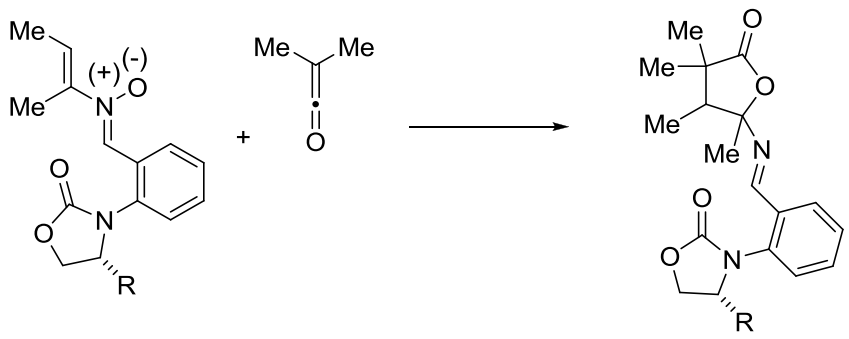
A review of the literature revealed several methods for the *N*-arylation of oxazolidinones; however, all of the reported methods either lack substrates that contain ortho substitution, or report low yields for this type of substitution.[13] We, therefore, set out to discover conditions that would suit our needs, initially focusing on the modern palladium and copper catalyzed variants as well as an S_NAr approach.[14] After extensive experimentation, we discovered the key to a successful transformation was the use of *o*-iodobenzoic acid as the coupling partner. Having discovered conditions for the successful *N*-arylation, we then synthesized the oxazolidinone substituted *N*-vinyl nitrone **3.59** (Scheme 3.15). Optimal conditions for the *N*-arylation consist of heating the oxazolidinone and *o*-iodobenzoic acid in the presences of catalytic CuI, 2 equivalents of K_2CO_3 and nitrobenzene as the solvent, without the need for any ligand.[15] Mild reduction of carboxylic acid **3.56** was accomplished by formation of the mixed anhydride, followed by filtration of the reaction into a flask containing an aqueous suspension of $NaBH_4$.[16] Removal of the triethylamine•HCl salts by filtration could be omitted, but lower yields and the need for a large excess of $NaBH_4$ render this process less attractive. The Mitsunobu reaction of the benzylic alcohol with bis-BOC-protected hydroxylamine proceeded in high yields when DEAD and DIAD where utilized; however, the separation of the generated hydrazine byproducts proved challenging. The purification of the protected hydroxylamine product could be greatly simplified by using Liptshultz's DCAD reagent, wherein the generated hydrazine is insoluble in the reaction media and precipitates.[17] Deprotection effected by the action of a dioxane solution of HCl provided the protected hydroxylamine, which was then utilized in our *N*-vinyl nitrone synthesis to provide compound **3.59**.

Scheme 3.15 Synthesis of Vinyl Nitrone **3.59**



We then subjected the substituted *N*-vinyl nitrones to reaction with ketene. Dimethyl ketene was chosen as the coupling partner to simplify interpretation of the resulting spectra. The use of phenyl substituted *N*-vinyl nitrone **3.60** resulted in a diastereomeric ratio of 4:1. This initial result was very promising as a validation that our designed chiral auxiliary is capable of high levels of diastereotopic face electivity in the nitrone π-faces in the [3 + 2]-dipolar cycloaddition. The use of benzyl substituted *N*-vinyl nitrone **3.61** provided an increase of the diastereomeric ratio to 12:1. When the *t*-butyl derived nitrone **3.62** was subjected to the reaction conditions, the resulting crude ^{1}H NMR spectra contained multiple rotamers due to the presence of *tert*-butyl group, making accurate analysis impossible. Additionally, we noticed that the imine contained in the *tert*-butyl derived product lactone, was undergoing hydrolysis after a short period in $CDCl_3$. This rapid hydrolysis calls into question the reliability of the diastereomeric ratios, leading us to consider another method of analysis.

Table 3.4 Asymmetric Induction

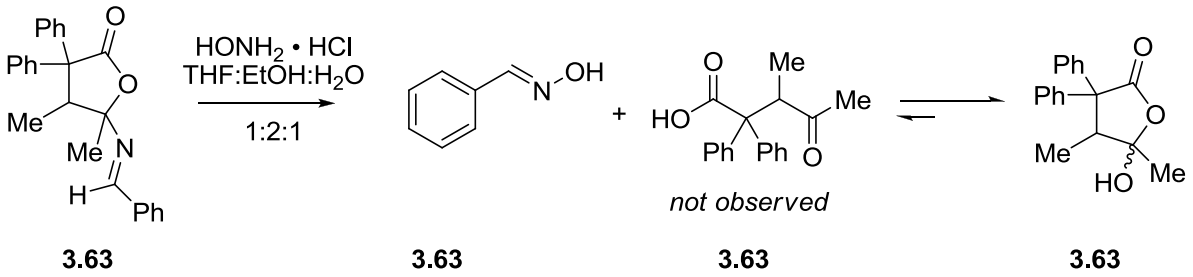


entry	nitrone	R	*dr*
1	**3.60**	Ph	4:1
2	**3.61**	Bn	12:1
3	**3.62**	*t*-Bu	see text

In order to determine the stereochemical outcome with high confidence, we concluded that hydrolysis, and analysis of the enantiomeric ratios of the resulting keto-acids via chiral HPLC, would be more appropriate. We, therefore, studied conditions for imine hydrolysis that would minimize epimerization of the resulting keto-acid. We chose lactone **3.63** for this study in order to minimize the number of diastereomers, simplifying analysis, in addition to the anticipation that the diphenyl substitution of the resulting keto-acid would facilitate separation on the chiral HPLC column. We sought to avoid the use of basic conditions out of concern for epimerization, and unfortunately, simple hydrolysis using mineral or organic acids in THF/water mixtures was slow providing incomplete conversion even with prolonged reaction times. Keeping in mind the need to recycle the chiral auxiliary, we found that imino-lactone **3.63**, when treated with hydroxylamine HCl followed by basic work-up, allowed the direct isolation of oxime **3.63** (Scheme 3.16). This eliminates a two-step, condensation/reduction, which would have been necessary had the product of aqueous hydrolysis, an aldehyde, been isolated. The

other product of the transamination was not the open γ-keto-acid, but a diastereomeric mixture consisting of the ring-chain tautomer, lactol **3.63**.[18]

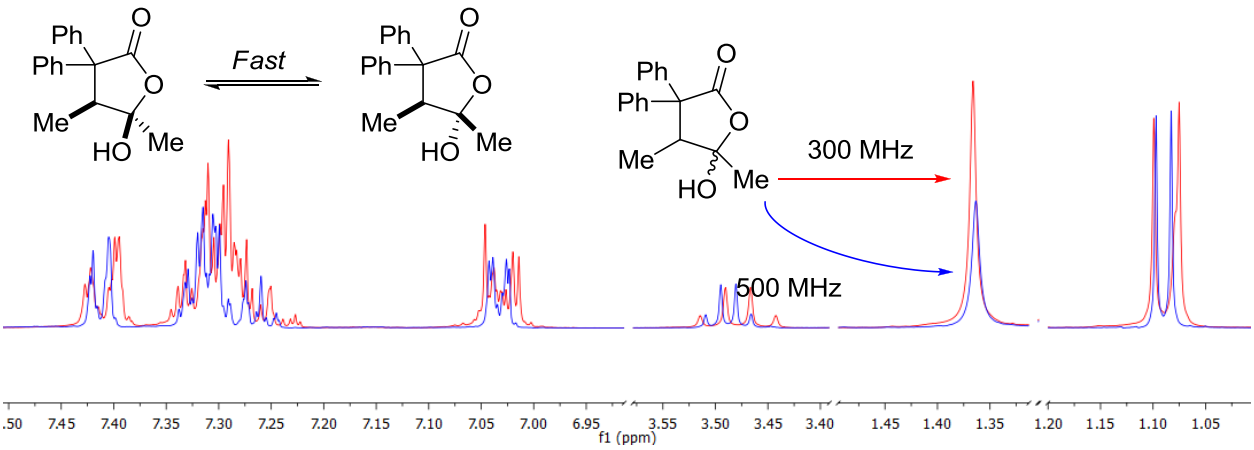
Scheme 3.16 Transamination and Ring-Chain Tautomerism



3.63 **3.63** **3.63** **3.63**

The 500 MHz ^{1}H NMR of lactol **3.63** in $CDCl_3$ showed a 1.35:1 mixture of the two anomeric diastereomers, with none of the open chain form present. Importantly, there was significant exchange broadening, which indicated the rate of exchange was in the intermediate regime. We reasoned that the rate of exchange should show a dependency on the solvent, and under the appropriate conditions, the rate of exchange could be fast on the NMR timescale thereby simplifying the spectra. Gratifyingly, a spectrum of the same sampled measured in *d4*-methanol did indeed show a single compound, albeit with a small amount of residual exchange broadening. Decreasing the field strength of the magnet used to measure the spectrum leads to an increase in the relative timescale of the exchange. This is a consequence of the rate of exchange remaining constant while the frequency difference of the two exchanging signals decreases with decreasing field strength. An overlay of the ^{1}H NMR spectra acquired in *d4*-methanol at the two different field strengths is shown in Figure 3.6. On decreasing the field strength from 500 MHz to 300 MHz, the resonance assigned to the methyl single does in fact sharpen considerably.

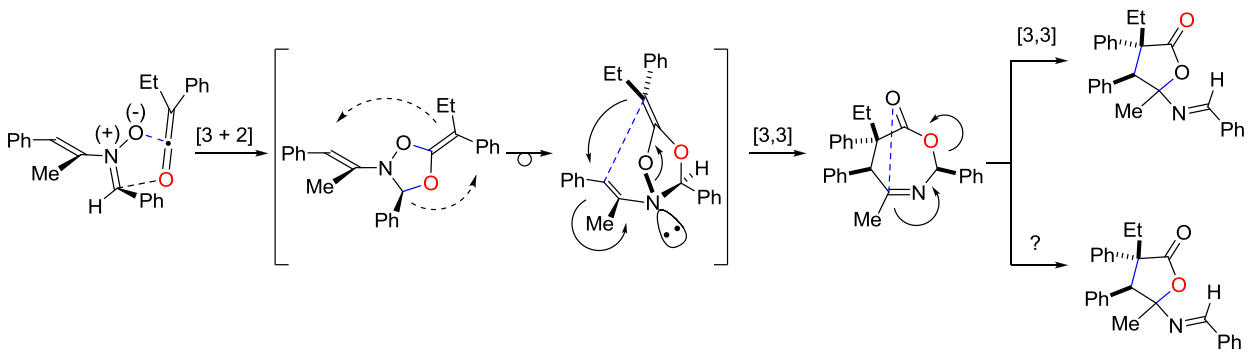
Figure 3.6 Residual Exchange Broadening



3.5 Concluding Remarks

In conclusion, we have developed a new reaction between *N*-vinyl nitrones and ketenes. This reaction is an overall oxidative coupling of two carbonyls, a challenging transformation in itself, that stereoselectively produces an all carbon quaternary center with adjacent to a tertiary center. Our mechanistic studies have provided evidence for a pericyclic reaction cascade proceeding through an initial [3 + 2]-dipolar cycloaddition, followed by one, possible two [3,3]-sigmatropic rearrangements. In order to elucidate whether the final step precedes via a [3,3]-sigmatropic rearrangement, we have designed an experiment that allows the fate of the oxygen in the starting ketene to be determined by utilizing ^{18}O labeled ketene **3.64** (Scheme 17). If a second [3,3]-sigmatropic rearrangement is operative, the oxygen from ketene **3.64** will correspond to the carbonyl oxygen and a shift of approximately 20 cm^{-1} of the carbonyl stretching frequency should be evident in the infra-red spectrum.[19] The lack of this shift would indicate another process is taking place. This experiment is currently underway.

Scheme 17 ^{18}O Labeled Ketene to Determine Mechanism of Last Step



We have also provided a means to achieve control of the absolute stereochemistry in this reaction with a chiral auxiliary based approach. Our initial experiments have proven this a viable approach that holds much promise. We hope to continue to apply the basic mechanistic principles that guided the work in this chapter to other systems as well. In the next chapter, we apply these concepts to the synthesis of oxindoles from phenylhydrazine and ketenes.

3.6 Experimental

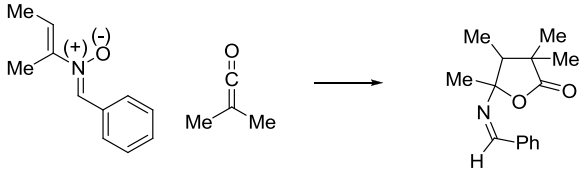
General: All glassware was oven-dried or flame-dried. All reactions were preformed under nitrogen or argon unless specifically stated otherwise. THF and Et_2O were distilled from sodium benzophenone ketyl under nitrogen; CH_2Cl_2, hexanes and toluene were distilled over CaH_2 under nitrogen. Unless specifically mentioned, all chemicals are commercially available and were used as received. Thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F254 glass plates. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^1H NMR spectra were recorded at 300, 400, or 500 MHz, and ^{13}C NMR spectra were recorded at either 75 MHz or 100 MHz. Chemical shifts are reported in ppm referenced to residual solvent

peaks as follows: $CDCl_3$, 7.24 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR. Infrared (FT-IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization.

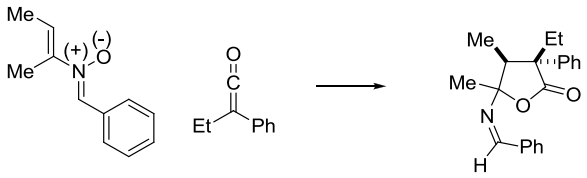
The preparation of the *N*-vinyl nitrones is described in the preceding chapter. 2-Phenylbutanoic acid and diphenylacetic acid were purchased from Aldrich. 2-(4-methoxyphenyl)butanoic acid, 2-(2-chlorophenyl)butanoic acid, and 2-(4-bromophenyl)butanoic acid and dimethyl ketene were prepared according to Fu's procedure.[20] Alkyl-aryl ketenes[21] and diphenyl ketene[22] were prepared by known methods.

The Data Presented in **Table 3.2**

General procedure: A flame dried 25 ml round bottom flask equipped with a septa, magnetic stirring and an N_2 inlet was charged with the vinyl nitrone (1.5mmol) and placed under N_2. THF (3.75 ml) was added, followed by a solution of freshly distilled ketene (1.8 mmol) in THF (3.75 ml) dropwise. The yellow color of the ketene solution dissipates immediately upon addition, until the last few drops when the yellow color persisted. The reaction is poured into a solution of sat aq $NaHCO_3$ and thoroughly shaken to hydrolyze the excess ketene. The solution is then extracted with 3, 10 ml portions of DCM. The organics are combined, washed with brine, dried over sodium sulfate and concentrated. Purification by flash chromatography (hexanes:EtOAc) resulted in the reported compounds.

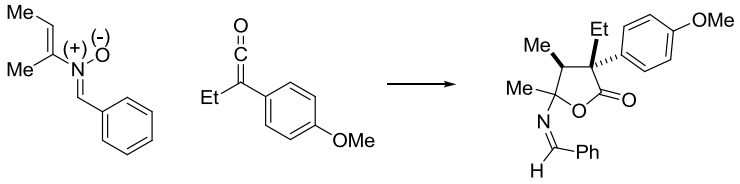


Entry 1: **(Z)-5-(benzylideneamino)-3,3,4,5-tetramethyldihydrofuran-2(3H)-one**: Prepared according to the general procedure except the ketene was prepared directly prior to use. A suspension of zinc dust (5 equiv with respect α-bromoacetyl bromide) (activated prior to use by sonication of a slurry in 1 M HCl followed by washing with water, EtOH, EtOAc, ether, and then dried under high vac.) in THF was cooled to 78 ° C under N_2. Neat, freshly distilled α-bromoacetyl bromide added dropwise via syringe an the suspension was stirred for 5 min at – 78 ° C and then an additional 25 min at 0 ° C. The suspension developed a yellow color during this time. This solution was then vacuum transferred into a dry conical flask and then cannulated into the solution of the *N*-vinyl nitrone. Purified by flash chromatography (hexanes:EtOAc 9:1 R_f =0.32). Clear oil (92 %). that solidified to a white solid in the freezer. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.41 (s, 1H), 7.79 – 7.69 (m, 2H), 7.46 – 7.34 (m, 3H), 2.32 (q, J = 7.2 Hz, 1H), 1.62 (s, 3H), 1.54 1.20 (s, 3H), 1.17 (d, J = 7.2 Hz, 3H), 0.92 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.03, 156.89, 135.90, 131.40, 128.83, 128.66, 99.22, 51.08, 42.84, 27.32, 25.49, 20.23, 9.25.; IR (thin film): 2983, 2934, 1771, 1647, 1581, 1451, 1389, 1379, 1343, 1312, 1276, 1230, 1213, 1190, 1175, 1104, 1075, 1047, 983, 913, 757, 694

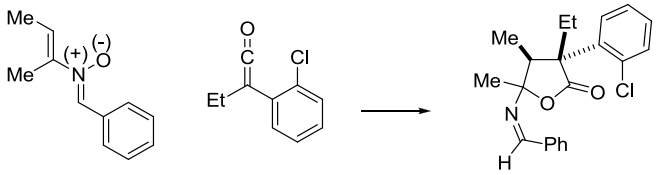


Entry 2: 5-((Z)-benzylideneamino)-3-ethyl-4,5-dimethyl-3-phenyldihydrofuran-2(3H)-one: Prepared according to the general procedure to give a 13.5:10:1 mixture of diastereomers as a white foam. (85%) Purified by flash chromatography (9:1 hexanes EtOAc Rf = 0.27 ^{1}H NMR

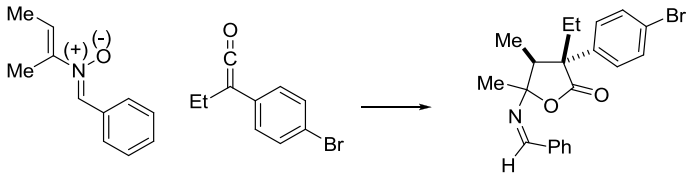
(300 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 8.26 (s, 1H), 7.85 – 7.73 (m, 2H), 7.55 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 – 7.15 (m, 12H), 2.79 (q, *J* = 7.4 Hz, 1H), 2.69 (q, *J* = 7.2 Hz, 1H), 2.28 – 1.84 (m, 3H), 1.61 (d, *J* = 1.1 Hz, 6H), 1.29 (d, *J* = 7.4 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.12, 177.61, 157.63, 156.86, 154.58, 141.14, 140.46, 135.94, 135.63, 131.46, 131.11, 131.05, 128.97, 128.86, 128.80, 128.72, 128.60, 128.56, 128.52, 128.48, 128.44, 127.69, 127.04, 126.90, 126.78, 126.74, 126.69, 100.08, 99.95, 98.68, 56.05, 55.52, 54.64, 50.89, 49.13, 30.98, 28.06, 27.28, 26.18, 24.28, 23.43, 12.01, 10.65, 9.24, 9.15, 8.99, 8.82. IR (thin film): 2959, 1811, 1769, 1646, 1494, 1452, 1381, 1237, 1213, 1053, 917, 157, 696.



Entry 3: **5-((Z)-benzylideneamino)-3-ethyl-3-(4-methoxyphenyl)-4,5-dimethyldihydrofuran-2(3H)-one:** Prepared according to the general procedure to give 9:2.5:1 ratio of diastereomers as a white foam. (89%) Rf = 0.55 (7:1 hexanes EtOAc). Major diastereomer 1H NMR (300 MHz, Chloroform-d) δ 8.55 (s, 1H), 7.89 – 7.75 (m, 2H), 7.49 (d, J = 1.8 Hz, 2H), 7.27 (d, J = 4.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 2.70 (d, J = 7.2 Hz, 1H), 2.01 (dd, J = 14.6, 7.3 Hz, 1H), 1.64 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR; IR (thin film): 2983, 2936, 2836, 1765, 1646, 1611, 1581, 1514, 1452, 1384, 1311, 1288, 1252, 1212, 1186, 1165, 1115, 1086, 1053, 982, 918, 872, 830, 806, 758, 731, 694

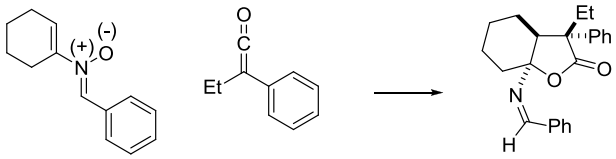


Entry4:**(Z)-benzylideneamino)-3-(2-chlorophenyl)-3-ethyl-4,5-dimethyldihydrofuran-2(3H)-one** Prepared according to the general procedure to give 5:3:1 mixture of diastereomers as a white foam. (73 %) ^{1}H NMR (300 MHz, Chloroform-d) δ 8.54 (s, 1H), 8.52 (s, 1H), 8.47 (s, 1H), 7.85 – 7.75 (m, 1H), 7.68 – 7.59 (m, 2H), 7.49 – 7.21 (m, 10H), 7.16 – 7.02 (m, 2H), 3.11 (q, J = 7.3 Hz, 1H), 2.91 (q, J = 7.4 Hz, 1H), 2.73 (dq, J = 14.6, 7.3 Hz, 1H), 2.17 (ddd, J = 23.2, 14.9, 7.3 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 2H), 1.67 – 1.58 (m, 1H), 1.52 (s, 1H), 1.06 (d, J = 7.3 Hz, 2H), 0.94 (dt, J = 17.6, 7.3 Hz, 6H), 0.80 (d, J = 7.4 Hz, 3H), 0.72 (t, J = 7.4 Hz, 3H).^{13}C NMR (75 MHz, CDCl3) δ 177.63, 176.33, 156.77, 155.96, 136.40, 136.03, 135.86, 134.71, 134.12, 133.95, 132.13, 132.04, 131.51, 131.45, 131.19, 129.88, 129.50, 128.88, 128.84, 128.74, 128.72, 128.70, 128.57, 128.55, 126.90, 126.81, 126.58, 100.11, 99.26, 98.82, 58.27, 54.49, 52.00, 50.48, 33.09, 29.26, 27.64, 24.68, 22.22, 14.84, 13.81, 9.74, 9.62, 8.86, 8.55; IR (thin film): 2984, 2936, 1766, 1647, 1580, 1475, 1451, 1382, 1310, 1211, 1168, 1084, 1052, 982, 904, 931, 756, 693,



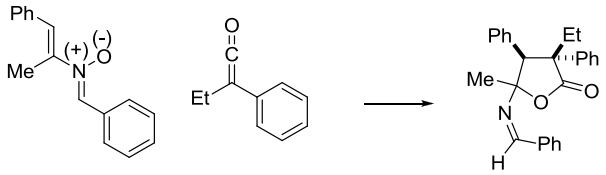
Entry 5: **(Z)-benzylideneamino)-3-(4-bromophenyl)-3-ethyl-4,5-dimethyldihydrofuran-2(3H)-one** Prepared according to the general procedure to give 5:3:1 mixture of diastereomers

as a yellow oil (77%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 8.51 (s, 2H), 8.50 (s, 0H), 8.24 (d, *J* = 4.6 Hz, 0H), 8.04 – 7.66 (m, 5H), 7.63 – 6.88 (m, 28H), 3.66 – 3.20 (m, 2H), 3.02 – 2.88 (m, 0H), 2.80 (q, *J* = 7.4 Hz, 0H), 2.67 (td, *J* = 7.3, 3.3 Hz, 2H), 2.22 – 1.64 (m, 6H), 1.28 (dd, *J* = 7.5, 0.6 Hz, 1H), 1.22 (d, *J* = 3.0 Hz, 3H), 1.19 (d, *J* = 3.0 Hz, 3H), 0.98 – 0.73 (m, 6H), 0.71 – 0.63 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.81, 178.58, 157.40, 157.32, 142.05, 141.58, 136.38, 136.36, 132.42, 132.34, 131.90, 131.87, 130.31, 130.08, 129.55, 129.35, 129.30, 129.26, 129.24, 129.23, 129.19, 129.16, 129.09, 129.05, 128.93, 128.64, 128.60, 128.58, 128.11, 128.08, 127.48, 127.34, 127.21, 127.08, 127.04, 99.19, 99.13, 55.97, 55.73, 55.13, 55.08, 54.74, 54.63, 35.70, 30.68, 29.86, 29.82, 28.50, 28.39, 26.63, 26.29, 23.87, 23.73, 23.64, 22.91, 14.51, 14.42, 14.36, 14.23, 12.34, 12.31, 9.58, 9.26.



Entry 6: **((Z)-benzylideneamino)-3-ethyl-3-phenylhexahydrobenzofuran-2(3H)-one**

Prepared according to the general procedure to give single diastereomer of a white foam. (86%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.36 – 7.25 (m, 1H), 7.23 (d, *J* = 1.0 Hz, 1H), 7.07 (dd, *J* = 8.3, 7.4 Hz, 1H), 6.84 – 6.73 (m, 1H), 3.31 (dd, *J* = 11.1, 6.1 Hz, 1H), 2.12 (ddd, *J* = 10.8, 4.6, 2.0 Hz, 1H), 2.04 – 1.72 (m, 6H), 1.69 (s, 0H), 1.58 – 1.41 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.38, 156.30, 139.78, 135.49, 130.71, 128.25, 128.12, 127.96, 126.82, 126.22, 98.39, 58.24, 46.63, 35.00, 28.15, 25.98, 23.59, 21.70, 9.11.



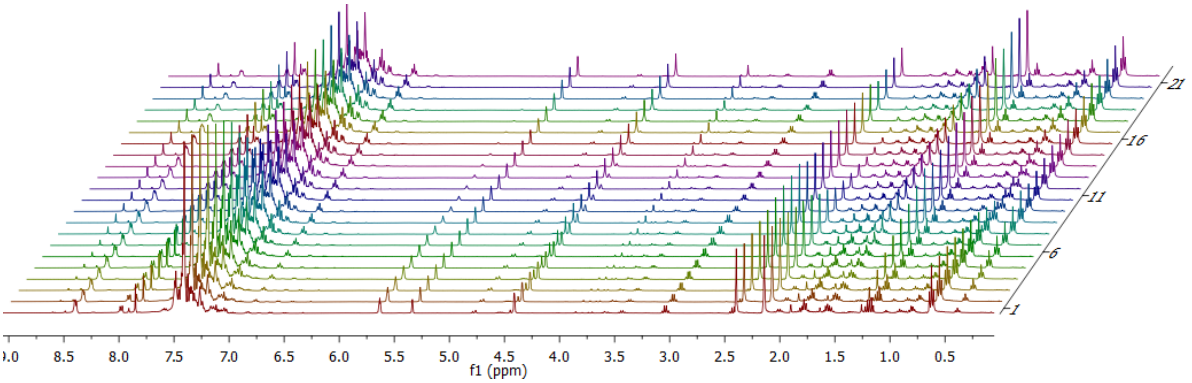
Entry 7 ***Z*-(benzylideneamino)-3-ethyl-5-methyl-3,4-diphenyldihydrofuran-2(3H)-one**

Prepared according to the general procedure to give 1:1 mixture of diastereomers. (90%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.91 (s, 1H), 7.77 – 7.70 (m, 1H), 7.56 – 7.19 (m, 12H), 7.14 – 7.01 (m, 4H), 6.84 – 6.74 (m, 1H), 4.44 (s, 1H), 3.81 (s, 1H), 1.98 – 1.58 (m, 5H), 1.55 (s, 3H), 1.27 (s, 4H), 0.69 (t, *J* = 7.4 Hz, 3H), 0.41 (t, *J* = 7.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.98, 156.64, 140.55, 139.56, 136.65, 135.91, 133.43, 132.45, 131.56, 130.95, 130.40, 128.96, 128.84, 128.66, 128.47, 128.26, 128.13, 127.96, 127.84, 127.74, 127.14, 127.03, 126.75, 126.59, 100.84, 98.72, 66.53, 59.96, 57.10, 57.01, 29.90, 28.67, 26.45, 25.74, 8.61, 8.20.

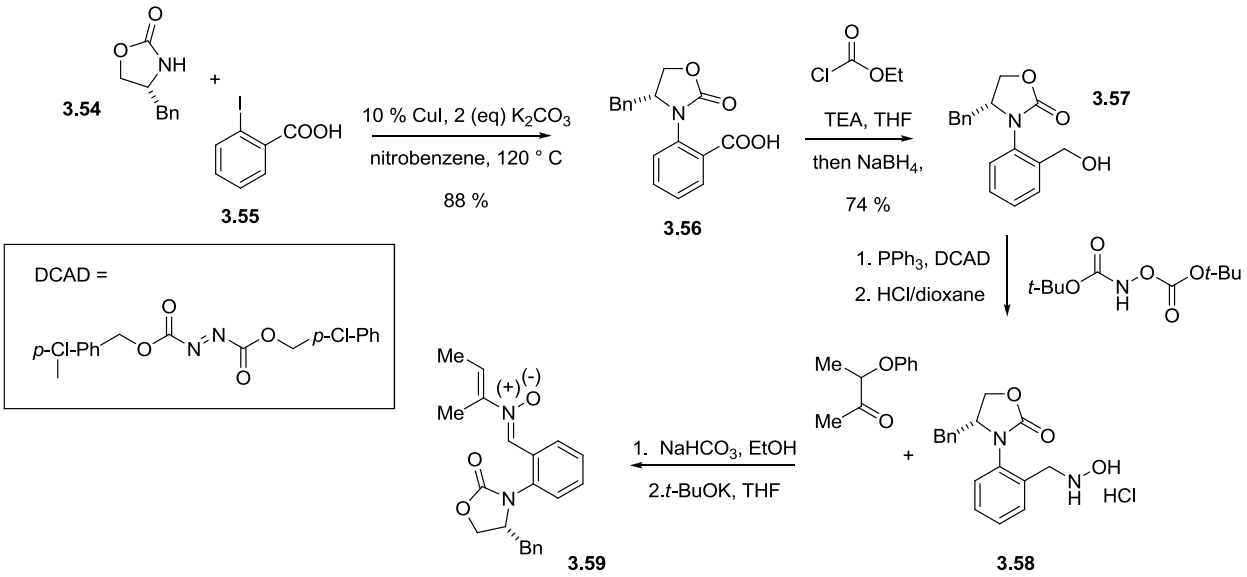
Mechanistic Studies:

Rate study: nitrone (.015 g, 0.063 mmol) was place into a oven dried NMR tube and a rubber septa was place on top. The tube was back filled with N2 and deutero DCM (0.243 ml) was added via syringe. The tube was then cooled to -78 an a solution of ketene (9.24 mg, 0.063 mmol) in deutero DCM (0.243 ml) was added. The NMR tube was briefly vortexed and the placed back into the cooling bath. This was repeated 3 times. The tube was then quickly transferred to the NMR probe that had been pre cooled to -80 °C. The probe was allowed to warm to – 50 ° C and spectra were acquired over the next hour.

The probe was then allowed to warm to – 35 °C and spectra were collected over the next four hours.

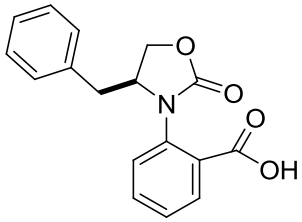


Synthesis of Chiral Auxiliaries:



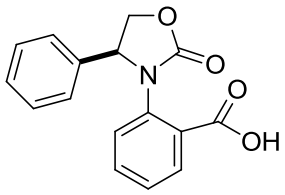
General procedure for *N*-arylation: Degassed nitroethane (concentration of 1M) was added to a flame dried round bottom flask containing benzoic acid (1 equiv), oxazolidinone (1 equiv) and K_2CO_3 (2 equivalents). The flask was back filled with N_2 and placed in an oil bath set at 110 ° C and allowed to stir for 16 hrs. The reaction turns dark green with the evolution of gas upon eating. After cooling, the reaction is diluted with water and washed with dichloromethane. The

aqueous phase is made acidic with 3 M HCl (color change from green to blue to yellow) and extracted with 4:1 chloroform/*iso*-propanol x 6. Saturated aqueous sodium thiosulphate was added dropwise with stirring until the solution becomes clear. The clear organic is washed with brine, the brine back extracted, and dried over magnesium sulphate. The *o*-oxazolidinone benzoic acid can be purified by recrystallization or flash chromatography.



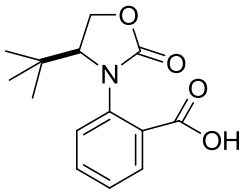
(S)-2-(4-benzyl-2-oxooxazolidin-3-yl)benzoic acid

Prepared according to the general procedure. White powder (72%) Precipitated from acetone with pentane and recrystallized from EtOH mp = 216-218° C. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.61 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.28 – 7.16 (m, 5H), 7.10 – 7.04 (m, 2H), 4.56 (ddt, *J* = 10.5, 6.5, 3.3 Hz, 1H), 4.42 (t, *J* = 8.5 Hz, 1H), 4.22 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.07 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.84 (dd, *J* = 13.5, 10.0 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 135.57, 133.95, 132.84, 129.07, 129.03, 128.34, 127.26, 68.26, 59.77, 39.52.



(S)-2-(2-oxo-4-phenyloxazolidin-3-yl)benzoic acid

Prepared according to the general procedure white crystalline solid (84%). rf .27 in 5% meoh dcm ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.87 (s, 2H), 8.06 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.52 – 7.21 (m, 8H), 6.91 (dd, *J* = 7.7, 1.4 Hz, 1H), 5.33 (dd, *J* = 9.0, 7.5 Hz, 1H), 4.88 (t, *J* = 8.8 Hz, 1H), 4.38 (dd, *J* = 8.6, 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 157.88, 137.89, 137.06, 133.61, 132.60, 129.30, 129.22, 128.43, 128.38, 127.88, 127.80, 70.98, 63.30.

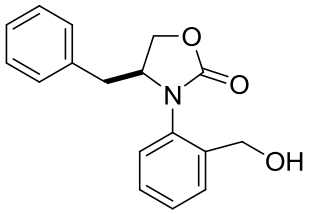


(S)-2-(4-tert-butyl-2-oxooxazolidin-3-yl)benzoic acid

Prepared according to the general procedure Needles (72%) . flashed with 1:1 to 100% hex/etoac. Recrystallized from water to give beautiful needles. rf 0.2 5% meoh.dcm ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.07 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.66 – 7.53 (m, 1H), 7.52 – 7.33 (m, 2H), 4.51 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.13 (s, 1H), 0.83 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.83, 132.80, 127.93, 67.29, 65.53, 35.36, 25.88.

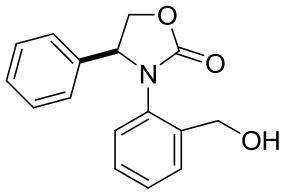
General procedure for the reduction:

Ethyl chloroformate (1,1 equiv) was added to a 0 °C solution of the acid (1 equiv) and TEA (1,1 equiv). After 15 min the tlc showed no starting material and a new spot with solvent front (1:1) hex EtOAc (starting acid Rf ~0.1). The reaction was filtered through a pad of Celite into a suspension of sodium borohydride (5 equiv) in 20 ml of water and allowed to stir for3 hrs. Neutralized with 1 M HCl and extracted with chloroform. Purification by flash chromatography.



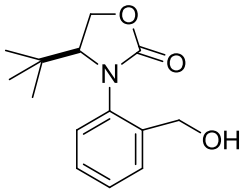
(S)-4-benzyl-3-(2-(hydroxymethyl)phenyl)oxazolidin-2-one

Prepared according to the general procedure (68%) clear oil. Flashed EtOAc/hexanes 1:2 Rf = .57 in 1:1. Second spot. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 – 7.51 (m, 1H), 7.48 – 7.13 (m, 6H), 7.09 – 6.96 (m, 2H), 4.71 – 4.34 (m, 4H), 4.22 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.33 (s, 1H), 2.96 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.68 (dd, *J* = 13.5, 10.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.85, 138.99, 135.07, 134.01, 131.37, 129.11, 128.99, 128.98, 128.76, 127.32, 126.06, 67.95, 61.59, 59.86, 38.90.



(S)-3-(2-(hydroxymethyl)phenyl)-4-phenyloxazolidin-2-one

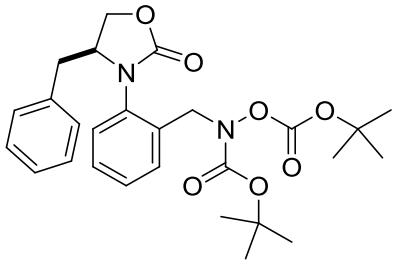
Prepared according to the general procedure (84%) clear oil. Flashed 1:1 hexanes: EtOAc ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.13 (m, 9H), 7.10 – 6.97 (m, 1H), 5.35 (dd, *J* = 8.8, 7.8 Hz, 1H), 4.86 (t, *J* = 8.9 Hz, 1H), 4.66 (d, *J* = 12.3 Hz, 1H), 4.49 – 4.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.02, 138.38, 137.01, 134.22, 131.50, 129.43, 129.36, 128.86, 128.47, 127.48, 125.39, 77.58, 70.46, 63.28, 61.79.



(S)-4-tert-butyl-3-(2-(hydroxymethyl)phenyl)oxazolidin-2-one

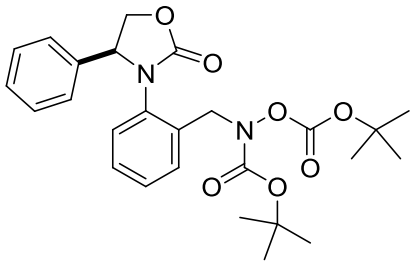
Prepared according to the general procedure (84%) clear oil. Flashed 1:1 hexanes: EtOAc ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 7.38 – 7.20 (m, 3H), 4.82 (d, *J* = 11.8 Hz, 1H), 4.59 – 4.18 (m, 4H), 3.81 (s, 1H), 0.80 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.17, 128.88, 128.34, 66.99, 65.25, 61.81, 35.41, 25.89, 24.89.

General Procedure for the Mitsunobu: A solution of DCAD (1.1 equiv) in DCM (overall concentration .25 M.) was slowly added at rt via cannula to a solution of triphenylphosphine (1.1 equiv), bis-Boc protected hydroxylamine (1.1 equiv), and benzyl alcohol (1 equiv) in DCM, and the resulting cloudy mixture was stirred at rt for 33 min. The reaction was filtered and concentrated in vacuo. Flash chromatography of the crude (EtOAc/hexanes) afforded the desired products.



(S)-tert-butyl 2-(4-benzyl-2-oxooxazolidin-3-yl)benzyl(tert-butoxycarbonyloxy)carbamate

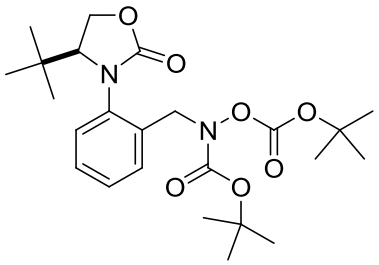
Prepared according to the general procedure clear oil (72%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.60 – 7.45 (m, 1H), 7.42 – 7.07 (m, 8H), 4.96 (s, 2H), 4.67 – 4.47 (m, 1H), 4.33 (t, *J* = 8.3 Hz, 1H), 4.17 (dd, *J* = 8.7, 6.6 Hz, 1H), 3.12 – 3.00 (m, 1H), 2.66 (dd, *J* = 13.2, 10.7 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.76, 152.12, 135.81, 134.48, 129.13, 128.88, 128.47, 127.09, 84.98, 83.00, 67.82, 59.69, 50.69, 38.90, 28.21, 27.59.



(S)-tert-butyl tert-butoxycarbonyloxy(2-(2-oxo-4-phenyloxazolidin-3-yl)benzyl)carbamate

Prepared according to the general procedure clear oil (82%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.25 (m, 6H), 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 7.03 (td, *J* = 7.7, 1.6 Hz, 1H), 6.69 – 6.60 (m, 1H), 5.35 – 5.23 (m, 1H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.84 (t, *J* = 8.7 Hz, 1H), 4.56 (d, *J* = 15.9 Hz, 1H), 4.40 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.49 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 156.71, 155.00, 152.11, 138.49, 134.99, 133.88, 130.64, 129.16, 129.06, 128.55, 128.12, 127.70, 84.96, 83.06, 76.74, 70.44, 62.67, 51.18, 28.20, 27.61



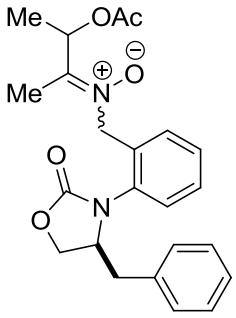
(S)-tert-butyltert-butoxycarbonyloxy(2-(4-tert-butyl-2-oxooxazolidin-3yl)benzyl)carbamate

Prepared according to the general procedure Clear oil (84%) flashed 4:1 hex EtOAc. rf 1:1 =0.48 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.17 (m, 3H), 5.16 (d, *J* = 23.2 Hz, 0H), 4.86 (d, *J* = 41.9 Hz, 0H), 4.86 (s, 1H), 4.63 – 4.43 (m, 1H), 4.29 (td, *J* = 5.7, 5.1, 3.4 Hz, 2H), 4.05 (d, *J* = 7.6 Hz, 0H), 1.55 (s, 3H), 1.48 (d, *J* = 1.7 Hz, 9H), 1.43 (s, 9H), 0.81 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.07, 134.06, 128.89, 127.76, 127.53, 123.71, 84.78, 66.66, 64.91, 35.21, 28.30, 28.21, 27.74, 27.70, 26.06, 25.73.

General procedure for deprotection and condensation with α-acyl butanone.

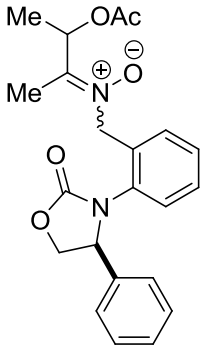
The protected hydroxylamine was taken up in 4M HCl in dioxane and let stir until the disappearance of starting material by tlc, concentrated and used without purification. The α-acyl ketone (1.1 equiv) and benzylhydroxylamine HCl (1 equiv) were dissolved in EtOH (0.5M). NaH_2CO (5 equiv) was added in one portion and the resulting suspension was allowed to stir at room temperature for 16 hours. The suspension was filtered through a pad of Celite, the filter cake rinsed with dichloromethane and concentrated at reduced pressure in room temperature

bath. The crude α-aryloxy or α-acyl nitrones were purified by flash chromatography (silica gel, hexanes:acetone)



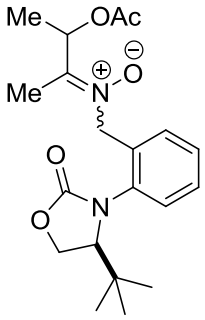
N-(3-acetoxybutan-2-ylidene)-1-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)phenyl)methanamine oxide

Prepared according to the general procedure white foam (77% brsm) Rf = .27 1:1 hexanes/acetone ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (ddd, *J* = 11.8, 6.2, 2.5 Hz, 3H), 7.32 – 7.15 (m, 8H), 7.06 (t, *J* = 7.8 Hz, 4H), 6.24 – 5.96 (m, 1H), 5.76 (q, *J* = 6.6 Hz, 0H), 5.45 – 4.85 (m, 2H), 4.57 (s, 2H), 4.47 – 4.30 (m, 2H), 4.31 – 4.13 (m, 2H), 3.08 (ddd, *J* = 13.8, 7.5, 4.1 Hz, 2H), 2.70 (ddd, *J* = 19.2, 13.5, 10.4 Hz, 2H), 2.15 (s, 3H), 2.09 (s, 2H), 1.99 (s, 2H), 1.97 (s, 2H), 1.44 (d, *J* = 6.7 Hz, 2H), 1.18 (d, *J* = 6.6 Hz, 1H).



N-(3-acetoxybutan-2-ylidene)-1-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)phenyl)methanamine oxide

Prepared according to the general procedure white foam (56% brsm) Rf = .30 1:1 hexanes/acetone ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.06 (m, 24H), 6.91 (s, 3H), 6.07 (dq, *J* = 9.6, 6.7 Hz, 2H), 5.38 – 5.27 (m, 4H), 5.22 (d, *J* = 15.1 Hz, 1H), 4.96 – 4.80 (m, 5H), 4.52 – 4.39 (m, 3H), 3.77 (s, 1H), 2.61 (s, 3H), 2.15 (d, *J* = 2.8 Hz, 14H), 2.10 – 2.01 (m, 12H), 1.89 (s, 3H), 1.46 – 1.35 (m, 7H), 1.23 (s, 8H), 1.10 (d, *J* = 6.6 Hz, 1H), 0.95 (d, *J* = 6.3 Hz, 2H).

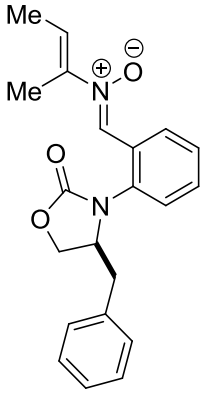


N-(3-acetoxybutan-2-ylidene)-1-(2-((S)-4-tert-butyl-2-oxooxazolidin-3-yl)phenyl)methanamine oxide

Prepared according to the general procedure white foam (35% brsm) Rf = .4 2:1 hexanes/acetone ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.23 (m, 5H), 6.12 (dq, *J* = 13.6, 7.0 Hz, 1H), 5.59 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.28 (s, 1H), 5.01 – 4.86 (m, 1H), 4.50 (q, *J* = 8.7 Hz, 1H), 4.35 – 4.22 (m, 2H), 2.17 – 1.96 (m, 7H), 1.50 (d, *J* = 6.6 Hz, 1H), 1.42 (dd, *J* = 21.7, 6.7 Hz, 2H), 1.25 – 1.16 (m, 1H), 0.89 – 0.76 (m, 12H).

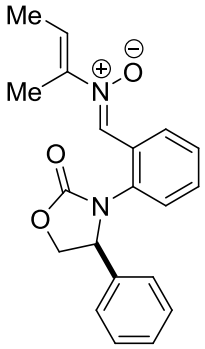
The α-acyl nitrone (1 equiv) was dissolved in THF (0.15 M), placed in a bath at - 78°C (dry ice/acetone) and allowed to stir for 15 min. t-BuOK solution (1 M in THF;1.1 equiv) was added

via syringe and the reaction allowed to stir until the starting material was no longer visible by tlc. The cold solution was then poured into a separatory funnel containing containing pH 7 buffer solution (potassium phosphate monobasic sodium hydroxide buffer) and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc x 3. The combined organic layers were washed with brine, the brine back extracted with EtOAc, the combined organic layers dried with magnesium sulfate and concentrated at reduced pressure in a room temperature bath. The crude N-vinyl nitrones were purified by flash chromatography (silica gel, hexanes:EtOAc).



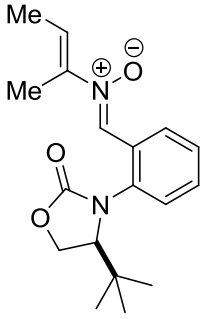
(2E,NZ)-N-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)benzylidene)but-2-en-2-amine oxide

Prepared according to the general procedure white foam (63% brsm) flashed .. 5:1 to 1:1 hexanes/acetone ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.31 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.68 (s, 1H), 7.52 – 7.42 (m, 2H), 7.36 – 7.18 (m, 4H), 7.05 – 6.98 (m, 2H), 6.08 (qq, *J* = 7.0, 1.1 Hz, 1H), 4.43 (q, *J* = 10.3, 8.1 Hz, 2H), 4.29 – 4.22 (m, 1H), 2.98 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.70 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.11 (t, *J* = 1.2 Hz, 3H), 1.76 (dq, *J* = 7.0, 1.2 Hz, 3H).



(2E,NZ)-N-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)benzylidene)but-2-en-2-amine oxide

Prepared according to the general procedure white foam (77% brsm) flashed with 5:1 to 1:1 hex acetone. third spot. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.99 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.71 (s, 1H), 7.36 – 7.20 (m, 9H), 7.05 – 6.99 (m, 1H), 6.11 – 6.02 (m, 1H), 5.28 (dd, *J* = 8.7, 7.0 Hz, 1H), 4.86 (t, *J* = 8.8 Hz, 1H), 4.46 (dd, *J* = 8.9, 7.0 Hz, 1H), 2.12 (p, *J* = 1.1 Hz, 3H), 1.79 (dq, *J* = 7.2, 1.2 Hz, 3H).



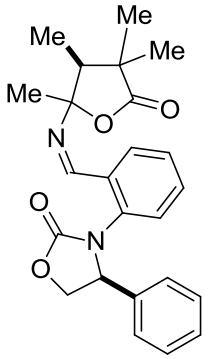
(2E,NZ)-N-(2-((S)-4-tert-butyl-2-oxooxazolidin-3-yl)benzylidene)but-2-en-2-amine oxide

Prepared according to the general procedure white foam yield not determined Flashed 5:1 to 1:1 hex/acetone. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.02 (s, 0H), 2.11 (dd, *J* = 2.6, 1.4 Hz, 3H), 0.78 (s, 10H), 2.08 – 2.00 (m, 3H), 6.24 (q, *J* = 5.7 Hz, 0H), 1.78 – 1.72 (m, 3H), 1.39 (d, *J* = 5.7 Hz, 1H), 1.29 – 1.20 (m, 5H), 4.14 – 4.05 (m, 2H), 9.42 (s, 1H), 7.87 (s, 1H), 7.40 (tt, *J* = 7.4,

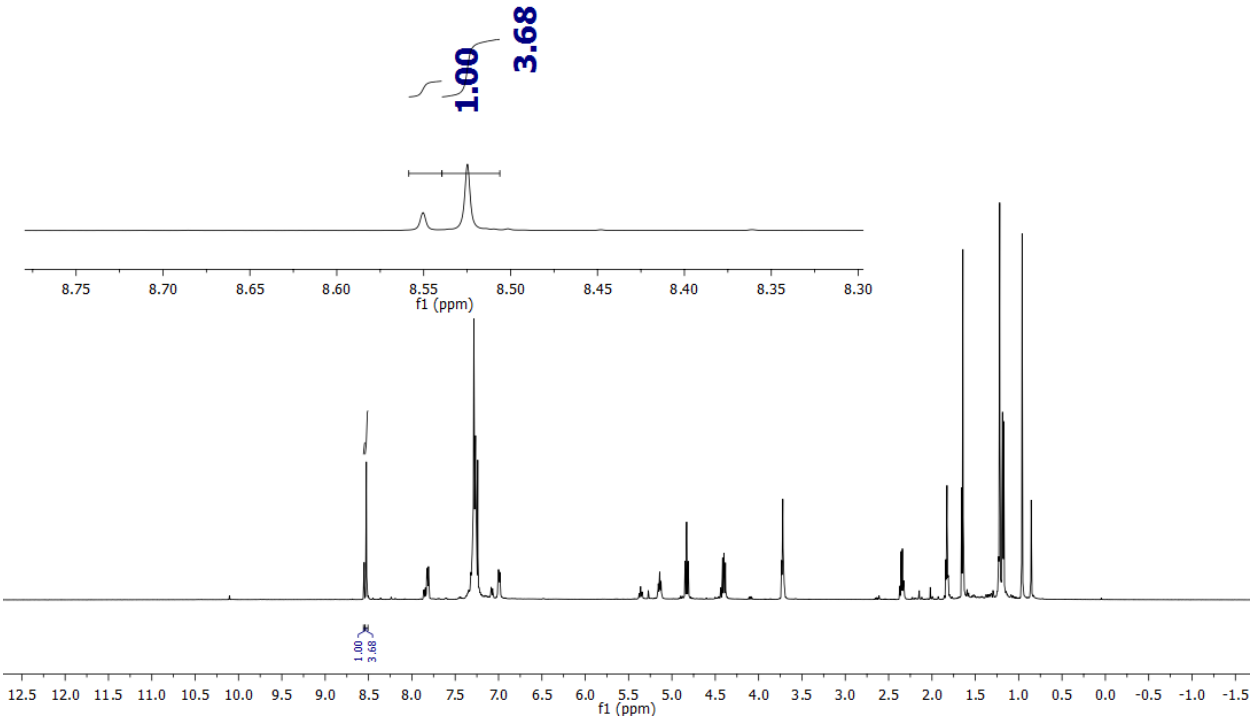
3.8 Hz, 2H), 7.29 (s, 1H), 6.11 (dddd, *J* = 8.3, 7.0, 6.0, 1.3 Hz, 1H), 4.51 (t, *J* = 9.0 Hz, 1H), 4.32 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.24 (s, 1H).

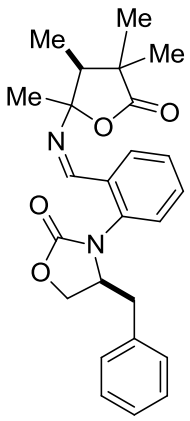
The data from Table 3.4.

Asymmetric *N*-vinyl nitrone/ketene reaction general procedure: The above general procedure for the racemic reaction was followed with the exception that the reaction was set up at -78°C, stired at – 20 for ~ 4 hrs and then allowed to warm to rt before workup. Yields were not determined. The absolute stereochemistry of the newly created center has not yet been determined.

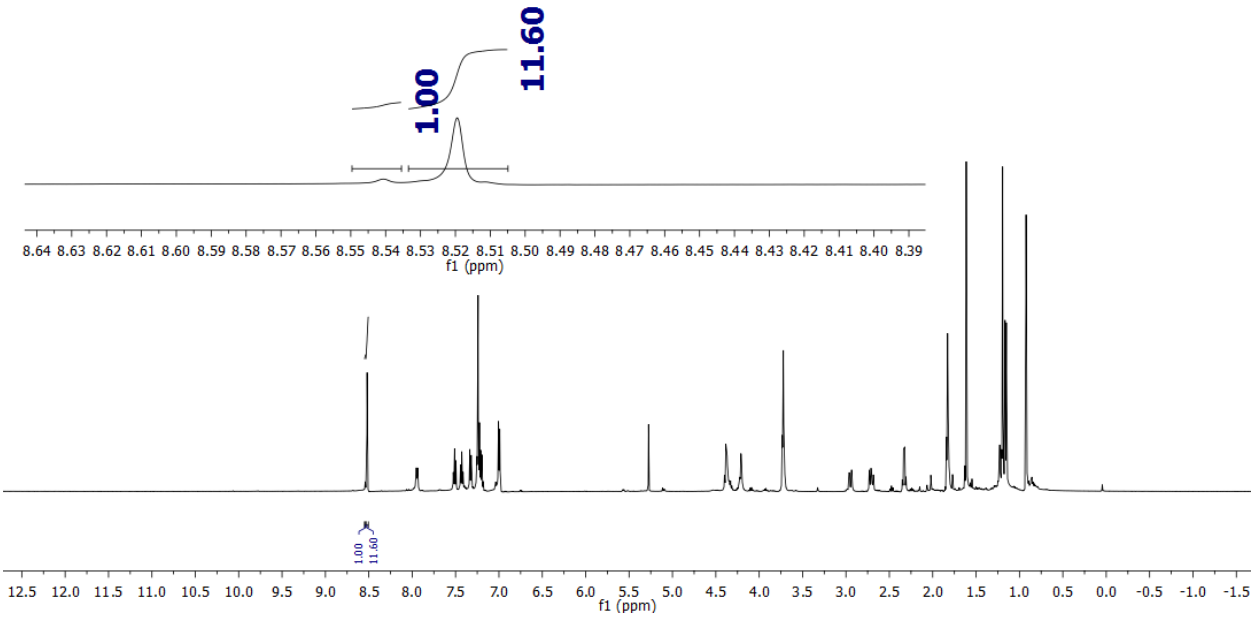


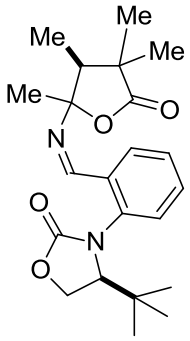
From the reaction of **3.60** with dimethyl ketene a ~ 4:1 *de* was recorded.





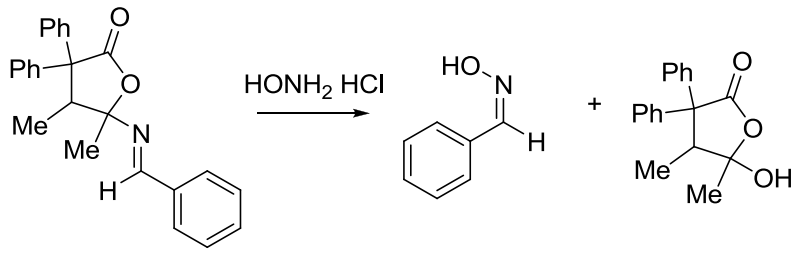
From the reaction of **3.61** with dimethyl ketene a ~ 12:1 *de* was recorded.

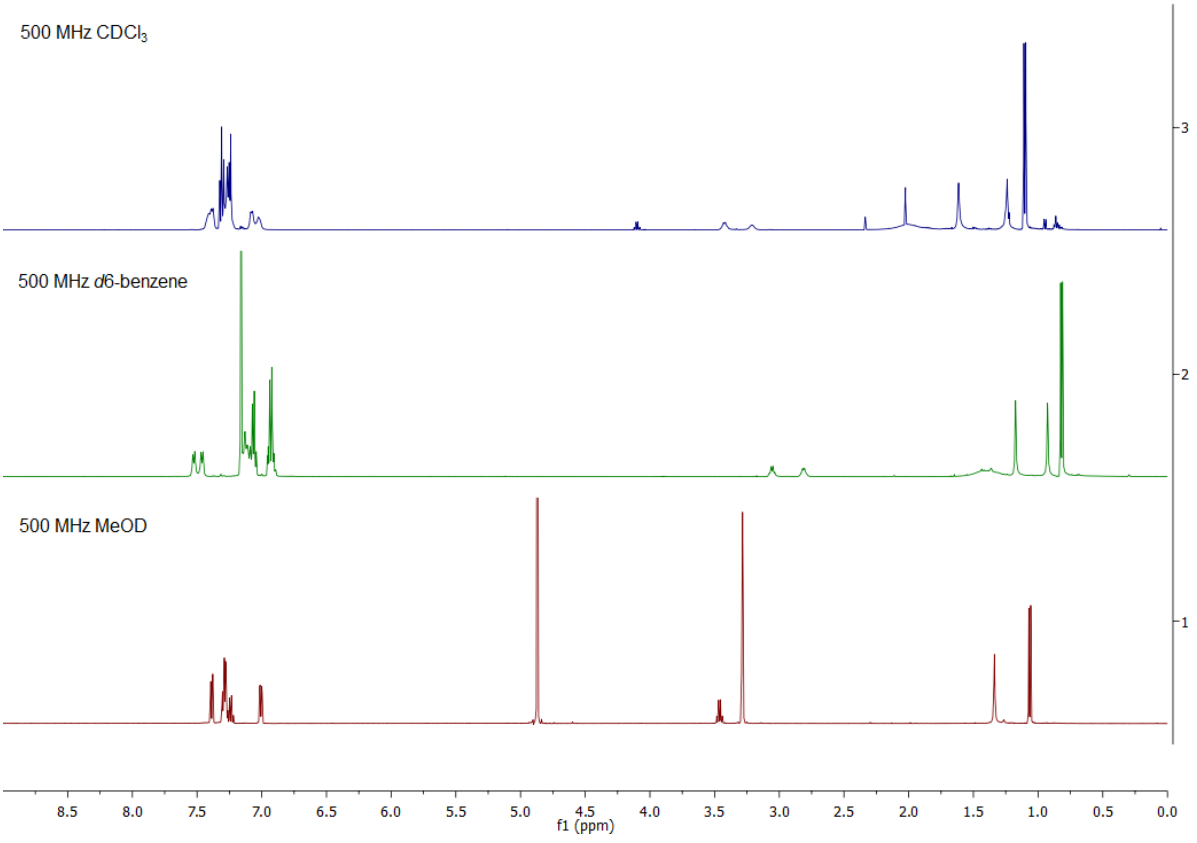




As noted in the text the data for **3.62** was not suitable for analysis.

Transamination was performed by adding 3 equivalent of hydroxylamine HCl to the crude reaction mixture of diphenyl ketene with **3.13** 2:1:1 ethanol, THF, water at 0.1M. After consumption of the starting material as indicated by tlc the reaction was extracted with chloroform, dried and concentrated. The solvent dependent spectra are displayed below.


Ph
Ph
O
O
Me
Me
N
H
HONH2 HCl
HO
N
H
+
Ph
Ph
O
O
Me
Me
OH


500 MHz CDCl3
500 MHz d6-benzene
500 MHz MeOD
3
2
1
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3.7 References

1 The values cited for the bond dissociation energy of a typical N-O bond range from approximately 43 kcal/mol (Lowry and Richardson) to 48 kcal/mol (Huheey). Given that homolytic cleavage of the N-O bond in compound 1.12.3 would produce an oxyallyl radical and an aniline radical, both of which enjoy enhanced stability, one might expect the N-O bond strength in this compound to be slightly lower than these average values. See: Lowry, T. H.; Richardson, K. S. Mechanism and Theory in Organic Chemistry, 3rd ed.; Harper and Row: New York, 1987; p 162; Huheey, J. E. Inorganic Chemistry: Principles of Structure and Reactivity, 2nd ed.; Harper and Row: New York, 1978; p 848

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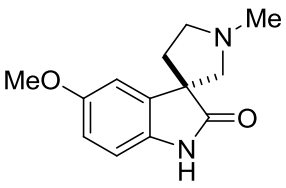
Chapter 4

The Reaction of Phenyl-Hydrazines and Ketenes

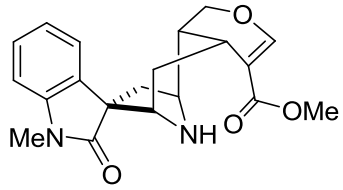
4.1 Introduction

3,3-Disubstituted oxindoles are found in many natural products and medicinally relevant molecules (Figure 4.1).[1] As such, the development of new and efficient methods for the construction of this structural motif remains an important challenge.

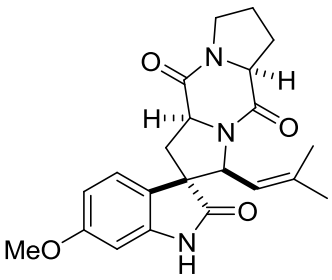
Figure 4.1 Examples of 3,3,-Disubstituted Oxindole Natural Products



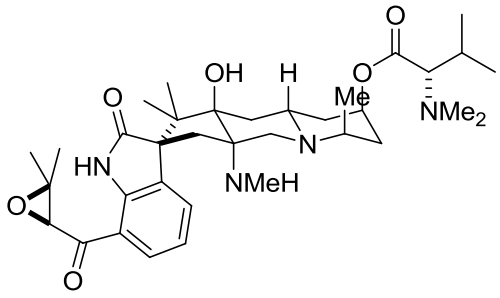
(-)-horsfiline



alstonisine



spirotryptostatin A

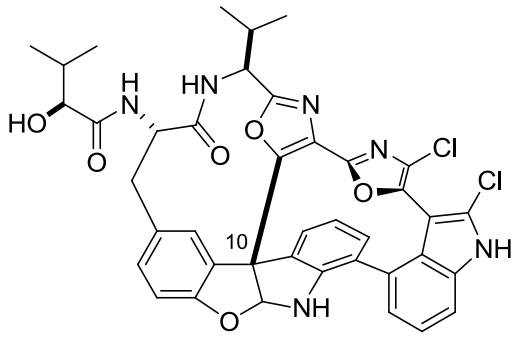


citrinadin A

Diazonamide A, a marine derived natural product, is of particular interest due to the limited supply available from natural sources, in addition to the intriguing biological activity possessed in the complex molecular structure.[2] Examining the structure of diazonamide A, the

C-10 all carbon quaternary center immediately reveals a daunting challenge for the synthesis and study of this molecular scaffold (Figure 4.2)

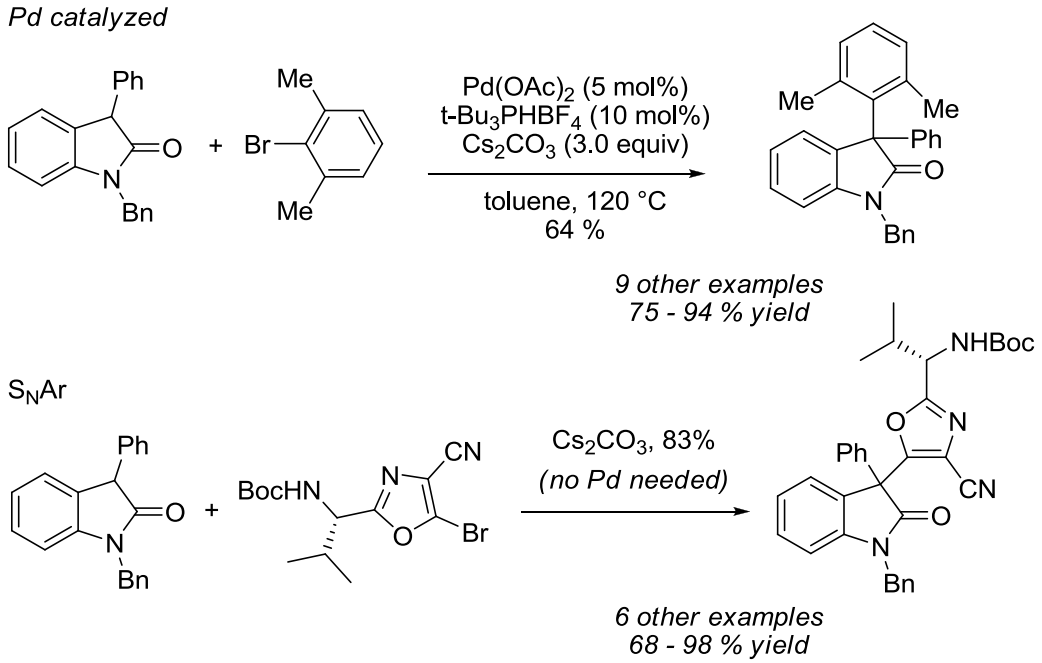
Figure 4.2 The Structure of the Marine Natural Product Diazonamide A



diazonamide A

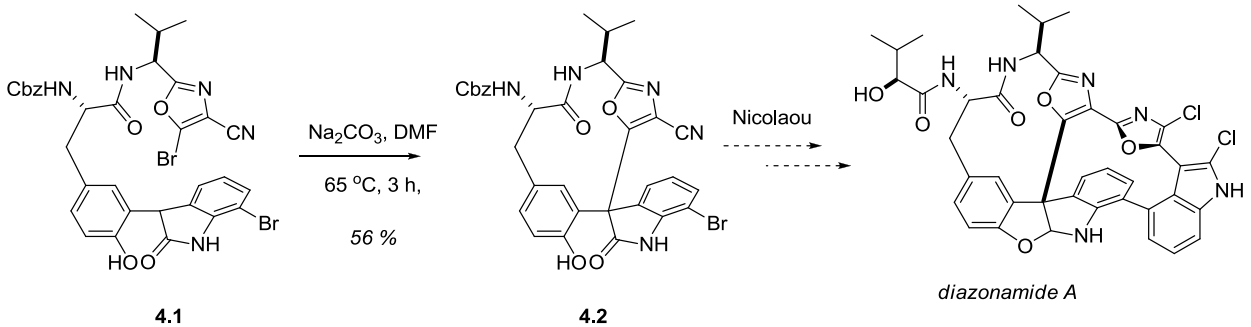
The elegant work of two former graduate students in the Sammakia group, Dr. Mathew Sammons and Dr. Cheng-Kang Mai, resulted in a formal total synthesis of diazonamide A.[3] The strategy to form the C-10 quaternary center was based on the Pd catalyzed arylation of an oxindole enolate that contained substitution at the 3-position. This Pd catalyzed arylation was developed into a general method for the synthesis of very hindered 3,3-diaryloxindoles, a motif that had been challenging to access (scheme 4.1).[4] Interestingly, control experiments demonstrated that with electron poor aryl halide coupling partners, the reaction could proceed via an S_NAr mechanism without the need for Pd catalysis. This work also provided a general solution to the formation of related sterically hindered bonds.[5]

Scheme 4.1 Sammakia, Mai and Sammons' α-Arylation of Oxindoles



The formation of the C-10 quaternary center during the formal total synthesis of diazonamide A was accomplished without the need for Pd catalysis (scheme 4.2). Heating electron deficient oxazole **4.1** in the presence of base led to the formation of **4.2**, an advanced intermediate that, in two steps, intercepted an intermediate in Nicolaou's total synthesis.[6]

Scheme 4.2 Sammakia's Formal Total Synthesis of Diazonamide A

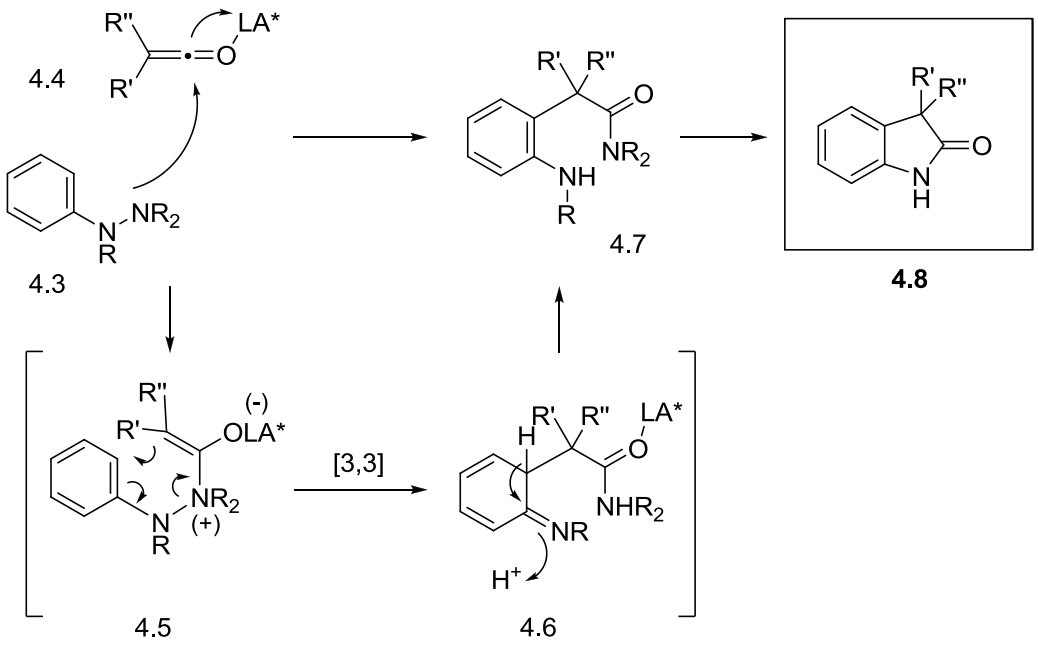


In our continuing efforts towards the development of [3,3]-sigmatropic rearrangements for the synthesis of quaternary carbons, we envisioned that the application of the general reaction principles outlined in the preceding chapters could be effectively applied to the synthesis of 3,3-disubstituted oxindole products. This chapter describes our efforts towards this goal.

4.2 The Reaction of Phenyl-Hydrazines and Ketenes for the Synthesis of 3,3-Disubstituted Oxindoles

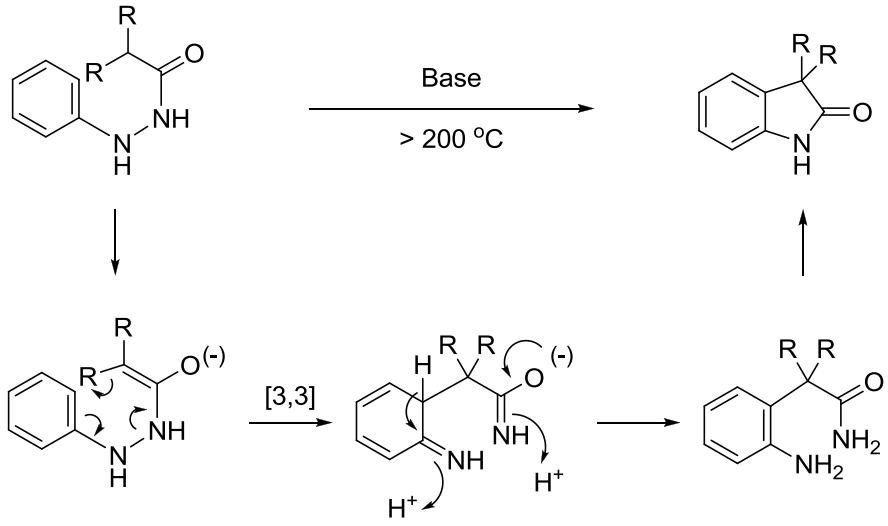
Our generalized mechanistic principles consist of the *in situ* formation of an intermediate bearing vicinal di-π groups capable of undergoing a [3,3] sigmatropic rearrangement wherein the rearrangement is driven by the cleavage of a weak heteroatom-heteroatom bond. We envisioned the application of this strategy to the synthesis of oxindoles using aryl hydrazines and ketenes. We reasoned the ketene would undergo nucleophilic attack by the terminal nitrogen of an aryl-hydrazine forming zwitterionic enolate **4.5**. Zwitterionic enolate **4.5** contains a vicinal di-π system poised to undergo a [3,3]-sigmatropic rearrangement that benefits from charge neutralization in addition to the cleavage of a weak N-N bond.[7] Rearomatization, followed by lactam formation, would provide the 3,3-disubstituted oxindole (scheme 4.3). In addition, analogous to MacMillan and Yoon's Lewis acid catalyzed Bellus-Mahlbery-Claisen,[8] the system should be amenable to Lewis acid catalysis , with the possibility of asymmetric induction by the use of a chiral Lewis acid.[9]

Scheme 4.3 General Scheme for the Phenyl-Hydrazine/ Ketene Reaction



This reaction can be thought of as a charged accelerated variant of the Brunner reaction which is the pyrolysis of an enolizable acyl phenylhydrazine in the presence of base to induce a [3,3] rearrangement (Scheme 4.4)[10]. While the Brunner reaction proceeds under forcing conditions, high temperatures in excess of 200° C are not uncommon as is the use of strong base, we believed that the charge neutralization inherent in our proposed reaction would allow for much milder conditions.

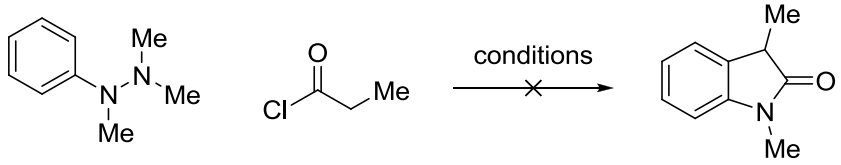
Scheme 4.4 The Brunner Oxindole Synthesis



While our ultimate goal was the synthesis of 3,3-disubstituted oxindoles, our initial attempts focused on a monosubstituted ketene reasoning that the less hindered bond may be easier to form. We began our study with the reaction of phenyltrimethyl-hydrazine and the ketene generated by *in-situ* dehydrohalogenation of propionyl chloride (Table 4.1). Addition of a solution of propionyl chloride to a solution of hydrazine **4.9** and TEA in DCM, led to complete recovery of the hydrazine (entry 1). Switching to Hunig's base under the same conditions produced an identical result (entry 2). We next attempted the conditions successfully employed by MacMillan and Yoon in their Lewis acid catalyzed Bellus-Malherbe-Claisen reaction;[8] unfortunately, the addition of 1 equivalent of $TiCl_4(THF)_2$ had no effect on the outcome of our reaction (entry 3). The dimerization of monosubstituted ketenes is known to be catalyzed by tertiary amine bases and we began to suspect phenylhydrazine **4.9** was assuming a similar role in our system (Scheme 4.4).[11] In the mechanism, nucleophilic addition of the tertiary amine to the ketene results in zwitterionic enolate **4.13**. The enolate (**4.13**) then attacks another ketene, generating intermediate **4.14**, which then cyclizes to give the ketene dimer with concomitant regeneration of the catalyst. Assuming ketene dimerization is second order with respect to the

ketene, we reasoned that by minimizing the concentration of the ketene, we might slow the dimerization enough to allow the desired [3,3]-sigmatropic rearrangement, which is first order, to occur. Reduction of the concentration of the ketene was accomplished by slow addition of the solution of propionyl chloride over several hours via syringe pump (entry 4), and while this had no immediate effect on the outcome of this reaction this procedure was used in all experiments from here on. Using half of a molar equivalent of promoter had no effect (entries 5 and 9). Switching the solvent to toluene only led to the decomposition of the starting materials (entry 6). We explored the use of other bases (entries 7 and 10) and $AlCl_3$ as the promoter (entries 9 and 10), but this also had no beneficial effect on the reaction outcome. MacMillan and Yoon's conditions were also applied while using phenylacetyl chloride as the ketene precursor, but this also led to recovery of the starting material (data not shown).

Table 4.1 Initial Study of the Reaction Conditions



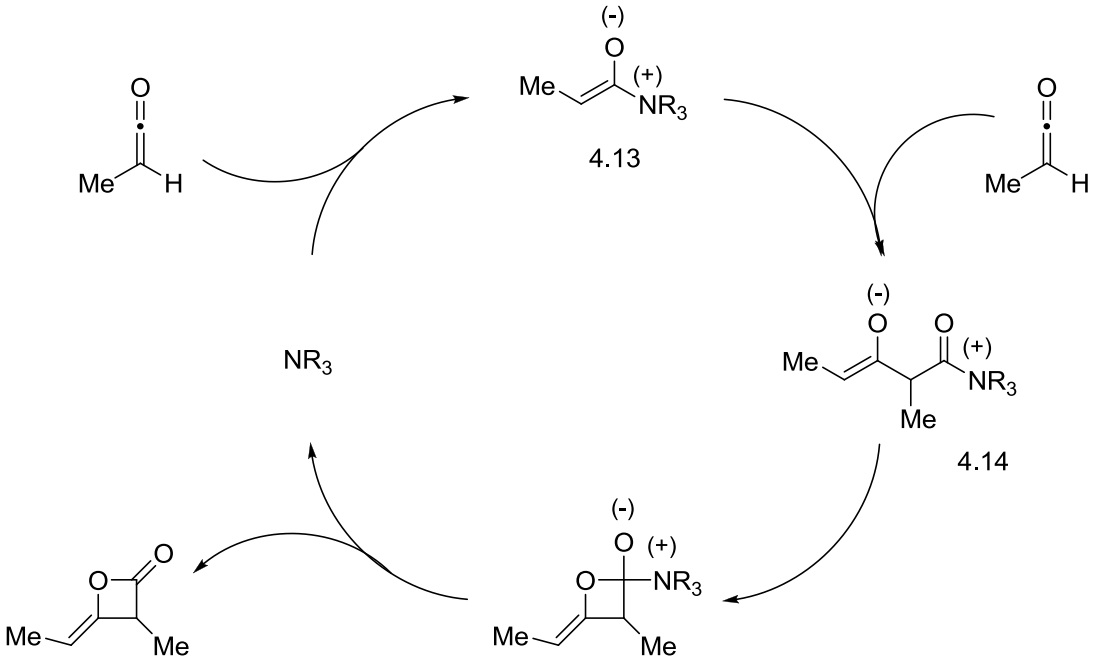
4.9 **4.10** **4.11**

entry[a]	base	solvent	additive	notes	result[b]
1	TEA	DCM	none	none	*n.r.*
2	Hunig's	DCM	none	none	*n.r.*
3	Hunig's	DCM	$TiCl_4(THF)_2$	none	*n.r.*
4	Hunig's	DCM	$TiCl_4(THF)_2$	slow addition	*n.r.*
5[c]	Hunig's	DCM	$TiCl_4(THF)_2$	slow addition	*n.r.*
6	Hunig's	tol	$TiCl_4(THF)_2$	slow addition	decomposition
7	K_2CO_3	DCM	$TiCl_4(THF)_2$	slow addition	*n.r.*
8	Hunig's	DCM	$AlCl_3$	slow addition	*n.r.*

9[c]	Hunig's	DCM	$AlCl_3$	slow addition	*n.r.*
10	P.S.[d]	DCM	$AlCl_3$	slow addition	*n.r.*

[a] Conditions: To a solution of the indicated base (1.5 equiv), hydrazine (1 equiv), and Lewis acid (1 equiv) in DCM (0.2 M with respect to the hydrazine), a solution of the acid chloride (1.5 equiv) in DCM (0.2 M) was added at the either at once or via syringe pump. [b] Judged by analysis of the crude ^{1}H NMR. [c] 0.5 equiv of Lewis acid was used. [d] P.S. = proton sponge.

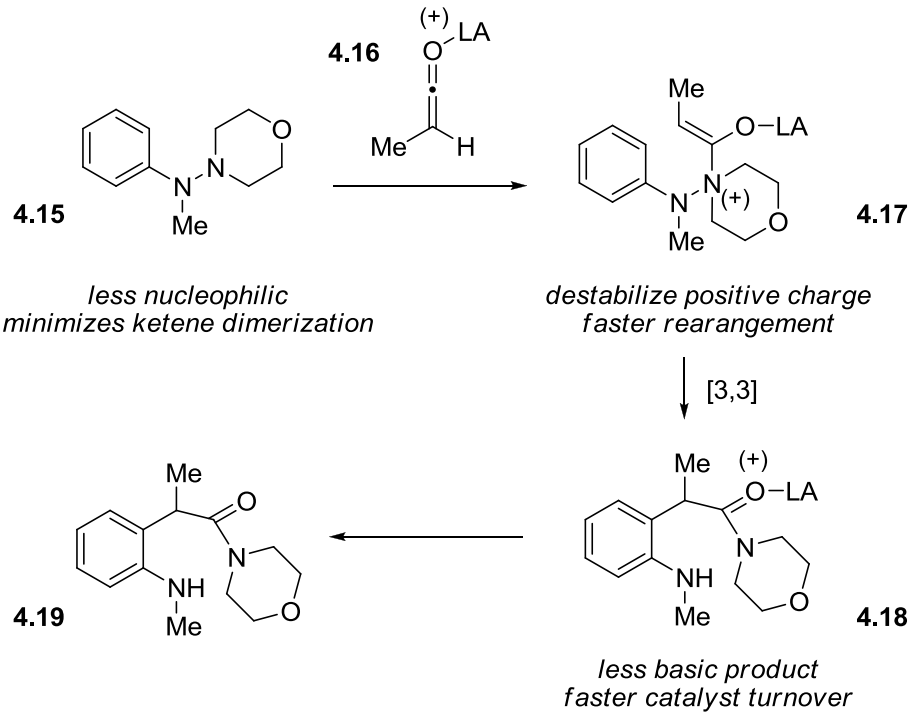
Scheme 4.5 The Mechanism of Ketene Dimerization



These disappointing results prompted us to consider ways in which we could increase the rate of the desired [3,3]-sigmatropic rearrangement, in addition to slowing the undesired ketene dimerization. We speculated that utilization of morpholine derived phenylhydrazine **4.15** may accomplish these goals by the addition of an oxygen atom in the ring (Figure 4.6). The electronegativity of the oxygen atom should provide an enhanced rate for the desired [3,3]-sigmatropic rearrangement by destabilizing the positive charge on the nitrogen atom in zwitterionic enolate **4.17**. The presence of an oxygen atom will also decrease the nucleophilicity

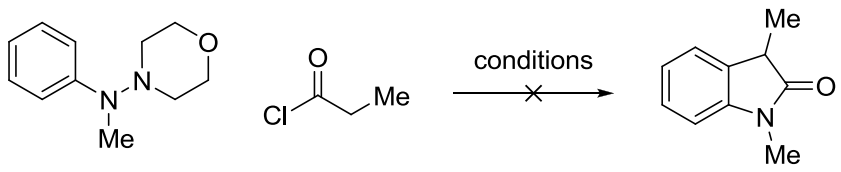
of phenylhydrazine **4.15**, possibly slowing the rate of ketene dimerization.[12] A Lewis acid catalyzed process would also presumably benefit from the decrease in basicity of the resulting amide **4.18**, allowing for more efficient catalyst turnover.

Scheme 4.6 Morpholine Derived Phenyl-Hydrazine's Advantages



We next screened conditions utilizing morpholine derived phenylhydrazine **4.19** and propionyl chloride as the ketene precursor (Table 4.2). Unfortunately, similar results were obtained and we observed no desired product under all conditions examined.

Table 4.2 Morpholine Derived Phenyl-Hydrazine as the Coupling Partner



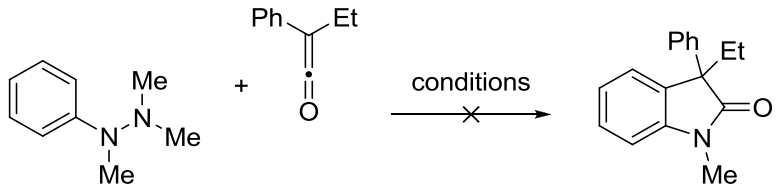
entry[a]	base	solvent	additive	notes	result[b]
1	Hunig's	DCM	none	slow additiom	*n.r.*
2	Hunig's	DCM	$TiCl_4(THF)_2$	slow addition	*n.r*
3	Hunig's	DCM	$TiCl_4(THF)_2$	slow addition	*n.r*
4[c]	Hunig's	DCM	$TiCl_4(THF)_2$	slow addition	*n.r*
5	K_2CO_3	DCM	$TiCl_4(THF)_2$	slow addition	*n.r*
6	Hunig's	DCM	$AlCl_3$	slow addition	*n.r*
7[c]	Hunig's	DCM	$AlCl_3$	slow addition	*n.r*
8	P.S.	DCM	$AlCl_3$	slow addition	*n.r*

[a] Conditions: To a solution of the indicated base (1.5 equiv), hydrazine (1 equiv), and Lewis acid (1 equiv) in DCM (0.2 M with respect to the hydrazine), a solution of the acyl chloride (1.5 equiv) in DCM (0.2 M) was added slowly via syringe pump. [b] Judged by analysis of the crude ^{1}H NMR. [c] 0.5 equiv of Lewis acid was used.

With our unsuccessful attempts to date, we decided to take a different approach that eliminated an uncertainty we had with the system we were studying. The uncertainty involved the *in-situ* generated monosubstituted ketene, the rate of generation and stability of which were two unknown factors. Both of these uncertainties can be eliminated with the use of the more stable, disubstituted ketenes. Disubstituted ketenes that possess an aryl group as one substituent typically can be prepared and purified by distillation prior to use.[13] Tertiary amine bases do not catalyzed the dimerization of disubstituted ketenes, which are commonly synthesized by triethylamine promoted dehydrohalogenation of the parent acid chloride.[14] We, therefore,

synthesized ethylphenyl ketene for use as the heterocumulene partner and screened a variety of Lewis acids with hydrazines **4.9** and **4.15** (Table 4.3 and Table 4.4). Of all the condition studied, the vast majority led to no reaction and recovered starting material. Further, of the conditions that did foster reactivity, four led to complex mixtures or decomposition (Table 4.3 entries 3 and 7, Table 4.4 entries 14 and 23), and two led to Friedel-Crafts products (Table 4.3 entry 3 and entries 16), only one Lewis acid led to the desired reactivity, $CuOTf_2$.

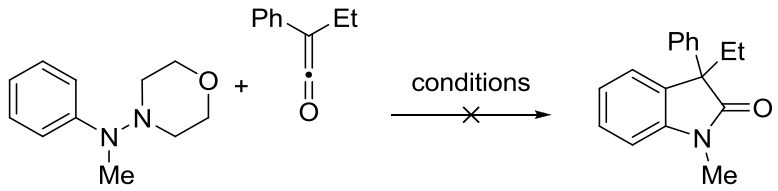
Table 4.3 Screen of Conditions Utilizing Phenyltrimethyl-hydrazine



entry[a]	promoter	solvent	temperature	result[b]
1	none	THF	reflux	*n.r.*
2	none	toluene	reflux	*n.r.*
3	TMSOTf	DCM	23	decomposition
4	$TiCl_4(THF)_2$	DCM	23	*n.r.*
5	$Sc(OTf)_3$	acetonitrile	23	*n.r.*
6	$Sc(OTf)_3$	acetonitrile	100	Friedel-Crafts
7	$IrCl_3$	DCM	23	complex mixture
8	AlCl3	DCM	23	*n.r*

[a] Conditions: To a solution of the hydrazine (1 equiv), and Lewis acid (1 equiv) in the indicated solvent (0.2 M with respect to the hydrazine), a solution of the ketene (1.5 equiv) in DCM (0.2 M) was added dropwise over five minutes. [b] Judged by analysis of the crude ^{1}H NMR. [c] 0.5 equiv of Lewis acid was used.

Table 4.4 Screen of Conditions Utilizing Morpholine Derived Phenyl-Hydrazine

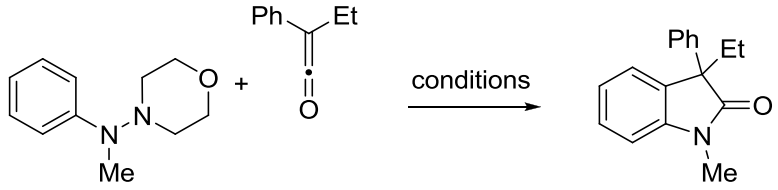


entry[a]	promoter	solvent	temperature	result[b]
1	none	THF	Reflux	*n.r.*
2	none	toluene	Reflux	*n.r.*
3	$TiCl_4(THF)_2$	THF	23	*n.r.*
4	$AlMe_3$	THF	23	*n.r.*
[c]5	$AlMe_3$	THF	23	*n.r.*
6	$AlCl_3$	THF	23	*n.r.*
7	$Sc(OTf)_3$	THF	23	*n.r.*
8	$Yt(OTf)_3$	THF	23	*n.r.*
9	**$Cu(OTf)_2$**	**THF**	**23**	**62 %[d]**
10	$Mg(OTf)_2$	THF	23	*n.r.*
11	$Sn(OTf)_2$	THF	23	*n.r.*
12	ZnBr	THF	23	*n.r.*
13	BF_3 OEt_2	DCM	23	*n.r.*
14	TMSOTf	THF	23	decomposition
15	AgOTf	DCM	23	*n.r.*
16	$AuCl_3$	DCM	23	Friedel-Crafts
17	$AuClPPh_3$[x]	DCM	23	*n.r.*
18	$Ni(ClO_4)_2$	DCM	23	*n.r.*
19	$Ni(PPh_3)_2Cl_2$	DCM	23	*n.r.*
20	$Pd(PPh_3)2Cl_2$	DCM	23	*n.r.*
21	$Pd(dba)_2$	DCM	23	*n.r.*
22	$Pd(OAc)_2$	DCM	23	*n.r.*
23	$RuCl_2(PPh_3)_3$	DCM	23	not characterized

[a] Conditions: To a solution of the hydrazine (1 equiv), and Lewis acid (1 equiv) in the indicated solvent (0.2 M with respect to the hydrazine), a solution of the ketene (1.5 equiv) in DCM (0.2 M) was added dropwise over five minutes. [b] Judged by analysis of the crude ^{1}H NMR. [c] 0.5 equiv of Lewis acid was used. [d] Isolated yield after column chromatography.

The fact that no other Lewis acids that were tested displayed the desired reactivity except $Cu^{(II)}(OTf)_2$ prompted the study of other copper-based Lewis acids (Table 4.5). Of the additional Lewis acids examined, only $(Cu^{(I)}OTf)_2$ tol (entry 6) was able to promote the desired reaction.

Table 4.5 Screen of Other Copper Based Lewis Acids



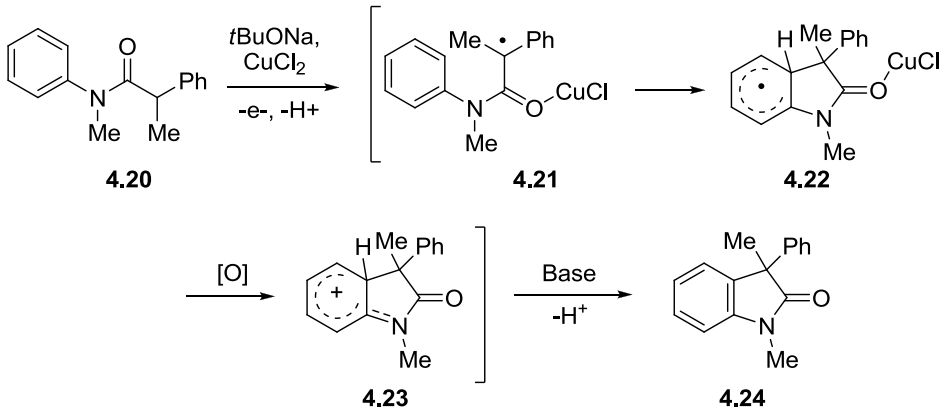
entry[a]	promoter	solvent	temperature °C	result[b]
1	CuCl2	DCM	23	*n.r.*
2	CuBr2	DCM	23	Friedel-Crafts
3	CuSO4	DCM	23	*n.r.*
4	Cu(acac)2	DCM	23	*n.r.*
5	Cu(II)-2-ethylhexanoate	DCM	23	decomp
6	$(CuOTf)_2$ tol	DCM	23	60 %[d]
7	CuI	DCM	23	*n.r.*
8	TsOH	DCM	23	*n.r.*
9[c]	TsOH	DCM	23	*n.r.*

[a] Conditions: To a solution of the hydrazine (1 equiv), and Lewis acid (1 equiv) in the indicated solvent (0.2 M with respect to the hydrazine), a solution of the ketene (1.5 equiv) in DCM (0.2 M) was added dropwise over five minutes. [b] Judged by analysis of the crude ^{1}H NMR. [c] 0.5 equiv of Lewis acid was used. [d] Isolated yield after column chromatography.

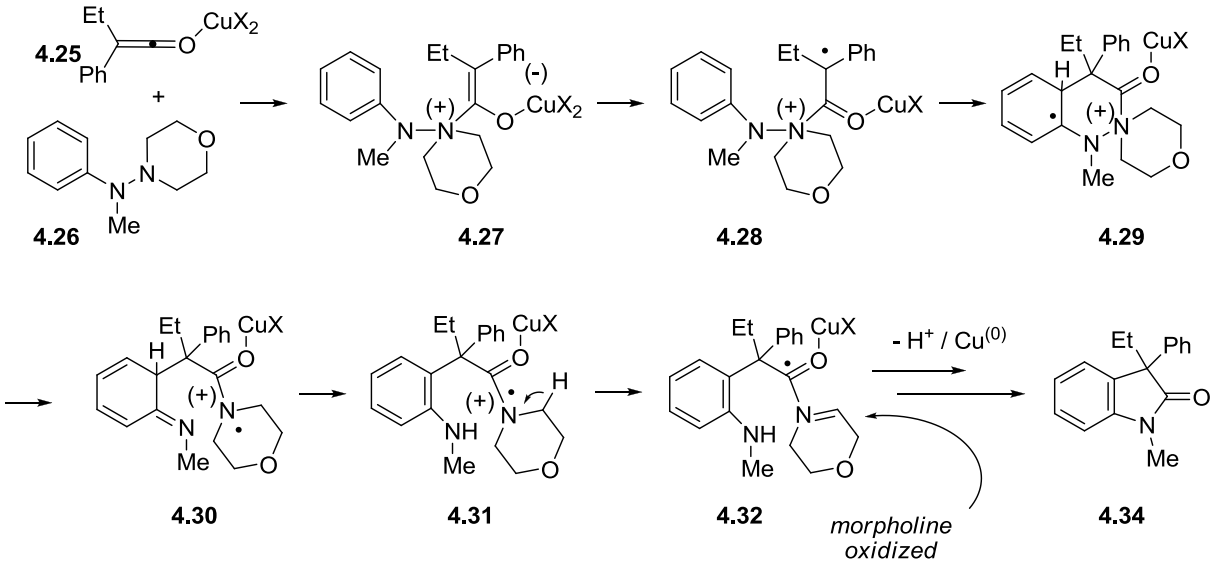
The Cu-specific Lewis acid dependence of this reaction is unusual and we speculate that the Cu is playing dual roles. First, it is likely that the copper is activating the ketene[15] and facilitating addition of the hydrazine. However, several of the Lewis acids studied should also facilitate this addition, yet are not effective, suggesting an additional role for copper. Kundig and Taylor have recently described a route to oxindoles wherein anilides such as **4.20** are treated with base and cupric salts (scheme 4.7).[16] These reactions are thought to proceed via an anilide enolate that is oxidized by Cu(II) to provide an oxyallyl radical (**4.21**) that then adds in an intramolecular fashion to the arene portion of the anilide to form the C-C bond. We suspect that Cu might be playing a similar role in our reaction, namely the oxidation of enolate **4.27**[17] that is produced upon addition of the hydrazine to the ketene. This would provide a copper-bound oxyallyl radical (4.**28**) that then adds to the arene in the key C-C bond-forming step to provide **4.29**. Radical promoted cleavage of the N-N bond would then provide imine **4.30** which would undergo rapid rearomatization to the aniline and eventual ring-closure to oxindole **4.34**. According to this mechanism, the terminal amine group should be produced as a byproduct. We have examined the crude reaction mixture and searched for this byproduct from the morpholine-derived substrate, but we have been unable to identify it. This suggests that the morpholine is being consumed, and we propose that it is being oxidized, ultimately reducing the Cu and leading to a requirement of a stoichiometric amount of this species. Rearomatization of the phenyl group and loss of a proton α-to the amino radical would provide a neutral, ketyl-type species (**4.28**) that can undergo nucleophilic attack at the carbonyl by the aniline nitrogen to provide the oxindole (**4.34**) and liberate Cu^0.[18] In this process, the morpholine is oxidized to the imine and would likely undergo hydrolysis on work up and not be present or detected.

Scheme 4.7 Proposed Mechanism

Kundig and Taylor:

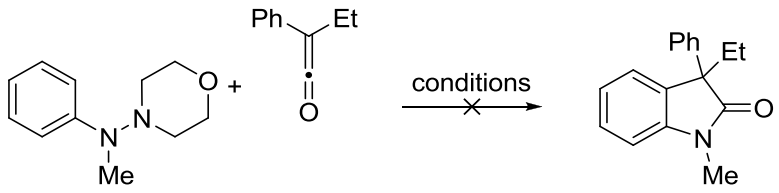


Proposed



We next examined weather other single electron oxidants[19] could promote the desired transformation (Table 4.6). All of the oxidants examined provided no reaction. The lack of reactivity of Lewis acids that are not redox active, and the failure of non-Lewis acidic oxidants support the general mechanism outlined above.

Table 4.6 Attempts With Non-Lewis Acidic Single Electron Oxidants



entry[a]	oxidant	result[b]
1	DDQ	*n.r.*
2	CAN	*n.r.*
3	$FeCl_3$	*n.r.*
4	ferrocenium tetrafluoroborate	*n.r*

[a] Conditions: To a solution of the hydrazine (1 equiv), and oxidant (1 equiv) in DCM solvent (0.2 M with respect to the hydrazine), a solution of the ketene (1.5 equiv) in DCM (0.2 M) was added dropwise over five minutes. [b] Judged by analysis of the crude ^{1}H NMR.

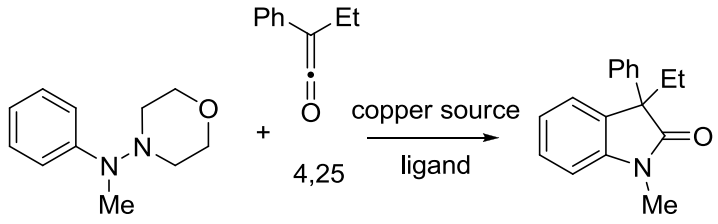
4.3 Investigations of an Enantioselective Phenyl-Hydrazine/Ketene Reaction

The long-term goal for this project is to devise a catalytic asymmetric processes using a chiral Lewis acid. Having discovered that copper triflate based Lewis acids promote the reaction described above, we were excited about the possibility of developing an asymmetric catalyst consisting of a chiral ligand bound to copper. We chose phenylethyl ketene (**4.25**) and the morpholine derived phenylhydrazine **4.26** as our model system (scheme 4.8). Utilizing both Cu(II)OTf_2 and (Cu(I)$OTf)_2$-toluene complex as the Lewis acid promoters, we began screening a number of chiral ligands (Table 4.7.)

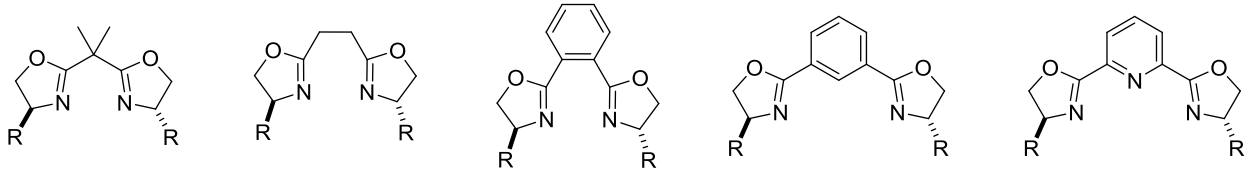
C-2 symmetric bis-oxazoline ligands, introduced in 1991 in two back to back articles in the *Journal of the American Chemical Society*, by Evans[20] and Corey,[21] have been shown to be highly efficient ligands for asymmetric catalysis (Table 4.7, L1 – L5).[22] We therefore studied

these ligands as well as ligands based upon the trans-cyclohexane diamine skeleton in the form of imines,[23] and sulfonamides. Table 4.7 tabulates our current progress thus far. Only two ligands have shown any asymmetric induction, *tert*-Bu-Box and *iso*-Pr-Box (entries 4,6,7,8,10,11,12,13,14). Unfortunately, only low *ee*'s have been realized thus far with these bisoxazoline ligands providing the highest to date (entry 6, 15 % *ee*). We examined other variables that could impact the stereochemical outcome including copper source, counter ion, exclusion or addition of moisture, premade complexes, and electronic properties, and found all to have little or no effect on the asymmetric induction in the systems studied to date. This work is ongoing.

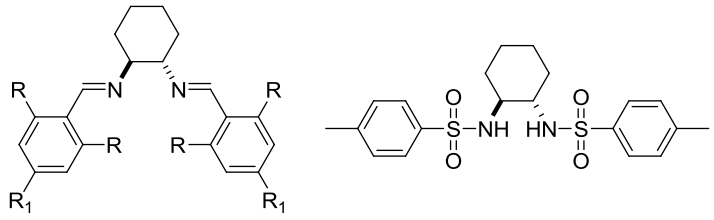
Table 4.7 Ligand Screen for Asymmetric Induction



4.26 4.34



L1 *L2* *L3* *L4* *L5*



L6 *L7*

entry	ligand	R	Cu source	ratio S:L:C	additive	temp	ee
1	L1	Ph	$Cu(OTf)_2$	1:0.5:1	none	23	0

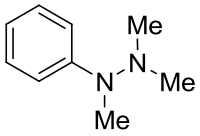
2	L1	Ph	$Cu(OTf)_2$	1:1:1	none	23	0
3	L1	Ph	$Cu(OTf)_2$	1:1:1	none	-78 to 23	0
4	L1	*i*-Pr	$Cu(OTf)_2$	1:1:0.98	none	0 to rt	9
5	L1	*i*-Pr	$Cu(OTf)_2$	1:1:0.98	mol sieves	0 to rt	0
6[c]	L1	*t*-Bu	$Cu(OTf)_2$	1:1.05:1	none	0 to rt	15
7[c]	L1	*i*-Pr	$Cu(OTf)_2$	1:1:0.98	2 equiv H_2O	0 to rt	10
8	L1	*t*-Bu	$Cu(OTf)_2$	1:1.05:1	2 equiv H_2O	0 to rt	15
9	L1	Ph	$Cu(SbF_6)_2$	1:1.05:1	none	0 to rt	0
10[d]	L1	*i*-Pr	$Cu(SbF_6)_2(H_2O)_2$	1:1	none	0 to rt	10
11[d]	L1	*i*-Pr	$Cu(SbF_6)_2(H_2O)_2$	1:1	mol sieves	0 to rt	10
12	L1	*i*-Pr	$Cu(OTf)_2$	1:2:1	none	0 to rt	10
13	L1	*i*-Pr	$Cu(OTf)_2$	1:2:2	none	0 to rt	9
14[d,e]	L1	*i*-Pr	$Cu(SbF_6)_2(H_2O)_2$	2:1	none	0 to rt	10
15	L1	*i*-Pr	$(CuOTf)_2$tol	1:1:0.5	none	0 to rt	0
16	L1	*t*-Bu	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0
17	L2	Bn	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	*n.r.*
18	L2	Bn	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0
19	L3	Ph	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
20	L3	Ph	$(CuOTf)_2$ tol	1:2:1	none	0 to rt	0
21	L4	Ph	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
22	L5	*i*-Pr	$(CuOTf)_2$ tol	1:2:1	none	0 to rt	0
23	L5	*i*-Pr	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
24	L6	R = R_1= H	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
25	L6	R = R_1= H	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0
26	L6	R = Cl; R_1 = H	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
27	L6	R = Cl; R_1 = H	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0
28	L6	R = H; R_1 = OMe	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
29	L6	R = H; R_1 = OMe	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0
30	L7	na	$Cu(OTf)_2$	1:1.1:1	none	0 to rt	0
31	L7	na	$(CuOTf)_2$ tol	1:1:0.5	none	0 to rt	0

[a] Conditions: see experimental for conditions.. [b] *ee*'s determined by HPLC chiralcel AD, 98:2 hexanes/*i*-PrOH, 1 ml/min. [c] hydrazine, copper source, and ligand were sonicated to gether for 2.5 hrs prior to addition of the ketene. [d] Catalyst complex was preformed. [e] trimethylphenyl hydrazine was used.

4.4 Concluding Remarks

Taylor was able to render his reaction catalytic in Cu by using a stoichiometric co-oxidant, air.[16] Should our reaction prove to be proceeding by a radical mechanism, we will similarly study co-oxidants including air as well as MnO_2, $PhI(OAc)_2$, oxone, Me_3NO, TEMPO, etc. In addition, we will study the use of a two-component system wherein a catalytic Lewis acid is used in conjunction with a stoichiometric single-electron oxidant consistent with the need for ketene activation[24] and SET. Our initial studies toward the discovery of an effective Cu ligand for asymmetric induction are described below.

4.5 Experimental



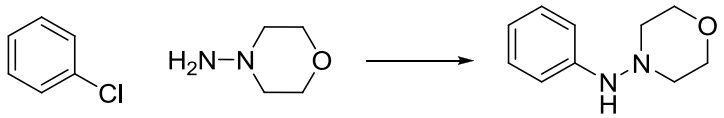
Phenyltrimethylhydrazine (4.15).

To a solution of 10.5 mL (31.5 mmol) of 3 M H_2SO_4, 12.5 mL (168 mmol) of 37% formaline solution, and 50 mL of THF was added a suspension of 2.75 mL (28 mmol) of phenylhydrazine, 9.53 g (0.25 mol) of $NaBH_4$, and 50 mL of dry THF; the temperature was maintained at 20-30 °C. When the addition was half finished, the reaction mixture was acidified by another 10.5 mL (31.5 mmol) of 3 M H_2SO_4. The addition of the $NaBH_4$ slurry was finished, and after

completion, the suspension was stirred for a further30 min. A 50 mL volume of H_2O was added, and the resulting suspension was made alkaline by addition of solid NaOH until pH > 11. The organic layer was separated and the aqueous layer extracted with two 50 mL portions of Et_2O. The combined organic phases were extracted with 50 mL of a saturated NaCl solution and dried over Mg_2SO_4. After removal of solvent in vacuo, the remaining brownish oil was distilled (133 °C), collected, and further purified by flash chromatography (40:1 PE/Et_2O, *Rf* = 0.26) to yield 2.94 g (70%). ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 6 H), 2.76 (s, 3 H), 6.74 (tt, J = 7 Hz, J = 1 Hz, 1 H), 7.01 (d, J = 8 Hz, 2 H), 7.23 (ddd, J = 8, J = 7, J = 2 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 26.6, 41.0, 112.9, 117.6, 128.8, 150.3. The spectral data is consistent with the literature.[25]

General procedure for the data collected in **Table 4.1.**:and **Table 4.2**

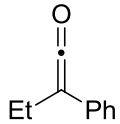
Trimethylphenyl-hydrazine (0.02 g, 0.133 mmol) was added to a small reaction vial and sealed with a Teflon septa lined screw cap. The vial was purged with N_2 and DCM (0.666 ml) was added via syringe. The Lewis acid (0.133 mmol) was added (if a solid, the cap was quickly removed and replaced followed by carefully backfilling with N_2; liquids were added via syringe) followed by the addition of the base (0.200 mmol) via syringe. Freshly distilled propionyl chloride (0.018 ml, 0.200 mmol) in DCM (0.666 ml) was then added via syringe at the rate indicated in the table. Reactions were monitored by tlc (hex:EtOAc 5:1) When tlc indicated a new spot or 16 hrs had passes, the reactions were diluted with water and DCM, the aq layer extracted with DCM. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated.



morpholin-4-yl-phenyl-amine [26]

Dioxane (31.3 ml) was degassed by passing a stream of N_2 through for 1 hr. $Pd_2(dba)_3$ (0.407 g, 0.444 mmol) and Xphos (0.411 g, 0.888 mmol) were placed in a 350 ml sealed flask under argon and dioxane (31.3 ml) was added via cannula. chlorobenzene (1.802 ml, 17.77 mmol) and 4-aminomorpholine (3.43 ml, 35.5 mmol) in Dioxane (31.3 ml) were degassed as above and then cannulated to the flask. Sodium *tert*-butoxide (2.391 g, 24.88 mmol) was added and the atmosphere purged with argon and the tube sealed and immersed in an oil bath at 120 °C and allowed to stir overnight. After cooling the solution was diluted with EtOAc and filtered through Celite then washed with sat $NaHCO_2$ x 3, dried with Mg_2SO_4. Flash with 7:1 hexanes:EtOAc to yield 2.9 g of a orange solid (92 %). mp:106-107 °C; IR (thin film) 3241, 2956, 2850, 1068 ; ^{1}H NMR ($CDCl_3$) δ 7.29-7.21 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.83 (t, *J* =7.3 Hz, 1H), 4.46 (bs, 1H), 3.85-3.82 (m, 4H), 2.78 (bs, 4H); ^{13}C NMR ($CDCl_3$) δ 147.1, 129.3, 119.8, 113.8, 67.1, 56.5.

Notes Dioxane was used fresh from a new anhydrous bottle. Ph-Cl was distilled from sieves and 4-aminomorpholine was use from a new bottle (Aldrich).



Phenyl ethyl ketene (4.25)

The preparation of this compound was described in the previous chapter.

General procedure for the data collected in **Table 4.3.**, **Table 4.4** and **Table4.5**

Trimethylphenyl-hydrazine **(4.9)** (0.02 g, 0.133 mmol) (1 equiv) (or morpholin-4-yl-phenyl-amine **(4.25))** was added to a small reaction vial and sealed with a Teflon septa lined screw cap. The vial was purged with N_2 and indicated solvent (0.666 ml) was added via syringe. The Lewis acid (0.133 mmol) (1 equiv) was added (if a solid, the cap was quickly removed and replaced followed by carefully backfilling with N_2; liquids were added via syringe) Freshly distilled phenyl ethyl ketene **(4.25)** (0.029 mg, 0..200 mmol) (1.5 equiv) in the indicated solvent (0.666 ml) was then added via syringe at the rate indicated in the table. Reactions were monitored by tlc (hex:EtOAc 5:1) When tlc indicated a new spot or 16 hrs had passes, the reactions were diluted with water and DCM, the aq layer extracted with DCM. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated.

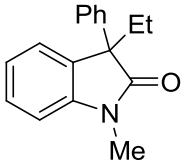


Table 4.4 entry 9: *N*-methyl-3,3-phenyl-ethyl oxindole white solid was isolated in 62 % yield after flash chromatography (9:1 hexanes:EtOAc) uv/Seabach's magic stains multi-colored blue/grey. m.p. = 81–84 °C. IR (thin film): 3053, 2963, 2934, 2877, 1732, 1618, 1500, 1381, 1259, 1038, 916, 763; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40–7.19 (m, 7H), 7.12 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 3.22 (s, 3H), 2.49–2.37 (m, 1H), 2.29–2.18 (m, 1H), 0.68 (t, J = 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 178.5, 144.0, 140.2, 132.0, 128.4, 128.0, 127.1, 126.9, 124.7, 122.5, 108.1, 57.2, 30.8, 26.2 , 9.0 .

Table 4.4 entry 6; *N*-methyl-3,3-phenyl-ethyl oxindole was isolated in 60 % yield after flash chromatography. The data is consistent with the published value.

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