Exploitation of Nitrone and Hydroxylamine N–O Bonds for the Construction of Functionalized Heterocycles

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THESIS
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This work is dedicated to my mother, Rebecca, who raised two boys on her own and exemplified perseverance every day to provide for our family.

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-TWR

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LIST OF ABBREVIATIONS

Å	Angstrom
Ac	Acetyl (MeCO)
acac	acetylacetonate
Ar	aryl
ATR	attenuated total reflection
bp	boiling point
Bn	benzyl
Boc	tert-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
CAM	ceric ammonium molybdate
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
Cu	copper
CuTC	copper(I) thiophenecarboxylate
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DHP	3,4-dihydro-2H-pyran
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
dt	doublet of triplets
equiv	molar equivalent
E	entgegen (opposite, trans)
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
FT	Fourier transform
GC	gas chromatography
h	hour
Hex	hexyl (C_6H_{13})
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz
i-	iso

IR	infrared
Ir	Iridium
J	coupling constant
LAH	lithium aluminum hydride ($LiAlH_4$)
LHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet
Me	methyl
MPLC	medium-pressure liquid chromatography
mmol	millimole
MS	molecular sieves
M/z	mass-to-charge
n-	normal
NMR	nuclear magnetic resonance
Pd	palladium
Ph	phenyl
PMP	para-methoxyphenyl
ppm	parts per million
Pr	propyl
PTFE	poly(tetrafluoroethylene)
py	pyridine
q	quartet
R	carbon-centered functional group
RT	room temperature
s	singlet
t	triplet
t-	tertiary
TBAF	tetra-n-butyl-ammonium fluoride
TBS	tert-butyl dimethylsilyl (also TBDMS)
td	triplet of doublets
TEA	triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf	triflate (F_3CSO_2)
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
Tol	tolyl
tt	triplet of triplets
UV	ultraviolet
wt	weight
Z	zussamen (together, cis)

SUMMARY

In this four part thesis, I will share my work in the formation of complex novel *N*-heterocycles from common intermediates such as *N*-vinylnitrones and *N,O*-divinylhydroxylamines. **Chapter 1** will describe the formation of azetidine nitrones via a thermal 4π-electrocyclization of an isolable *N*-vinylnitrone intermediate. The scope of the substituents on the nitrone, kinetic reaction parameters, and diverse functionalizations of these azetidine nitrones will be discussed. After discovery of the reaction utilizing α-ketooximes to facilitate 6π-electrocyclization by my coworker, Dr. Jongwoo Son, I took over this project, with my contribution involving optimization and scope of thermal reaction conditions, substrate scope, and functionalization of these privileged scaffolds. Dr. Son contributed to the project by synthesizing several boronic acids, oximes, and nitrones. **Chapter 2** will discuss the addition of *N*-vinylhydroxylamines to electron-deficient allenoates for the selective formation of 2-aminotetrahydrofurans. In this work, my contribution included rapid synthesis of a variety of vinyl iodides for use in the Ullmann coupling with protected hydroxylamines, deprotection to give novel hydroxylamine intermediates, and optimization of base, ligand, and copper in the Ullmann coupling. Dr. Son discovered this transformation and performed initial screenings of Michael acceptors. **Chapter 3** will discuss my final project in the group, involving an enantioselective 4π-electrocyclization route to enantioenriched azetidine nitrones through chiral Lewis acid catalysis. Mike Shevlin, Associate Principal Scientist at Merck, performed HTE screening to identify reaction conditions and I determined viable conditions on a larger scale in order to translate to laboratory settings. Furthermore, I was able to determine the optimal catalyst, solvent, and HPLC separation conditions for this project. This work is expected to be elaborated on in the near future. **Chapter 4** will discuss a novel [3+2]-cycloaddition/(3,3')-sigmatropic rearrangement cascade of *N*-vinylnitrones with internal and terminal alkynes, benzyne, and cyclic alkyne intermediates to provide 4-acyl-1-pyrrolines with high levels of diastereoselectivity. While my labmate Abdullah Alshreimi initially investigated this reaction, I determined the reaction outcome, alkyne scope, rearrangement conditions, and functionalization of 4-acyl-1-pyrroline products and Robert Zhang contributed to this project by optimization and scope of the cyclic alkyne adducts.

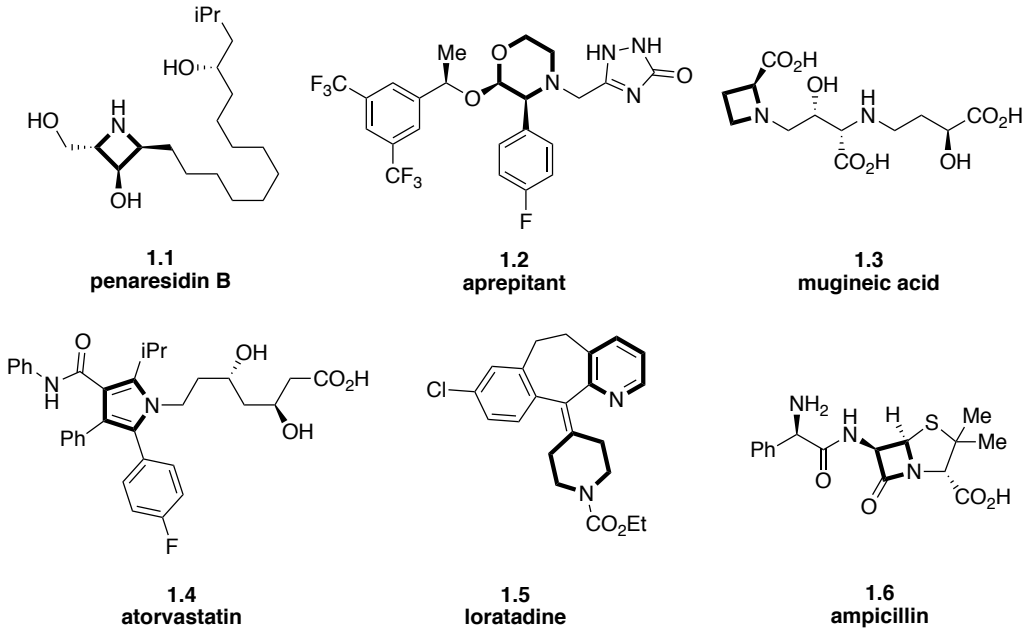
1. *N*-Vinylnitrones for the Synthesis of Functionalized Azetidines

Angew. Chem. Int. Ed., **2017**, *56*, 11579-11583.

1.1 Introduction

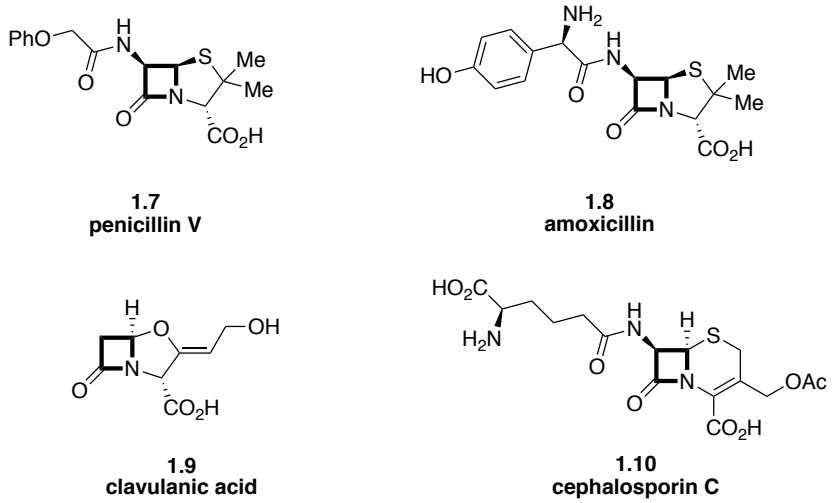
1.1.1 Biological Importance of *N*-Heterocycles

Nitrogen-containing heterocycles are prevalent scaffolds found in both natural products and medicinal targets. As of 2014, 84% of FDA-approved small-molecule drugs contained at least one nitrogen atom and 59% contained some sort of nitrogen heterocycle[1]. There have also been a number of natural products isolated, which contain heterocycles in their core structure. Some of these nitrogen-containing heterocycles such as penaresidin B[2] **1.1**, aprepitant[3] **1.2**, mugineic acid[4] **1.3**, atorvastatin[5] **1.4**, loratidine[6] **1.5**, and ampicillin[7] **1.6** contain azetidine, morpholine, pyrrole, β-lactam, piperidine, and pyridine moieties embedded within their core (Scheme 1.1).



Scheme 1.1 Examples of *N*-heterocycles in pharmaceuticals

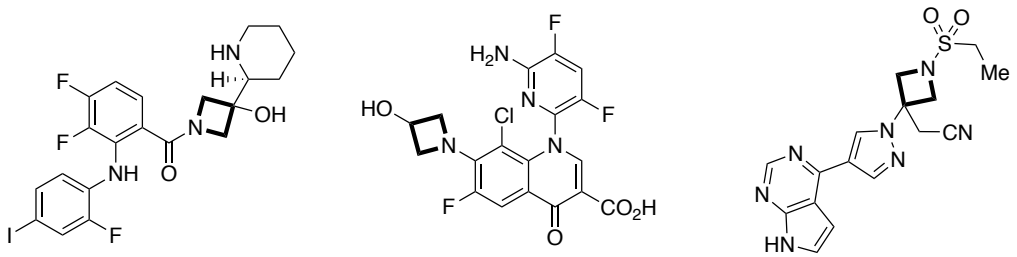
Saturated four-membered *N*-heterocycles are prevalent in well-known antibiotics in the form of β-lactams such as penicillin V[8] **1.7**, amoxicillin[9] **1.8,** clavulanic acid[10] **1.9**, and cephalosporin C[11] **1.10** (Scheme 1.2). These β-lactam structures have been shown to be valuable in the development of antibiotics and as important reactive intermediates in organic synthesis and methodology; however, engineering of new classes of antibiotics are continually needed due to the inevitable development of antibiotic resistance by certain strains of bacteria. Perhaps alternative *N*-heterocycles could be substituted for these beta-lactams in order to increase efficacy of these drugs. Azetidines, their saturated four-membered counterpart, could be part of the solution.



Scheme 1.2 Some common β-lactam antibiotics

Azetidines are known to exhibit rigid conformation and superior physiochemical properties and metabolic stability when exchanged for 5- or 6-membered analogous structures. In spite of their positive attributes, azetidines are vastly underrepresented in drugs, at least in part due to the inefficient methods traditionally used to access these valuable motifs. As a result, no azetidine containing drug candidate had made it through the approval process to be brought to market before 2018. Recently, a number of

azetidine containing pharmaceutical candidates have been introduced into clinical trials. These include cobimetinib[12] **1.11** (MEK inhibitor), delafloxicin[13] **1.12** (antibiotic), and baricitinib[14] **1.13** (JAK1/JAK2 inhibitor) (Scheme 1.3).



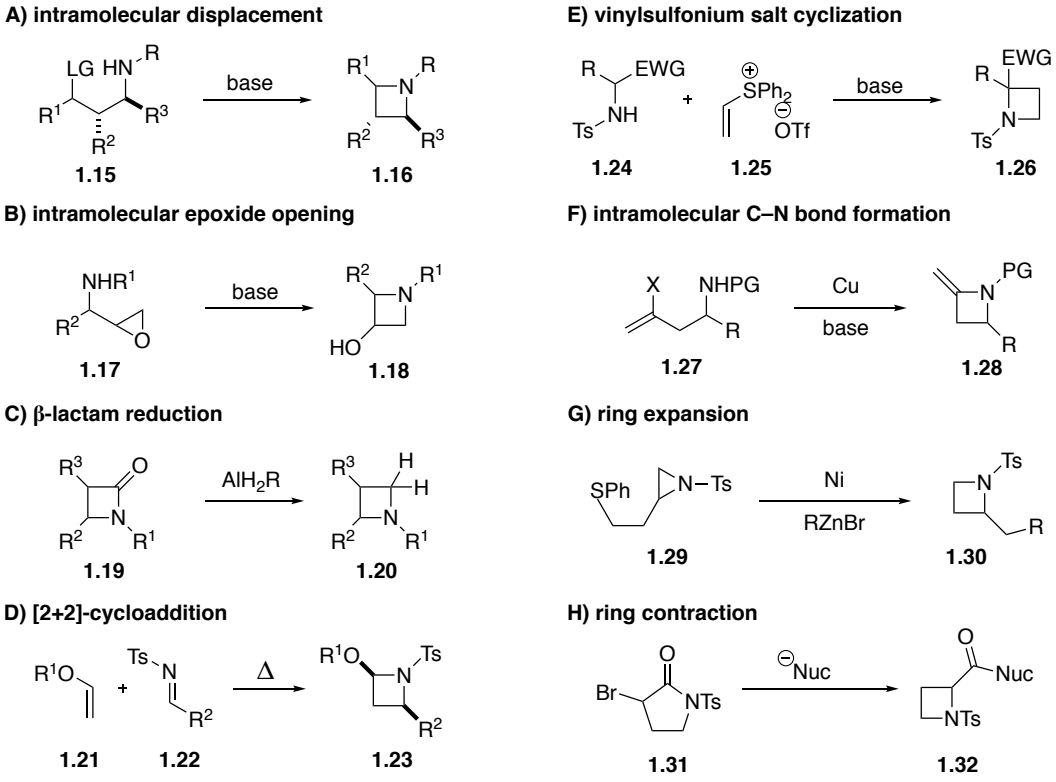
Scheme 1.3 Examples of recently approved azetidine drug candidates

The recent success of **1.11–1.13** as FDA clinical candidates highlights the potential for azetidine-containing drugs for the treatment of disease. The development of mild and general strategies to access azetidine scaffolds would be highly valuable, as this would allow both synthetic and medicinal chemists to begin to tap into the potential of azetidine containing drug-candidates as viable therapeutics to treat today's diseases.

1.1.2 Previous Strategies Toward Azetidines

Traditional methods to access azetidine scaffolds include SN_2 displacement, β-lactam reduction, [2+2]-cycloaddition, ring-expansion or -contraction, and C–H functionalization. Eight strategies to prepare azetidines are shown in Scheme 1.4. The most common methods utilize γ-amino tosylate (LG= OTs) or γ-amino alkyl halide (LG= X) **1.15** to facilitate an SN_2 displacement[15] (Scheme 1.4A) or employ nucleophilic epoxide opening[16] of **1.17** as an alternative to a leaving group to form **1.16** or **1.18**, respectively (Scheme 1.4B). Typical problems encountered in these types of reactions,

which require the use of strong bases, include epimerization of stereocenters and generally low yields. Another method is reduction of previously constructed β-lactam **1.19** with aluminum hydrides[17] (Scheme 1.4C). Thermal [2+2]-cycloaddition[18] has also been shown to provide azetidines from electron-rich alkene **1.21** and electron-deficient imine **1.22** (Scheme 1.4D). These selected methods require the use of pre-installed functional groups and lack modularity resulting in linear syntheses of specific classes of azetidine that lack diversity.

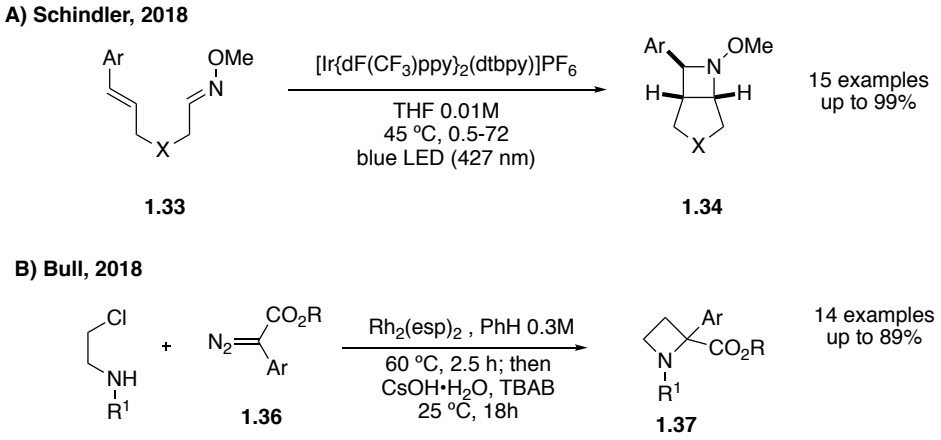


Scheme 1.4 Common routes to azetidine

To address this lack of modularity, Aggarwal[19] and coworkers developed an improved method for azetidine synthesis through an efficient approach utilizing vinyl sulfonium salt **1.25**, however the scope of vinyl sulfonium reagents was limited and only amine **1.24** bearing a vicinal electron-withdrawing group could affect the reaction

(Scheme 1.4E). Copper catalyzed intramolecular C–N bond formation of vinyl halide **1.27** has been used to access exo-methylene azetidine[20] **1.28** (Scheme 1.4F). Ring-expansion of protected aziridine **1.29** in the presence of Nickel and organozinc reagents has been used to access azetidines[21] **1.30** (Scheme 1.4G), and ring-contraction of α-bromopyrrolidinone[22] **1.31** has been used to access **1.32** (Scheme 1.4H). These methods require specific engineering of substrates prior to azetidine formation, which limits the synthetic utility of these transformations.

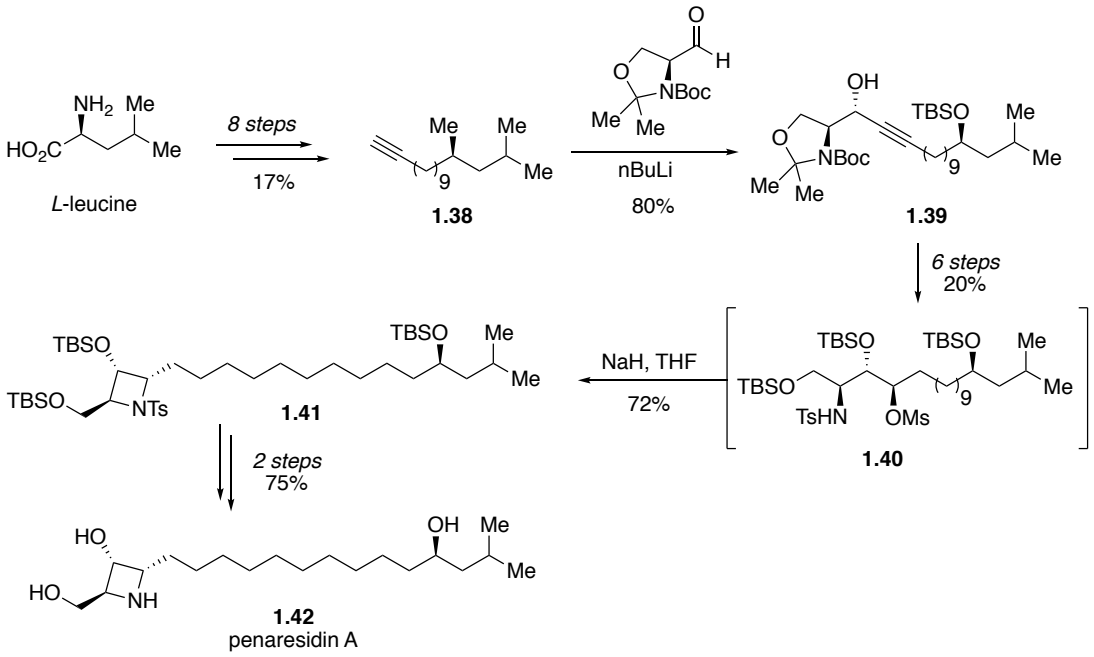
Two recent novel strategies toward azetidine synthesis are described in Scheme 1.5. Photocatalytic [2+2]-cycloaddition of a tethered imine with styrene **1.33** by the Schindler group in 2018[23] (Scheme 1.5A) offers a mild, functional-group tolerant route to fused bicyclic azetidine **1.34**. The Bull lab in 2019[24] (Scheme 1.5B) reported the N–H bond insertion by a rhodium carbene generated from diazo compound **1.36** followed by displacement of a chloride leaving group in amine **1.35** provides a modular approach to these privileged *N*-heterocycles. These methods improved on some of the problems associated with the common routes to azetidines discussed previously, however they are limited by narrow substrate scope and pre-activated reagents such as diazo compounds. A more desirable advancement would not only include a high level of modularity, but would also proceed under mild conditions to efficiently generate a diverse scope of azetidine scaffolds. Nonetheless, these improvements could prove to be useful in future drug-discovery and natural product syntheses.



Scheme 1.5 Recent advances on azetidine synthesis

1.1.3 Selected Examples of Azetidine Construction in Natural Product Synthesis

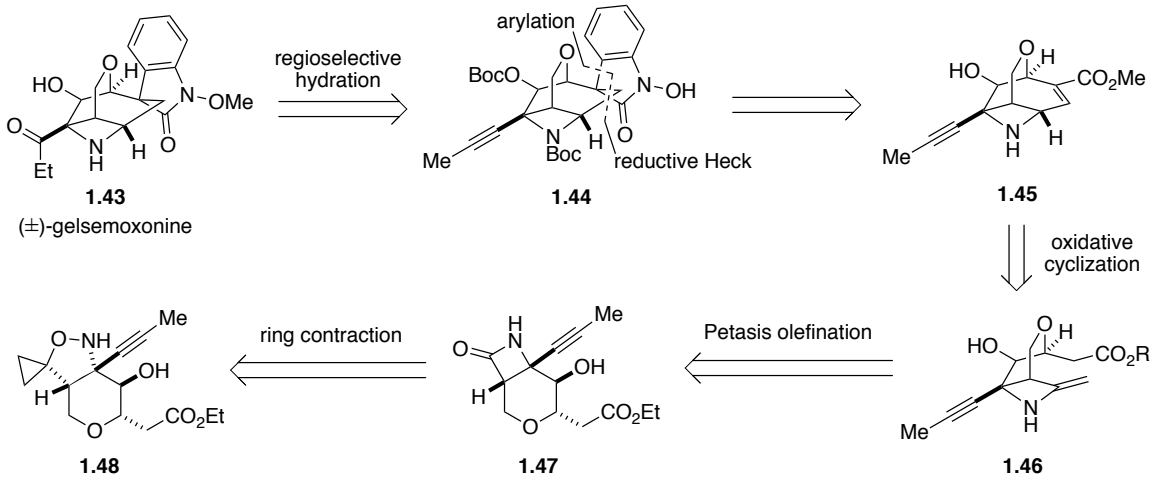
Azetidine construction in natural product synthesis has been limited by the previously discussed problems associated with traditional methods. In 1995 the Kenji Mori group demonstrated the construction of the actomyosin ATPase-inhibiting target penaresidin A[25] **1.42**. They achieved azetidine formation through an SN_2 reaction of stereodefined *cis*-γ-amino alcohol derivative **1.40** (Scheme 1.6). This synthetic route required a 15-step synthesis from commercially available *L*-leucine before a base mediated intramolecular cyclization, forging the crucial C–N bond of the azetidine core. Their total synthesis exemplifies the limitations of nucleophilic displacement reactions for the formation of azetidine scaffolds, as it required a lengthy multi-step synthesis to install the required functionality to access their key intermediate with the necessary stereochemistry and functional groups needed to affect the transformation.



Scheme 1.6 Construction of azetidine containing penaresidin A

A more recent example of azetidine construction in total synthesis came from the Carreira group in 2013[26] when they reported a 21-step synthesis of (±)-gelsemoxonine **1.43**, an alkaloid isolated from the Asian medicinal plant *Gelsemium elegans benth*. Their retrosynthetic analysis encompassed reductive Heck-type coupling and arylation of unsaturated ester **1.45** to afford *N*-hydroxy-2-indolinone **1.44**. Intermediate **1.45** could be accessed from β-lactam **1.47** via reduction and Petasis olefination followed by oxidative cyclization of azetidine **1.46**. The important azetidine was accessed via a unique ring contraction of spiro-cyclopropane isoxazolidine **1.48** to afford β-lactam **1.47** (Scheme 1.7). While this method afforded the required 4-membered fused azetidine tetracyclic core, it was still limited by the use of harsh reduction conditions for **1.47** and required pre-installation of a β-lactam. A mild and modular method toward these privileged heterocycles would streamline natural product syntheses and allow synthetic chemists more opportunity to study azetidine-containing natural products. It was hypothesized by

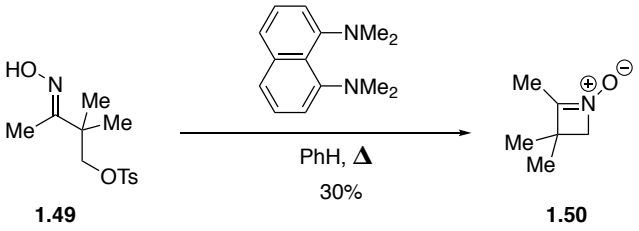
our group that unsaturated azetidine analogues might provide a useful entry into highly substituted examples of azetidine scaffolds.



Scheme 1.7 Carreira's total synthesis of (±)-gelsemoxonine

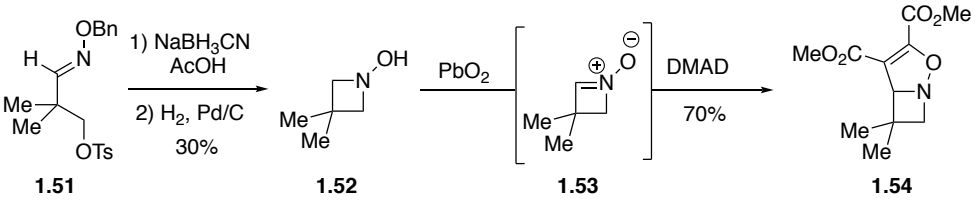
1.1.4 Previous Reports of Unsaturated Azetidines

Unsaturated azetidine *N*-oxides were first isolated in the lab of R.F.C. Brown[27] in 1974 (Scheme 1.8). While investigating the reactivity of 5- and 6-membered ring nitrones, they surprisingly found that when γ-tosyloxy ketooxime **1.49** was treated with 1,8-bis(dimethylamino)naphthalene, C–N bond formation was observed affording strained cyclic nitrone **1.50** (Scheme 1.8). Identification of this structure was supported by NMR and UV spectroscopies, however the resulting products were unstable and could not be isolated. This proof of principle that these strained *N*-heterocycles could be accessed inspired subsequent work for the development of more stable analogues.



Scheme 1.8 Initial discovery of unsaturated azetidine *N*-oxide structure

Expanding on their initial efforts to synthesize stable strained *N*-heterocycles, Reinhoudt and coworkers demonstrated that unsaturated azetidine *N*-oxides could be accessed from *N*-hydroxyazetidines[28]. As shown in Scheme 1.9, reduction of *O*-benzyl oxime ether **1.51** and cyclization of the resulting benzoxyamine followed by hydrogenolysis afforded *N*-hydroxy azetidine **1.52**. Oxidation with "active lead (IV) oxide" afforded intermediate unsaturated azetidine *N*-oxide **1.53**, which was found to be unstable and required trapping through [3+2]-cycloaddition to afford isoxazoline **1.54** (Scheme 1.9). This report further highlighted the need for stable azetidine precursors in order to perform controlled reactivity studies to access diverse azetidine scaffolds other than [3+2]-cycloaddition products.

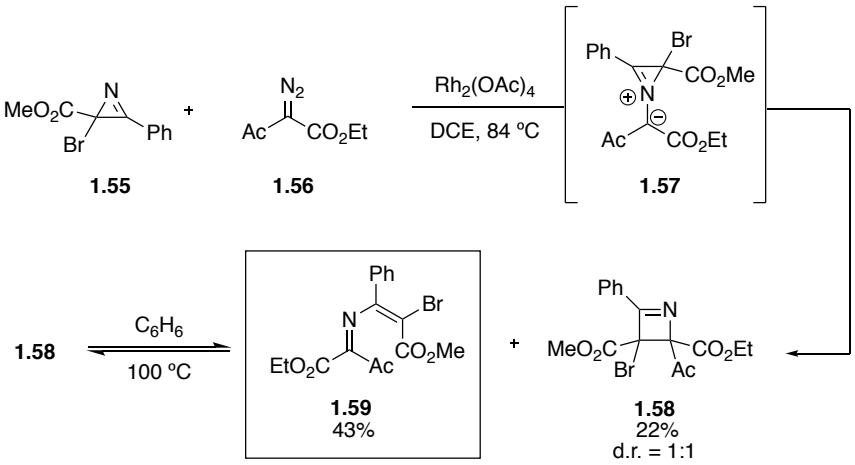


1.51 **1.52** **1.53** **1.54**

Scheme 1.9 Accessing azetidine *N*-oxides via oxidation of *N*-hydroxy azetidines

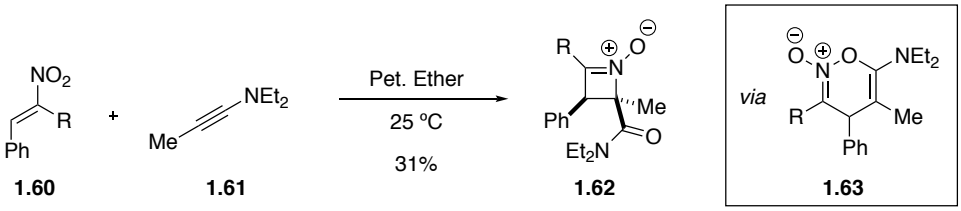
Recently, Novikov and coworkers[29] reported the generation of 2,3-dihydroazetes via treatment of substituted 2*H*-azirine **1.55** with a rhodium carbenoid generated from stabilized diazo compound **1.56** (Scheme 1.10). The authors proposed that azirinium ylide **1.57** was generated and underwent rearrangement and ring-opening to give 2-aza-1,3-butadienes **1.59** in modest yield, as well as 2,3-dihydroazete **1.58** as a 1:1 diastereomeric mixture. The authors postulated that **1.59** could be transformed to **1.58** during the reaction through 4π-electrocyclization. After isolating **1.59**, they found that

1.58 could be formed at elevated temperature as a 1:1 mixture of diastereomers. Because of these observations, it was proposed that this 4π-electrocyclization was reversible due to the instability of both **1.58** and **1.59**. While this method lends a level of modularity to the formation of azetidine precursors via 4π-electrocyclization, the instability of both the starting material azirine and diazo compounds, as well as instability of the products leaves room for improvements.



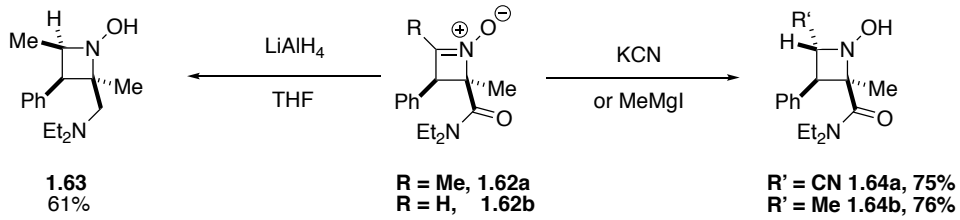
Scheme 1.10 4π-Electrocyclization of 2-azadienes to form dihydroazetes

An entry toward the generation of stable unsaturated azetidine *N*-oxides came from Reinhoudt[30] in 1982. Their work demonstrated that nitroolefin **1.60** could undergo cycloaddition with alkyne **1.61** to generate nitronate intermediate **1.63** (Scheme 1.11). The authors proposed that this intermediate then undergoes a [1,3]-sigmatropic rearrangement, forging a new C–N bond to afford azetidine *N*-oxide **1.62,** albeit in attenuated yield. This chemistry was limited to nitroolefins and side-products such as nitrocyclobutenes and 2-azetidine *N*-oxides were also generated during the course of the reaction, which caused the observed diminished yields.



Scheme 1.11 Azetidine nitrone synthesis via [1,3]-sigmatropic rearrangement

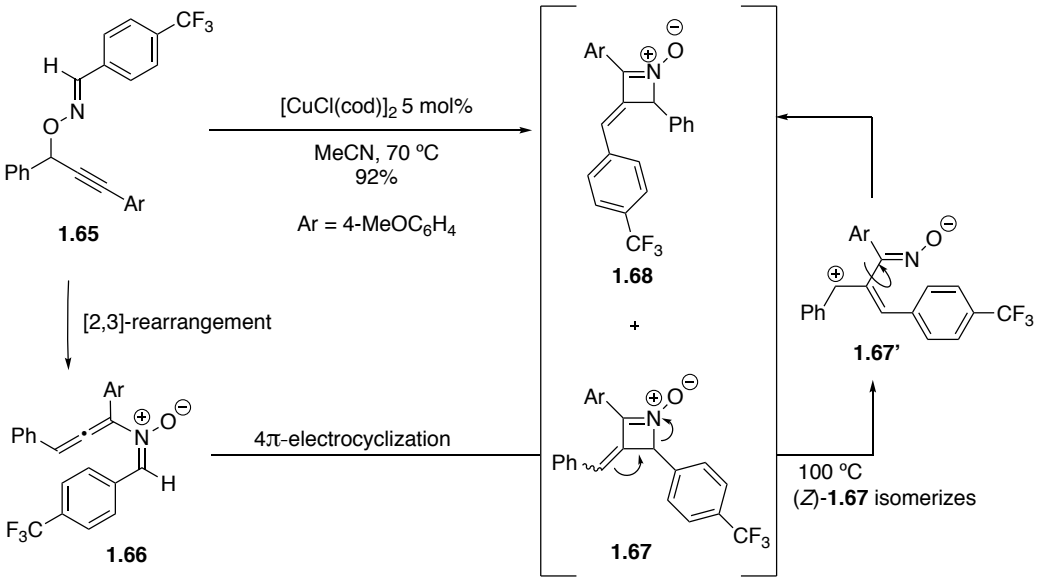
Shortly thereafter, Reinhoudt and coworkers examined the reactivity of the azetidine nitrones previously synthesized in their lab[31]. Treating azetidine nitrone **1.62a** with $LiAlH_4$ led to the reduced *N*-hydroxy azetidine amine **1.63**. Nucleophilic addition to **1.62b** afforded the corresponding *N*-hydroxy azetidines **1.64a** and **1.64b** (Scheme 1.12). These reports by Reinhoudt showed that not only could stable azetidine nitrones be accessed, they could be used to generate functionalized azetidines. A more general approach to these stabilized *N*-heterocycles could be used to access a wide array of azetidine-containing products.



Scheme 1.12 Azetidine nitrones as precursors for functionalized azetidines

As a more consistent alternative to the cycloaddition and rearrangement reactivity discovered by Reinhoudt, Nakamura and coworkers recently discovered a copper-catalyzed [2,3]-sigmatropic rearrangement of *O*-propargylic oxime ether[32] **1.65** to generate *N*-allenylnitrone intermediate **1.66**. This *N*-allenylnitrone undergoes 4π-electrocyclization to afford a mixture of azetidine nitrones **1.67** and **1.68** bearing an

exocyclic styrene (Scheme 1.13). To determine whether these products were independently formed, the authors investigated the thermal isomerization of (*E*)-**1.67** and (*Z*)-**1.67**. It was found that (*E*)-**1.67** was unreactive even when heated to 100 ºC, but (*Z*)-**1.67** underwent a proposed benzylic cation **1.67'** and cyclization to give **1.68** exclusively. This methodology lent evidence that it could be possible to construct unsaturated azetidine nitrones via 4π-electrocyclization of *N*-vinylnitrones; however a modular route to N-vinylnitrones was required to develop this desirable transformation.

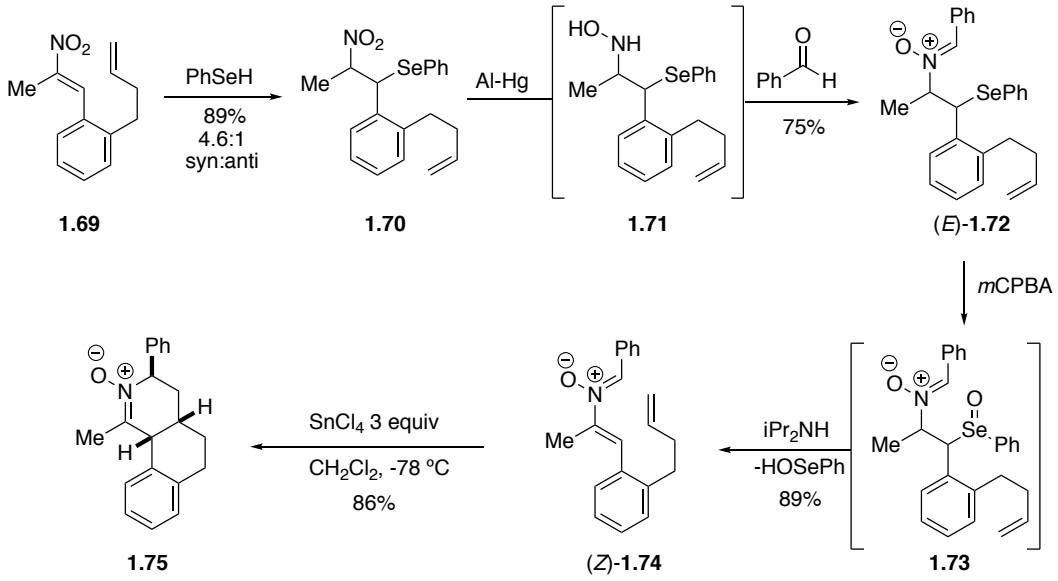


Scheme 1.13 4π-Electrocyclization of (*Z*)-*N*-allenylnitrone intermediate

1.1.5 Synthesis of *N*-Vinylnitrones and Their Reactivity

In late 2006, the Denmark group developed a novel method to access *N*-vinylnitrones in order to test their reactivity in [4+2]-cycloadditions to directly access piperidine scaffolds[33] (Scheme 1.14). This was an important discovery since *N*-vinyl nitrones cannot be prepared by traditional condensation techniques. The Denmark methodology began with hydroselenation of nitroolefin **1.69** to afford **1.70**. After reduction, the corresponding alkyl hydroxylamine **1.71** was condensed with

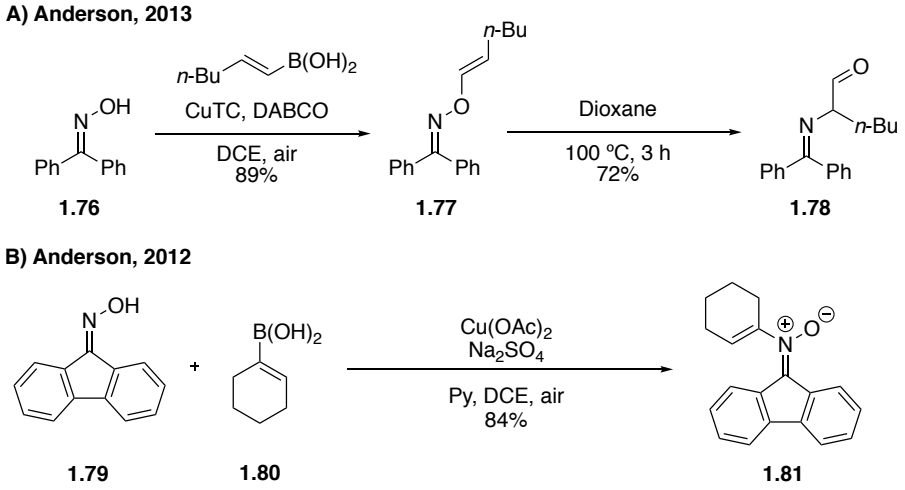
benzaldehyde to provide (*E*)-**1.72**. Finally, elimination of PhSeOH through *m*CPBA oxidation selectively led to formation of the (*Z*)-**1.74**. Subjection of this nitrone to super-stoichiometric $SnCl_4$ gave a single example of [4+2]-cycloaddition of a tethered alkene to yield piperidine nitrone **1.75**. This method established the first route to *N*-vinylnitrones and showed that these privileged heterocycles could be used as reactive intermediates in further reactions such as cycloaddition. However, the lengthy stepwise synthesis and use of selenium make this strategy problematic for a modular synthesis of *N*-vinylnitrones. A more mild and modular method would help to streamline *N*-vinylnitrone synthesis in order to further investigate their reactivity.



Scheme 1.14 First synthesis of *N*-vinylnitrones

The need for a concise modular synthesis of *N*-vinylnitrones and our group's previous work on *O*-vinylation for accessing *O*-vinyl oxime ethers led us to wonder if Chan-Lam coupling could be used to achieve *N*-vinylation of similar substrates. Our group first investigated the copper-mediated Chan-Lam coupling of keto-oxime **1.76** with vinylboronic acids and found efficient C–O bond formation occurred to afford *O*-vinyl

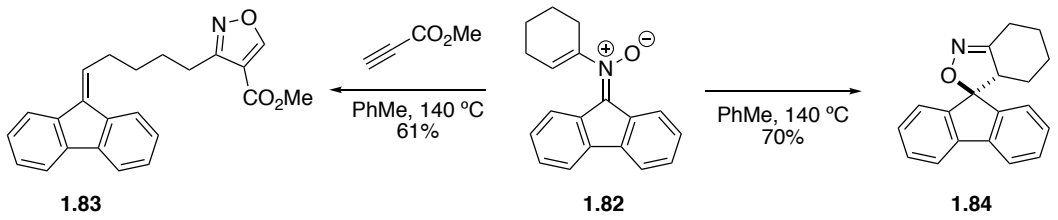
oxime ether[34] **1.77** (Scheme 1.15A). These substrates were then subjected to high temperature to trigger a [1,3]-sigmatropic rearrangement to give α-imino aldehyde **1.78**. Hoping to extend this reactivity to a diverse range of oxime substrates, fluorenone oxime **1.79** was employed under similar Chan-Lam coupling conditions with vinylboronic acid **1.80**. Pleasingly, the isolated product of this reaction was *N*-vinylnitrone[35] **1.81** (Scheme 1.15B). This lent an attractive alternative to the Denmark strategy for the synthesis of *N*-vinylnitrones and suggested that this reactivity could be used as a tool for the modular generation of *N*-vinylnitrones to be used for screening of 4π-electrocyclization.



Scheme 1.15 Chan-Lam coupling of ketooximes and vinylboronic acids

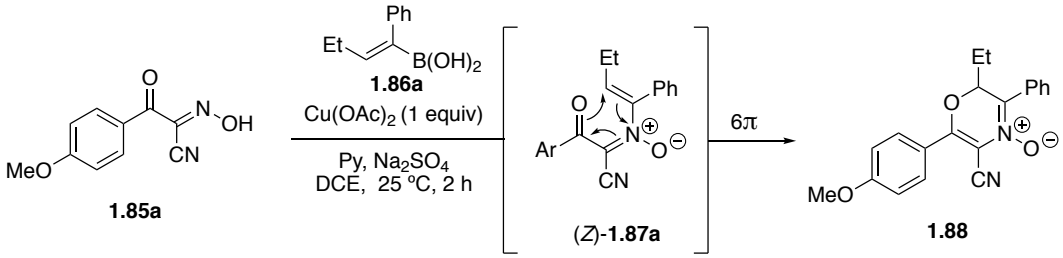
In the Anderson group's initial dissemination of a novel Chan-Lam coupling of ketooximes with vinyl boronic acids to afford *N*-vinylnitrones, the reactivity of 9-fluorenone nitrone **1.82** was studied[35]. It was found that this nitrone was reactive toward rearrangement and upon heating, novel spirocyclic isoxazoline **1.84** was formed. In the presence of Michael acceptors, 9-fluorenone tethered isoxazole **1.83** was isolated (Scheme 1.16). To further investigate the scope of these transformations, a diverse

selection of oxime precursors were screened in hopes that similar products could be formed.



Scheme 1.16 Reactivity studies of 9-fluorenone *N*-vinylnitrone[35] **1.82**

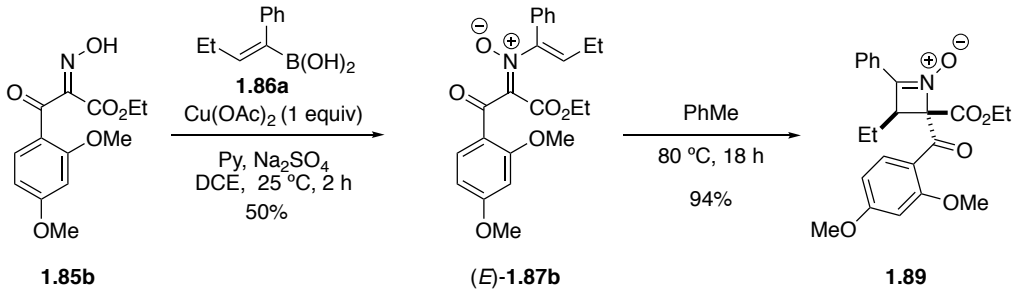
To examine the reactivity of alternative *N*-vinylnitrones, a variety of ketooximes were screened using the Chan-Lam reaction described in Scheme 1.15B. Electron-deficient oximes were shown to give excellent reactivity under these conditions. Surprisingly, when oxime **1.85a** was utilized with vinylboronic acid **1.86a**, unsaturated morpholine *N*-oxide **1.88** was formed, presumably via a 6π-electrocyclization of transient *N*-vinylnitrone[36] **1.87a** (Scheme 1.17). This pathway is favorable because of the relatively nucleophilic ketone situated in close proximity to the vinyl group in and because of the electron-deficient nature of (*Z*)-**1.87a**.



Scheme 1.17 6π-Electrocyclization of transient *N*-vinylnitrone **1.87a**

In order to determine if the transient *N*-vinylnitrone intermediate could be detected prior to 6π-electrocyclization, further testing of less electrophilic oxime substrates was performed. Ketoester oxime **1.85b** was employed in the Chan-Lam reaction with vinylboronic acid **1.86a** and after 2 hours, (*E*)-**1.87b** was isolated (Scheme

1.18). The nitrone isomer was confirmed via nOe analysis. Although this isomer was not the expected configuration for 6π-electrocyclization, we wondered if isomerization to the active isomer would occur with elevated temperature. By heating (*E*)-**1.87b**, unsaturated azetidine nitrone **1.89** was formed[37] (Scheme 1.18). It was proposed that this product was formed via 4π-electrocyclization of the (*E*)-isomer while the (*Z*)-isomer leads to 6π-electrocyclization to afford unsaturated morpholine *N*-oxide **1.88**. The potential for further functionalization of these products was envisioned because of the inherent reactivity embedded within the nitrone moiety.



Scheme 1.18 4π-Electrocyclization from (*E*)-nitrone isomer

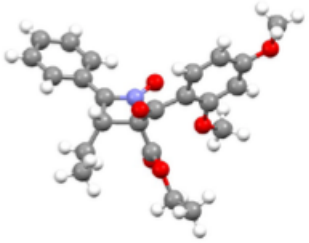
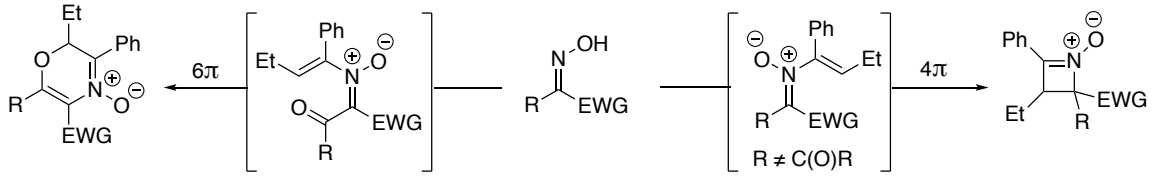


Figure 1.1 X-Ray Crystallography of **1.89** – Prof. Donald J. Wink

1.2 Initial Hypothesis

Based on our findings, it was reasoned that these 4π-electrocyclization and 6π-electrocyclization products could be accessed from the same ketone-bearing oxime, depending on reaction and isolation conditions. In the case of unsaturated morpholine *N*-

oxide synthesis, performing the reaction under standard Chan-Lam conditions leads to C–N bond formation followed by isomerization and spontaneous 6π-electrocyclization through a copper-mediated process. Isolation of the intermediate *N*-vinylnitrone and heating could lead exclusively to the azetidine nitrone. It was hoped that competing 6π-electrocyclization could be avoided by substituting the nucleophilic ketone substituent of the oxime for another electron-withdrawing group (Scheme 1.20). It was hoped that this divergent access to both products would provide a modular route to a diverse library of functionalized *N*-heterocycles.

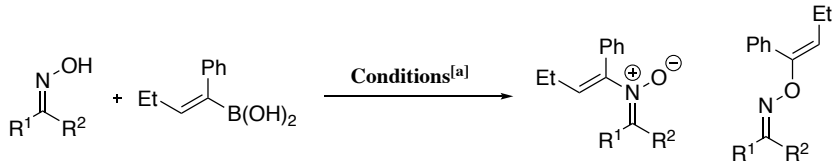


Scheme 1.19 Goal: Substrate design for selective azetidine formation

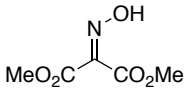
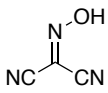
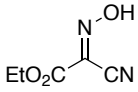
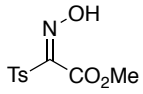
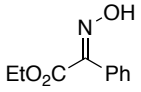
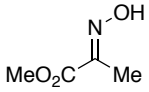
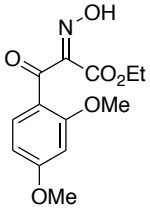
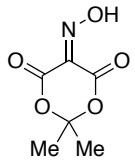
1.2.1 Optimization and Scope of *N*-Vinylnitrone Synthesis

Based on our previous success of C–N bond formation with ketoester oxime (*E*)-**1.90b** with vinyl boronic acid **1.86a**, the scope of the oxime reagent was investigated by screening of a variety of electron-deficient oximes with **1.86a** under standard Chan-Lam conditions (Table 1.1). It was found that dimethylmalonate oxime **1.90a** was most efficient for C–N coupling, affording only *N*-vinylnitrone **1.91a** in excellent yield and selectivity. Phenylglyoxalate oxime (*E*)-**1.90c** led to **1.91c** as the sole product. Oximes that gave a mixture of C–N and C–O coupling products included (*E*)-**190b** and pyruvate oxime (*E*)-**190g**. All other **1.90** tested resulted in decomposition or were unreactive under these conditions. These screenings hinted that the pKa of **1.90** might have a strong

effect on the outcome of the Chan-Lam reaction. Oxime **1.90a** has a calculated pKa of about 5.59 (95% MeCN/H_2O[38]). Lower pKa oximes such as (*E*)-**1.90b** (4.36 in 95% MeCN/H_2O) perform poorly giving a mixture of products in low yield. Higher pKa oximes such as benzaldehyde oxime (20.2 in DMSO[39]) were unreactive, resulting in hydrolysis of the oxime substrate. It was postulated that the pKa of oxime **1.90** should be between 5.5 – 6.5 in order to selectively form *N*-vinylnitrones in high yield. These parameters were important for future expansion of our nitrone synthesis and functionalization.



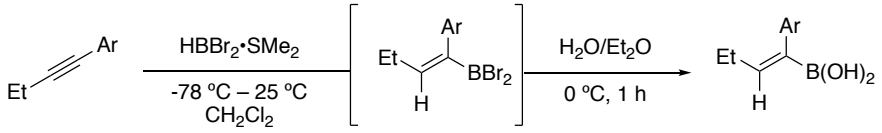
1.90 **1.86a** **1.91** **1.91'**

Entry	Oxime	% Yield 1.91/1.91'[b]	Entry	Oxime	% Yield 1.91/1.91'[b]
1	 **1.90a**	95/0	5	 **1.90e**	0/0
2	 (*E*)-**1.90b**	42/40	6	 (*E*)-**1.90f**	0/0
3	 (*E*)-**1.90c**	63/0	7	 (*E*)-**1.90g**	19/10
4	 (*E*)-**1.90d**	50/0	8	 **1.90h**	0/0

[a] Conditions: $Cu(OAc)_2$ (1 equiv), **1.86a** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1M DCE, 25 ºC, 18 h, air [b] %Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference. Py = pyridine, DCE = 1,2-dichloroethane.

Table 1.1 Oximes tested under Chan-Lam reaction conditions with **1.86a**

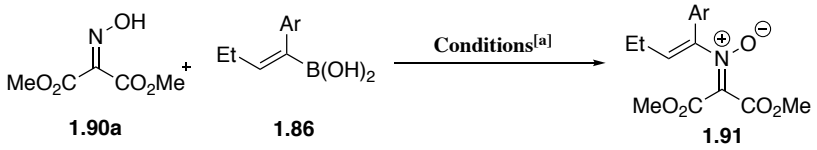
After determining the optimal oxime substrate to be **1.90a**, the scope of the vinylboronic acid **1.86** was investigated. As was the case in the previously reported synthesis of unsaturated morpholine *N*-oxides by our group, vinylboronic acids bearing an α-aryl substituent and an alkyl group at the β-position proved to be the best coupling partner for this reaction. Because of this fact, a robust and general procedure had to be developed in order to produce these reagents. Previous reports from our lab in the synthesis of **1.86** gave sloppy reagents, which provided inconsistent results, making optimization troublesome. By modifying the method for quenching used in the previous method, a scalable preparation of **1.86** was developed which gave a reagent that was easy to handle and store and gave consistent results in our coupling reactions (Scheme 1.20, see Supplemental Materials for modification to previous literature). Using the previous method, 5 equivalents of **1.86** were required to obtain 95% yield, however with this modified procedure, only 2.5 equivalents could be used and only a slight decrease in yield to 79% was observed.



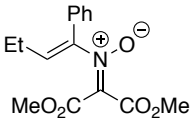
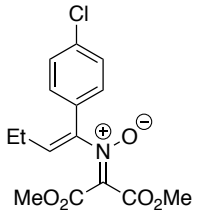
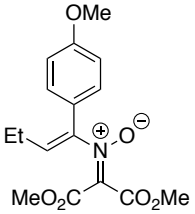
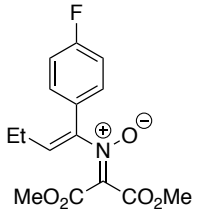
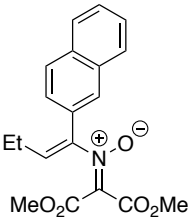
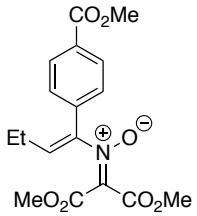
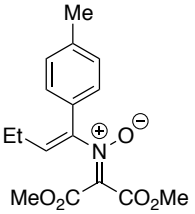
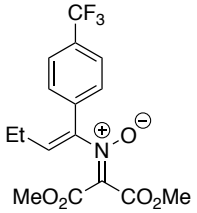
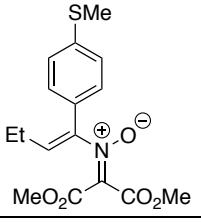
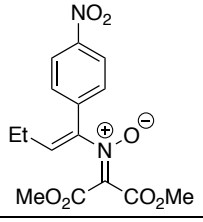
Scheme 1.20 Modified vinylboronic acid synthesis

With these vinylboronic acids in hand, it was found that optimal results were attained when 5 equivalents were used in the coupling reaction utilizing **1.90a** and **1.86a**, resulting in 95% of **1.91a** (Table 1.2). Both electron-withdrawing and electron-donating groups on the aryl ring were well tolerated, however it was found that strongly electron-donating **1.90b**, **1.90d**, and **1.90e** resulted in a small amount of 4π-electrocyclization in the Chan-Lam reaction mixture. At extended reaction times, electron-withdrawing **1.87f-**

j resulted in dimerization of the **1.91f-j**, which was confirmed by HRMS. Gratifyingly, this could be avoided by monitoring the reaction progress closely by TLC and stopping the reaction after complete consumption of **1.86a**, typically within 2-6 hours. These mechanistic parameters were essential for efficient *N*-vinylnitrone synthesis.



1.90a **1.86** **1.91**

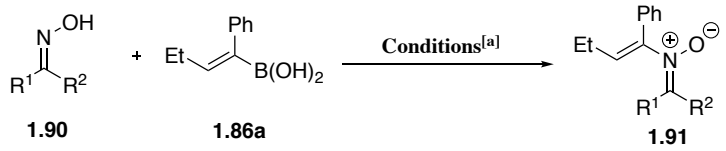
Entry	Nitrone	%Yield[b]	Entry	Nitrone	%Yield[b]
1	 **1.91a**	95 79%[f]	**6**	 **1.91f**	82[c]
2	 **1.91b**	75	**7**	 **1.91g**	85[c]
3	 **1.91c**	60	**8**	 **1.91h**	75[c]
4	 **1.91d**	77	**9**	 **1.91i**	86[d]
5		51	**10**		76[e]

1.91e	1.91j

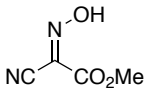
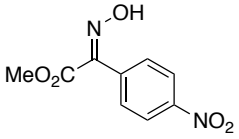
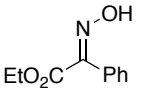
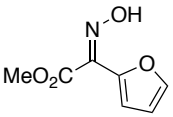
[a] Conditions: $Cu(OAc)_2$ (1 equiv), **1.90a** (1 equiv), **1.86** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1M in DCE, 25 ºC, air, 2 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Isolated yield. [c] reaction time: 8 h [d] reaction time: 6 h. [e] reaction time: 5 h. [f] Conditions: **1.90a** (1 equiv), **1.86a** (2.5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1M in DCE, 25 ºC, air, 3 h.

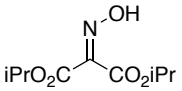
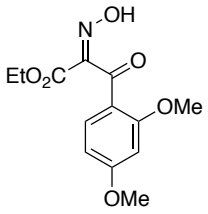
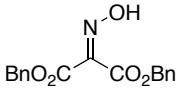
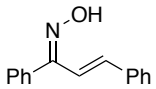
Table 1.2 Scope of boronic acid **1.86** for *N*-vinylnitrone formation

Since it was clear that a wide scope of these vinylboronic acids were shown to give the desired *N*-vinylnitrones in high yield, the scope of the oxime substitution was investigated next. It was already known that strongly withdrawing groups such as esters resulted in the most efficient coupling, so oximes bearing at least one ester were targeted (Table 1.3). Changing the esters in **1.90j** and **1.90k** resulted in slightly diminished yields, while changing the electronics of the aryl groups in (*E*)-**1.90l** and (*E*)-**1.90m** gave comparable results to that of (*E*)-**1.90i**. Chalcone oxime **1.90n** also showed C–N coupling under slightly modified Chan-Lam reaction conditions. These entries gave an expanded variety of *N*-vinylnitrones and allowed us to investigate the scope of the reactivity of 4π-electrocyclization.



1.90 **1.86a** **1.91**

Entry	Nitrone	%Yield[b]	Entry	Nitrone	%Yield[b]
1	 **1.90b**	42	**6**	 (*E*)-**1.90l**	77
2	 (*E*)-**1.90i**	63	**7**	 (*E*)-**1.90m**	63

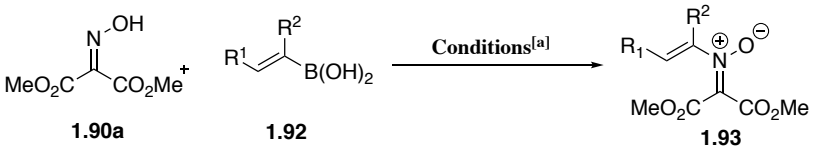
3	 **1.90j**	79	**8**	 **1.90d**	50
4	 **1.90k**	61	**9**	 **1.90n**	57[c]

[a] Conditions: $Cu(OAc)_2$ (1 equiv), **1.90** (1 equiv), **1.86a** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1M in DCE, 25 ºC, air, 18 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Isolated yield. [c] COD as ligand

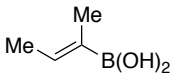
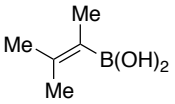
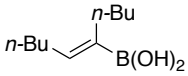
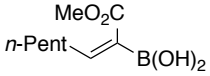
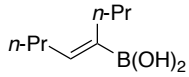
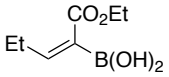
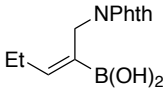
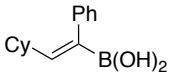
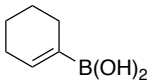
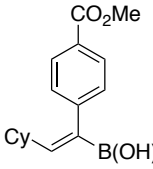
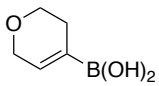
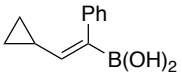
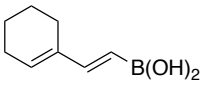
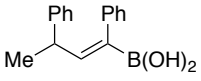
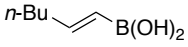
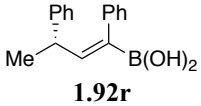
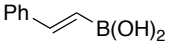
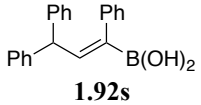
Table 1.3 Scope of unsymmetrical oximes **1.90** for *N*-vinylnitrone formation

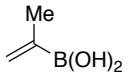
Having established that a range of electron-deficient oximes could be used to efficiently generate a library of *N*-vinylnitrones using **1.86**, we wondered if other vinylboronic acids not bearing an α-aryl group could participate in this Chan-Lam coupling reaction to give the desired reactivity (Table 1.4). Thus, vinylboronic acids derived from internal alkynes such as **1.92a-d** were tested and showed excellent reactivity. Cyclic alkyl vinylboronic acids **1.92e** and **1.92f** gave *N*-vinylnitrones in almost quantitative yield. Exchanging a proton for one of the alkyl substituents in **1.92g-j** gave attenuated yields. Fully substituted **1.92k** was successfully utilized, albeit in low yield. Next, the electronic nature of the boronic acid was studied by coupling **1.92l** and **1.92m**, which bear an α-ester substituent. Satisfyingly, these boronic acids also gave the *N*-vinylnitrone products. Finally, the sterics of the β-substituent was investigated. It was hypothesized that aryl substituted vinylboronic acids with secondary carbons at the β-position might be too sterically encumbered to participate in the coupling reaction, however **1.92n and 1.92o** gave the desired C–N coupling products. Interestingly, *N*-vinylnitrone from cyclopropyl-substituted **1.92p** could not be isolated and instead, the corresponding azetidine *N*-oxide was isolated. It was also postulated that a vicinal

stereocenter might direct the torquoselectivity of 4π-electrocyclization, so **1.92q** and **1.92r** were synthesized to test this hypothesis. These substrates were important to investigate since the steric environment could have an impact on the 4π-electrocyclization.



1.90a **1.92** **1.93**

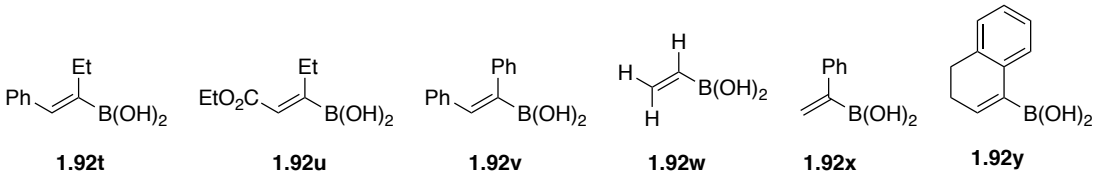
Entry	1.92	%Yield[b]	Entry	1.92	%Yield[b]
1	 **1.92a**	56	**11**	 **1.92k**	31
2	 **1.92b**	71	**12**	 **1.92l**	50
3	 **1.92c**	75	**13**	 **1.92m**	60
4	 **1.92d**	40	**14**	 **1.92n**	80
5	 **1.92e**	95	**15**	 **1.92o**	83
6	 **1.92f**	96	**16**	 **1.92p**	82[c]
7	 **1.92g**	81	**17**	 ***rac*-1.92q**	60
8	 **1.92h**	96	**18**	 **1.92r**	57
9	 **1.92i**	40	**19**	 **1.92s**	95

10	 **1.92j**	53

[a] Conditions: $Cu(OAc)_2$ (1 equiv), **1.90a** (1 equiv), **1.92** (3 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1M in DCE, 25 ºC, air, 18 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Isolated yield [c] only azetidine nitrone was isolated

Table 1.4 Scope of boronic acid derivatives **1.92** for formation of *N*-vinylnitrones

Through our successful establishment of Chan-Lam coupling to generate *N*-vinylnitrones, we also encountered some vinylboronic acids that failed to couple under our standard conditions. Specifically, 1-phenylbut-1-en-2-yl **1.92t**, acrylate **1.92u,** diphenyl **1.92v**, vinyl **1.92w**, α-styrenyl **1.92x**, and α-tetralone **1.92y** failed to give the desired *N*-vinylnitrones (Scheme 1.21). Also worth noting, any pinacol esters of boronic acids **1.86** or **1.92** were unreactive in this Chan-Lam reaction.



1.92t **1.92u** **1.92v** **1.92w** **1.92x** **1.92y**

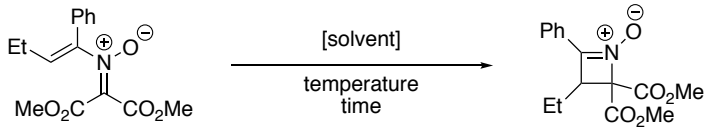
Scheme 1.21 Boronic acids that did not participate in the Chan-Lam reaction

1.2.2 Investigation of 4π-Electrocyclization Reaction Parameters

With a number of *N*-vinylnitrones in hand, reaction conditions were explored to determine optimal parameters of 4π-electrocyclization for the conversion to azetidine nitrones. Utilizing *N*-vinylnitrones **1.90a** and **1.93a** as model substrates, solvents were first tested at room temperature and conversion was measured by ^{1}HNMR spectroscopic analysis.

First, a range of solvents was tested for conversion at room temperature. In almost all solvents, low conversion of **1.90a** was achieved, with moderate reactivity seen

in MeOH and DMSO (Table 1.6, entries 4 and 5). Increasing the temperature to 40 ºC resulted in increased conversion in all solvents, again with MeOH and DMSO giving the best reactivity and resulting in almost quantitative yield of azetidine nitrone **1.94a** (Table 1.6, entries 12 and13). Further increase of temperature to 60 ºC in MeOH and DMSO gave similar results (Table 1.5, entries 14 and 15). This data showed that aryl-substituted **1.90a** can be converted to **1.94a** most efficiently in MeOH and DMSO.



1.91a **1.94a**

Entry	Solvent	[M]	Temp. (ºC)	Time (h)	% Yield[a]
1	PhMe	0.1	25	18	11
2	DCE	0.1	25	18	39
3	THF	0.1	25	18	-
4	DMSO	0.1	25	18	51
5	MeOH	0.1	25	18	60
6	iPrOAc	0.1	25	18	29
7	CF_3Ph	0.1	25	18	20
8	PhMe	0.1	40	4	19
9	DCE	0.1	40	4	61
10	DMSO	0.1	40	4	77
11	MeOH	0.1	40	4	65
12	DMSO	0.1	40	18	>95
13	MeOH	0.1	40	18	>95
14	DMSO	0.1	60	18	Quant.
15	MeOH	0.1	60	18	Quant.

[a] % Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference.

Table 1.5 Optimization for 4π-electrocyclization of **1.91a**

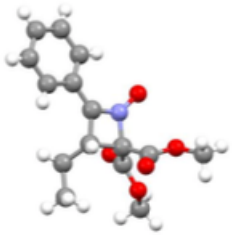
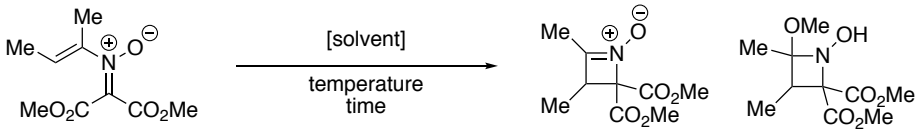


Figure 1.2 X-Ray Crystallography of **1.91a** – Prof. Donald J. Wink

When screening for conversion of **1.93a**, a more narrow range of solvent and temperature tolerance was observed for conversion to **1.95a**. In nonpolar solvents, very low conversion was observed at 40 ºC and decomposition was observed at 60 ºC (Table 1.6, entries 6-10). Once again, in MeOH and DMSO, modest conversion to azetidine nitrone **1.95a** was observed at low temperatures (Table 1.6, entries 1-3). In MeOH at 40 ºC, quantitative conversion of **1.93a** to **1.95a** was achieved, however further temperature increase led to the formation of hemiaminal **1.95a'** (Table 1.6, entry 4). Due to this undesirable byproduct formation, the optimal solvent and temperature was chosen to be anhydrous MeOH at 40 ºC for 18 h.



1.93a **1.95a** **1.95a'**

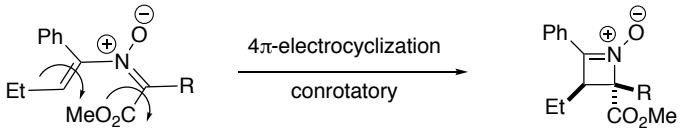
Entry	Solvent	[M]	Temp. (ºC)	Time (h)	% Yield[a]
1	MeOH	0.1	25	18	39
2	DMSO	0.1	40	18	46
3	MeOH	0.1	40	8	31
4	MeOH	0.1	40	18	97
5	MeOH	0.1	60	18	27[b]
6	PhMe	0.1	40	18	18
7	PhMe	0.1	60	18	dec.
8	iPrOAc	0.1	40	18	11

9	iPrOAc	0.1	60	18	dec.
10	DCE	0.1	40	18	49

[a] %Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference.
[b] Hemiaminal **1.95a'** was formed in 27% yield.

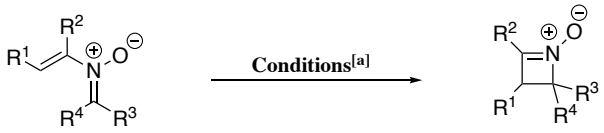
Table 1.6 Optimization for 4π-electrocyclization of **1.93a**

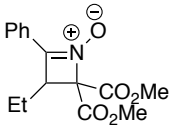
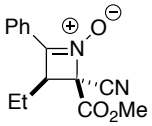
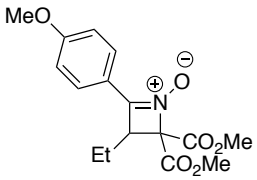
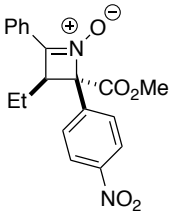
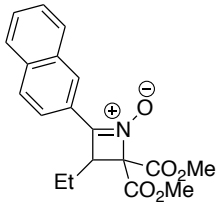
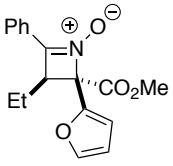
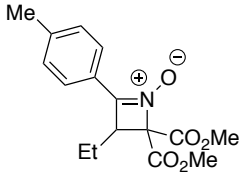
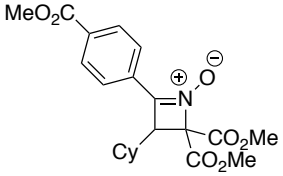
With optimal conditions for 4π-electrocyclization established, the previously discussed *N*-vinylnitrones **1.91** and **1.93** were converted to **1.94** and **1.95**. Substituted aryl rings at the α-position gave high yields of the corresponding azetidine nitrones (Table 1.7, entries 1-9). Differentiating the ester substitution resulted in comparable conversion (Table 1.7, entries 10-11). Nitrones derived from unsymmetrical oximes showed excellent reactivity under these conditions and provided unsymmetrical azetidine nitrones as a single diastereomer dependent on the nitrone isomer (Table 1.7, entries 12-16) suggesting that this 4π-electrocyclization occurs via a conrotatory motion (Scheme 1.22). Secondary carbons at the β-position of the vinyl group also showed high conversion to the desired products (Table 1.7, entries 17-21). It is worth noting that an enantiodefined stereocenter did not control the torquoselectivity of 4π-electrocyclization for **1.94u**. Alkyl substrates also showed reactivity to afford a range of substituted azetidine nitrones (Table 1.7, entries 22-25). Surprisingly, trisubstituted *N*-vinylnitrone bearing three methyl groups cleanly afforded the desired product, albeit in attenuated yield.

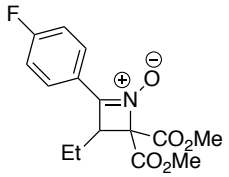
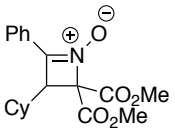
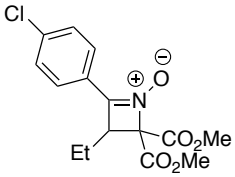
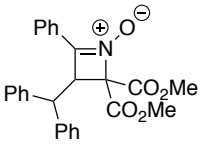
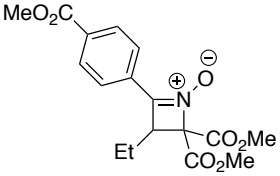
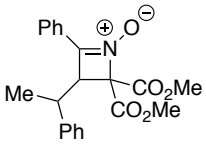
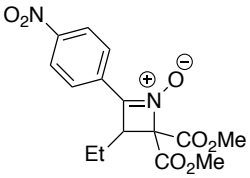
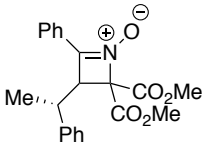
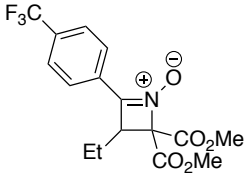
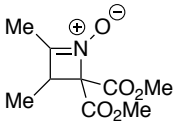
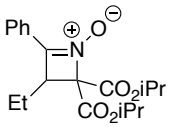
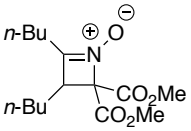
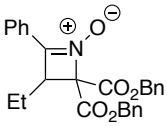
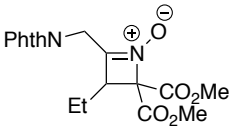
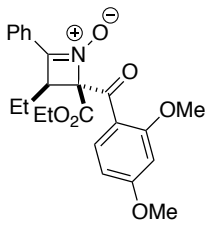
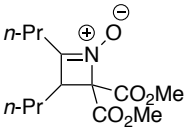


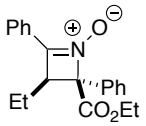
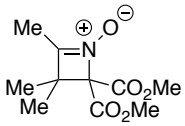
Scheme 1.22 Conrotatory 4π-electrocyclization

In the case of cyclic alkyl *N*-vinylnitrone **1.93e**, attempts at inducing 4π-electrocyclization under standard conditions resulted in the isolation of interesting isoxazolidines **1.96a** and **1.96b**, presumably due to alcohol addition to an oxaziridine intermediate (Scheme 1.23). Regardless, this showed that a library of substituted unsaturated azetidine *N*-oxides could be accessed from *N*-vinylnitrones via a mild and modular pathway to afford azetidine scaffold precursors that could be further functionalized to efficiently generate substituted azetidines.



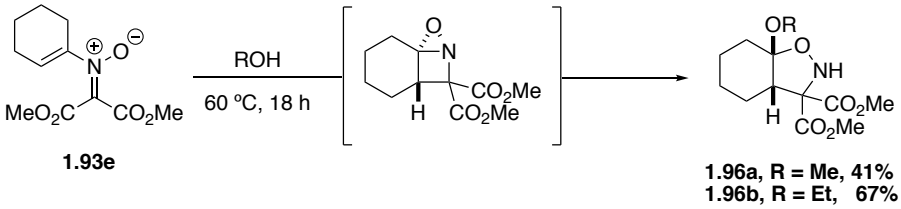
Entry		% Yield[b]	Entry		% Yield[b]
1	 **1.94a**	98	**14**	 **1.94n**	95[c]
2	 **1.94b**	95	**15**	 **1.94o**	93[c]
3	 **1.94c**	88	**16**	 **1.94p**	95[c]
4	 **1.94d**	95	**17**	 **1.94q**	45

5	 **1.94e**	93	**18**	 **1.94r**	91
6	 **1.94f**	90	**19**	 **1.91s**	95
7	 **1.94g**	93	**20**	 **1.94t**	92
8	 **1.94h**	83[d]	**21**	 **1.94u**	90[e][f]
9	 **1.94i**	94	**22**	 **1.95a**	97
10	 **1.94j**	87	**23**	 **1.95b**	79
11	 **1.94k**	90	**24**	 **1.95c**	68
12	 **1.89**	95[c]	**25**	 **1.95d**	82

13	 **1.94m**	94[c]	**26**	 **1.95e**	30

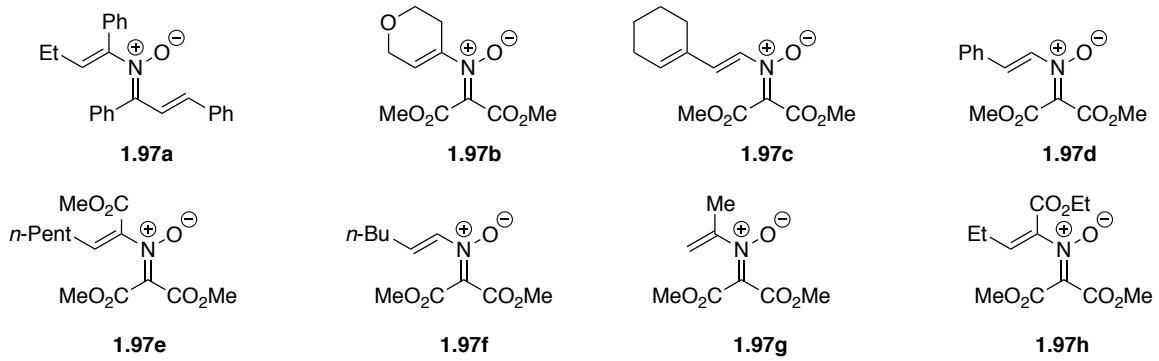
[a] Conditions: 0.1M in MeOH, 40 ºC, 18 h. [b] Isolated yield. [c] d.r. = ≥20:1 [d] DMSO, 60 ºC, 18 h [e] d.r. = 1:1 [f] 0.1 M in PhMe, 80 ºC, 18 h.

Table 1.7 Scope of 4π-electrocyclization of *N*-vinylnitrones



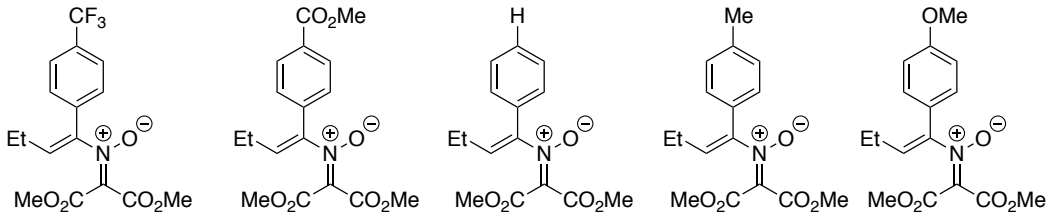
Scheme 1.23 Isoxazolidine formation from nitrone **1.93e**

Despite the robust and wide ranging tolerance of the thermal 4π-electrocyclization of these *N*-vinylnitrones, a few substrates showed no reactivity in this transformation (Scheme 1.24). Notably, chalcone nitrone **1.97a**, which has previously been shown to be reactive in a thermal rearrangement for the formation of substituted pyridines[41], was not reactive under these conditions for 4π-electrocyclization. Analogous to observation of **1.93e**, **1.97b** showed no 4π-electrocyclization product formation. The *N*-vinylnitrones **1.97c-f** were also screened under these conditions and their corresponding azetidine nitrones were not isolated due to messy reactions, low conversion, and unstable products. This can be attributed to the relatively low stability of the resulting unsaturated azetidine *N*-oxide, which does not have a stabilizing group on the iminium carbon, and thus is prone to hydrolysis, rearrangement, and decomposition. Ester substituted **197e** and **1.97h** were also shown to be unreactive perhaps due to the electronic destabilization of the transition state of 4π-electrocyclization.



Scheme 1.24 Unreactive **1.97** in thermal 4π-electrocyclization reaction

In order to further evaluate the mechanistic details of this 4π-electrocyclization, a variety of *N*-vinylnitrones were chosen for a Hammett study (Scheme 1.25). Five substrates bearing substituents on the aryl ring that are electron withdrawing (**1.91h** and **1.91i**) and electron donating (**1.91b** and **1.91d**) were chosen, along with neutral **1.91a**. Variable temperature reaction monitoring by ^{1}H NMR spectroscopy was performed for each substrate to determine rate constants for 4π-electrocyclization at 50 ºC in PhMe-*d*8. These rates were then plotted against the σ-value to obtain a linear correlation (Figure 1.1). By graphing the σ_p value vs. Log(k_R/k_H), a strong linear correlation is obtained with a slope of -0.5275, suggesting that the 4π-electrocyclization is proceeding through an intermediate with a buildup of partial cationic character at the imine carbon, as evidenced by the relative rate of **1.91b** being nearly two times faster than that of **1.91i**. This gave us important kinetic parameters, which are crucial for future synthetic reactivity studies of these privileged structures. Additional Hammett studies at different temperatures need to be performed to determine if the Hammett value of <1 is due to an approaching isokinetic point.



	1.91i	1.91h	1.91a	1.91d	1.91b
σ_p =	0.54	0.45	0	-0.17	-0.27

Scheme 1.25 Nitrones **1.91** utilized in 4π-electrocyclization Hammett Study

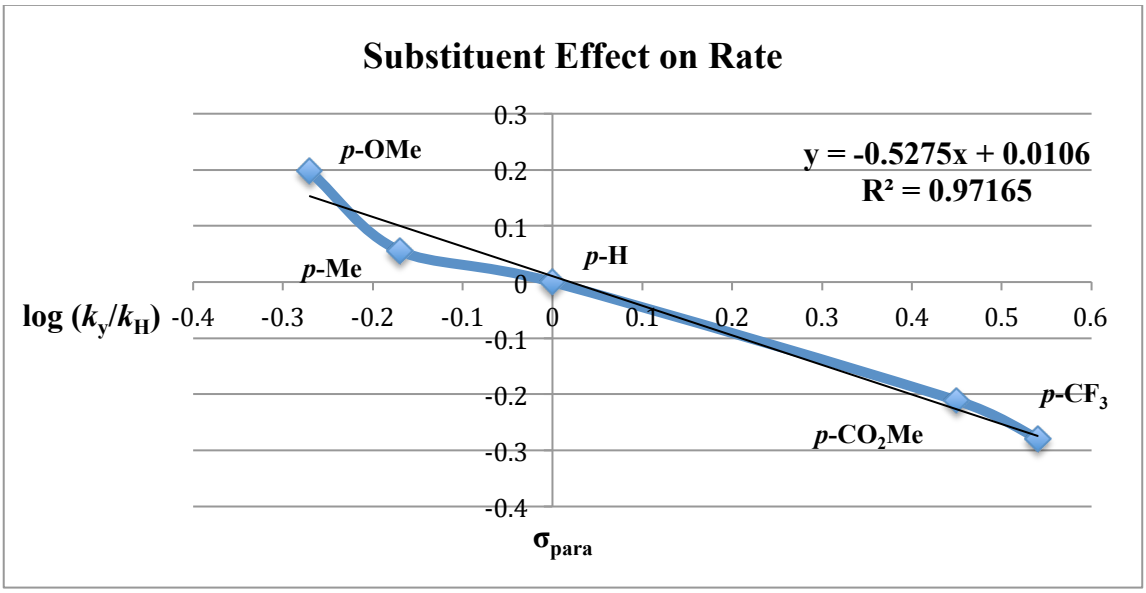


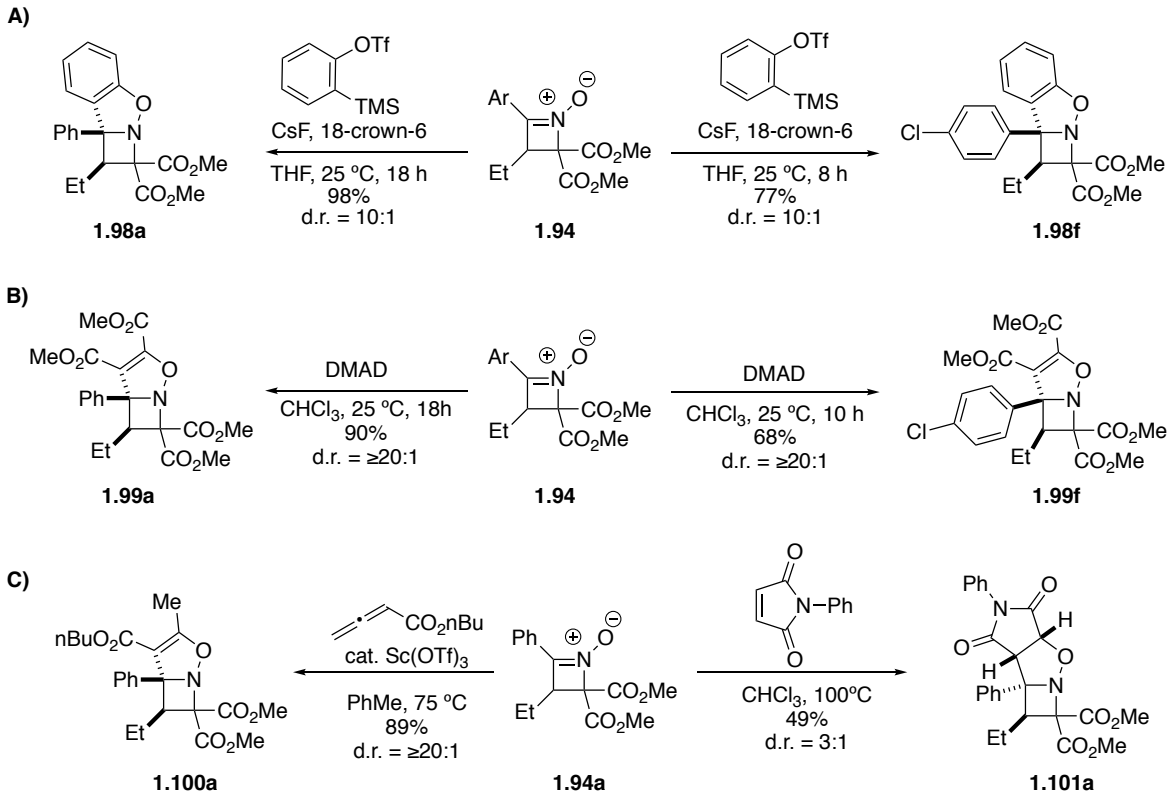
Figure 1.3 Hammett plot of 4π-electrocyclization

With the optimization, scope, and mechanistic details elucidated, it was postulated that these unsaturated azetidine *N*-oxides might be suitable substrates for a myriad of functionalization reactions. If successful, this would result in the rapid construction of densely substituted azetidine scaffolds and might lend the possibility of accessing a broad range of unique azetidine products. It was hoped that these functionalization studies

might offer a synthetic alternative to the problematic nucleophilic displacement reactions associated with azetidine synthesis in the past.

1.2.3 Cycloaddition Reactions of Azetidine Nitrones

Having established a robust and efficient route to azetidine *N*-oxide that have inherent reactivity embedded within the nitrone functionality, studies on the synthetic utility were begun. The most common functionalization of nitrones is through cycloaddition chemistry to generate isoxazolidine, isoxazoline, and further rearrangement products. Analogous cycloadditions to those previously reported in the [3+2]-cycloaddition of unsaturated morpholine *N*-oxide from our lab were attempted. First, azetidine nitrones **1.94a** and **1.94f** were subjected to reaction with in-situ generated benzyne to efficiently generate fused isoxazolines **1.95a** and **1.95f** (Scheme 1.26A). Next, these same unsaturated azetidine *N*-oxides could be diastereoselectively added via cycloaddition to electron-deficient DMAD to afford isoxazolines **1.99a** and **1.99f** (Scheme 1.26B). Cycloaddition with an electron-deficient allenoate gave **1.100a** as a single diastereomer, while cycloaddition with *N*-phenylmaleimide afforded **1.100a** in attenuated yield and diminished selectivity (Scheme 1.26C). These products represent an efficient, mild, and modular route to a novel class of fused bicyclic azetidines, which could find use in drug discovery and natural product synthesis, but we wondered if more could be done to functionalize azetidine nitrone **1.94a**.



Scheme 1.26 [3+2]-cycloaddition of azetidines **1.94a** and **1.94f**

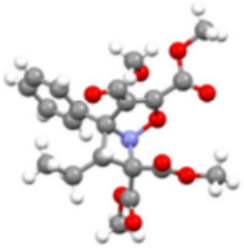
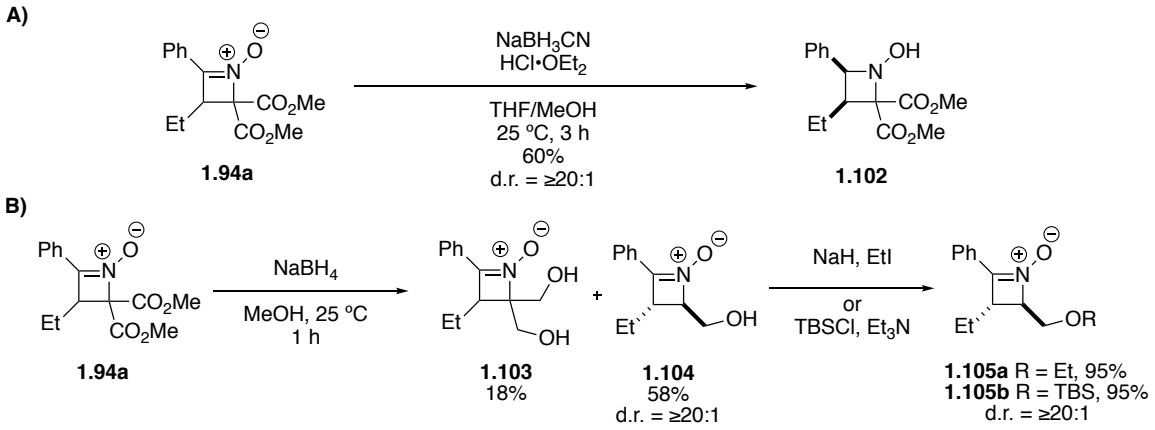


Figure 1.4 X-Ray Crystallography of **1.99a** (CCDC 1551509) – Prof. Donald J. Wink

1.2.4 Reduction of Azetidine Nitrones

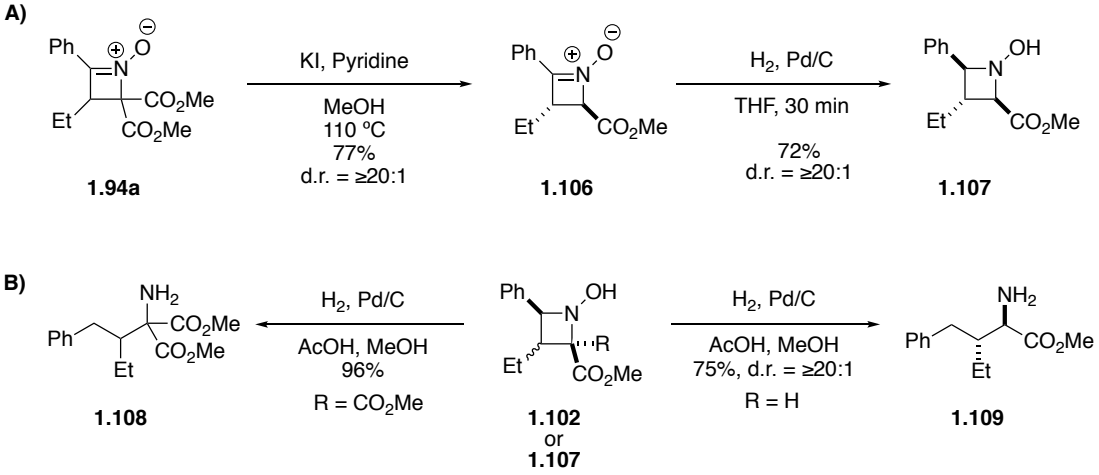
To determine the reactivity of these azetidine nitrones, the reduction of strained azetidine nitrones was explored through traditional reductive methods. The resulting *N*-hydroxy azetidines could be used as useful synthetic intermediates in a number of organic transformations such as electrophilic amination, deoxygenation, and oxidative

sulfonylation. Initial efforts using $NaBH_3CN$ were successful at reducing the nitrone functionality in **1.94a** to afford *N*-hydroxy azetidine **1.102** as a single diastereomer (Scheme 1.27A). With this result, it was postulated that other reducing agents might be employed. A stronger reducing agent, $NaBH_4$ was used and dramatically different reactivity was observed. Rather than reduction of the nitrone, surprisingly, a 3:1 mixture of diol **1.103** and alcohol **1.104** was obtained with the nitrone functionality intact (Scheme 1.27B). This lack of reactivity could be rationalized by the inherent stability of the azetidine *N*-oxide to reduction without activating the oxygen first. The alcohol **1.104** could then be protected as the ethyl ether **1.105a** or silyl ether **1.105b** in excellent yield as a single diastereomer. It was hypothesized that **1.103** was formed via a double reduction of the malonate esters, while alcohol **1.104** was formed through an initial nucleophilic hydride decarboxylation to generate $CH_{4(g)}$, $CO_{2(g)}$ and an amino ester, which is then reduced by $NaBH_4$. The mechanism of this dealkoxycarbonylation has been studied in detail in the past. With this knowledge, it was hoped the reactivity could be leveraged to access other reduced azetidine *N*-oxides.



Scheme 1.27 Borohydride reduction of azetidine nitrone **1.94a**

With the knowledge that **1.104** can be formed via dealkoxycarbonylation, we postulated that this transformation might be stopped before reduction to the alcohol. The Krapcho dealkoxycarbonylation reaction is known to selectively transform geminal-diesters to esters through nucleophilic attack of a "hard" anionic species. The byproducts are gaseous in nature and the reaction results in an enolate anion, which is protonated from solvent or from water. Azetidine nitrone **1.94a** was subjected to Krapcho conditions with KI as the nucleophile. (Scheme 1.28A) Gratifyingly, azetidine ester **1.106** was isolated as a single diastereomer. This unsaturated azetidine *N*-oxide was then reduced under standard Pd/C, H_2 conditions to give *N*-hydroxy azetidine **1.107.** Further hydrogenolysis of *N*-hydroxy azetidines **1.102** and **1.107** was achieved via hydrogenolysis in the presence of acetic acid to provide amino esters **1.108** and **1.109** (Scheme 1.28B).



Scheme 1.28 Dealkoxycarbonylation and hydrogenolysis of azetidines

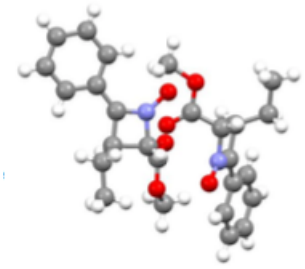
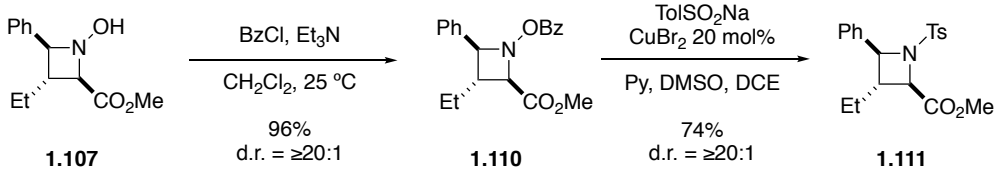


Figure 1.5 X-Ray Crystallography of **1.106** – Prof. Donald J. Wink

With functionalized *N*-hydroxy azetidines in hand, further synthetic utility was envisioned. Previous reports by Buchwald, Miura, and Bower have demonstrated elegant use of *N*-acyloxy amines as tools for electrophilic amination using copper, palladium, and ruthenium to achieve selective amination of alkenes, sulfinates, and alkynes. It was hoped that similar transformations could be leveraged with these hydroxylamine products. After efficient *O*-benzoylation of **1.107**, employing catalytic $CuBr_2$ in the presence of DMSO as an oxidant, sulfonylation of intermediate **1.110** with sodium *p*-toluenesulfinate was achieved, affording functionalized azetidine sulfonamide **1.11**. These sulfonamides could prove to be useful as antibiotic derivatives, as both sulfonamides and β-lactams have been known to exhibit high levels of antibiotic activity.

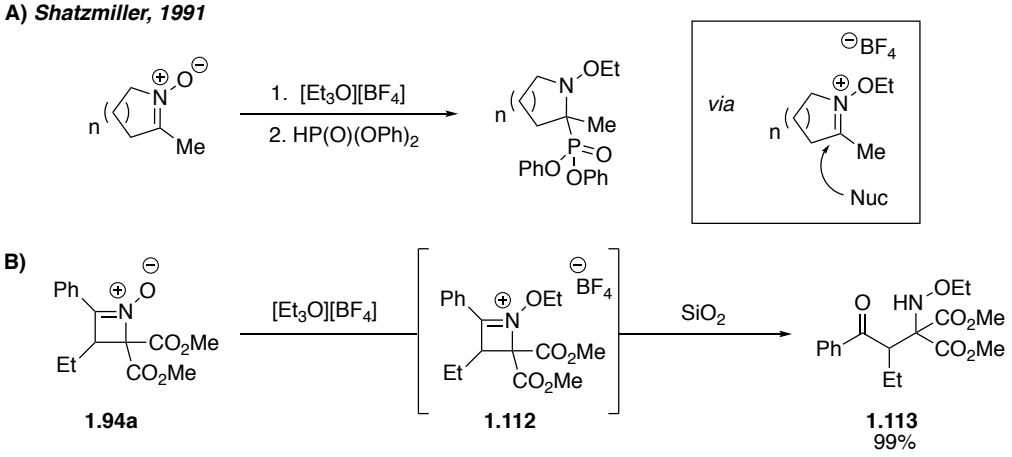


Scheme 1.29 Electrophilic amination for sulfonamide formation

1.2.5 Electrophilic Activation and Nucleophilic Trapping of Azetidine Nitrones

After having successfully achieved functionalization of unsaturated azetidine nitrones via borohydride reduction, hydrogenolysis, and dealkoxycarbonylation, we next

aimed at exploring the reactivity of the nitrone functionality of these products. Previous reports of *C*-alkylation of nitrones using Grignard reagents seemed like a logical place to start, however the functional groups of our substrates proved to be too reactive toward these reagents. It was clear that a more mild and general strategy would be necessary to utilize alkylation reactions of our azetidine nitrones.

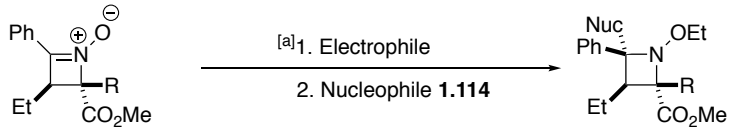


Scheme 1.30 Nucleophilic addition to electrophile activated nitrones

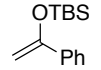
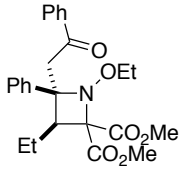
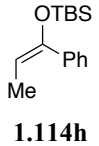
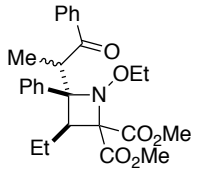
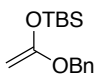
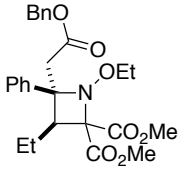
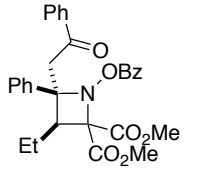
One report from the Shatzmiller lab[42] involved activation of cyclic nitrones with Meerwein's salt to generate an iminium ion, which could then be trapped by phosphinic acids (Scheme 1.30A). This method was intriguing as it used relatively mild activation conditions and was trapped by a mild nucleophile. It was hypothesized that we could harness the propensity of nitrones toward *O*-alkylation by Meerwein's salts to activate our unsaturated azetidine *N*-oxides toward nucleophilic addition. In that case, the intermediate iminium azetidine might be trapped by a variety of mild nucleophiles. After addition of $[Et_3O][BF_4]$ to a CH_2Cl_2 solution of **1.94a**, a noticeable change was immediately observed by TLC. Hoping to isolate the intermediate *N*-ethoxy azetidinium salt **1.112**, subsequent SiO_2 column chromatography resulted in isolation of ring-opened

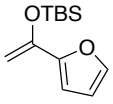
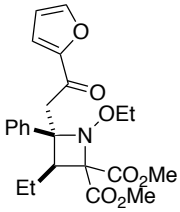
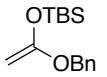
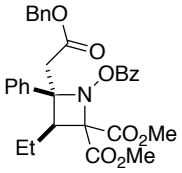
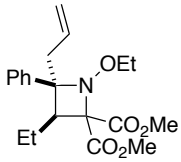
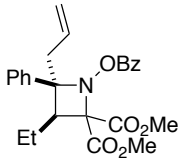
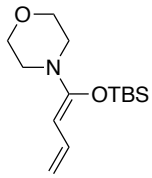
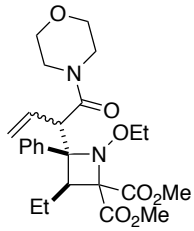
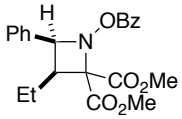
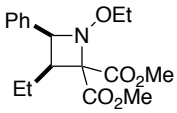
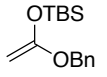
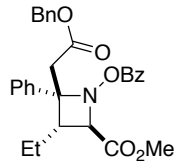
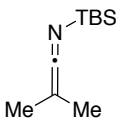
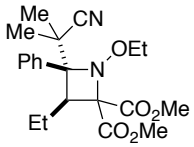
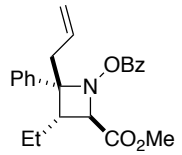
β-amino ketone **1.113**, formed through hydrolysis of **1.112** (Scheme 1.30B). Hoping to trap **1.112**, in-situ trapping with nucleophiles was proposed.

Azetidine *N*-oxide **1.94a** was activated with Meerwein's salt, followed by slow addition of silyl enol ethers **1.114a** and **1.114c**, allyltributylstannane **1.114d**, and silyl ketene acetal **1.114b** to trap **1.112**. These products were afforded as a single diastereomer and in excellent yield to efficiently generate a variety of densely substituted azetidine scaffolds (Table 1.8, entries 1-4). Conjugated silyl amidyl ether **1.114e** gave a mixture of diastereomers with attenuated yield, while trapping with tin hydride resulted in poor yield and selectivity (Table 1.8, entries 5 and 6). Silyl ketene imine **1.114g** was found to be incompatible under these conditions (Table 1.8, entry 7), as was the case for sterically encumbered **1.114h** (Table 1.8, entry 8). Other nucleophiles such as aryl aluminum, arylzinc, aryl Grignard, azide, and alcohols were unsuccessful and resulted in either decomposition or hydrolysis when subjected to SiO_2.



1.94a/1.106 **1.115**

Entry	Nuc	Product	% Yield[d] (d.r)	Entry	Nuc	Product	% Yield[d] (d.r)
1	 **1.114a**	 **1.115a**	69[a] (≥20:1)	**8**	 **1.114h**	 **1.115h**	–[a]
2	 **1.114b**	 **1.115b**	97[a] (≥20:1)	**9**	 **1.114a**	 **1.115i**	70[b] (2:1)

3	 **1.114c**	 **1.115c**	68[a] (≥20:1)	**10**	 **1.114b**	 **1.115j**	73[b] (4:1)
4	**1.114d**	 **1.115d**	72[a] (≥20:1)	**11**	**1.114d**	 **1.115k**	95[b] (1:1)
5	 **1.114e**	 **1.115e**	51[a] (3:1)	**12**	Bu_3SnH **1.114f**	 **1.115l**	50[b] (1:1)
6	$HSnBu_3$ **1.114f**	 **1.115f**	25[a] (2:1)	**13**	 **1.114b**	 **1.115m**	73[c] (≥20:1)
7	 **1.114g**	 **1.115g**	–[a]	**14**	**1.114d**	 **1.115n**	85[c] (≥20:1)

[a] Conditions: 1. **1.94a** (1 equiv), $[Et_3O][BF_4]$ (1.1 equiv). 0.1 M CH_2Cl_2, 25 ºC, 30 min; 2. Nuc (2 equiv), 0.1 M CH_2Cl_2, 0–25 ºC. [b] Conditions: 1. **1.94a** or **1.106** (1 equiv), BzCl (2 equiv), AgOTf (4 equiv), 0.03 M CH_2Cl_2, 0 ºC, 30 min; 2. Nuc (2 equiv), 0.01 M CH_2Cl_2, –78-25 ºC, 2–3 h. [c] Nuc added first, followed by electrophile. [d] Isolated Yield

Table 1.8 Nucleophilic trapping of activated **1.94a** and **1.106**

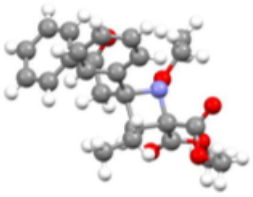
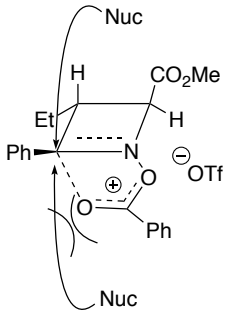


Figure 1.6 X-Ray Crystallography of **1.115a** – Prof. Donald J. Wink

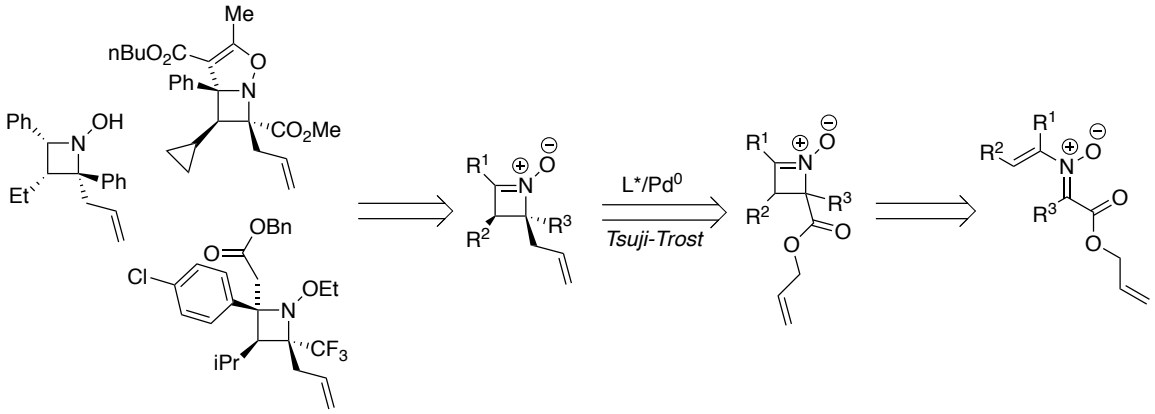
Other activation reagents were also explored. It was found that benzoyl chloride, benzoyl bromide, and benzoyl fluoride were successful in activating **1.94a**, however the reactions were messy and hard to reproduce. Benzoyl triflate was found to be much more consistent at activating the nitrone functionality. Furthermore, in-situ generation of benzoyl triflate was conveniently the most efficient condition. By introducing **1.94a** to the presence of benzoyl chloride and AgOTf to achieve complete activation, these azetidines could be trapped by the same nucleophiles used previously, however a substantial loss in selectivity was observed (Table 1.8, entries 9-12). By switching from **1.94a** to **1.106**, under the same conditions, diastereoselectivity was restored (Table 1.8, entries 13 and 14). This could be due to the stabilization of the cationic iminium intermediate from the face opposite of the ester group, which could cause steric repulsion resulting in facial selectivity of the approaching nucleophile (Scheme 1.31).



Scheme 1.31 Steric repulsion of approaching nucleophile

1.2.6 Future Goals

Our group plans to explore the enantioselective Tsuji-Trost allylation of these azetidine nitrones to achieve asymmetric allylation. This will allow us to access stereodefined azetidine nitrones with substituents which we are currently unable to access due to limitations with our Chan-Lam protocol. Once successful, we expect that the previously discussed diastereoselective functionalizations outlined in this work will be applicable to these substrates to access densely substituted chiral azetidine scaffolds. This will provide a highly valuable, mild & modular route toward enantiodefined azetidine-containing pharmaceutical targets and natural products.



Scheme 1.32 Future works: asymmetric Tsuji-Trost allylation of azetidine nitrones

1.3 Conclusion

To summarize, a mild and modular route to densely substituted azetidines has been realized. This method proceeds initially from a Chan-Lam reaction of keto-oxime and vinylboronic acids for the preparation of *N*-vinylnitrones, which then efficiently undergo thermal 4π-electrocyclization to afford intermediate unsaturated azetidine *N*-oxides. These reactive intermediates are then used in subsequent diastereoselective cycloaddition, reduction, and electrophilic activation/nucleophilic addition reactions to

afford functionalized azetidine scaffolds. This is a major advancement on the previous literature, as it allows azetidine construction in a mild facially-selective manner and allows for further functionality to be installed following azetidine construction. Further reactivity will be investigated in the future to advance these methods for potential use in structure-activity relationship studies.

1.4 Supporting Information

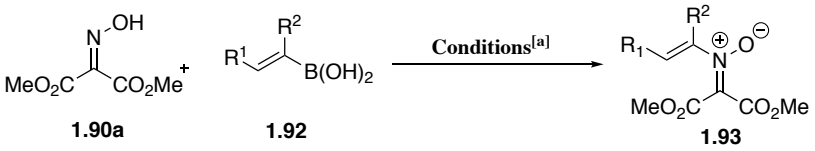
1.4.1 General Experimental Information

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded at ambient temperature using ATR sampling. High-resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed using force flow of the indicated solvent system down columns packed with 60 Å (40 – 60 μm) mesh silica gel (SiO_2). Samples purified by medium pressure liquid chromatography were dry-loaded onto celite. Unless otherwise noted, all reagents and solvents were obtained from commercial sources and, where appropriate, purified prior to use. Unless otherwise noted, all reactions were performed under N_2 using standard Schlenk techniques. CH_2Cl_2, toluene, and THF were dried by filtration through alumina according to the procedure of Grubbs.[43] MeOH was dried by filtration through a column loaded with activated 4 Å molecular sieves. Oximes

1.90a – 1.90n were prepared by known methods.[44-46] Alkenyl boronic acids 1.86a – 1.86j and 1.92a – 1.92s were prepared by known methods.[47] Nitrone *E*-1.87b was prepared as previously reported. Silyl enol ether and silyl ketene acetal nucleophiles used in Table 1.8 were prepared by known methods.

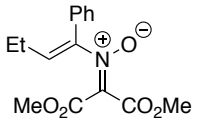
1.4.2 Experimental Procedures and Characterization Data

1.4.3 Synthesis of *N*-Vinylnitrones 1.91a – 1.91r, 1.93a – 1.93s



1.90a **1.92** **1.93**

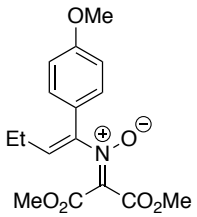
General Procedure A: A scintillation vial was charged with oxime substrate **1.90** (0.30 mmol, 1.0 equiv), alkenylboronic acid **2** (3 – 5 equiv), $Cu(OAc)_2$ (1.0 equiv), and anhydrous Na_2SO_4 (8.0 equiv). These solids were diluted with 1,2-dichloroethane (DCE) to form a 0.1 M solution of oxime **1.90**. Pyridine (3.0 equiv) was then added to the resulting slurry via syringe. The scintillation vial was capped with a septum, pierced with a ventilation needle, and the reaction mixture was allowed to stir at 25 °C for 2 – 18 h. The reaction mixture was then filtered through a plug of silica gel covered with a layer of celite and washed with EtOAc (3 x 10 mL). The filtrate was then concentrated under vacuum to give the crude product mixture that was dry-loaded using EtOAc or Et_2O onto celite and purified by medium pressure column chromatography (1:20 – 1:3, EtOAc: hexanes) to afford nitrone **1.91** or **1.93** as a white solid or light-yellow oil.



1.91a

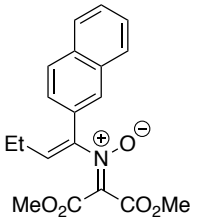
Nitrone 1.91a: Nitrone **1.91a** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:3, EtOAc:

hexanes) afforded **1.91a** as a white solid (0.087 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.48 – 7.46 (m, 2H), 7.38 – 7.34 (m, 3H), 5.95 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 2.27 –2.21 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 159.0, 145.9, 132.1, 131.2, 129.2, 129.1, 128.8, 128.4, 53.1, 52.8, 21.4, 13.3; IR (thin film) 2992, 2975, 2950, 1739, 1529, 1443, 1340, 1304, 1226, 1111 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}NO_5$ $(M+H)^+$ 292.1185, found 292.1179; m.p: 92 – 96 °C.



1.91b

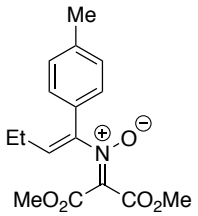
Nitrone 1.91b: Nitrone **1.91b** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-methoxyphenyl)but-1-en-1-yl)boronic acid **1.86b** (0.309 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred 5 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91b** as a light yellow oil (0.073 g, 75%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41 – 7.40 (m, 2H), 6.91 – 6.89 (m, 2H), 5.89 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 2.27 –2.20 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 160.2, 159.1, 145.8, 132.0, 130.5, 130.3, 123.6, 113.8, 55.3, 53.2, 52.8, 21.4, 13.3; IR (thin film) 2953, 2339, 1742, 1590, 1510, 1439, 1430, 1375, 1231, 1135 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_6$ $(M+H)^+$ 322.1291, found 322.1282.



1.91c

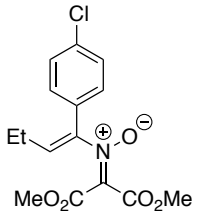
Nitrone 1.91c: Nitrone **1.91c** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (*Z*)-(1-(naphthalen-2-yl)but-1-en-1-yl)boronic acid **1.86c** (0.339 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol),

and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.91c** as a yellow oil (0.067 g, 65%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.99 – 7.98 (m, 1H), 7.87 – 780 (m, 4H), 7.51 – 7.48 (m, 2H), 3.91 (s, 3H), 3.71 (s, 3H), 2.35 (m, 2H), 1.01 (td, *J* = 7.0 Hz, 0.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 159.0, 146.0, 133.4, 131.6, 128.9, 128.7, 128.5, 127.7, 127.0, 126.7, 126.6, 126.5, 126.2, 122.5, 53.2, 52.9, 21.5, 13.3.



1.91d

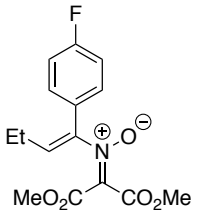
Nitrone 1.91d: Nitrone **1.91d** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(*p*-tolyl)but-1-en-1-yl)boronic acid **1.86d** (0.285 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91d** as an off-white solid (0.070 g, 77%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37 – 7.35 (m, 2H), 7.19 – 7.17 (m, 2H), 5.91 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 2.34 (s, 3H), 2.27 – 2.21 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 159.0, 146.0, 139.3, 132.0, 130.7, 129.1, 128.9, 128.4, 53.1, 52.8, 21.4, 21.3, 13.3; IR (thin film) 2955, 2359, 2341, 1733, 1730, 1510, 1435, 1344, 1294, 1182 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_5$ $(M+H)^+$ 306.1341, found 306.1340; m.p.: 97 – 100 °C.



1.91f

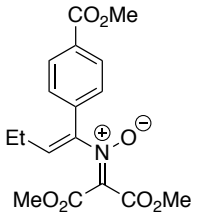
Nitrone 1.91f: Nitrone **1.91f** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-chlorophenyl)but-1-en-1-yl)boronic acid **1.86f** (0.316 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography

(1:4, EtOAc: hexanes) afforded **1.91f** as a light-yellow solid (0.064 g, 65%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.44 – 7.42 (m, 2H), 7.36 – 7.35 (m, 2H), 5.96 (t, *J* = 7.5 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 2.24 –2.18 (m, 2H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.9, 144.7, 135.3, 132.2, 131.7, 130.5, 129.6, 128.7, 53.2, 52.9, 21.4, 13.2; IR (thin film) 2950, 2361, 2341, 1737, 1732, 1584, 1491, 1435, 1409, 1265 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}ClNO_5$ $(M+H)^+$ 326.0795, found 326.0787; m.p.: 86 – 89 °C.



1.91g

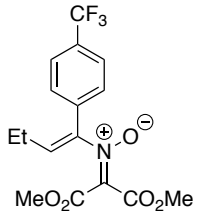
Nitrone 1.91g: Nitrone **1.91g** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-fluorophenyl)but-1-en-1-yl)boronic acid **1.86g** (0.291 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE. Chromatography (1:3, EtOAc: hexanes) afforded **1.91g** as a light yellow solid (0.079 g, 85%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.48 – 7.46 (m, 2H), 7.07 – 7.04 (m, 2H), 5.93 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.21 –2.15 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1 (d, *J* = 248.0 Hz), 160.8, 159.0, 144.7, 132.1, 131.4, 131.2 (d, *J* = 8.3 Hz), 127.2 (d, *J* = 3.3 Hz), 115.5 (d, *J* = 21.8 Hz), 53.2, 52.9, 21.3, 13.1; IR (thin film) 2956, 2360, 2340, 1732, 1601, 1506, 1435, 1343, 1296, 1219 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}FNO_5$ $(M+H)^+$ 310.1091, found 310.1085; m.p.: 98 – 100 °C.



1.91h

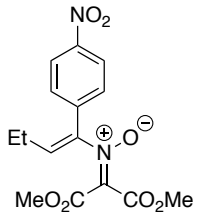
Nitrone 1.91h: Nitrone **1.91h** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-(methoxycarbonyl)phenyl)but-1-en-1-yl)boronic acid **1.86h** (0.351 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4

(0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91h** as a white solid (0.079 g, 75%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.03 – 8.02 (m, 2H), 7.55 – 7.53 (m, 2H), 6.01 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.70 (s, 3H), 2.26 –2.20 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 160.8, 158.8, 145.0, 135.5, 132.5, 130.7, 129.6, 129.0, 124.7, 53.2, 52.9, 52.2, 21.4, 13.1; IR (thin film) 2958, 2360, 2341, 1732, 1713, 1609, 1532, 1423, 1291, 1193 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}NO_7$ $(M+H)^+$ 350.1240, found 350.1233; m.p.: 95 – 98 °C.



1.91i

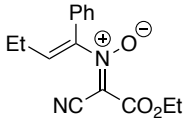
Nitrone 1.91i: Nitrone **1.91i** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)boronic acid **1.86i** (0.366 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91i** as an off-white solid (0.093 g, 86%). ^{1}H NMR (500 MHz; C_6D_6): δ 7.63 – 7.61 (m, 2H), 7.38 – 7.36 (m, 2H), 5.69 (t, *J* = 7.5 Hz, 3H), 3.62 (s, 3H), 3.25 (s, 3H), 1.91 – 1.85 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 161.0, 158.7, 144.5, 132.2, 132.0, 130.8 (q, *J* = 32.5 Hz), 129.7, 128.1, 125.3, 124.7 (q, *J* = 270 Hz), 52.5, 52.0, 21.1, 12.7; IR (thin film) 2958, 2359, 2341, 1733, 1516, 1437, 1323, 1296, 1166 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{17}F_3NO_5$ $(M+H)^+$ 360.1059, found 360.1055; m.p.: 98 – 100 °C.



1.91j

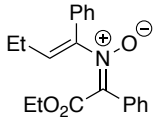
Nitrone 1.91j: Nitrone **1.91j** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (1-(4-nitrophenyl)but-1-en-1-yl)boronic acid **1.86j** (0.332

g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91j** as a yellow solid (0.077 g, 76%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.22 – 8.22 (m, 2H), 7.57 – 7.55 (m, 2H), 6.18 (t, J = 7.5 Hz, 1H), 3.98 (s, 3H), 3.71 (s, 3H), 2.30 – 2.24 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 157.7, 147.7, 144.3, 138.7, 133.9, 130.6, 125.6, 124.2, 53.6, 53.0, 21.5, 13.0; IR (thin film) 2956, 2761, 1732, 1721 1597, 1516, 1436, 1297, 1217 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}N_2O_7$ $(M+H)^+$ 337.1036, found 337.1030; m.p.: 129 – 131 °C.



1.91k

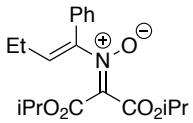
Nitrone 1.91k: Nitrone **1.91k** was prepared by general procedure **A**. Oxime **1.90b** (0.142 g, 1.0 mmol, 1.0 equiv) was treated with ((1-phenylbut-1-en-1-yl)boronic acid **1.86a** (0.880 g, 5.0 mmol, 5.0 equiv), $Cu(OAc)_2$ (0.182 g, 1.0 mmol, 1.0 equiv), Na_2SO_4 (1.14 g, 8.0 mmol, 8.0 equiv), and pyridine (0.237 g, 3.0 mmol, 3.0 equiv) in 10.0 mL DCE and stirred for 48 h. Chromatography (1:7, Et_2O: hexanes) afforded **3q** as a yellow oil (0.163 g, 60%, *E*:*Z* = 1:6). This mixture was then triturated with 5.0 mL hexane and 1 drop of EtOAc to obtain **(*Z*)-3q** as a yellow solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 – 7.33 (m, 5H), 5.98 (t, J = 15.0, 7.5 Hz, 1H), 4.23 – 4.19 (m, 2H), 2.22 – 2.07 (m, 2H), 1.26 (t, J = 14.0, 7.0 Hz, 3H), 1.10 (t, J = 15.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 146.9, 132.2, 129.3, 128.9, 127.6, 125.1, 118.1, 111.4, 63.1, 21.4, 13.9, 13.2.



1.91l

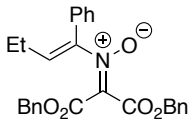
Nitrone 1.91l: Nitrone **1.91l** was prepared by general procedure **A**. Oxime **1.90i** (0.0580 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.341 g, 2.50 mmol), and pyridine (0.0712 g, 0.900 mmol) in 5.0 mL DCE and stirred for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91l** as a yellow oil (0.0610 g, 63%). ^{1}H NMR (500 MHz;

$CDCl_3$): δ 8.16 – 8.14 (m, 2H), 7.60 – 7.59 (m, 2H), 7.43 – 7.35 (m, 6H), 6.08 (t, *J* = 7.5 Hz, 1H), 4.30 (q, *J* = 7.5 Hz, 2H), 2.29 – 2.23 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 146.7, 140.5, 133.2, 131.9, 130.8, 130.6, 130.0, 129.4, 129.1, 128.7, 128.4, 62.5, 21.5, 13.9, 13.6; IR (thin film) 2970, 2936, 2341, 1734, 1592, 1493, 1448, 1386, 1267, 1223 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.1600, found 324.1599.



1.91m

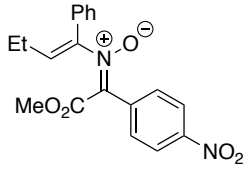
Nitrone 1.91m: Nitrone **1.91m** was prepared by general procedure **A**. Oxime **1.90j** (0.065 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 12 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.91m** as a yellow oil (0.0782 g, 75%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.51 – 7.49 (m, 2H), 7.40 – 7.35 (m, 3H), 5.99 (t, *J* = 7.0 Hz, 1.0 Hz, 1H), 5.27 – 5.22 (m, 1H), 5.03 – 4.98 (m, 1H), 2.28 – 2.22 (m, 2H), 1.32 (d, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 7.0 Hz, 6H), 1.07 (t, *J* = 7.0 Hz, 1.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 158.5, 145.9, 133.1, 131.4, 131.1, 129.2, 128.7, 128.3, 70.3, 70.2, 21.6, 21.5, 21.4, 13.3; IR (thin film) 2978, 2935, 2360, 1735, 1715, 1509, 1464, 1444, 1356, 1327 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{26}NO_5$ $(M+H)^+$ 348.1811, found 348.1803; m.p: 88 – 91 °C.



1.91n

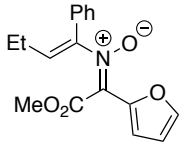
Nitrone 1.91n: Nitrone **1.91n** was prepared by general procedure **A**. Oxime **1.90k** (0.094 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91n** as a yellow oil (0.0931 g, 70%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.47 – 7.45 (m, 2H), 7.39 – 7.35 (m, 4H), 7.34 – 7.28 (m, 9H), 5.97 (t, *J* = 7.5 Hz, 1H),

5.33 (s, 2H), 5.12 (s, 2H), 2.22 – 2.16 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 158.6, 146.0, 134.8, 134.5, 132.3, 131.5, 131.2, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 128.4, 128.2, 127.0, 67.9, 67.7, 21.4, 13.2.



1.91o

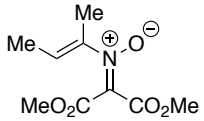
Nitrone 1.91o: Nitrone **1.91o** was prepared by general procedure **A**. Oxime **1.90l** (0.0673 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.91o** as an off-white solid (0.101 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.24 (s, 4H), 7.55 – 7.54 (m, 2H), 7.42 – 7.40 (m, 3H), 6.08 (t, J = 7.5 Hz, 1H), 3.84 (s, 3H), 2.29 – 2.24 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 147.9, 147.2, 138.2, 135.1, 131.5, 129.5, 129.4, 129.3, 128.5, 123.5, 53.3, 21.5, 13.6.; IR (thin film) 3726, 2959, 2872, 1727, 1595, 1515, 1487, 1444, 1294, 1214 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{19}N_2O_5$ $(M+H)^+$ 355.1294, found 355.1288; m.p: 92 – 96 °C.



1.91p

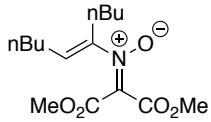
Nitrone 1.91p: Nitrone **1.91p** was prepared by general procedure **A**. Oxime **1.90m** (0.051 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 12 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.91p** as a white solid (0.0566 g, 63%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.99 – 7.98 (m, 1H), 7.54 – 7.53 (m, 1H), 7.51 – 7.49 (m, 2H), 7.41 – 7.36 (m, 3H), 6.58 – 6.57 (m, 1H), 6.02 (t, J = 7.5 Hz, 1H), 3.86 (s, 3H), 2.25 – 2.19 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 145.7, 144.8, 144.6, 132.9, 131.9, 130.8, 129.4, 129.2, 128.7, 128.5, 117.5, 112.5, 53.2, 21.4, 13.6; IR (thin film) 3150, 2360,

1730, 1596, 1521, 1484, 1375, 1316, 1281, 1182 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{18}NO_4$ $(M+H)^+$ 300.1236, found 300.1230; m.p: 92 – 95 °C.



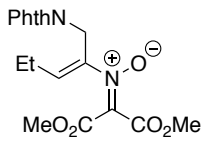
1.93a

Nitrone 1.93a: Nitrone **1.93a** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with 2-butenylboronic acid **1.92a** (0.090 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.92a** as a yellow oil (0.036 g, 56%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.68 (qd, *J* = 7.0 Hz, 1.0 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.06 (s, 3H), 1.71 (td, *J* = 7.0 Hz, 0.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 159.5, 144.3, 131.5, 122.0, 53.1, 52.9, 14.1, 12.6; IR (thin film) 2956, 1732, 1632, 1514, 1435, 1384, 1346, 1293, 1219, 1192 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_9H_{14}NO_5$ $(M+H)^+$ 216.0872, found 216.0869.



1.93b

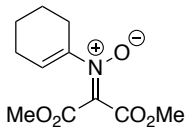
Nitrone 1.93b: Nitrone **1.93b** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (*Z*)-dec-5-en-5-ylboronic acid **1.92b** (0.166 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 6 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93b** as a yellow oil (0.0539 g, 60%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.63 (t, *J* = 7.0 Hz, 1.0 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 2.46 – 2.39 (m, 2H), 2.13 – 2.05 (m, 2H), 1.39 – 1.26 (m, 8H), 0.93 – 0.84 (m, 6H).



1.93d

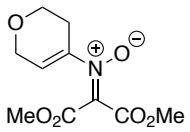
Nitrone 1.93d: Nitrone **1.93d** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(1-(1,3-dioxoisoindolin-2-yl)pent-2-en-2-

yl)boronic acid **1.92d** (0.233 g, 0.900 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.11 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.93d** as a white solid (0.0451 g, 40%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.86 – 7.84 (m, 2H), 7.71 – 7.70 (m, 2H), 5.85 (t, *J* = 8.0 Hz, 1H), 4.72 (s, 2H), 3.87 (s, 3H), 3.64 (s, 3H), 2.48 (m, *J* = 7.5 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5 (2*C*), 160.6, 159.4, 140.8, 134.3, 134.0 (2*C*), 132.6, 132.1 (2*C*), 123.5 (2*C*), 53.2, 53.0, 34.0, 20.8, 12.9; IR (thin film) 2955, 1774, 1714, 1614, 1518, 1466, 1423, 1391, 1336, 1297 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{19}N_2O_7$ $(M+H)^+$ 375.1187, found 375.1192; m.p.: 119 – 120 °C.



1.93e

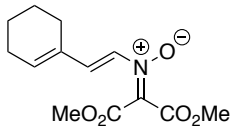
Nitrone 1.93e: Nitrone **1.93e** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (0.113 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93e** as a white solid (0.0695 g, 96%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.92 – 5.87 (m, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.44 – 2.38 (m, 2H), 2.18 – 2.11 (m, 2H), 1.83 – 1.76 (m, 2H), 1.67 – 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 159.5, 146.6, 131.7, 124.1, 53.2, 52.9, 25.8, 24.1, 21.9, 20.9. IR (thin film) 3726, 3628, 2952, 2859, 2359, 1731, 1515, 1440, 1356, 1192 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{16}NO_5$ $(M+H)^+$ 242.1028, found 242.1024; m.p: 118 – 119 °C.



1.93f

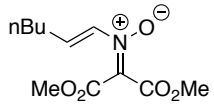
Nitrone 1.93f: Nitrone **1.93f** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (3,6-dihydro-2*H*-pyran-4-yl)boronic acid **1.92f** (0.115 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 6 h. Chromatography (1:4, EtOAc:

hexanes) afforded **1.93f** as a yellow oil (0.0467 g, 64%).[1]H NMR (500 MHz; $CDCl_3$): δ 5.91 – 5.87 (m, 1H), 4.22 – 4.20 (m, 2H), 3.89 – 3.88 (m, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 2.51 – 2.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 159.2, 143.4, 132.0, 122.3, 63.8, 63.7, 53.2, 53.1, 26.2. IR (thin film) 2992, 2975, 2950, 1739, 1529, 1443, 1340, 1304, 1226, 1111 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{14}NO_6$ $(M+H)^+$ 244.0821, found 244.0819.



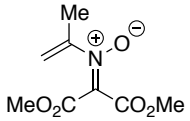
1.93g

Nitrone 1.93g: Nitrone **1.93g** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (*E*)-(2-(cyclohex-1-en-1-yl)vinyl)boronic acid **1.92g** (0.137 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 16 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93g** as a yellow oil (0.0649 g, 81%). [1]H NMR (500 MHz; PhMe-d_8): δ 8.61 (d, 1H), 7.47 (d, 1H), 5.72 (m, 1H), 3.58 (s, 3H), 3.27 (s, 3H), 1.95 – 1.92 (m, 2H), 1.83 – 1.80 (m, 2H), 1.40 – 1.35 (m, 2H), 1.32 – 1.28 (m, 2H); ^{13}C NMR (125 MHz, PhMe-d_8): δ 161.4, 159.1, 140.1, 137.1, 132.9, 128.5, 128.3, 521., 51.7, 26.4, 24.2, 21.8, 21.7.



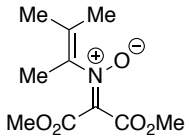
1.93h

Nitrone 1.93h: Nitrone **1.93h** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (*E*)-hex-1-en-1-ylboronic acid **1.92h** (0.115 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 4 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93h** as a yellow oil (0.0409 g, 56%). [1]H NMR (500 MHz; $CDCl_3$): δ 8.29 (d, 1H), 7.00 – 6.95 (m, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.22 – 2.18 (m, 2H), 1.44 – 1.38 (m, 2H), 1.33 – 1.25 (m, 2H), 0.84 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 158.8, 138.0, 132.2, 129.2, 53.1, 52.9, 30.3, 29.0, 22.1, 30.3, 29.0, 22.1, 13.7.



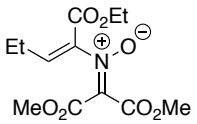
1.93j

Nitrone 1.93j: Nitrone **1.93j** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with prop-1-en-2-ylboronic acid **1.92j** (0.0773 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 5 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93j** as a yellow oil (0.032 g, 53%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.06 (s, 1H), 5.01 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 159.2, 151.2, 131.6, 110.6, 53.1, 53.0, 18.5.



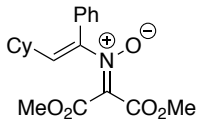
1.93k

Nitrone 1.93k: Nitrone **1.93k** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (3-methylbut-2-en-2-yl)boronic acid **1.92k** (0.102 g, 0.900 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.11 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **3n** as a colorless oil as a 4:1 mixture of rotamers (0.0213 g, 31%). Major rotamer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.91 (s, 3H), 3.79 (s, 3H), 2.04 (s, 3H), 1.74 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 158.4, 137.7, 132.2, 127.2, 53.2, 52.8, 25.9, 18.9, 16.3; Minor rotamer diagnostic peaks: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.89 (s, 3H), 3.82 (s, 3H), 2.22 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 162.3, 53.5, 52.7, 24.9, 19.1; IR (thin film) 2955, 2917, 2849, 1732, 1519, 1436, 1377, 1347, 1296, 1258 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{16}NO_5$ $(M+H)^+$ 230.1028, found 230.1027.



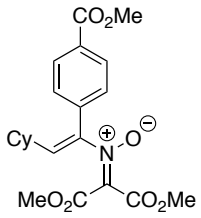
1.93l

Nitrone 1.93l: Nitrone **1.93l** was prepared by general procedure **A**. Oxime **1.90a** (0.048 g, 0.30 mmol) was treated with (*Z*)-(1-ethoxy-1-oxopent-2-en-2-yl)boronic acid **1.92l** (0.180 g, 0.90 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 16h. Chromatography (1:4, EtOAc: hexanes) afforded **1.93l** as a yellow oil (0.0709 g, 78%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.87 – 6.83 (m, 1H), 4.33 –4.24 (m, 2H), 3.96 (s, 3H), 3.79 (s, 3H), 2.31 – 2.27 (m, 1H), 2.22 – 2.18 (m, 1H), 1.30 (t, 3H), 1.09 (t, 3H).



1.93n

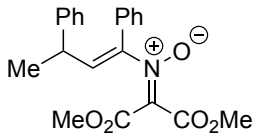
Nitrone 1.93n: Nitrone **1.93n** was prepared by general procedure A. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(2-cyclohexyl-1-phenylvinyl)boronic acid **1.92n** (0.345 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.11 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 16 h. Chromatography (1:6, EtOAc:hexanes) afforded **1.93n** as a yellow oil (0.0933 g, 90%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.48 – 7.46 (m, 2H), 7.36 – 7.34 (m, 3H), 5.79 (d, J = 10.5 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 2.31 – 2.22 (m, 1H), 1.73 – 1.58 (m, 6H), 1.23 – 1.10 (m, 4H).



1.93o

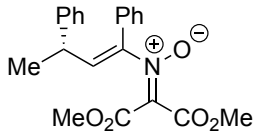
Nitrone 1.93o: Nitrone **1.93o** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(2-cyclohexyl-1-(4-(methoxycarbonyl)phenyl)vinyl)boronic acid **1.92o** (0.363 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.11 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:6, EtOAc:hexanes) afforded **1.93o** as a yellow oil (0.101 g, 83%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.04 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 5.84 (d, J = 10.5 Hz, 1H), 3.91 (s, 3H), 3.89 (s,

3H), 3.74 (s, 3H), 2.25 – 2.23 (m, 1H), 1.74 – 1.62 (m, 5H), 1.23 – 1.16 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 160.7, 159.1, 143.8, 135.86, 135.81, 132.3, 130.7, 129.6, 129.1, 53.2, 52.9, 52.2, 36.8, 31.9, 25.6, 25.0; IR (thin film) 2927, 2851, 1722, 1609, 1514, 1435, 1405, 1344, 1276, 1218 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}NO_7$ $(M+H)^+$ 404.1704, found 404.1703.



***rac*-1.93q**

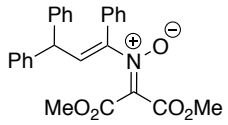
***rac*-Nitrone 1.93q:** Nitrone ***rac*-1.93q** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(1,3-diphenylbut-1-en-1-yl)boronic acid ***rac*-1.92q** (0.378 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.341 g, 2.40 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 18 h. Chromatography (1:9, EtOAc: hexanes) afforded ***rac*-1.93q** as a yellow oil (0.0672 g, 61%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.55 – 7.53 (m, 2H), 7.42 – 7.41 (m, 3H), 7.34 – 7.31 (m, 2H), 7.26 – 7.19 (m, 3H), 6.10 (d, *J* = 10.5 Hz, 1H), 3.90 (s, 3H), 3.75 – 3.66 (m, 1H), 3.58 (s, 3H), 1.43 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 159.3, 145.2, 143.5, 133.3, 132.4, 131.0, 129.6, 129.4, 128.8, 128.5, 126.9, 126.8, 53.2, 52.8, 37.8, 21.3; IR (thin film) 2995, 2977, 2819, 1761, 1758, 1405, 1329, 1299, 1261, 1100 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1498, found 368.1490.



1.93r

Nitrone 1.93r: Nitrone **1.93r** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*S*)-(*Z*)-(1,3-diphenylbut-1-en-1-yl)boronic acid **1.92r** (0.378 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.341 g, 2.40 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 18 h. Chromatography (1:9, EtOAc: hexanes) afforded **1.93r** as an off-white solid (0.0628 g, 57%, ee = 95% (Daicel Chiralpak IA-3 column, 5% MeOH in hexane, column temperature: 45 °C, flow rate: 1.0 mL/min, λ = 254 nm), t_{minor}= 7.29 min, t_{major} = 7.61 min)). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.56 – 7.53 (m, 2H), 7.44 – 7.40 (m, 3H), 7.34 –

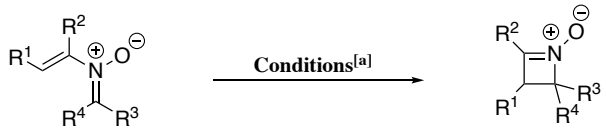
7.31 (m, 2H), 7.25 – 7.20 (m, 3H), 6.11 (d, J = 10.5 Hz, 1H), 3.90 (s, 3H), 3.74 – 3.67 (m, 1H), 3.58 (s, 3H), 1.43 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 159.3, 145.2, 143.5, 133.3, 132.4, 131.0, 129.6, 129.4, 128.8, 128.5, 126.9, 126.8, 53.2, 52.8, 37.8, 21.3; IR (thin film) 2994, 2969, 2825, 1759, 1750, 1401, 1301, 1289, 1262, 1111 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1498, found 368.1508; m.p.: 91 – 95 °C.



1.93s

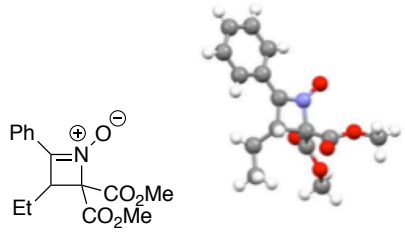
Nitrone 1.93s: Nitrone **1.93s** was prepared by general procedure **A**. Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(1,3,3-triphenylprop-1-en-1-yl)boronic acid **1.92s** (0.471 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.341 g, 2.40 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 18 h. Chromatography (1:9, EtOAc: hexanes) afforded **1.93s** as an off-white solid (0.121 g, 94%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.53 – 7.51 (m, 2H), 7.41 – 7.40 (m, 3H), 7.33 – 7.30 (m, 2H), 7.26 – 7.24 (m, 3H), 7.15 – 7.13 (m, 5H), 6.44 (d, J = 10.5 Hz, 1H), 4.88 (d, J = 10.5 Hz, 1H), 3.90 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 159.4, 146.5, 142.1, 130.7, 130.3, 129.58, 129.3, 128.8, 128.6, 128.3, 128.0, 127.0, 53.2, 52.8, 49.1. IR (thin film) 3025, 2952, 2359, 1733, 1596, 1514, 1492, 1435, 1344, 1296 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{26}H_{24}NO_5$ $(M+H)^+$ 430.1654, found 430.1649; m.p: 90 – 92 °C.

1.4.4 Synthesis of Azetidine Nitrones 1.94 (Table 1.7)



General Procedure B: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91**, diluted with anhydrous MeOH to form a 0.1 M solution, and sealed with a Teflon screw cap. The solution was heated at 40 °C for 18 h. The reaction mixture was allowed to cool to 25 °C, then condensed under vacuum to give the crude product mixture, which was dry-loaded onto celite with EtOAc and purified by medium

pressure chromatography (1:5 – 1:2, EtOAc: hexanes) to afford azetidine nitrones **1.94**.



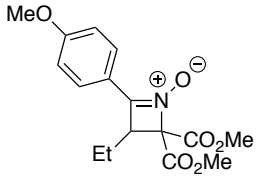
1.94a

Azetidine Nitrone 1.94a: Azetidine nitrone **1.94a** was prepared by general procedure **B** using nitrone **1.91a** (0.0870 g, 0.298 mmol) in MeOH (2.9 mL) and heating for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94a** as a white solid (0.085 g, 98%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.96 – 7.95 (m, 2H), 7.43 – 7.42 (m, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.80 (dd, J = 10.0, 4.0 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.78 – 1.72 (m, 1H), 1.04 (dd, J = 10.0, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 164.1, 152.9, 130.9, 128.8, 127.1, 126.6, 86.7, 54.0, 53.5, 43.8, 20.4, 11.7; IR (thin film) 2955, 2885, 1734, 1592, 1493, 1435, 1377, 1275, 1103, 1033 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}NO_5$ $(M+H)^+$ 292.1185, found 292.1176; m.p.: 164 – 168 °C. Purified **1.94a** was further dissolved in a minimal amount of EtOAc, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.

Gram Scale/One-Pot Synthesis of 1.94a: Azetidine nitrone **1.94a** was prepared using a general procedure **A** and a modified general procedure **B** in sequence on a 1 g scale. Oxime **1.90a** (1.00 g, 6.21 mmol, 1.0 equiv) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (3.28 g, 18.6 mmol, 3.0 equiv), $Cu(OAc)_2$ (1.13 g, 6.21 mmol, 1 equiv), Na_2SO_4 (7.50 g, 52.8 mmol, 8.5 equiv), and pyridine (1.47 g, 18.6 mmol, 3.0 equiv) in 62.1 mL DCE and stirred for 15 h. The crude reaction mixture was filtered through a short column of silica gel topped with a pad of celite to remove copper and inorganic salts and washed with EtOAc (200 mL). The crude product mixture was then concentrated under vacuum to remove EtOAc and DCE, and dissolved in dry MeOH to form a 0.1 M solution and heated at 40 °C in an oil bath for 18 h. The reaction mixture was then cooled to 25 °C and concentrated under vacuum again. Et_2O (10.0 mL) was added to the crude product to form a solution, followed by 200 mL of hexanes to

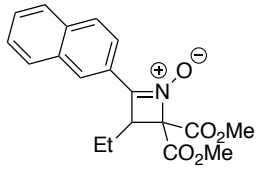
precipitate the desired clean product, which was filtered over a fritted funnel to afford azetidine **1.94a** as a light yellow solid (1.54 g, 85%).

Gram Scale/One-Pot Synthesis of 1.94a with 20 mol% $Cu(OAc)_2$: Azetidine nitrone **1.94a** was prepared using a modified general procedure **A** with 20 mol % $Cu(OAc)_2$ and a modified general procedure **B** in sequence on a 1 g scale. Oxime **1.86a** (1.00 g, 6.21 mmol, 1.0 equiv) was treated with (1-phenyl-1-butenyl)boronic acid **1.86a** (3.28 g, 18.6 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.226 g, 1.24 mmol, 0.20 equiv), Na_2SO_4 (7.50 g, 52.8 mmol, 8.5 equiv), and pyridine (1.47 g, 18.6 mmol, 3.0 equiv) in 62.1 mL DCE and stirred for 18 h. The crude reaction mixture was filtered through a short column of silica gel topped with a pad of celite to remove copper and inorganic salts and washed with EtOAc (200 mL). The crude product mixture was then concentrated under vacuum to remove EtOAc and DCE, and dissolved in dry MeOH to form a 0.1 M solution and heated at 40 °C in an oil bath for 18 h. The reaction mixture was then cooled to 25 °C and concentrated under vacuum again. Et_2O (10.0 mL) was added to the crude product to form a solution, followed by 200 mL of hexanes to precipitate the desired clean product, which was filtered over a fritted funnel to afford azetidine **1.94a** as a light yellow solid (1.50 g, 83%).



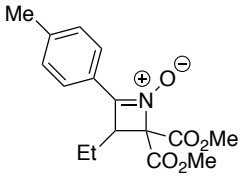
1.94b

Azetidine Nitrone 1.94b: Azetidine nitrone **1.94b** was prepared by general procedure **B**. Nitrone **1.91b** (0.0258 g, 0.0803 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc:hexanes) afforded 4c as a white solid (0.0245 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.92 – 7.90 (m, 2H), 6.92 – 6.90 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.73 (dd, J = 10.0, 4.0 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.76 – 1.66 (m, 1H), 1.00 (dd, J = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 164.2, 161.4, 152.8, 128.6, 120.0, 114.2, 86.2, 55.4, 53.9, 53.4, 43.8, 20.4, 11.7; IR (thin film) 2956, 2349, 2342, 1739, 1592, 1567, 1510, 1383, 1251, 1130 cm^{-1}; HRMS (ESI) *m/z* calcd. for C16H20NO6 $(M+H)^+$ 322.1291, found 322.1287; m.p.: 94 – 96 °C.



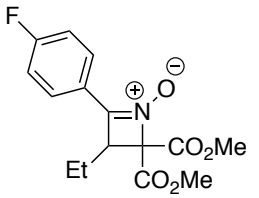
1.94c

Azetidine Nitrone 1.94c: Azetidine nitrone **1.94c** was prepared by general procedure **B**. Nitrone **1.91c** (0.0341 g, 0.1 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, Et_2O: hexanes) afforded **1.94c** as a yellow oil (0.0307 g, 90%). ^1H NMR (500 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.92 – 7.80 (m, 4H), 7.54 – 7.49 (m, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.88 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.89 – 1.77 (m, 1H), 1.08 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 164.1, 153.1, 134.1, 132.8, 128.9, 128.8, 128.6, 127.8, 127.6, 127.3, 127.0, 122.8, 86.7, 54.0, 44.0, 53.5, 20.5, 11.7.



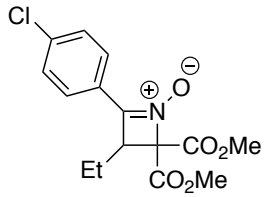
1.94d

Azetidine Nitrone 1.94d: Azetidine nitrone **1.94d** was prepared by general procedure B. Nitrone **1.91d** (0.0339 g, 0.111 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, Et_2O: hexanes) afforded **1.94d** as a white solid (0.0322 g, 95%). ^1H NMR (500 MHz; $CDCl_3$): δ 7.86 – 7.84 (m, 2H), 7.23 – 7.22 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.76 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.36 (s, 3H), 2.04 – 1.95 (m, 1H), 1.78 – 1.68 (m, 1H), 1.02 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 164.1, 153.0, 141.5, 129.4, 126.6, 124.4, 86.5, 53.9, 53.4, 43.7, 21.8, 20.4, 11.7; IR (thin film) 2955, 2356, 2342, 1739, 1590, 1509, 1435, 1386, 1262, 1219 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_5$ $(M+H)^+$ 306.1341, found 306.1340; m.p.: 101-104 °C.



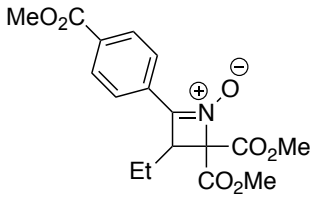
1.94e

Azetidine Nitrone 1.94e: Azetidine nitrone **1.94e** was prepared by general procedure **B** using nitrone **1.91g** (0.0160 g, 0.0517 mmol) in dimethyl sulfoxide (0.5 mL) and heating at 60 ˚C for 18 h. Chromatography (1:2, Et_2O: hexanes) afforded **1.94e** as a white solid (0.0149 g, 93%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.99 – 7.96 (m, 2H), 7.12 – 7.09 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.76 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.78 – 1.68 (m, 1H), 1.01 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 164.0 (d, *J* = 26.4 Hz), 162.6, 151.8, 128.9 (d, *J* = 8.3 Hz), 123.6, 116.1 (d, *J* = 8.3 Hz), 86.7, 54.0, 53.5, 20.3, 11.6; IR (thin film) 2956, 2359, 2341, 1739, 1592, 1582, 1508, 1435, 1386, 1264 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}FNO_5$ $(M+Na)^+$ 332.0910, found 332.0904; m.p.: 142 – 144 °C.



1.94f

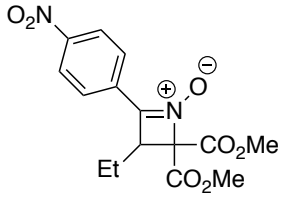
Azetidine Nitrone 1.94f: Azetidine nitrone **1.94f** was prepared by general procedure **B** using nitrone **1.91f** (0.0977 g, 0.30 mmol) in methanol (3.0 mL) and heating at 40 ˚C for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94f** as a white solid (0.0880 g, 90%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.91 – 7.89 (m, 2H), 7.40 – 7.39 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.79 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.79 – 1.69 (m, 1H), 1.03 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 163.8, 151.8, 136.6, 129.2, 127.8, 125.5, 86.9, 54.0, 53.5, 43.8, 20.3, 11.7; IR (thin film) 2956, 2359, 2341, 1739, 1585, 1558, 1490, 1435, 1410, 1263 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}ClNO_5$ $(M+H)^+$ 327.0795, found 327.0790; m.p.: 84 – 86 °C.



1.94g

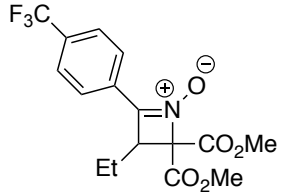
Azetidine Nitrone 1.94g: Azetidine nitrone **1.94g** was prepared by general procedure **B.** Nitrone **1.91h** (0.0370 g, 0.106 mmol) was heated at 40 °C in MeOH for 18 h.

Chromatography (1:2, EtOAc: hexanes) afforded **1.94g** as a white solid (0.0344 g, 93%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.07 – 8.06 (m, 2H), 8.00 – 7.96 (m, 2H), 3.90 (s, 6H), 3.89 (s, 3H), 3.82 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.81 – 1.72 (m, 1H), 1.03 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 163.9, 163.7, 151.9, 131.5, 130.6, 130.0, 126.2, 87.2, 54.0, 53.6, 52.4, 43.8, 20.4, 11.7; IR (thin film) 2951, 2341, 1745, 1741, 1737, 1592, 1582, 1508, 1386, 1218 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}NO_7$ $(M+H)^+$ 350.1240, found 350.1235; m.p.: 95 – 98 °C.



1.94h

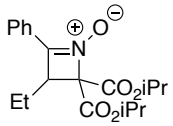
Azetidine Nitrone 1.94h: Azetidine nitrone **1.94h** was prepared by general procedure **B** using nitrone **1.91j** (0.0189 g, 0.0562 mmol) in dimethyl sulfoxide (0.5 mL) and heating at 60 ˚C for 18 h. Chromatography (1:2, Et_2O: hexanes) afforded **1.91h** as a white solid (0.0126 g, 83%). ^{1}H NMR (500 MHz; C_6D_6): δ 7.86 – 7.85 (m, 2H), 7.71 – 7.69 (m, 2H), 3.75 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.44 (s, 3H), 3.37 (s, 3H), 1.72 – 1.64 (m, 1H), 1.62 – 1.55 (m, 1H), 0.91 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 164.0, 163.8, 149.3, 147.5, 132.1, 126.1, 123.8, 88.4, 53.2, 52.6, 43.4, 20.2, 11.4; IR (thin film) 2971, 2359, 2342, 1742, 1661, 1534, 1438, 1345, 1294, 1242 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}N_2O_7$ $(M+H)^+$ 336.1036, found 336.1030; m.p.: 126 – 128 °C.



1.94i

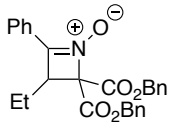
Azetidine Nitrone 1.94i: Azetidine nitrone **1.94i** was prepared by general procedure **B** using nitrone **1.91i** (0.0471 g, 0.131 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94i** as a yellow viscous oil (0.0442 g, 94%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.07 – 8.06 (m, 2H), 7.69 – 7.67 (m, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.83 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.82 – 1.73 (m,

1H), 1.05 (dd, J = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 163.7, 151.4, 131.9 (q, J = 32.5 Hz), 130.0, 126.6, 125.8, 123.6 (q, J = 270 Hz), 87.3, 54.1, 53.6, 43.8, 20.4, 11.7; IR (thin film) 2975, 2361, 1739, 1736, 1535, 1439, 1344, 1290, 1212, 1117 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{17}F_3NO_5$ $(M+H)^+$ 360.1059, found 360.1057.



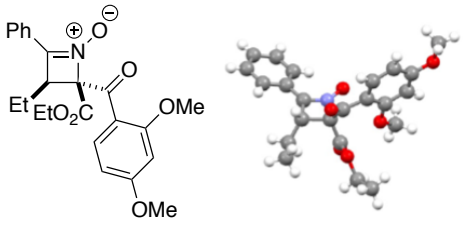
1.94j

Azetidine Nitrone 1.94j: Azetidine nitrone **1.94j** was prepared by general procedure **B** using nitrone **1.91m** (0.0347 g, 0.10 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94j** as a yellow oil (0.0330 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.97 – 7.96 (m, 2H), 7.65 – 7.63 (m, 3H), 5.28 – 5.18 (m, 2H), 3.81 – 3.78 (m, 1H), 2.05 – 1.98 (m, 1H), 1.83 – 1.74 (m, 1H), 1.34 –1.32 (m, 12H), 1.08 (t, 3H).



1.94k

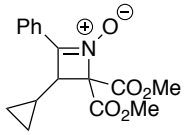
Azetidine Nitrone 1.94k: Azetidine nitrone **1.94k** was prepared by general procedure **B** using nitrone **1.91n** (0.0444 g, 0.10 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94k** as a yellow viscous oil (0.0404 g, 91%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.94 – 7.92 (m, 2H), 7.40 – 7.37 (m, 4H), 7.34 – 7.27 (m, 9H), 5.34 – 5.21 (m, 4H), 3.77 (dd, J = 10.0, 4.0 Hz, 1H), 1.94 – 1.86 (m, 1H), 1.67 – 1.58 (m, 1H), 0.86 (dd, J = 10.0, 5.5 Hz, 3H).



1.89

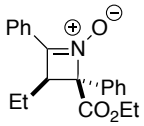
Azetidine Nitrone 1.89: Azetidine nitrone **1.89** was prepared by general procedure **B**. Nitrone **1.87b** (0.100 g, 0.243 mmol) was heated at 40 °C in MeOH (2.0 mL) for 18 h.

Chromatography (1:3, EtOAc:hexanes) afforded **1.89** as a white solid (0.0950 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.95 – 7.94 (m, 2H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.38 – 7.36 (m, 3H), 6.51 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 6.47 – 6.46 (m, 1H), 4.37 – 4.27 (m, 2H), 3.96 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.10 – 2.00 (m, 1H), 1.83 – 1.72 (m, 1H), 1.28 (dd, *J* = 8.0 Hz, 7.5 Hz, 3H), 1.15 (dd, *J* = 8.0 Hz, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.6, 165.8, 164.4, 162.2, 152.4, 133.5, 130.3, 128.6, 127.4, 126.7, 118.9, 106.1, 98.2, 93.7, 62.0, 55.6, 55.2, 44.2, 20.3, 14.1, 12.5; IR (thin film) 3726, 3627, 2359, 2341, 1732, 1654, 1596, 1504, 1464, 1387, 1268 cm-1; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_6$ $(M+H)^+$ 412.1760, found 412.1763; m.p.: 99 – 102 °C. Purified **1.89** was further dissolved in a minimal amount of Et2O, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



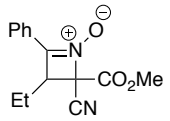
1.93p

Azetidine Nitrone 1.93p: Azetidine nitrone **1.93p** was prepared by general procedure **A**: Oxime **1.90a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(2-cyclopropyl-1-phenylvinyl)boronic acid **1.92p** (0.282 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.11 mmol), and pyridine (0.0710 g, 0.900 mmol) in 3.0 mL DCE and stirred for 4 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.93p** as a pale yellow solid (0.0743 g, 82%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.09 – 8.07 (m, 2H), 7.47 – 7.45 (m, 3H), 3.91 (s, 3H), 3.91 (s, 3H), 3.13 (d, *J* = 10.5 Hz, 1H), 0.98 – 0.92 (m, 1H), 0.88 – 0.83 (m, 1H), 0.70 – 0.64 (m, 1H), 0.61 – 0.56 (m, 1H), 0.53 – 0.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.09, 164.04, 152.7, 130.9, 128.7, 127.2, 126.8, 87.3, 53.8, 53.4, 47.5, 7.6, 6.2, 3.9; IR (thin film) 3011, 2954, 1737, 1590, 1492, 1448, 1432, 1384, 1322, 1271 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{18}NO_5$ $(M+H)^+$ 304.1179,
found 304.1182; m.p.: 138–140 °C.



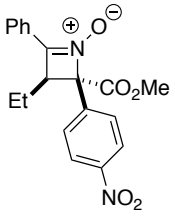
1.94m

Azetidine Nitrone 1.94m: Azetidine nitrone **1.94m** was prepared by general procedure **B**. Nitrone **1.91l** (0.0650 g, 0.200 mmol) was heated at 40 °C in MeOH (2.0 mL) for 18 h. Chromatography (1:4, EtOAc: hexanes) afforded **1.94m** as a yellow amorphous solid (0.0610 g, 94%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.03 – 7.99 (m, 2H), 7.81 – 7.77 (m, 2H), 7.44 – 7.34 (m, 6H), 4.33 (q, *J* = 7.5 Hz, 2H), 3.57 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.95 – 1.85 (m, 1H), 1.29 (t, *J* = 5.5 Hz, 3H), 1.20 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 150.1, 134.6, 130.4, 128.8, 128.7, 128.5, 127.5, 126.9, 126.5, 87.9, 62.5, 48.6, 20.9, 14.1, 12.4; IR (thin film) 3726, 3059, 2970, 2935, 2359, 2341, 1733, 1591, 1448, 1266, 1222 cm-1; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.1600, found 324.1607.



1.94n

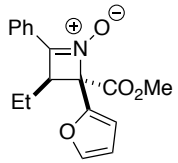
Azetidine Nitrone 1.94n: Azetidine nitrone **1.94n** was prepared by general procedure **B**. Nitrone **1.91k** (0.129 g, 0.500 mmol) was heated at 40 °C in MeOH (5.0 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94n** as white crystals (0.106 g, 82%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.94 – 7.92 (m, 2H), 7.49 – 7.48 (m, 3H), 3.99 (s, 3H), 3.74 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.82 – 1.73 (m, 1H), 1.07 (dd, *J* = 10.0, 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 152.9, 131.6, 129.0, 126.7, 126.5, 112.6, 83.1, 54.6, 47.6, 20.2, 11.6.



1.94o

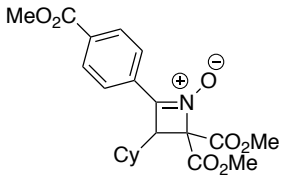
Azetidine Nitrone 1.94o: Azetidine nitrone **1.94o** was prepared by general procedure **B**. Nitrone **1.91o** (0.0354 g, 0.100 mmol) was heated at 40 °C in MeOH (1.0 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94o** as a colorless solid (0.0350 g, 99%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.31 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H),

7.43 – 7.38 (m, 3H), 7.22 – 7.19 (m, 2H), 4.11 – 4.08 (m, 1H), 3.77 (s, 3H), 1.56 – 1.47 (m, 2H), 1.21 (t, 3H).



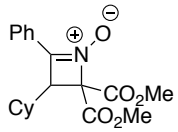
1.94p

Azetidine Nitrone 1.94p: Azetidine nitrone **1.94p** was prepared by general procedure **B**. Nitrone **1.91p** (0.0449 g, 0.150 mmol) was heated at 40 °C in MeOH (1.0 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94p** as a white solid (0.0427 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.00 – 7.98 (m, 2H), 7.44 – 7.41 (m, 4H), 6.73 – 6.72 (m, 1H), 6.40 – 4.39 (m, 1H), 3.90 (s, 3H), 3.79 (dd, *J* = 8.0, 7.5 Hz, 1H), 2.12– 2.05 (m, 1H), 1.80 – 1.71 (m, 1H), 1.04 (t, 3H).



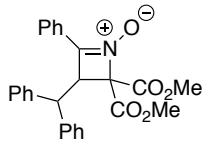
1.94q

Azetidine Nitrone 1.94q: Azetidine nitrone **1.94q** was prepared by general procedure **B**. Nitrone **1.93o** (0.0319 g, 0.0791 mmol) was heated at 40 °C in MeOH (0.8 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94q** as a colorless oil (0.0144 g, 45%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.08 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 6H), 3.89 (s, 3H), 3.77 (d, *J* = 7.5 Hz, 1H), 1.84 – 1.80 (m, 2H), 1.77 – 1.75 (m, 1H), 1.68 – 1.64 (m, 3H), 1.27 – 1.19 (m, 2H), 1.17 – 1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 164.1, 164.0, 152.2, 131.4, 131.3, 129.7, 126.9, 86.9, 54.1, 53.6, 52.4, 48.6, 37.2, 32.4, 31.4, 26.2, 26.0, 25.8; IR (thin film) 2928, 2852, 1741, 1720, 1581, 1557, 1506, 1434, 1412, 1387 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}NO_7$ $(M+H)^+$ 404.1704, found 404.1713.



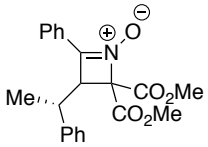
1.94r

Azetidine Nitrone 1.94r: Azetidine nitrone **1.94r** was prepared by general procedure **B**. Nitrone **1.94n** (0.0345 g, 0.1 mmol) was heated at 40 °C in MeOH (0.8 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94r** as a colorless oil (0.0269 g, 78%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.95 – 7.93 (m, 2H), 7.40 – 7.38 (m, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.71 (d, J = 7.5 Hz, 1H), 1.83 – 1.56 (m, 6H), 1.26 – 1.00 (m, 5H).



1.94s

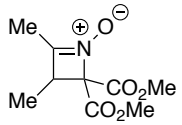
Azetidine Nitrone 1.94s: Azetidine nitrone **1.94s** was prepared by general procedure **B**. Nitrone **1.94s** (0.0859 g, 0.200 mmol) was heated at 40 °C in MeOH (0.8 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **1.94s** as a colorless solid (0.0842 g, 98%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.46 – 7.44 (m, 2H), 7.33 – 7.31 (m, 2H), 7.21 – 7.18 (m, 7H), 7.15 – 7.13 (m, 2H), 7.06 – 7.03 (m, 2H), 4.89 (d, 1H), 4.38 (d, 1H), 3.90 (s, 3H), 3.21 (s, 3H).



1.94u

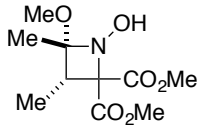
Azetidine Nitrone 1.94u: Azetidine nitrone **1.94u** was prepared by general procedure **B**. Nitrone **1.93r** (0.114 g, 0.31 mmol) was heated at 80 °C in toluene (0.8 mL) for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **1.94u** as an off-white solid (0.103 g, 90%, dr = 1:1). Major diastereomer ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.92 – 7.91 (m, 2H), 7.27 – 7.25 (m, 3H), 7.20 – 7.15 (m, 5H), 4.05 (d, J = 10.0 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.25 – 3.19 (m, 1H), 1.42 (d, J = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 164.1, 153.4, 143.2, 130.8, 129.1, 128.8, 128.5, 127.9, 127.3, 127.0, 86.2, 54.0, 53.8, 50.6, 38.7, 21.9; Minor diastereomer ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.44 – 7.40 (m, 3H), 7.35 – 7.32 (m, 2H), 7.24 – 7.20 (m, 3H), 7.06 – 7.03 (m, 2H), 4.41 (d, J = 10.0 Hz, 1H), 3.85 (s, 3H), 3.48 (s, 3H), 3.39 – 3.33 (m, 1H), 1.38 (d, J = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 163.5, 153.3, 143.1, 130.1, 129.0, 128.7, 128.1,127.5, 127.2, 126.9, 86.1, 53.9, 53.3, 47.7, 38.3, 20.2;IR (thin film) 2951, 2886, 1742, 1586,

1443, 1430, 1307, 1270, 1111, 1030 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}NO_7$ $(M+H)^+$ 404.1704, found 404.1713; m.p.: 131 – 135 °C.



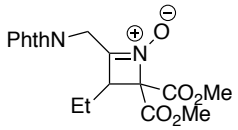
1.95a

Azetidine Nitrone 1.95a: Azetidine nitrone **1.95a** was prepared by general procedure **B**. Nitrone **1.93a** (0.0183 g, 0.0850 mmol) was heated at 40 °C in MeOH (0.8 mL) for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded azetidine nitrone **1.95a** as a pale-yellow oil (0.0177 g, 97%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.88 (s, 6H), 3.46 (q, *J* = 7.0 Hz, 1H), 2.07 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 163.8, 155.7, 87.3, 53.9, 53.3, 38.6, 11.0, 10.2; IR (thin film) 2956, 2930, 2872, 2359, 2341, 1745, 1435, 1268, 1224, 1109 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_9H_{14}NO_5$ $(M+H)^+$ 216.0872, found 216.0868.



1.95a'

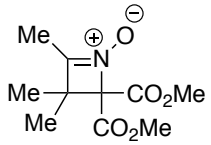
Azetidine 1.95a': Azetidine **1.95a'** was prepared by general procedure **B** at 60 °C. Nitrone **1.95a'** (0.140 g, 0.651 mmol) was heated at 60 °C in MeOH (7.0 mL) for 18 h. Chromatography (1:5, EtOAc: hexanes) afforded azetidine hemiaminal **1.95a'** as a yellow oil (0.0441 g, 27%). ^{1}H NMR (500 MHz; C_6D_6): δ 7.08 (br, 1H), 3.34 (s, 3H), 3.32 – 3.25 (m, 1H), 3.24 (s, 3H), 2.97 (s, 3H), 1.11 (s, 3H), 1.06 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 169.4, 168.2, 110.2, 77.6, 53.6, 52.5, 52.0, 48.2, 15.0, 12.2; IR (thin film) 2954, 1732, 1435, 1383, 1264, 1177, 1155, 1135, 1095, 1062 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{18}NO_6$ $(M+H)^+$ 248.1129, found 248.1141.



1.95c

Azetidine Nitrone 1.95c: Azetidine nitrone **1.95c** was prepared by general procedure **B** using nitrone **1.93d** (0.0241 g, 0.0644 mmol) in DCE (0.6 mL) and heating at 60 ˚C for

18 h. Chromatography (1:50, MeOH:CH_2Cl_2) afforded **1.95c** as a colorless oil (0.0165 g, 68%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.89 – 7.87 (m, 2H), 7.76 – 7.74 (m, 2H), 4.78 (dd, *J* = 7.0 Hz, 1.0 Hz, 1H), 4.53 (dd, *J* = 16.5 Hz, 1.5 Hz, 1H), 3.874 (s, 3H), 3.872 (s, 3H), 3.46 – 3.43 (m, 1H), 1.72 – 1.61 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 163.5, 163.4, 150.3, 134.4, 131.8, 123.8, 87.4, 54.0, 53.5, 45.0, 31.8, 19.9, 11.7; IR (thin film) 2956, 2927, 1741, 1714, 1614, 1466, 1435, 1417, 1386, 1310 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{19}N_2O_7$ $(M+H)^+$ 375.1187, found 375.1200.



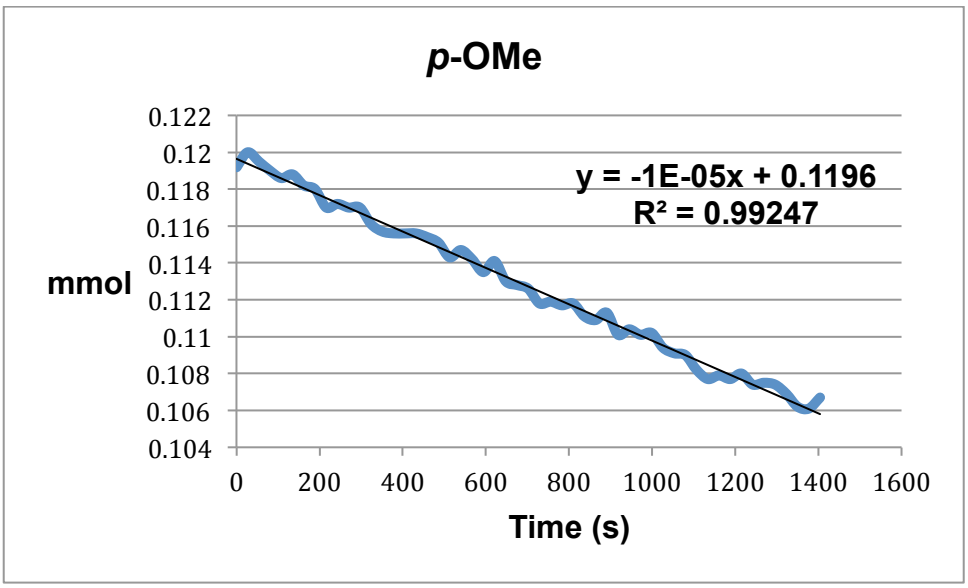
1.95e

Azetidine Nitrone 1.95e: Azetidine nitrone **1.95e** was prepared by general procedure **B** using nitrone **1.93k** (0.0458 g, 0.200 mmol) in MeOH (2.0 mL) and heating for 18 h. Chromatography (1:50, MeOH: CH_2Cl_2) afforded **1.95e** as a colorless oil (0.0101 g, 22%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.87 (s, 6H), 2.03 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 157.6, 89.7, 53.4, 46.6, 20.1, 8.2; IR (thin film) 2956, 1745, 1633, 1464, 1435, 1391, 1371, 1330, 1266, 1195 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{16}NO_5$ $(M+H)^+$ 230.1023, found 230.1033.

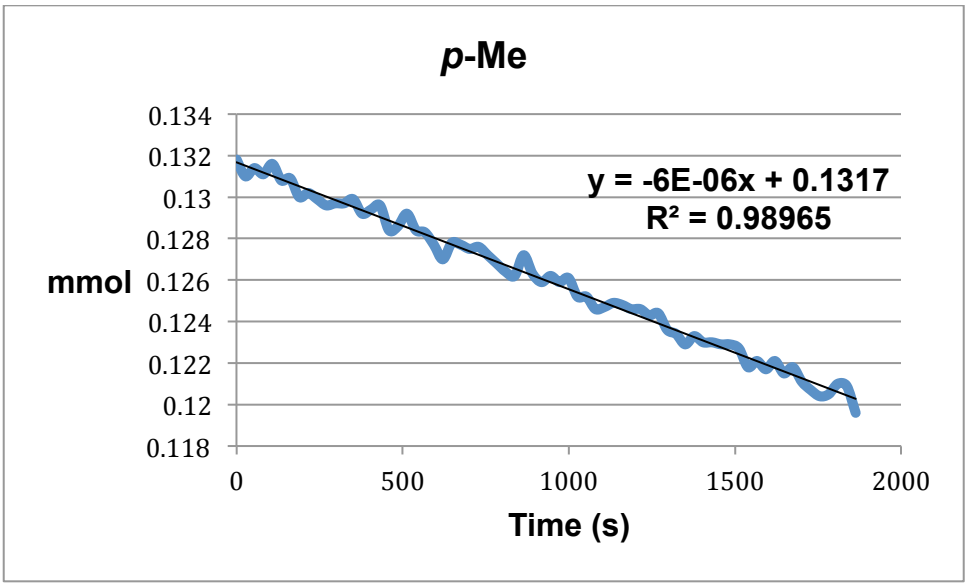
1.4.5 Hammett Study

To determine the electronic parameters of the electrocyclization, nitrones **3** were heated in toluene at 50 °C and the electrocyclization was monitored to 10% disappearance of the vinyl resonance of the nitrone to obtain initial rates. Rate data was collected in toluene because the reaction was difficult to monitor in MeOH due to rapid conversion to the azetidine nitrone products.

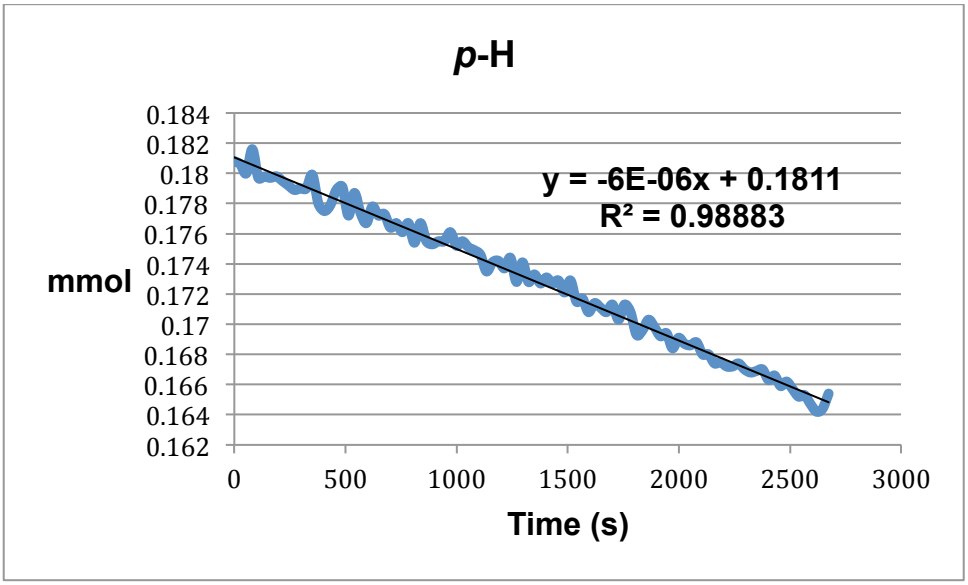
Concentration vs. Time Plot for the Conversion of **3c** to **4c** (*p*-OMe):



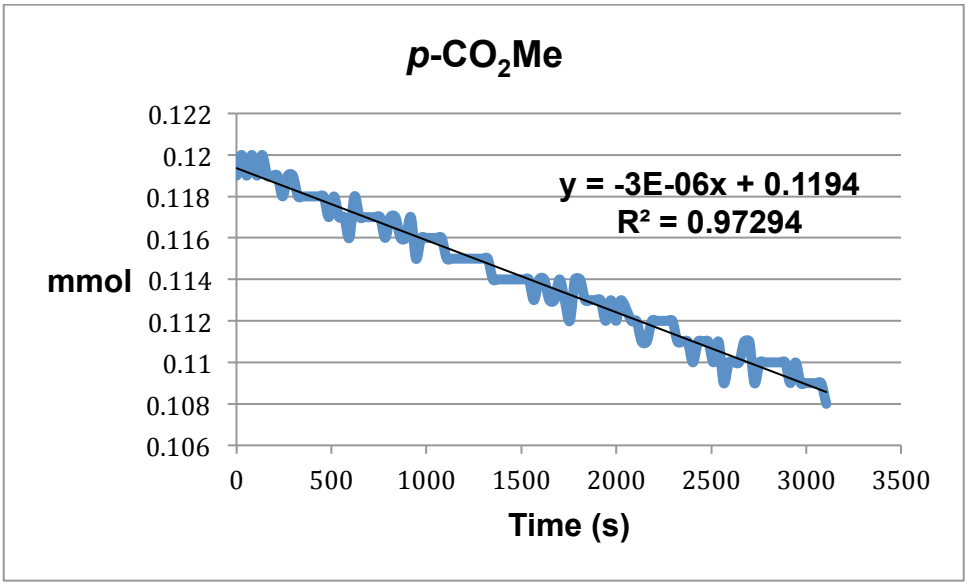
Concentration vs Time Plot for the Conversion of **3d** to **4d** (*p*-Me):



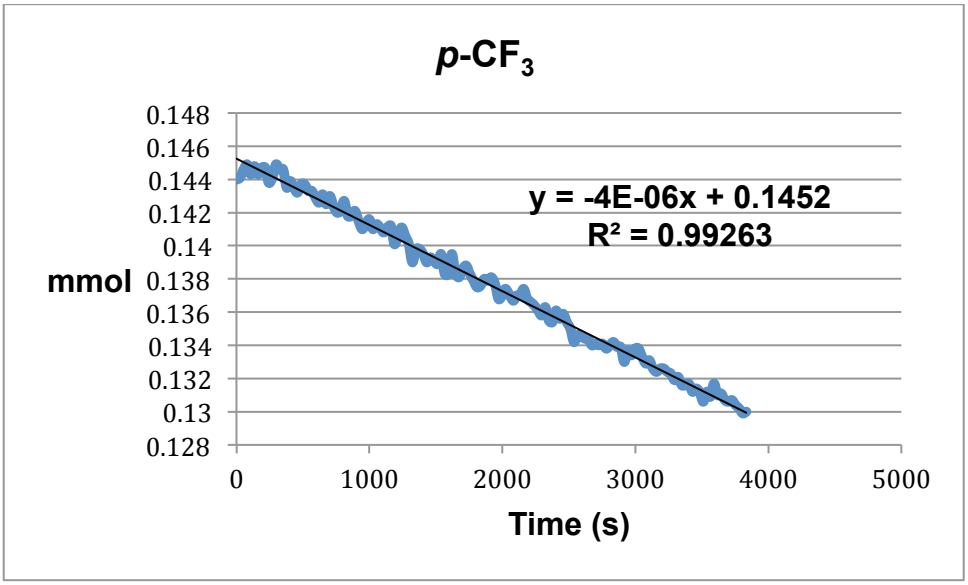
Concentration vs Time Plot for the Conversion of **3a** to **4a** (*p*-H):



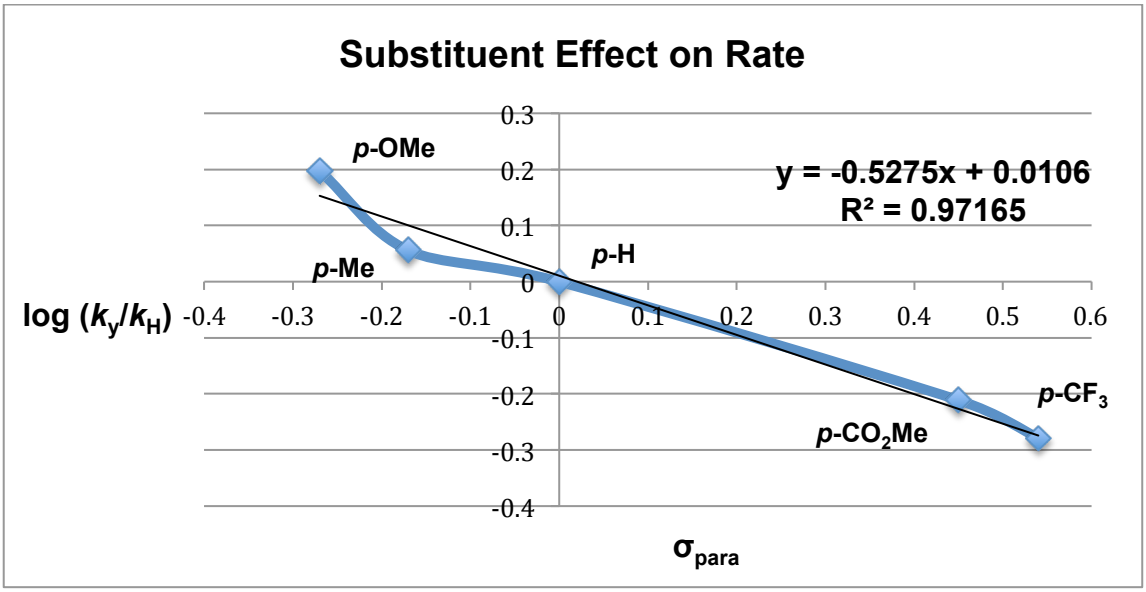
Concentration vs Time Plot for the Conversion of **3k** to **4k** (*p*-CO_2Me):



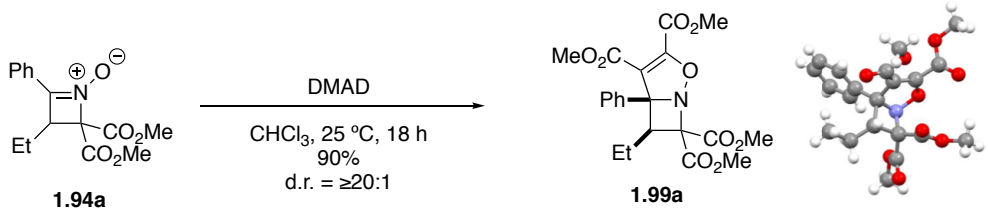
Concentration vs Time Plot for the Conversion of **3h** to **4h** (*p*-CF_3):



Hammett Plot for σ_p:

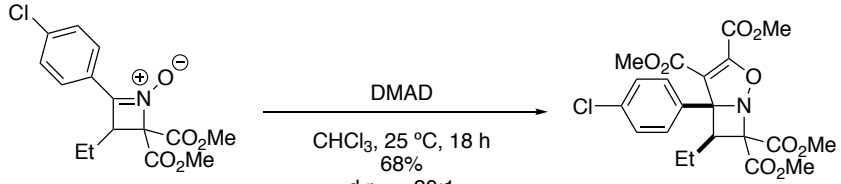


1.4.6 Cycloaddition, Reduction, and Dealkoxycarbonylation of 1.94



1.94a **1.99a**

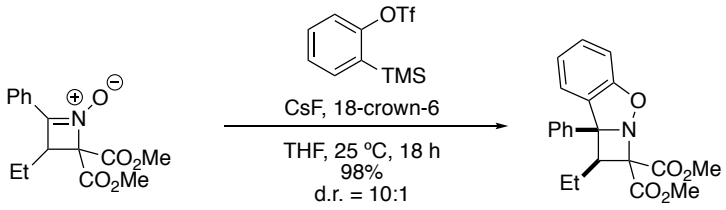
Cycloaddition of 1.94a with DMAD:[36] A flame-dried 25-mL round bottom flask was charged with azetidine **1.94a** (0.150 g, 0.515 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate (DMAD) (0.146 g, 1.03 mmol, 2.0 equiv), and $CHCl_3$ (5.0 mL). The reaction mixture was stirred for 18 h and then concentrated under vacuum. The crude product mixture was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:40 – 1:20; Et_2O: hexanes) to afford isoxazoline **1.99a** (0.200 g, 90%, dr >20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.68 – 7.66 (m, 2H), 7.37 – 7.34 (m, 2H), 7.31 – 7.28 (m, 1H), 4.15 (t, J = 7.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 1.39 – 1.30 (m, 1H), 1.27 – 1.18 (m, 1H), 0.64 (dd, J = 8.0, 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 166.1, 162.4, 159.0, 154.0, 137.4, 128.3, 128.1, 126.7, 113.7, 80.1, 79.0, 53.8, 53.2, 52.7, 52.2, 48.9, 20.5, 11.2; IR (thin film) 2608, 2339, 1741, 1736, 1731, 1728, 1589, 1469, 1444, 1260, 1130 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{24}NO_9$ $(M+H)^+$ 434.1451, found 434.1436. Purified **1.99a** was further dissolved in a minimal amount of EtOAc, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



1.94f **1.99f**

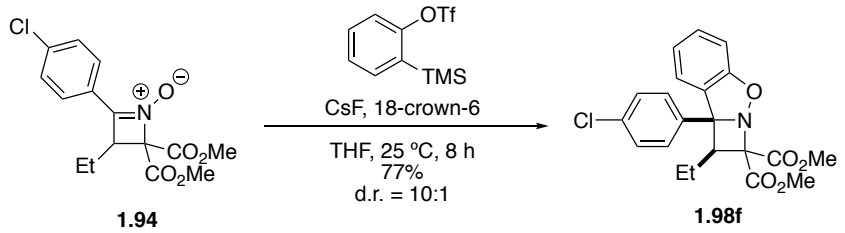
Cycloaddition of 1.94f with DMAD:[36] A flame-dried 25-mL round bottom flask was charged with azetidine **1.94f** (0.163 g, 0.500 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate (DMAD) (0.142 g, 1.00 mmol, 2.0 equiv), and $CHCl_3$ (5.0 mL). The reaction mixture was stirred for 18 h and then concentrated under vacuum. The crude product mixture was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:40 – 1:20; Et_2O: hexanes) to afford isoxazoline **1.99f** (0.159 g, 68%, dr ≥20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.64 – 7.62 (m, 2H),

7.33 – 7.31 (m, 2H), 4.11 (t, J = 7.5 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 1.33 – 1.20 (m, 1H), 1.19 – 1.14 (m, 1H), 0.65 (dd, J = 8.0, 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 166.0, 162.3, 158.9, 154.4, 135.9, 134.2, 128.5, 128.3, 113.2, 79.5, 79.0, 53.8, 53.3, 52.8, 52.3, 48.8, 20.5, 19.0, 11.3.



1.94 **1.98a**

Cycloaddition of 1.94a with benzyne:[36] A flame-dried 25-mL round bottom flask was charged with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.400 g, 1.34 mmol, 2.0 equiv), 18-crown-6 (0.707 g, 2.68 mmol, 4.0 equiv), azetidine **1.94a** (0.195 g, 0.670 mmol, 1.0 equiv), 4 Å MS (0.050 g), and THF (10.0 mL). The reaction mixture was stirred at 25 °C for 20 min, then solid CsF (0.407 g, 2.68 mmol, 4.0 equiv) was added in one portion. After 2 h, the reaction mixture was filtered through a plug of celite and washed with EtOAc (3 x 10 mL). The filtrate was then concentrated under vacuum and the crude product mixture was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:20 – 1:9; Et_2O: hexanes) to afford benzisoxazoline **1.98a** (0.241 g, 98%, dr = 10:1) as a colorless solid. Major Diastereomer: ^{1}H NMR (500 MHz; C_6D_6): δ 7.95 – 7.93 (m, 2H), 7.38 – 7.36 (m, 1H), 7.23 – 7.20 (m, 2H), 7.10 – 7.07 (m, 1H), 6.98 – 6.94 (m, 1H), 6.91 – 6.89 (m, 1H), 6.68 – 6.67 (m, 1H), 4.18 (t, J = 7.5 Hz, 1H), 3.45 (s, 3H), 3.36 (s, 3H), 1.61 – 1.52 (m, 1H), 1.52 – 1.43 (m, 1H), 0.70 (dd, J = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 167.5, 166.6, 158.8, 138.8, 132.0, 129.1, 128.3, 127.8, 127.6, 124.2, 122.7, 108.5, 78.4, 78.2, 52.7, 51.8, 50.5, 21.1, 11.6; Minor Diastereomer diagnostic peaks: ^{1}H NMR (500 MHz; C_6D_6): δ 7.67 – 7.65 (m, 2H), 6.85 – 6.81 (m, 2H), 3.64 – 3.60 (m, 1H), 3.48 (s, 3H), 3.25 (s, 3H), 2.34 – 2.24 (m, 1H), 1.96 – 1.86 (m, 1H), 1.03 (dd, J = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 128.6, 128.1, 124.9, 121.7, 108.3, 52.0, 20.5, 11.8; IR (thin film) 2652, 2360, 1742, 1738, 1592, 1493, 1471, 1455, 1261, 1212 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1498, found 368.1511; m.p.: 65 – 67 °C.



1.94 **1.98f**

Cycloaddition of 1.94f with benzyne:[48] A flame-dried 25-mL round bottom flask was charged with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.366 g, 1.22 mmol, 2.0 equiv), 18-crown-6 (0.649 g, 2.46 mmol, 4.0 equiv), azetidine **1.94f** (0.200 g, 0.614 mmol, 1.0 equiv), 4 Å MS (0.050 g), and THF (10.0 mL). The reaction mixture was stirred at 25 °C for 20 min, then solid CsF (0.374 g, 2.46 mmol, 4.0 equiv) was added in one portion. After 2 h, the reaction mixture was filtered through a plug of celite and washed with EtOAc (3 x 10 mL). The filtrate was then concentrated under vacuum and the crude product mixture was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:20 – 1:9; Et_2O: hexanes) to afford benzisoxazoline **1.98f** (0.190 g, 77%, dr = 10:1) as a colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.70 – 7.68 (d, 2H), 7.54 – 7.52 (m, 1H), 7.35 – 7.33 (d, 2H), 7.22 – 7.18 (m, 1H), 7.09 – 7.06 (m, 1H), 6.79 – 6.78 (m, 1H), 3.85 (t, J = 7.5 Hz, 1H), 3.83 (s, 3H), 3.61 (s, 3H), 1.39 – 1.27 (m, 2H), 0.66 (dd, J = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 166.3, 158.2, 136.7, 133.8, 130.9, 129.7, 129.5, 128.8, 128.5, 128.0, 126.5, 125.3, 123.9, 123.1, 122.2, 108.6, 108.3, 53.4, 52.7, 50.1, 20.6, 11.6.

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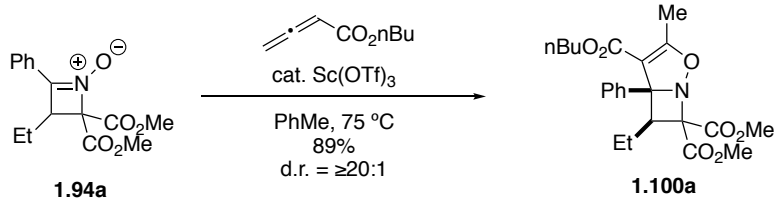
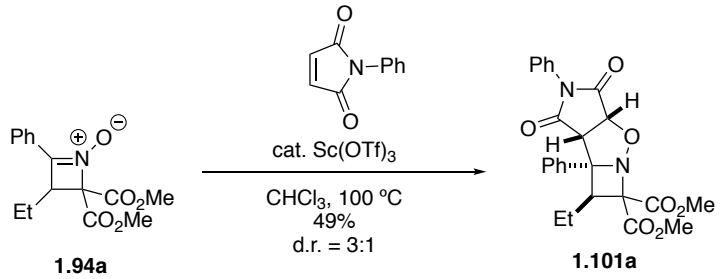


1.94a **1.100a**

Cycloaddition of **1.94a** with *n*-butylallenoate: A flame-dried 25-mL round bottom flask was charged with azetidine **1.94a** (0.150 g, 0.515 mmol, 1.0 equiv), *n*-butyl buta-2,3-dienoate (0.144 g, 1.03 mmol, 2.0 equiv),[49] $Sc(OTf)_3$ (0.0131 g, 0.0258 mmol, 0.05 equiv), and toluene (5.0 mL). The reaction mixture was heated to 75 °C and stirred for 1 h and then concentrated under vacuum. The crude product mixture was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:40 – 1:20;

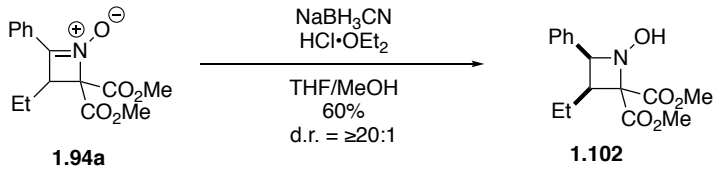
EtOAc: hexanes) to afford isoxazoline **1.100a** (0.198 g, 89%, dr ≥20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.69 – 7.68 (m, 2H), 7.34 – 7.31 (m, 2H), 7.27 – 7.24 (m, 1H), 4.31 – 4.21 (m, 2H), 4.05 – 4.02 (m, 1H), 3.80 (s, 6H), 2.11 (s, 3H), 1.72 – 1.67 (m, 2H), 1.47 – 1.40 (m, 2H), 1.37 – 1.28 (m, 1H), 1.27 – 1.19 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.61 (dd, *J* = 8.0, 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 167.0, 166.9, 164.3, 139.0, 128.0, 127.7, 127.0, 108.9, 79.2, 78.5, 64.1, 53.2, 52.6, 48.6, 30.8, 20.6, 19.3, 13.7, 12.6, 11.3; IR (thin film) 2957, 2359, 1741, 1698, 1644, 1447, 1434, 1375, 1336, 1309, 1125 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{30}NO_7$ $(M+H)^+$ 432.2022, found 432.2022.



1.94a **1.101a**

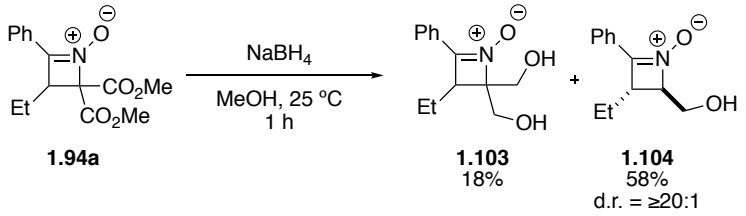
Cycloaddition of 1.94a with *N*-phenyl maleimide:[36] A flame-dried 25-mL round bottom flask was charged with azetidine **1.94a** (0.050 g, 0.172 mmol, 1.0 equiv), *N*-phenylmaleimide (0.0446 g, 0.257 mmol, 1.5 equiv), and anhydrous $CHCl_3$ (2.0 mL). The reaction mixture was heated to 100 °C and stirred for 48 h and then concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (1:9 – 1:4; Et_2O: hexanes) to afford isoxazoline **1.101a** (0.0391 g, 49%, dr = 3:1) as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$) (major diastereomer): δ 7.37 – 7.31 (m, 5H), 7.24 – 7.23 (m, 3H), 6.42 – 6.38 (m, 2H), 5.77 (d, *J* = 8.7 Hz, 1H), 4.67 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.13 (t, *J* = 7.9 Hz, 1H), 2.15 – 2.09 (m, 2H), 1.16 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 172.4, 170.8, 169.1, 165.8, 140.3, 130.7, 128.9, 128.6, 128.5, 128.1, 125.8, 125.3, 85.5, 80.2, 78.1, 55.6, 53.2, 53.1, 46.0, 21.0, 11.6; ^{1}H NMR (500 MHz; $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 7.37 – 7.21 (m, 5H), 7.24 – 7.23 (m, 3H), 6.35 – 6.33 (m, 2H), 5.41 (d, *J* = 8.7 Hz, 1H), 4.77 (d, *J* = 8.7 Hz, 1H), 3.92 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.82 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.78 (s, 3H), 1.58 – 1.51 (m, 1H), 1.30 – 1.25 (m, 1H), 0.81 (dd, *J* = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 171.3, 170.6, 168.6, 167.2, 134.6, 129.8, 129.0,

128.3, 126.0, 83.9, 80.1, 77.9, 61.7, 54.0, 52.7, 48.1, 20.9, 11.8; IR (thin film) 3725, 3702, 3628, 2359, 2341, 1745, 1716, 1724, 1497, 1457, 1385 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}N_2O_7$ $(M+H)^+$ 465.1662, found 465.1677; m.p.: 106 – 110 °C.

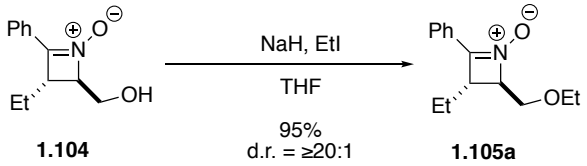


1.94a **1.102**

Reduction of 1.94a with $NaBH_3CN$:[49] A flame-dried 10-mL round bottom flask was flushed with N_2, charged with azetidine **1.94a** (0.075 g, 0.26 mmol, 1.0 equiv), and sealed with a rubber septum. Anhydrous THF (3.0 mL) was then added to the reaction flask via syringe, followed by a addition of a solution of $NaBH_3CN$ (0.018 g, 0.29 mmol, 1.1 equiv) in MeOH (1.0 mL), and a solution of HCl (0.143 mL, 2.0 M in Et_2O, 0.286 mmol, 1.1 equiv) at 25 °C. The reaction mixture was allowed to stir for 20 min at 25 °C. At this time, the reaction mixture was quenched with 2.0 mL sat. $NaHCO_3$ and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried over Na_2SO_4, filtered through cotton, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (1:10 – 1:5; EtOAc: hexanes) to afford hydroxylamine **1.102** (0.045 g, 60%, dr = >20:1) as a white solid. ^1H NMR (500 MHz; $CDCl_3$): δ 7.44 – 7.43 (m, 2H), 7.31 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 6.41 (brs, 1H), 5.02 (d, J = 9.2 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.16 – 3.11 (m, 1H), 1.32 – 1.17 (m, 2H), 0.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 167.5, 136.8, 128.1, 127.9, 127.7, 78.6, 69.9, 52.9, 52.2, 41.3, 19.0, 11.7; IR (thin film) 3459, 3401, 2995, 1740, 1736, 1495, 14893, 1469, 1369, 1260, 1201 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{20}NO_5$ $(M+H)^+$ 294.1341, found 294.1331; m.p.: 98 – 102 °C. Characterization of the major diastereomer was determined by comparison of the methine coupling constants to literature values for similar azetidine structures.[50]

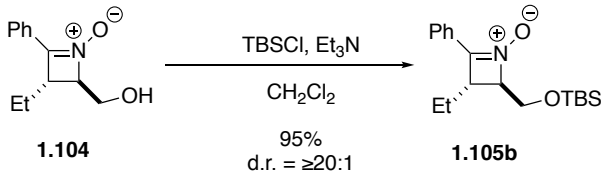


Reduction of 1.94a with $NaBH_4$: A flame-dried 10-mL round bottom flask was flushed with N_2, charged with azetidine **1.94a** (0.500 g, 1.72 mmol, 1.0 equiv), and sealed with a rubber septum and dissolved in MeOH to form a 0.1 M solution. Solid $NaBH_4$ (0.0716 g, 1.90 mmol, 1.1 equiv) was added at 25 °C in one portion. The reaction mixture was allowed to stir for 1 hour at 25 °C. At this time, the reaction mixture was quenched with 2.0 mL sat. $NaHCO_3$ and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried over Na_2SO_4, filtered through cotton, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (1:10 – 1:5; EtOAc: hexanes) to afford diol **1.103** (0.073 g, 18%) as a white solid and alcohol **1.104** (0.205 g, 58%, d.r. = ≥20:1) as a white solid. **1.103:** ^{1}H NMR (500 MHz; MeOH-d_4): δ 7.99 – 7.98 (m, 2H), 7.45 – 7.44 (m, 3H), 4.01 – 3.95 (m, 3H), 3.83 – 3.80 (m, 1H), 3.39 (t, 1H), 2.02 – 1.96 (m, 2H), 1.11 (t, 3H); ^{13}C NMR (125 MHz, MeOH-d_4): δ 152.4, 130.5, 128.5, 127.1, 126.9, 86.0, 59.3, 58.7, 42.1, 18.8, 12.4. **1.104:** ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.82 – 7.81 (m, 2H), 7.28 – 7.27 (m, 3H), 4.72 (brs, 1H), 4.14 – 4.12 (d, 1H), 4.09 – 4.08 (m, 1H), 3.76 – 3.72 (d, 1H), 3.18 – 3.15 (m, 1H), 1.95 – 1.87 (m, 1H), 1.62 – 1.53 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.5, 130.2, 128.6, 127.6, 126.4, 80.1, 57.9, 37.4, 22.5, 11.3.



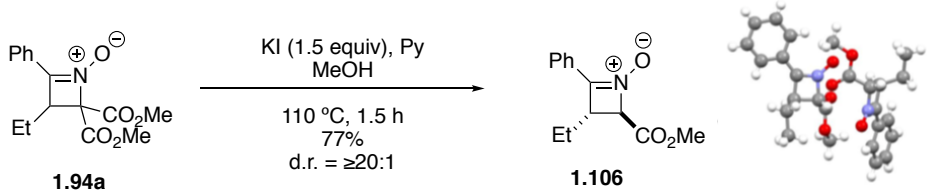
Etherification of 1.04: A 25-mL round bottom flask was flame-dried under N_2, allowed to cool to 25 ºC and charged with **1.104** (0.050 g, 0.244 mmol, 1.0 equiv) and dissolved in THF (2.5 mL, 0.1 M). To this mixture was added NaH (60% in mineral oil, 0.0107 g, 0.268 mmol, 1.1 equiv) in one portion. After 10 min, EtI (0.0571 g, 0.366 mmol,1.5 equiv) in one portion. After 1 h, the reaction was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:10 – 1:8; EtOAc:hexanes) to afford

azetidine nitrone ether **1.105a** (0.054 g, 95%, dr = >20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.96 – 7.95 (m, 2H), 7.43 – 7.36 (m, 3H), 4.20 – 4.19 (m, 1H), 3.99 – 3.96 (m, 1H), 3.84 – 3.82 (m, 1H), 3.61 – 3.54 (m, 2H), 3.23 – 3.20 (m, 1H), 2.10 – 2.00 (m, 1H), 1.74 – 1.65 (m, 1H), 1.15 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 129.9, 128.7, 128.1, 126.1, 78.8, 67.2, 66.1, 38.5, 22.8, 15.1, 11.4.



1.104 **1.105b**

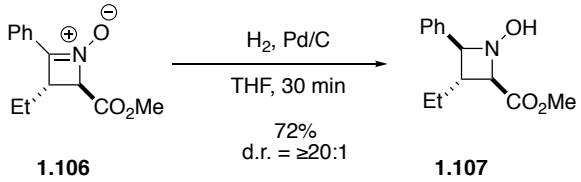
Silylation of 1.04: A 25-mL round bottom flask was flame-dried under N_2, allowed to cool to 25 ºC and charged with **1.104** (0.050 g, 0.244 mmol, 1.0 equiv) and dissolved in CH_2Cl_2 (2.5 mL, 0.1 M). To this mixture was added Et_3N (0.0271 g, 0.268 mmol, 1.1 equiv) in one portion. After 10 min, TBSCl (0.0441 g, 0.293 mmol,1.2 equiv) in one portion. After 1 h, the reaction was dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:10 – 1:5; EtOAc:hexanes) to afford azetidine nitrone ether **1.105b** (0.093 g, 95%, dr = >20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.88 – 7.86 (m, 2H), 7.33 – 7.26 (m, 3H), 4.11 – 4.08 (m, 1H), 4.06 – 4.05 (m, 1H), 3.91 – 3.89 (m, 1H), 3.15 – 3.11 (m, 1H), 2.00 – 1.92 (m, 1H), 1.65 – 1.56 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.73 (s, 9H), 0.00 ((s, 3H), -0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.0, 129.7, 128.5, 128.0, 125.9, 80.1, 58.9, 37.9, 25.6, 22.8, 18.0, 11.5, -5.4, -5.5.



1.94a **1.106**

Dealkoxycarbonylation of 1.94a: A 25-mL round bottom flask was flame-dried under N_2, allowed to cool to 25 °C and charged with azetidine **1.94a** (0.150 g, 0.515 mmol, 1.00 equiv) and KI (0.128 g, 0.772 mmol, 1.50 equiv). The reaction mixture was then diluted with pyridine and MeOH (1:1 mixture, 5.2 mL) to form a 0.1 M solution of **1.94a** and heated at 110 °C for 1.5 h. The reaction mixture was then cooled to 25 °C, diluted with

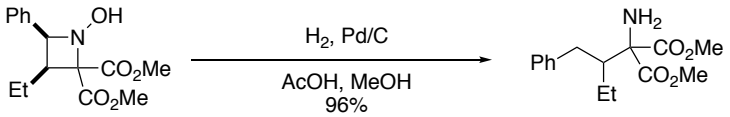
EtOAc (20 mL), filtered through a silica plug, and concentrated under vacuum at 40 °C. The crude product mixture was then dry-loaded onto celite using EtOAc and purified by medium pressure chromatography (1:3 – 1:1; EtOAc:hexanes) to afford dealkoxycarbonylated azetidine nitrone **1.106** (0.093 g, 77%, dr = >20:1) as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.89 – 7.88 (m, 2H), 7.37 – 7.35 (m, 3H), 4.66 – 4.65 (m, 1H), 3.78 (s, 3H), 3.22 – 3.19 (m, 1H), 2.09 – 2.01 (m, 1H), 1.75 – 1.66 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 152.1, 130.5, 128.8, 127.5, 126.1, 77.4, 53.0, 40.4, 23.1, 11.0; IR (thin film) 2956, 2359, 2342, 1711, 1589, 1495, 1449, 1389, 1202, 1100 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{16}NO_3$ $(M+H)^+$ 234.1130, found 234.1124; m.p.: 99 – 102 °C. Purified **1.106** was further dissolved in a minimal amount of EtOAc, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



1.106 **1.107**

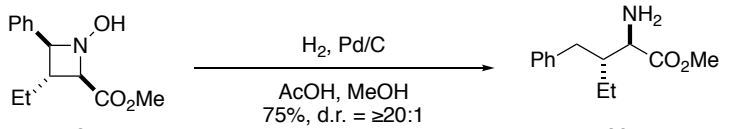
Hydrogenation of 1.106: A flame-dried 10-mL round bottom flask equipped with a magnetic stirring bar was charged with 10 wt% Pd on activated carbon (0.029 g, 0.027 mmol, 0.1 equiv), diluted with anhydrous THF (10.0 mL), sealed with a rubber septum, and flushed with N_2. A balloon of H_2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine nitrone **1.106** (0.063 g, 0.27 mmol, 1.0 equiv) in 5.0 mL THF was added to the activated Pd/C slurry in one portion via syringe. The reaction mixture was allowed to stir at 25 °C for 1 h under an H_2 atmosphere, then filtered through a plug of celite, rinsed with EtOAc (3 x 10 mL), and concentrated under vacuum. The crude product mixture was dry-loaded onto celite and purified by medium pressure chromatography (1:3 – 1:1; EtOAc:hexanes) to afford hydroxylamine azetidine **1.107** (0.046 g, 72%, dr = >20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.63 (brs, 1H), 7.31 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 4.01 (d, J = 8.5 Hz, 1H), 3.72 (d, J = 8.5 Hz, 1H), 3.60 (s, 3H), 2.06 – 2.00 (m, 1H), 1.74 – 1.65 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 139.6, 128.3, 127.8, 127.3, 76.1, 71.8, 51.8, 41.5, 26.0, 11.3; IR (thin film) 3512, 2945, 2356, 2332, 1709, 1575, 1480, 1381, 1101 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{18}NO_3$

$(M+H)^+$ 236.1287, found 236.1285. Characterization of the major diastereomer was determined by comparison of the methine coupling constants to literature values for similar azetidine structures and in analogy to the azetidine nitrone precursor **1.106**.[53]



1.102 **1.108**

N–O Reduction and Ring-Opening of 1.102: A flame-dried 10-mL round bottom flask was charged with 10wt% Pd on activated carbon (0.0553 g, 0.0522 mmol, 0.100 equiv), diluted with MeOH (2.5 mL), sealed with a rubber septum, and flushed with N_2. A balloon of H_2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine hydroxylamine **1.102** (0.153 g, 0.522 mmol, 1.00 equiv) and AcOH (0.0323 g, 0.522 mmol, 1.00 equiv) in 2.5 mL MeOH was added to the activated Pd/C slurry in one portion via syringe. The reaction mixture was allowed to stir at 25 °C for 18 h under an H_2 atmosphere, then filtered through a plug of celite, rinsed with Et_2O (3 x 10 mL), and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (1:5 – 1:4; Et_2O:hexanes) to afford amino ester **1.108** (0.140 g, 96%) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.28 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 5.70 (brs, 2H), 3.75 (s, 6H), 2.93 (dd, J = 14.0, 4.5 Hz, 1H), 2.60 (dd, J = 14.0, 4.5 Hz, 1H), 2.30 – 2.25 (m, 1H), 1.66 – 1.57 (m, 1H), 1.43 – 1.34 (m, 1H), 0.74 (dd, J = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 169.6, 140.7, 129.1, 128.3, 126.1, 78.1, 52.6, 52.5, 46.5, 37.2, 24.2, 13.3; IR (thin film) 2953, 2359, 1734, 1730, 1602, 1559, 1495, 1455, 1434, 1379, 1207 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{22}NO_4$ $(M+H)^+$ 280.1549, found 280.1545.

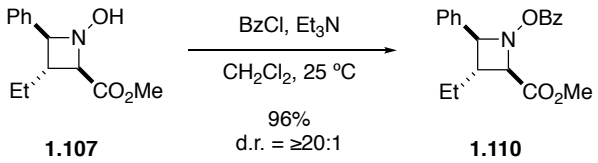


1.107 **1.109**

N–O Reduction and Ring-Opening of 1.107: A flame-dried 10-mL round bottom flask was charged with 10 wt% Pd on activated carbon (0.114 g, 0.107 mmol, 0.100 equiv), diluted with MeOH (5.0 mL), sealed with a rubber septum, and flushed with N_2. A

balloon of H_2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine hydroxylamine **1.107** (0.250 g, 0.107 mmol, 1.00 equiv) and AcOH (0.0643 g, 1.07 mmol, 1.00 equiv) in 5.0 mL MeOH was added to the activated Pd/C slurry in one portion via syringe. The reaction mixture was allowed to stir at 25 °C for 2 h under an H_2 atmosphere, then filtered through a plug of celite, rinsed with Et_2O (3 x 10 mL), and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (1:5 – 1:4; Et_2O:hexanes) to afford α-amino ester **1.109** (0.177 g, 75%, dr = >20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.28 – 7.25 (m, 2H), 7.19 – 7.15 (m, 3H), 3.63 (s, 3H), 3.58 (d, *J* = 10.0 Hz, 1H), 2.61 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.52 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.76 (brs, 2H), 1.49 – 1.40 (m, 1H), 1.37 – 1.28 (m, 1H), 0.92 (dd, *J* = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 140.4, 129.3, 128.2, 125.9, 55.3, 51.8, 45.8, 35.7, 23.2, 11.8; IR (thin film) 3726, 3709, 3026, 2957, 2359, 1732, 1721, 1602, 1558, 1455, 1379 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1498.

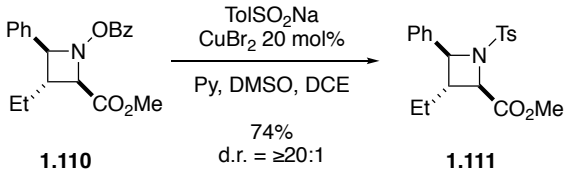
1.4.7 Benzoylation and Sulfonylation of *N*-Hydroxy Azetidines



1.107 **1.110**

Benzoylation of 1.107: A flame-dried 10-mL round bottom flask was charged azetidine hydroxylamine **1.107** (0.235 g, 1.00 mmol, 1.0 equiv), and diluted with CH_2Cl_2 (10.0 mL, 0.1M). The reaction flask was placed in an ice-bath and Et_3N (0.202 g, 2.00 mmol, 2.0 equiv) was added with vigorous stirring followed by BzCl (0.281 g, 2.00 mmol, 2.0 equiv) in one portion. The reaction mixture was allowed to warm to 25 °C for 1 h and then dry-loaded onto celite using Et_2O and purified directly by medium pressure chromatography (1:20 – 1:9; Et_2O:hexanes) to afford *O*-benzoylhydroxylamine azetidine **1.110** (0.322 g, 95%, dr = 20:1) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.96 – 7.94 (m, 2H), 7.57 – 7.56 (m, 2H), 7.53 – 7.50 (m, 1H), 7.40 – 7.36 (m, 4H), 7.32 – 7.29 (m, 1H), 4.46 (d, *J* = 8.5 Hz, 1H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 2.45 – 2.39 (m, 1H),

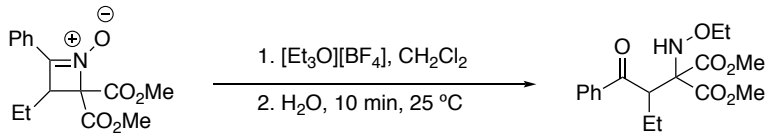
1.88 – 1.76 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 164.5, 138.8, 133.1, 129.5, 128.7, 128.5, 128.4, 128.2, 127.2, 75.0, 72.0, 52.3, 42.8, 26.0, 11.2; IR (thin film) 3469, 2959, 2539, 2350, 1760, 1481, 1451, 1420, 1370, 1110 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}NO_4$ $(M+H)^+$ 340.1549, found 340.1562. Characterization of the major diastereomer was determined by comparison of the methine coupling constants to literature values for similar azetidine structures and in analogy to the azetidine nitrone precursor **1.106**.[50,51]



1.110 **1.111**

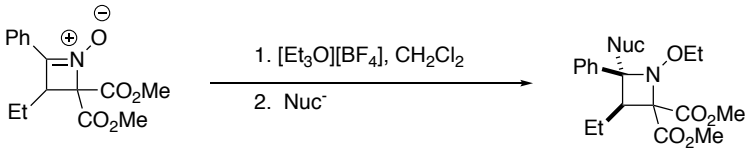
***N*-Tosylazetidine 1.111:**[55] A flame dried 25-mL round bottom flask was charged with azetidine **1.110** (0.126 g, 0.370 mmol, 1.00 equiv), $CuBr_2$ (0.017 g, 0.074 mmol, 0.20 equiv), and sodium 4-methylbenzenesulfinate (0.132 g, 0.740 mmol, 2.0 equiv). These reagents were diluted with DCE to form a 0.1 M solution of **1.110**. The resulting mixture was treated with pyridine (0.059 g, 0.740 mmol, 2.0 equiv) and DMSO (0.003 g, 0.037 mmol, 0.1 equiv) and allowed to stir for 18 h at 25 °C. The crude product mixture filtered through a plug of SiO_2, dry-loaded onto celite using Et_2O, and purified by medium pressure chromatography (0:100 – 1:5; Et_2O: hexanes) to give *N*-tosylazetidine **1.111** (0.102 g, 74%, dr = ≥20:1) as a white solid. ^{1}H NMR (500 MHz; C_6D_6): δ 7.66 – 7.65 (m, 2H), 7.40 – 7.38 (m, 2H), 7.29 – 7.20 (m, 5H), 4.61 (d, J = 6.8 Hz, 1H), 4.29 (d, J = 7.0 Hz, 1H), 3.74 (s, 3H), 2.40 (s, 3H), 2.39 – 2.35 (m, 1H), 1.63– 1.54 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 170.4, 143.2, 140.2, 136.2, 129.2, 128.5, 128.2, 127.6, 127.0, 68.7, 63.0, 51.6, 46.0, 25.7, 20.9, 10.4; IR (thin film) 3001, 2935, 2539, 2333, 1762, 1489, 1450, 1444, 1360 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}NO_4S$ $(M+H)^+$ 374.1426, found 374.1420; m.p.: 91 – 98 °C. Characterization of the major diastereomer was determined by comparison of the methine coupling constants to literature values for similar azetidine structures and in analogy to the azetidine nitrone precursor **1.106**.[50,51]

1.4.8 Electrophilic Activation and Nucleophilic Addition to Azetidine Nitrones



1.94a **1.113**

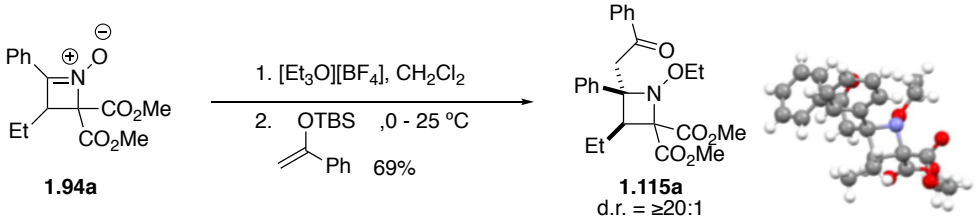
β-Aminoketone 1.113: A flame-dried 50-mL round bottom flask was allowed to cool to 25 °C under N_2, charged with azetidine nitrone **1.94a** (0.100 g, 0.343 mmol, 1.00 equiv) and CH_2Cl_2 (5.0 mL), and sealed with a rubber septum. A solution of $[Et_3O][BF_4]$ (0.065 g, 0.38 mmol, 1.1 equiv) in CH_2Cl_2 (1.0 mL) was added in one portion via syringe. The reaction mixture was then allowed to stir for 30 min at 25 °C. After 30 min, 5.0 mL deionized H_2O was added and allowed to stir for 10 min. The reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product mixture was then purified by medium pressure chromatography (1:20 – 1:3; EtOAc:hexanes) to give β-aminoketone **1.113** (0.111 g, 96%) as a clear oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.01 – 8.00 (m, 2H), 7.57 – 7.54 (m, 1H), 7.47 – 7.44 (m, 2H), 6.35 (s, 1H), 4.42 (dd, J = 10.5, 3.0 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.63 – 3.52 (m, 2H), 2.06 – 2.00 (m, 1H), 1.93 – 1.84 (m, 1H), 1.03 (t, J = 7.5 Hz, 3H), 0.83 (dd, J = 10.0, 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4, 168.8, 168.2, 138.4, 133.2, 128.6, 128.5, 75.1, 69.8, 52.8, 52.7, 49.2, 23.3, 13.8, 13.0; IR (thin film) 2983, 2953, 2876, 2360, 1737, 1677, 1450, 1443, 1217, 1049 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{24}NO_6$ $(M+H)^+$ 338.1604, found 338.1598.



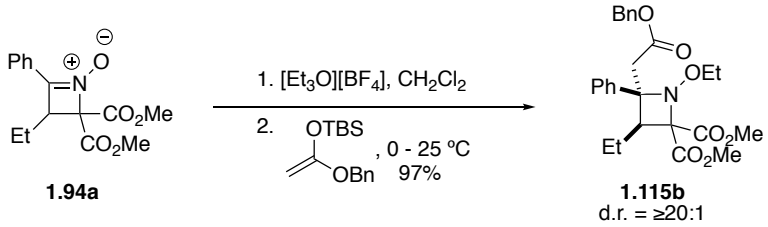
1.94a **1.115**

General Procedure C: A flame-dried 10-mL round bottom flask was charged with azetidine **1.94a** (1.00 equiv) and CH_2Cl_2 (5.0 mL) and sealed with a rubber septum. The resulting solution was then treated with a solution of $[Et_3O][BF_4]$ (1.1 equiv) in anhydrous CH_2Cl_2 (1.0 mL) via syringe. The reaction mixture was then allowed to stir for 30 min at 25 °C. At this time, the reaction flask was cooled in an ice-bath and the nucleophile (2.0 equiv, in 2.0 mL of CH_2Cl_2) was added via syringe at 0 °C and allowed

to warm to 25 °C and stir for 1 – 4 h. The reaction mixture was then concentrated under vacuum, dry-loaded onto celite using Et_2O, and purified by medium pressure chromatography (Et_2O: hexanes) to afford azetidine ethers **1.115**.

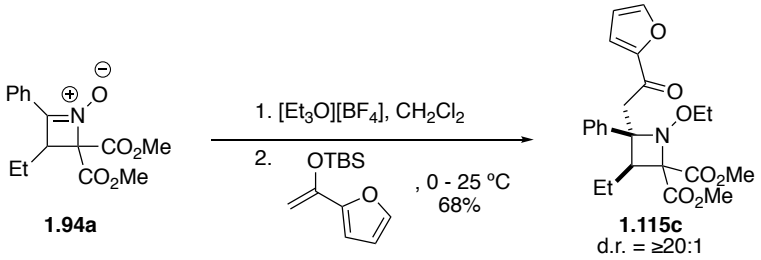


***N*-Ethoxyazetidine 1.115a:** Azetidine **1.115a** was prepared using general procedure C with azetidine nitrone **1.94a** (0.150 g, 0.515 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.108 g, 0.566 mmol, 1.1 equiv) and *tert*-butyldimethyl((1-phenylvinyl)oxy)silane (0.241 g, 1.03 mmol, 2.0 equiv). After the addition of the silyl enol ether, the reaction mixture was allowed to stir for 4 h. The crude product was purified by medium pressure chromatography (1:20 – 1:5; Et_2O:hexanes) to afford *N*-ethoxyazetidine **1.115a** (0.156 g, 69%, dr = ≥20:1) as a colorless solid. ^{1}H NMR (500 MHz; C_6D_6): δ 8.08 – 8.07 (m, 2H), 7.94 – 7.93 (m, 2H), 7.35 – 7.32 (m, 2H), 7.22 – 7.17 (m, 2H), 7.16 – 7.13 (m, 2H), 4.50 (d, J = 18.5 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.03 – 3.96 (m, 1H), 4.00 (d, J = 18.5 Hz, 1H), 3.80 (t, J = 7.5 Hz, 1H), 3.49 (s, 3H), 3.48 (s, 3H), 1.38 – 1.25 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H), 0.76 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 195.6, 169.2, 168.7, 142.6, 138.1, 132.3, 128.4, 128.0, 127.8, 127.6, 126.8, 78.7, 74.0, 70.3, 52.2, 51.4, 46.6, 42.0, 20.5, 14.0, 12.1; IR (thin film) 2978, 2950, 2892, 1752, 1732, 1695, 1596, 1494, 1434, 1263 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{30}NO_6$ $(M+H)^+$ 440.2073, found 440.2068; m.p.: 112 – 115 °C. Purified **1.115a** was further dissolved in a minimal amount of Et_2O, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



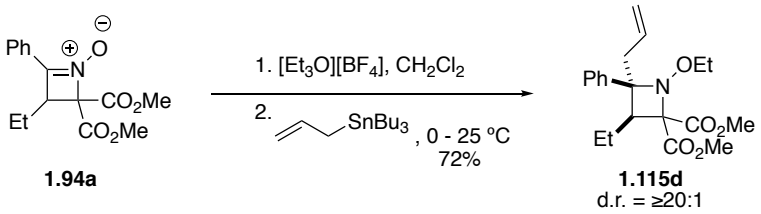
***N*-Ethoxyazetidine 1.115b:** Azetidine **1.115b** was prepared using general procedure C with azetidine nitrone **1.94a** (0.200 g, 0.687 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.143 g,

0.755 mmol, 1.10 equiv), and ((1-(benzyloxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (0.545 g, 2.06 mmol, 3.00 equiv). After the addition of the silyl ketene acetal, the reaction mixture was allowed to stir for 1 h. The crude product mixture was concentrated under vacuum and then dry-loaded onto celite and purified by medium pressure chromatography (1:30 – 1:20; Et_2O: hexanes) to afford *N*-ethoxyazetidine **1.115b** (0.313 g, 97%, dr = ≥20:1) as a colorless oil. ^{1}H NMR (500 MHz; C_6D_6): δ 7.87 – 7.85 (m, 2H), 7.31 – 7.28 (m, 2H), 7.19 – 7.13 (m, 4H), 7.11 – 7.08 (m, 2H), 4.99 – 4.97 (m, 2H), 4.12 – 4.06 (m, 1H), 3.95 – 3.88 (m, 1H), 3.83 (d, *J* = 17.5 Hz, 1H), 3.67 (t, *J* = 7.5 Hz, 1H), 3.56 (d, *J* = 17.5 Hz, 1H), 3.53 (s, 3H), 3.45 (s, 3H), 1.21 – 1.14 (m, 2H), 1.08 (dd, *J* = 8.0, 7.5 Hz, 3H), 0.61 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 170.1, 168.7, 168.6, 142.1, 136.5, 128.3, 128.2, 128.0, 127.6, 127.5, 126.9, 78.5, 72.8, 70.3, 65.7, 52.3, 51.4, 46.3, 38.6, 20.4, 14.0, 11.9; IR (thin film) 2980, 2359, 2340, 1736, 1446, 1434, 1261, 1213, 1182, 1147 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{26}H_{32}NO_7$ $(M+H)^+$ 470.2179, found 470.2176. The diastereoselectivity of **1.115b** was determined in analogy to **1.115a**.



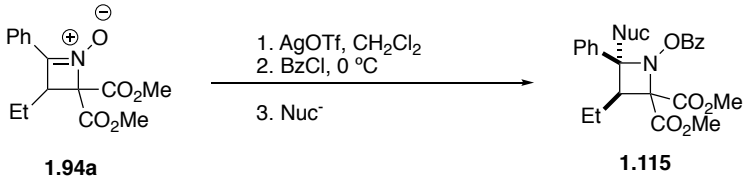
***N*-Ethoxyazetidine 1.115c:** Azetidine **1.115c** was prepared using general procedure C with azetidine nitrone **1.94a** (0.150 g, 0.515 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.108 g, 0.566 mmol, 1.10 equiv), and *tert*-butyl((1-(furan-2-yl)vinyl)oxy)dimethylsilane (0.127 g, 0.566 mmol, 1.1 equiv). After the addition of the nucleophile, the reaction mixture was allowed to stir for 2 h. The reaction mixture was then quenched by the addition of H_2O (5.0 mL) and allowed to stir for 10 min. The reaction mixture was then extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite and purified by medium pressure chromatography (0:100 – 2:98; Et_2O: hexanes) to afford *N*-ethoxyazetidine **1.115c** (0.134 g, 72%, dr = ≥20:1) as a colorless solid. ^{1}H NMR (500 MHz; C_6D_6): δ 7.96 – 7.95 (m, 2H), 7.32 – 7.30 (m, 2H),

7.25 (s, 1H), 7.18 – 7.16 (m, 1H), 7.01 – 6.98 (m, 1H), 6.95 – 6.94 (1H), 5.95 – 5.94 (m, 1H), 4.40 (d, J = 10.0 Hz, 1H), 4.19 – 4.13 (m, 1H), 4.06 – 4.02 (m, 2H), 3.82 (t, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 1.35 – 1.24 (m, 2H), 1.08 (dd, J = 8.0, 7.5 Hz, 3H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 185.2, 169.0, 168.7, 153.7, 145.0, 142.4, 127.8, 127.6, 126.9, 115.4, 111.8, 78.7, 73.7, 70.3, 52.2, 51.3, 46.5, 42.0, 20.5, 14.0, 12.0.; IR (thin film) 2951, 2361, 2341, 1762, 1737, 1493, 1445, 1433, 1382, 1256 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{28}NO_5$ $(M+H)^+$ 362.1967, found 362.1953; m.p.: 86 – 88 °C. The diastereoselectivity of **1.115c** was determined in analogy to **1.115a**.



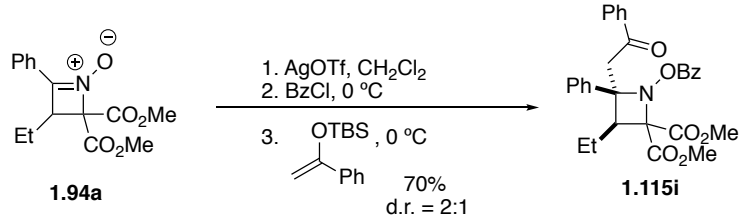
***N*-Ethoxyazetidine 1.115d:** Azetidine **1.115d** was prepared using general procedure C with azetidine nitrone **1.94a** (0.150 g, 0.515 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.108 g, 0.566 mmol, 1.10 equiv), and allyltributylstannane (0.187 g, 0.566 mmol, 1.1 equiv). After the addition of allyltributylstannane, the reaction mixture was allowed to stir for 2 h. The reaction mixture was then quenched by the addition of H_2O (5.0 mL) and NEt_3 (1.0 mL) and allowed to stir for 10 min. The reaction mixture was then extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite and purified by medium pressure chromatography (0:100 – 2:98; Et_2O: hexanes) to afford *N*-ethoxyazetidine **1.115d** (0.134 g, 72%, dr = ≥20:1) as a colorless solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 – 7.64 (m, 2H), 7.35 – 7.32 (m, 2H), 7.23 – 7.20 (m, 1H), 5.69 – 5.61 (m, 1H), 5.02 (d, J = 17.5 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.85 (s, 3H), 3.86 – 3.79 (m, 1H), 3.75 (s, 3H), 3.34 (dd, J = 15.0, 5.0 Hz, 1H), 3.17 (t, J = 7.5 Hz, 1H), 2.91 (dd, J = 15.0, 8.0 Hz, 1H), 1.07 (dd, J = 8.0, 7.5 Hz, 3H), 0.95 – 0.90 (m, 2H), 0.54 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 168.7, 141.1, 135.9, 128.1, 127.6, 126.7, 116.8, 78.1, 74.1, 69.7, 52.7, 52.0, 46.7, 38.9, 20.1, 14.1, 11.9; IR (thin film) 2951, 2361, 2341, 1762, 1737, 1493, 1445, 1433, 1382, 1256 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{28}NO_5$ $(M+H)^+$ 362.1967,

found 362.1953; m.p.: 86 – 88 °C. The diastereoselectivity of **1.115d** was determined in analogy to **1.115a**.



1.94a **1.115**

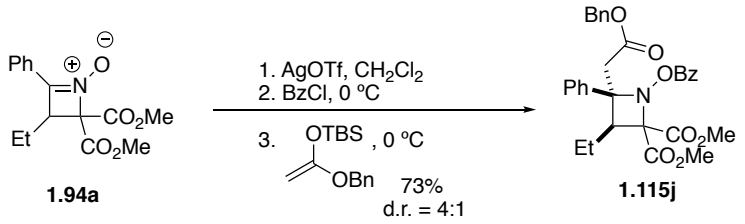
General procedure D: A flame-dried 10-mL round bottom flask was charged with azetidine **1.94a** (1.00 equiv), AgOTf (4.00 equiv), and CH_2Cl_2 (5.0 mL) and sealed with a rubber septum. The reaction mixture was then cooled to 0 °C and benzoyl chloride (0.048 g, 0.34 mmol, 2.0 equiv) was added in one portion via syringe and precipitation of AgCl was immediately observed. The reaction mixture was then allowed to stir for 30 min at 0 °C. At this time, the reaction mixture was filtered through a celite plug and the filter cake was washed with CH_2Cl_2 (3 x 4.0 mL). The organic extracts were combined in a second flame- dried 25-mL flask equipped with a stir bar, and sealed with a rubber septum. The reaction mixture was then cooled to -78 °C in a $CO_{2(s)}$/acetone bath and the nucleophile (2.0 equiv) was added via syringe, and the reaction mixture was allowed to stir for 2 - 3 h. The crude product mixture was concentrated under vacuum, dry-loaded onto celite using Et_2O, and purified by medium pressure chromatography (0:100 – 1:20; Et_2O: hexanes) to give *N*-benzoyloxyazetidines **1.115**.



1.94a **1.115i**

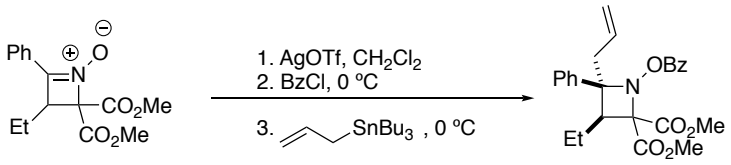
***N*-Benzoyloxyazetidine 1.115i:** Azetidine **1.115i** was prepared using general procedure D with azetidine nitrone **1.94a** (0.050 g, 0.172 mmol, 1.00 equiv), AgOTf (0.135 g, 0.515 mmol, 3.00 equiv), benzoyl chloride (0.048 g, 0.34 mmol, 2.0 equiv), and *tert*-butyldimethyl((1-phenylvinyl)oxy)silane (0.081 g, 0.344 mmol, 2.0 equiv). After the addition of the silyl enol ether, the reaction mixture was allowed to stir for 2 h. At this time, the reaction mixture was concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (0:100 – 1:20; Et_2O: hexanes) to give *N*-benzoyloxyazetidine **1.115i** (0.062 g, 70%, dr =

2:1) as a light yellow solid. Major Diastereomer: ^{1}H NMR (500 MHz; C_6D_6): δ 8.21 – 8.20 (m, 2H), 8.13 – 8.10 (m, 2H), 7.95 – 7.94 (m, 2H), 7.85 – 7.83 (m, 2H), 7.33 – 7.30 (m, 3H), 7.18 – 7.12 (m, 3H), 6.94 – 6.91 (m, 1H), 4.52 (d, *J* = 18.0 Hz, 1H), 4.17 (d, *J* = 18.0 Hz, 1H), 4.04 (t, *J* = 15.0, 7.5 Hz, 1H), 3.54 (s, 3H), 3.38 (s, 3H), 1.52 – 1.42 (m, 2H), 0.85 (t, *J* = 15.0, 7.5 Hz, 3H); 13C NMR (125 MHz, C6D6): δ 194.9, 169.1, 167.8, 162.8, 141.2, 137.6, 132.5, 129.4, 128.5, 128.0, 127.9, 127.8, 127.6, 127.5, 127.0, 124.9, 78.5, 75.4, 52.6, 51.9, 47.5, 43.2, 20.7, 12.0; Minor Diastereomer diagnostic peaks: ^{1}H NMR (500 MHz; C_6D_6): δ 7.92 – 7.90 (m, 2H), 7.08 – 7.05 (m, 9H), 6.94 – 6.93 (m, 4H), 5.33 (d, *J* = 18.0 Hz, 1H), 5.90 – 5.88 (m, 1H), 5.15 (d, *J* = 18.0 Hz, 1H), 3.94 (d, *J* = 18.0 Hz, 1H), 3.33 (s, 3H), 3.28 – 3.25 (m, 1H), 2.03 – 1.94 (m, 1H), 1.86 – 1.77 (m, 1H), 1.01 (dd, *J* = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 194.4, 167.2, 163.6, 146.8, 138.1, 132.3, 129.8, 128.3, 126.6, 79.4, 76.3, 52.3, 52.0, 49.7, 39.0, 19.1, 11.8; IR (thin film) 2961, 2539, 2340, 1765, 1741, 1490, 1444, 1430, 1369, 1250 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{30}H_{30}NO_7$ $(M+H)^+$ 516.2022, found 516.2022; m.p.: 86 – 88 °C. The diastereoselectivity of **1.115i** was determined in analogy to **1.115a**.



***N*-Benzoyloxyazetidine 1.115j:** Azetidine **1.115j** was prepared using general procedure D with azetidine nitrone **1.94a** (0.150 g, 0.515 mmol, 1.00 equiv), AgOTf (0.199 g, 0.772 mmol, 1.50 equiv), benzoyl chloride (0.087 g, 0.618 mmol, 1.2 equiv), and ((1-(benzyloxy)vinyl)oxy)(tert-butyl)dimethylsilane (0.272 g, 1.03 mmol, 2.0 equiv). After the addition of silyl enol ether, the reaction mixture was allowed to stir for 2 h. At this time, the reaction mixture was concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (0:100 – 1:20; Et_2O: hexanes) to give *N*-benzoyloxyazetidine **1.115j** (0.205 g, 73%, dr = 4:1) as a clear oil. Major Diastereomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.86 – 7.84 (m, 2H), 7.82 – 7.80 (m, 2H), 7.53 – 7.50 (m, 1H), 7.38 – 7.31 (m, 5H), 7.21 – 7.17 (m, 3H), 6.89 – 6.88 (m, 2H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.71 (d, *J* = 17.0 Hz, 1H), 3.54 (t, *J* = 7.4 Hz, 1H), 3.51 (d, *J* = 17.0 Hz, 1H),

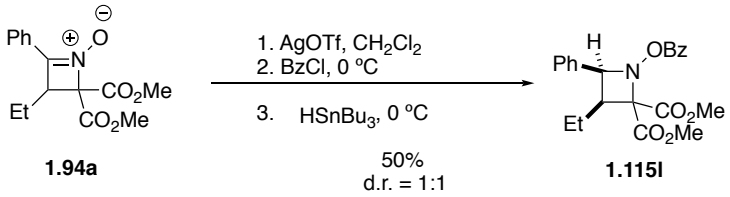
1.14 – 1.08(m, 2H), 0.64 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 168.3, 167.4, 163.0, 139.9, 135.2, 133.1, 129.8, 129.4, 128.4, 128.3, 128.0, 127.3, 127.1, 126.9, 124.6, 77.3, 74.5, 66.3, 53.3, 52.5, 47.4, 40.0, 20.2, 11.8; Minor Diastereomer diagnostic peaks: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.98 – 7.96 (m, 2H), 7.72 – 7.70 (m, 2H), 6.79 – 6.78 (m, 2H), 4.55 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 17.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.33 (d, J = 17.0 Hz, 1H), 2.88 – 2.84 (m, 1H), 1.90 – 1.80 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 169.1, 166.3, 163.7, 145.4, 135.3, 133.0, 128.8, 128.2, 127.8, 78.8, 77.9, 75.4, 66.2, 52.9, 52.8, 49.2, 35.7, 18.7, 11.9; IR (thin film) 2959, 2540, 2341, 1766, 1735, 1730, 1489, 1450, 1421, 1370, 1101 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{31}H_{32}NO_8$ $(M+H)^+$ 546.2128, found 546.2122. The diastereoselectivity of **1.115j** was determined in analogy to **1.115a**.



1.94a 95% d.r. = 1:1 **1.115k**

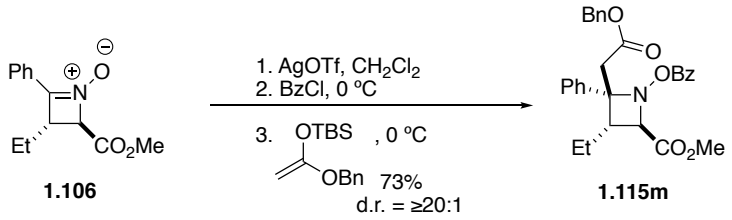
***N*-Benzoyloxyazetidine 1.115k:** Azetidine **1.115k** was prepared using general procedure **D** with azetidine nitrone **1.94a** (0.050 g, 0.172 mmol, 1.00 equiv), AgOTf (0.177 g, 0.688 mmol, 4.00 equiv), benzoyl chloride (0.048 g, 0.34 mmol, 2.0 equiv), and allyltributylstannane (0.114 g, 0.344 mmol, 2.00 equiv). After the addition of allyltributylstannane, the reaction mixture was allowed to stir for 3 h. At this time, the reaction mixture was quenched by the addition of H_2O (1.0 mL) and Et_3N (2.0 mL) and allowed to stir for 10 min. The reaction mixture was then extracted with CH_2Cl_2 (2 x 20.0 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (0:100 – 1:20; Et_2O: hexanes) to give *N*-benzoyloxyazetidine **1.115k** (0.071 g, 95%, dr = 1:1) as a colorless oil. Diastereomer A: ^{1}H NMR (500 MHz; C_6D_6): δ 8.34 – 8.32 (m, 2H), 8.08 – 8.06 (m, 2H), 7.34 – 7.29 (m, 2H), 7.22 – 7.09 (m, 4H), 5.72 – 5.62 (m, 1H), 5.09 (dd, J = 20.0, 17.5 Hz, 1H), 4.76 (dd, J = 26.0, 10.0 Hz, 1H), 4.14 (dd, J = 15.0, 7.5 Hz, 1H), 3.66 – 3.62 (m, 2H), 3.52 (s, 3H), 3.49 (s, 3H), 1.98 – 1.94 (m, 1H), 1.79 – 1.71 (m, 1H), 0.98 (dd, J = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 169.0, 167.6, 164.1, 145.9,

134.7, 133.0, 130.0, 129.2, 128.5, 128.2, 127.6, 127.1, 117.2, 79.3, 77.5, 52.6, 52.3, 49.1, 40.1, 20.6, 12.0; Diastereomer B: ^{1}H NMR (500 MHz; C_6D_6): δ 8.04 – 8.03 (m, 2H), 7.94 – 7.92 (m, 2H), 7.34 – 7.29 (m, 2H), 7.22 – 7.09 (m, 4H), 5.72 – 5.62 (m, 1H), 5.09 (dd, *J* = 20.0, 17.5 Hz, 1H), 4.76 (dd, *J* = 26.0, 10.0 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.20 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.09 (dd, *J* = 16.0, 6.5 Hz, 1H), 3.03 (dd, *J* = 15.0, 6.5 Hz, 1H), 1.32 – 1.22 (m, 2H), 0.71 (dd, *J* = 8.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 168.6, 166.6, 163.2, 140.0, 134.6, 132.9, 129.5, 129.2, 128.4, 127.8, 126.8, 125.4, 117.1, 78.0, 76.2, 51.9, 51.8, 48.3, 35.4, 19.1, 11.9; IR (thin film) 2941, 2541, 2339, 1760, 1742, 1480, 1439, 1421, 1366, 1110 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{28}NO_6$ $(M+H)^+$ 437.4931, found 437.4921.

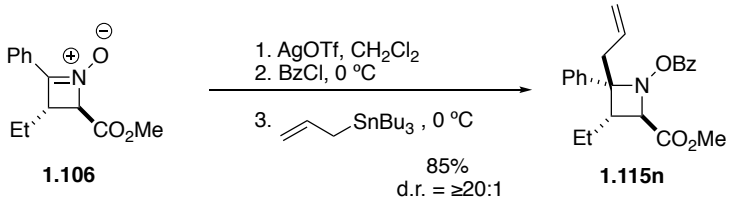


1.94a **1.115l**

***N*-Benzoyloxyazetidine 1.115l:** Azetidine **1.115l** was prepared using general procedure **D** with azetidine nitrone **1.94a** (0.050 g, 0.172 mmol, 1.00 equiv), AgOTf (0.177 g, 0.688 mmol, 4.00 equiv), benzoyl chloride (0.048 g, 0.34 mmol, 2.0 equiv), and tributyltin hydride (0.055 g, 0.189 mmol, 1.1 equiv). After the addition of the nucleophile, the reaction mixture was allowed to stir for 3 h. The reaction mixture was then quenched by the addition of H_2O (5.0 mL) and NEt_3 (1.0 mL) and allowed to stir for 10 min. The reaction mixture was then extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product mixture was dry-loaded onto celite and purified by medium pressure chromatography (0:100 – 2:98; Et_2O: hexanes) to afford *N*-benzoyl azetidine **1.115l** (0.0342 g, 50%, dr = 1:1) as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.90 – 7.88 (m, 2H), 7.51 – 7.49 (m, 2H), 7.41 – 7.39 (m, 1H), 7.30 – 7.25 (m, 5H), 5.10 – 5.08 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 2.61 – 2.56 (m, 1H), 1.78 – 1.73 (m, 2H), 1.15 (t, 3H).

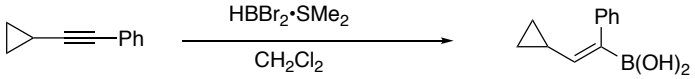


***N*-Benzoyloxyazetidine 1.115m:** A flame dried 25 mL round bottom flask was charged with decarboxylated azetidine nitrone **1.106** (0.150 g, 0.643 mmol, 1.00 equiv) and AgOTf (0.248 g, 0.965 mmol, 1.50 equiv), and diluted with CH_2Cl_2 to form a 0.1 M solution. ((1-(benzyloxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (0.255 g, 0.772 mmol, 1.2 equiv) was diluted with CH_2Cl_2 (2.0 mL) and added to the reaction mixture. The reaction flask was then cooled to -78 °C. Benzoyl chloride (0.109 g, 0.772 mmol, 1.2 equiv) was added via syringe and the reaction mixture was allowed to stir for 30 min. At this time, TBAF (0.772 mL, 1.0 M, 1.2 equiv) was added to the reaction mixture, which was then allowed to warm to 25 °C for 1 h. The reaction mixture was then concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (0:100 – 1:10; Et_2O: hexanes) to give *N*-benzoyloxyazetidine **1.115m** (0.229 g, 73%, dr = >20:1) as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.88 – 7.86 (m, 2H), 7.56 – 7.54 (m, 2H), 7.52 – 7.49 (m, 1H), 7.36 – 7.31 (m, 4H), 7.27 – 7.22 (m, 1H), 7.23 – 7.20 (m, 3H), 7.03 – 7.01 (m, 2H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 3.78 (d, *J* = 16.5 Hz, 1H), 3.74 (s, 3H), 3.56 (d, *J* = 16.5 Hz, 1H), 3.01 – 2.93 (m, 1H), 1.39– 1.29 (m, 1H), 1.21 – 1.13 (m, 1H), 0.78 (dd, *J* = 8.0, 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.1, 164.3, 139.1, 135.5, 133.0, 129.4, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.2, 127.0, 77.1, 70.5, 66.2, 52.4, 45.0, 43.5, 23.4, 11.3; IR (thin film) 2959, 2541, 2342, 1766, 1740, 1489, 1444, 1430, 1371, 1242 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{29}H_{30}NO_6$ $(M+H)^+$ 488.2073, found 488.2063; m.p.: 86 – 88 °C. Diastereoselectivity determined in analogy to **1.115n**.



***N*-Benzoyloxyazetidine 1.115n:** Azetidine **1.115n** was prepared using general procedure D with decarboxylated azetidine nitrone **1.106** (0.150 g, 0.643 mmol, 1.00 equiv), AgOTf (0.248 g, 0.965 mmol, 1.50 equiv), benzoyl chloride (0.108 g, 0.772 mmol, 1.20 equiv), and allyltributylstannane (0.426 g, 1.29 mmol, 2.00 equiv). After the addition of allyltributylstannane, the reaction mixture was allowed to stir for 2 h. At this time, the reaction mixture was concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et_2O and purified by medium pressure chromatography (0:100 – 1:20; Et_2O: hexanes) to give *N*-benzoyloxyazetidine **1.115n** (0.207 g, 85%, dr = >20:1) as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.93 – 7.92 (m, 2H), 7.56 – 7.55 (m, 2H), 7.53 – 7.50 (m, 1H), 7.40 – 7.36 (m, 4H), 7.26 – 7.23 (m, 1H), 5.82 – 5.74 (m, 1H), 5.09 (d, *J* = 18.0 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.35 (dd, *J* = 15.0, 6.8 Hz, 1H), 3.10 (dd, *J* = 15.0, 6.8 Hz, 1H), 2.83 – 2.79 (m, 1H), 1.37 – 1.28 (m, 1H), 1.21 – 1.12 (m, 1H), 0.76 (dd, *J* = 8.0, 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 164.6, 139.3, 134.2, 133.0, 129.4, 128.9, 128.4, 127.9, 127.5, 127.0, 117.8, 78.9, 70.1, 52.3, 44.9, 43.0, 23.4, 11.4; IR (thin film) 2960, 2540, 2351, 1760, 1749, 1481, 1442, 1425, 1366, 1112 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_4Na$ $(M+H)^+$ 380.1862, found 380.1871; m.p.: 86 – 88 °C. Diastereoselectivity determined by nOe correlations.

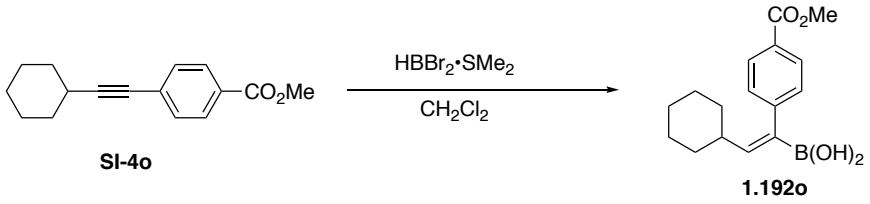
1.4.9 Preparation of Vinylboronic Acids



SI-4p **1.192p**

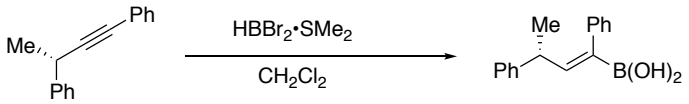
Preparation of Vinylboronic Acid 1.192p: A 50-mL flame-dried round bottom flask was cooled to 25 °C under N2, charged with alkyne **SI-4p**[54] (1.00 g, 7.03 mmol, 1.0 equiv) and diluted with CH_2Cl_2 (7.0 mL). The reaction flask was cooled to -78 °C in a $CO_{2(s)}$/acetone bath and $HBBr_2$•SMe_2 (7.73 mL, 1M in CH_2Cl_2, 1.1 equiv) was added dropwise over 1 h and warmed to 25 °C for 16 h. The reaction mixture was then heated for 4 h at 70 °C. At this time, the reaction mixture was concentrated under vacuum and the crude product mixture was dissolved in 15 mL Et_2O. The reaction flask was the sealed with a rubber septum equipped with a vent needle in a fume hood (***Caution***: HBr gas evolution) and cooled to 0 °C. H_2O (6 mL) was added dropwise over 1 h. The

reaction mixture was then warmed to room temperature and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to give alkenylboronic acid **1.192p** (1.31 g, 99%), which was used without further purification. ^1H NMR (500 MHz; $CDCl_3$): δ 7.40-7.37 (m, 2H), 7.29-7.26 (m, 3H), 5.96 (d, J = 10.5 Hz, 1H), 4.46 (br, 2H), 1.55-1.48 (m, 1H), 0.85-0.77 (m, 4H).



SI-4o **1.192o**

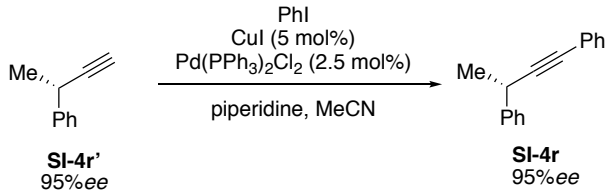
Preparation of Vinylboronic Acid 1.192o: A 50-mL flame-dried round bottom flask was cooled to 25 °C under N_2, charged with alkyne **SI-4o**[55] (1.00 g, 4.12 mmol, 1.0 equiv) and diluted with CH_2Cl_2 (4.0 mL). The reaction flask was cooled to -78 °C in a $CO_{2(s)}$/acetone bath and $HBBr_2$•SMe_2 (4.53 mL, 1M in CH_2Cl_2, 1.1 equiv) was added dropwise over 1 h and warmed to 25 °C for 16 h. The reaction mixture was then heated for 4 h at 70 °C. At this time, the reaction mixture was concentrated under vacuum and the crude product mixture was dissolved in 15 mL Et_2O. The reaction flask was the sealed with a rubber septum equipped with a vent needle in a fume hood (***Caution***: HBr gas evolution) and cooled to 0 °C. H_2O (6 mL) was added dropwise over 1 h. The reaction mixture was then warmed to room temperature and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to give alkenylboronic acid **1.192o** (0.890 g, 75%), which was used without further purification. ^1H NMR (500 MHz; $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.5, 2H), 6.44 (d, J = 10.0 Hz, 1H), 4.15 (br, 2H), 3.91 (s, 3H), 2.27-2.25 (m, 1H), 1.66-1.64 (m, 4H), 1.15-1.13 (m, 6H).



SI-4r **1.192r**

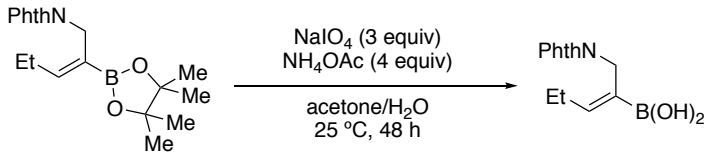
Preparation of Vinylboronic Acid 1.192r: A 50-mL flame-dried round bottom flask was cooled to 25 °C under N_2, charged with **SI-4r** (0.774 g, 3.75 mmol, 1.0 equiv), and diluted with CH_2Cl_2 (5.0 mL). The reaction flask was cooled to -78 °C in a $CO_{2(s)}$/acetone bath and $HBBr_2$•SMe_2 (4.12 mL, 1M in CH_2Cl_2, 1.1 equiv) was added dropwise over 1 h

and warmed to 25 °C for 16 h. At this time, the reaction mixture was concentrated under vacuum and the crude product mixture was dissolved in 15 mL Et_2O. The reaction flask was the sealed with a rubber septum equipped with a vent needle in a fume hood (***Caution***: HBr gas evolution) and cooled to 0 °C. H_2O (6 mL) was added dropwise over 1 h. The reaction mixture was then warmed to room temperature and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to give alkenylboronic acid **1.192r** (0.860 g, 91%), which was used without further purification. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 – 7.23 (m, 10H), 6.20 (d, J = 10.8 Hz, 1H), 3.68 – 3.61 (m, 1H), 1.88 – 1.76 (m, 2H), 1.41 (d, J = 7.0 Hz, 3H).



SI-4r' 95%*ee* **SI-4r** 95%*ee*

Preparation of Alkyne SI-4r: A 50-mL flame-dried round bottom flask was cooled to 25 °C under N_2 and charged with **SI-4r'** (0.887 g, 6.81 mmol, 1.0 equiv), iodobenzene (1.53 g, 7.49 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.119 g, 0.170 mmol, 0.025 equiv), CuI (0.065 g, 0.340 mmol, 0.050 equiv), PPh_3 (0.089 g, 0.340 mmol, 0.050 equiv), piperidine (1.74 g, 20.4 mmol, 3.0 equiv), and diluted with MeCN (15.0 mL). The reaction mixture was stirred for 4 h and then concentrated under vacuum. The crude reaction mixture was purified directly by medium pressure chromatography (0:100 – 1:99; EtOAc: hexanes) to afford **SI-4r** as a yellow liquid (1.19 g, 85%, *ee* = 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.46- 7.19 (m, 10 H), 3.97 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 6.9 Hz, 3H). The spectral data matched the literature.



SI-4d **1.192d**

Preparation of 1.192d: To a solution of vinyl pinacolborane **SI-4d** (1.90 g, 5.57 mmol) in acetone (140 mL) and water (140 mL) were added NH_4OAc (1.72 g, 22.3 mmol) and $NaIO_4$ (3.57 g, 16.7 mmol), and stirred for 2 d at 25 °C. The mixture was then concentrated to remove acetone and extracted with Et_2O (3 x 40 mL). The organic

extracts were combined, dried with Na_2SO_4, and concentrated under vacuum. The crude white solid **1.192d** (1.21 g, 84%) was used without further purification. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.85- 7.83 (m, 2H), 7.73-7.72 (m, 2H), 6.67 (t, *J* = 7.0 Hz, 1H), 5.80 (br, 2H), 4.36 (s, 2H), 2.51 (p, *J* = 7.5 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H).

Chapter 2: Synthesis of Nucleoside Analogues via [3,3']-Sigmatropic Rearrangement of *N,O*-Divinylhydroxylamines

Angew. Chem. Int. Ed., **2018**, *57*, 6597-6600.

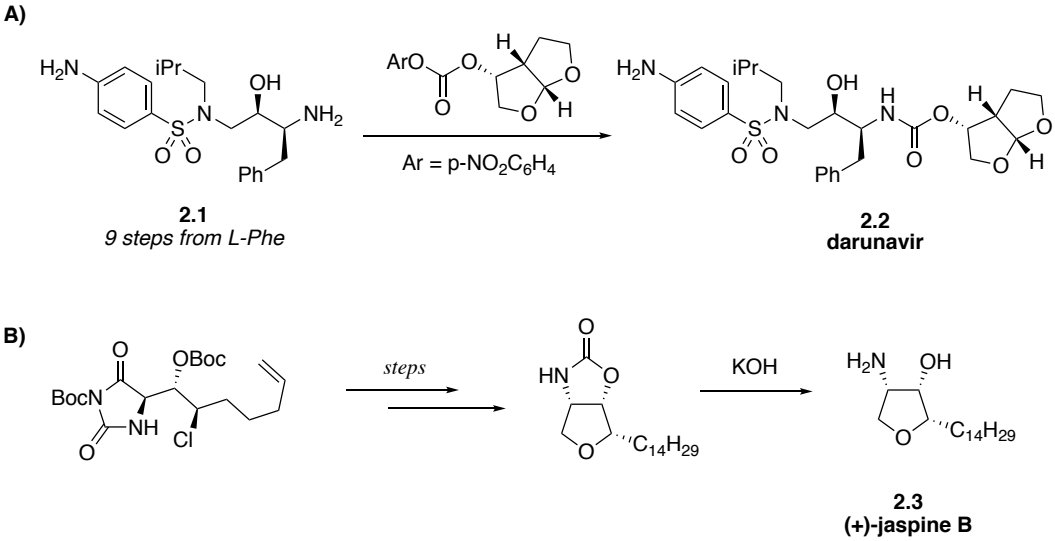
2.1 Introduction

2.1.1 Synthetic and Biological Importance of Tetrahydrofuran Scaffolds

There have been a variety of synthetic routes established to access substituted tetrahydrofuran scaffolds, which are common in both natural products and biologically relevant molecules. Traditional routes toward stereodefined tetrahydrofuran-containing targets suffer from the need to start from stereodefined starting materials in order to achieve stereospecific or stereoselective product formation. A general method toward these molecules that does not require complex starting materials would greatly benefit synthetic and medicinal chemists, alike.

Tetrahydrofuran scaffolds have been shown to be extremely valuable in applications towards the inhibition of HIV treatment and cancer cell lines.[56a] In 2006, darunavir, a tetrahydrofuran-containing drug developed at the University of Illinois at Chicago by Ghosh and coworkers, was approved by the FDA for treatment of HIV under the trade name Prezista[56b] **2.2** (Scheme 2.1A). Intermediate **2.1** was constructed in 9 steps from *L*-phenylalanine and subjected to a peptide coupling to install the necessary fused bis-tetrahydrofuranyl carbonate. The strategy in targeting this scaffold was to

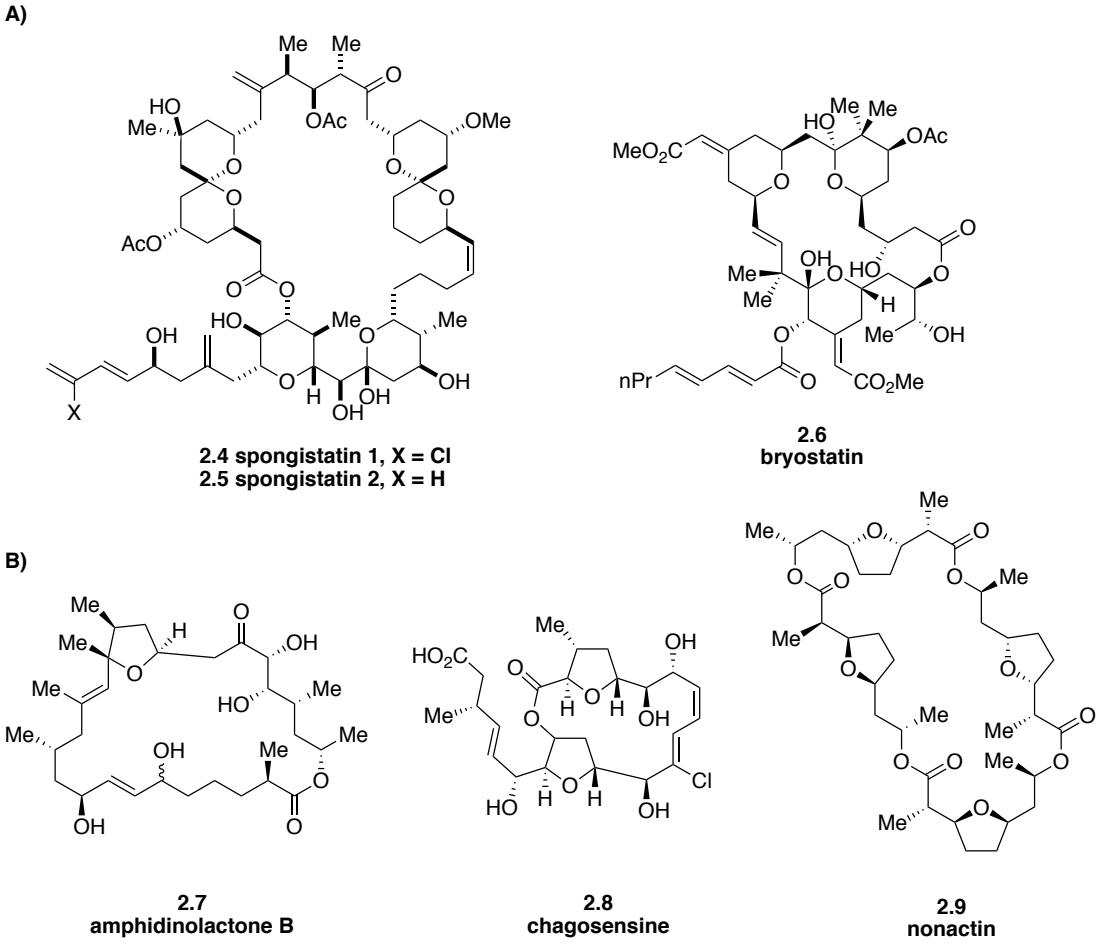
increase binding affinity and selectively bind Asp25 and Asp25' residues in the HIV-1 protease binding site to prevent viral replication. Similarly, Britton and coworkers reported in 2013 the asymmetric total synthesis of jaspine B **2.3**, a tetrahydrofuran containing marine natural product known to induce apoptosis in melanoma cells by interfering with ceramide metabolism to inhibit replication[57] (Scheme 2.1B). These examples represent the importance of tetrahydrofuran scaffolds in biologically active molecules as well as the inefficiency of traditional routes to compounds containing these motifs that require pre-installation of stereodefined centers in order to access stereodefined tetrahydrofuran products.



Scheme 2.1 Synthesis of darunavir and (+)-jaspine B

In addition to drug targets, tetrahydrofurans make up the core structure of a variety of natural products. Many marine organisms produce defensive secondary metabolites, which are comprised of diverse oxygen containing heterocycles and serve as neurotoxins and cell proliferation inhibitors to deter predators. The most common marine macropolyketides are assembled around tetrahydropyran cores, such as the spongistatins **2.4**[58] and **2.5**[59], and bryostatin[60] **2.6**, which have been heavily studied because of their

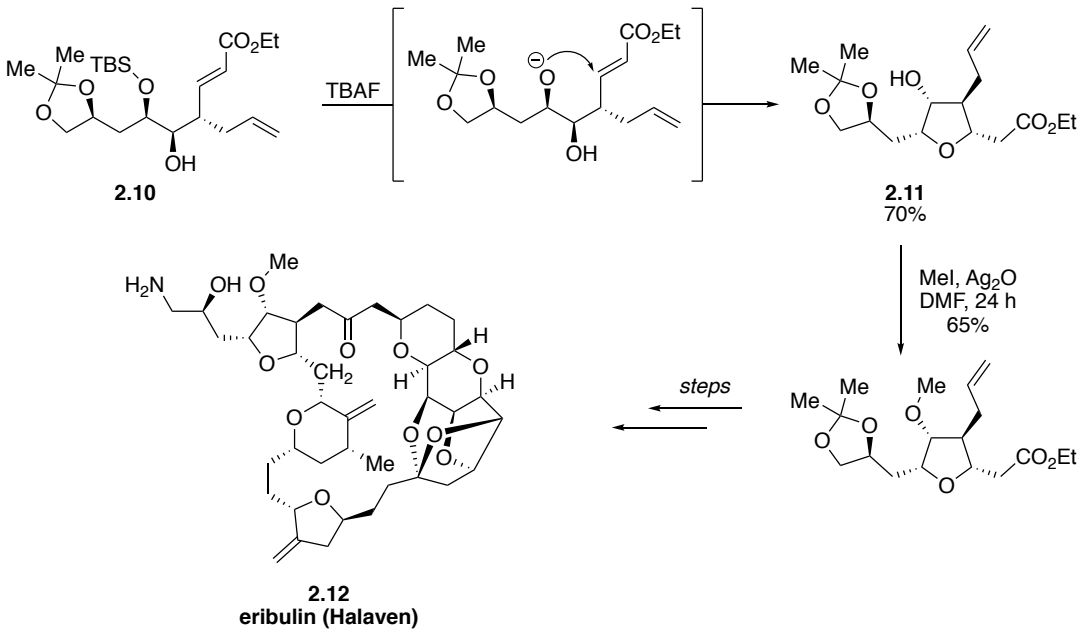
modulation of protein kinase C and chemoresistant tumor growth inhibition (Scheme 2.2A). Some common tetrahydrofuran containing marine natural products include **2.7**, **2.8**, and **2.9** (Scheme 2.2B). These molecules have also been extensively studied and many strategies have been explored for the construction of other tetrahydrofuran scaffolds via C–O or C–C bond formation using S_N2 type chemistry, radical processes, and cycloaddition chemistry. Selected examples will be discussed in order to highlight the growing need for new methods for tetrahydrofuran constructions as well as to address some of the inherent limitations associated with these syntheses.



Scheme 2.2 Selected examples of biologically relevant tetrahydrofurans

2.1.2 Construction of Tetrahydrofurans via C–O Bond Formation

The most common methods for the preparation of stereoselective tetrahydrofuran derivatives involve nucleophilic displacement of a tethered leaving group by an oxygen nucleophile.[61a] This transformation is typically applied in synthetic strategies using stereodefined starting materials such as alcohols, epoxides, acetonides, benzyl ethers, and silyl-enol ethers. These classical approaches to cyclic ether synthesis have been extensively studied in natural product synthesis as an efficient strategy for the rapid construction of many biologically active compounds. Arya and coworkers demonstrated this strategy in the stereoselective construction of fragments of eribulin[61b] **2.12** (Scheme 2.3). Their strategy involved the deprotection of stereodefined silyl ether **2.10** with a subsequent oxy-Michael addition to α,β-unsaturated ester to forge desired furan **2.11** in 70% yield. From here, subsequent steps afforded a diverse array of macrocyclic tethered furan scaffolds that could be used to screen derivative of Eribulin for biological activity, however the authors were still limited to using enantiopure starting materials to obtain stereoselective products.

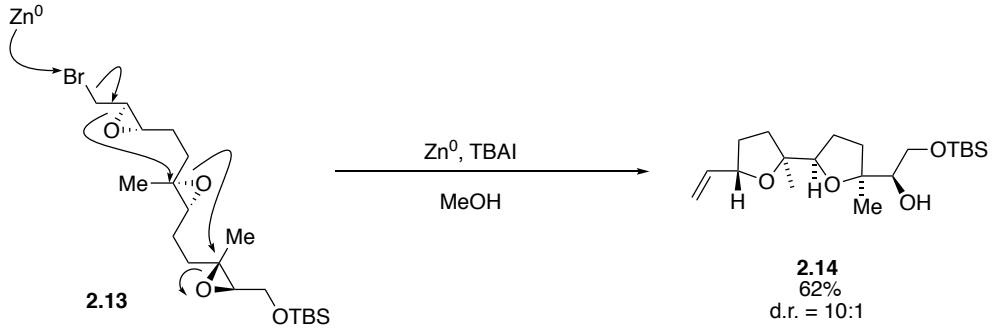


2.10 **2.11** 70%

2.12
eribulin (Halaven)

Scheme 2.3 Tetrahydrofuran construction via C–O bond formation for eribulin[61]

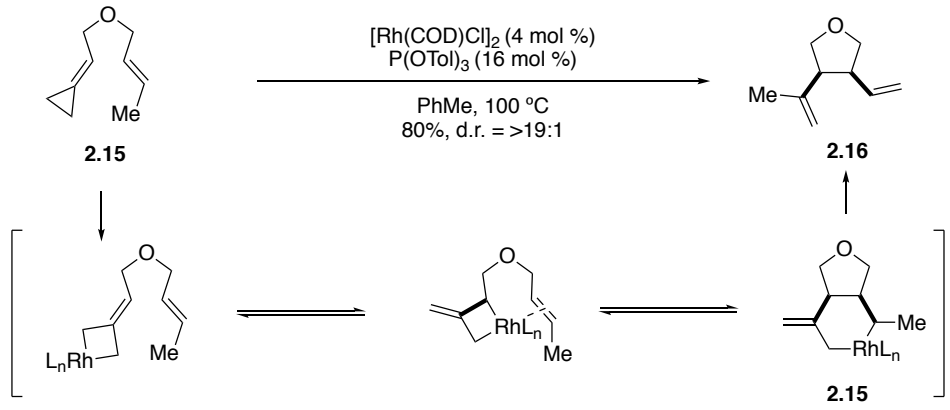
Another method for tetrahydrofuran preparation via C–O bond formation involves epoxide opening and cyclization of the resulting nucleophilic oxygen and a leaving group as demonstrated by the Marshall lab. Treatment of tris-epoxide **2.13** with zinc triggered a ring-expansion and cyclization cascade reaction for the synthesis of the bis-tetrahydrofuran core of **2.14**.[62] This method exemplified the use of oxygen nucleophiles other than alcohols, however it still required the starting material to be stereodefined prior to cyclization in order to achieve stereoselective tetrahydrofuran formation.



Scheme 2.4 Zinc mediated epoxide ring-expansion cascade for tetrahydrofurans

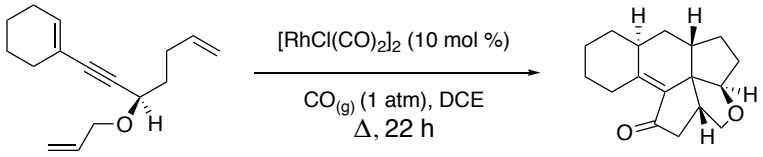
2.1.3 Construction of Tetrahydrofurans via C–C Bond Formation

An alternative approach towards the construction of tetrahydrofurans is the cycloisomerization of acyclic ethers. In 2012, Evans and coworkers reported the rhodium-catalyzed cycloisomerization of vinylidene cyclopropane ether **2.15** to afford 1,5-diene substituted tetrahydrofuran **2.16** via rhodacycle **2.15**.[63] The authors showed that this strategy could be highly diastereoselective, however it is limited to simple tethered ether substrates with relatively low levels of functionality due to incompatibility with the reaction conditions.



Scheme 2.5 Cycloisomerization of vinylidene cyclopropanes

Pu and coworkers accessed complex pentacyclic tetrahydrofuran scaffolds by forging a new C–C bond in a domino cyclization reaction from enantioenriched starting materials (Scheme 2.6).[64] A rhodium catalyzed Pauson-Khand reaction of enyne allyl ether (*R*)-**2.17** under an atmosphere of carbon monoxide gave a diene intermediate which then underwent a Diels-Alder cycloaddition to afford complex oxacyclic scaffolds such as **2.18** with high yields and high levels of diastereoselectivity. This method could find use in natural product synthesis, but is limited by functional group tolerance and the need for enantiodefined starting materials in order to access stereodefined scaffolds.



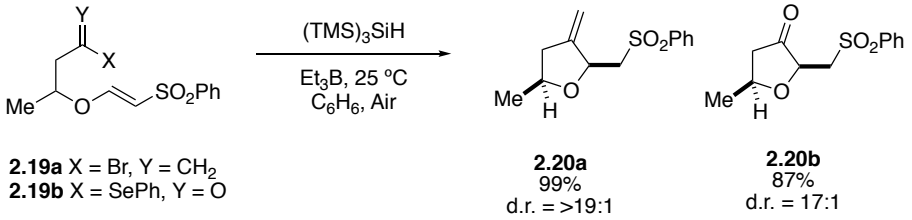
(*R*)-**2.17**
(90% *ee*)

2.18
71%
(90% *ee*)

Scheme 2.6 Domino cyclization and cycloaddition approach to tetrahydrofurans

2.1.4 Radical Processes for Tetrahydrofuran Construction

Radical C–C bond formation is an attractive method for the construction of tetrahydrofurans because of the plethora of radical group precursors that could be used. These reactions typically involve addition of a carbon-centered radical derived from an organostannane, organoselenium, or organohalide reagent to either an alkene or alkyne to forge a new C–C bond. Evans and coworkers showed an example of radical C–C bond formation for tetrahydrofuran construction utilizing (*E*)-vinylogous sulfonates **2.19** in the presence of Et_3B to generate a vinyl radical that cyclizes in a highly selective manner to afford exomethylene tetrahydrofurans **2.20** (Scheme 2.7).[65] The authors found that the cyclization gave excellent diastereoselectivity of the *cis*-disubstituted tetrahydrofuran, however, in an attempt to trap the resulting α-sulfonyl radical with allylstannane, they found that this second step was unselective. While this transformation provides a novel approach to tetrahydrofuran synthesis, the multi-step starting material synthesis limits the general applicability.



2.19a X = Br, Y = CH_2
2.19b X = SePh, Y = O

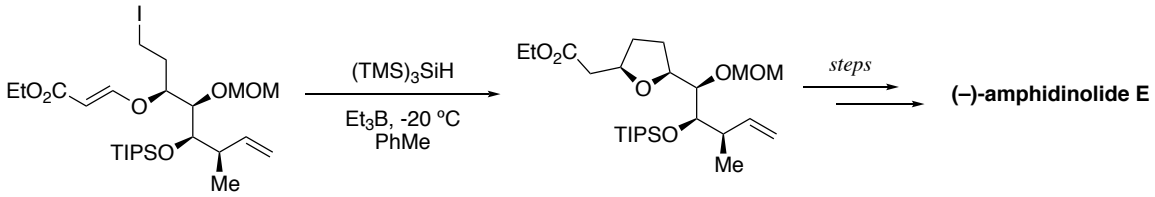
2.20a
99%
d.r. = >19:1

2.20b
87%
d.r. = 17:1

Scheme 2.7 Diastereoselective cyclization of vinyl radicals with vinyl sulfones

Similarly, in 2006 Eun Lee and coworkers demonstrated a radical cyclization of β-alkoxy acrylate **2.21** to construct the tetrahydrofuran core of (–)-amphidinolide E (Scheme 2.8).[66] Using an enantiopure precursor and installing an acrylate ether, radical cyclization conditions similar to those used by Evans could be used to trigger ring-closure of iodoalkyl ether to afford tetrahydrofuran fragment **2.22** with high levels of stereoselectivity. This stereoselective cyclization step was crucial for the process because

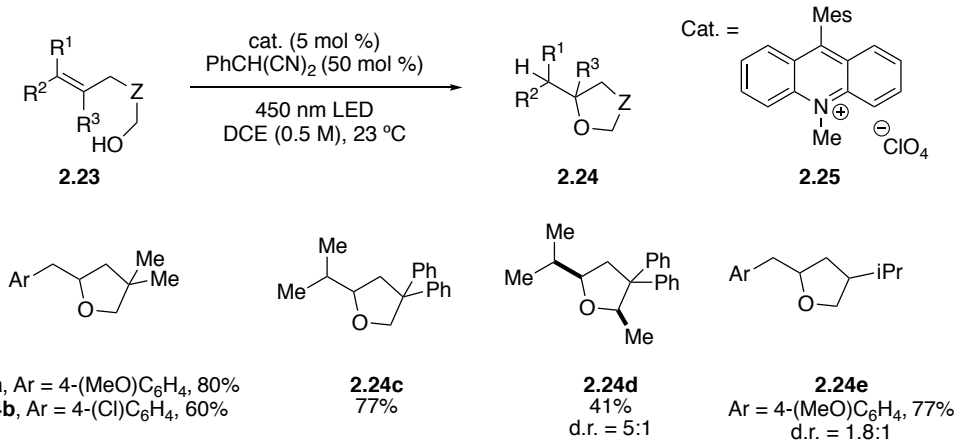
it helped establish that the (*S*,*S*)-conformation of the natural product was the naturally occurring isomer when isolated from dinoflagellate *Amphidinium* species and exhibited IC_{50} values of 2.0 mg/mL and 4.8 mg/mL against murine leukemia L1210 and L5178Y strains, respectively. This method demonstrated the viability of radical cyclization in total synthesis for the construction of tetrahydrofurans but was limited by the lengthy protecting group installation and removal throughout the synthesis.



2.21 **2.22**

Scheme 2.8 Construction of tetrahydrofuran core of (–)-amphidinolide E

Nicewicz and coworkers showed that organic dye catalyst **2.25** enabled the hydroetherification of tethered alkenols **2.23** with high levels of regioselectivity for the anti-Markovnikov product and afforded a diverse range of tetrahydrofuran products **2.24** (Scheme 2.9).[67] This novel use of organic dye was found to proceed with low levels of diastereoselectivity due to the ambiguous nature of the intermediate radical cation. Nonetheless, the authors showed a remarkable switch in selectivity from the previously reported Markovnikov cyclization of the same class of substrates by using an acridinium catalyst in place of ammonium salt catalysts and transition metals.



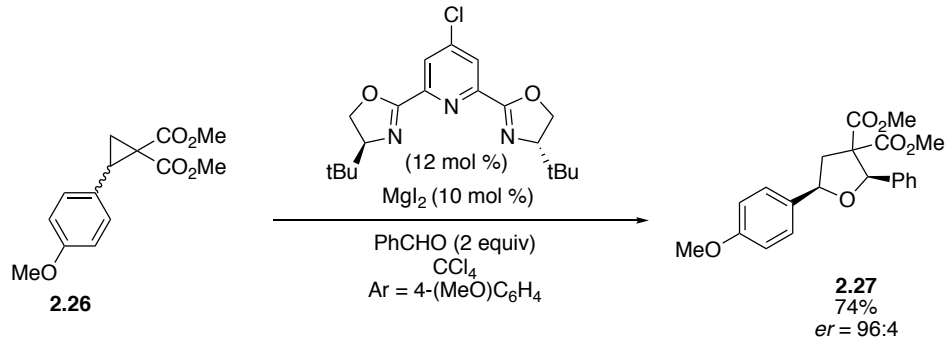
Scheme 2.9 Photoredox enabled radical cyclization of tetrahydrofurans[67]

2.1.5 Construction of Tetrahydrofurans via Cycloaddition

While previously discussed strategies toward tetrahydrofuran scaffolds have targeted the formation of either a new C–C or C–O bond, cycloadditions have emerged as a valuable tool for the construction of these privileged heterocycles through the formation of two bonds in a single step. An attractive route to diastereoselective tetrahydrofuran synthesis is the use of classical cycloaddition chemistry because of mild reaction conditions. New advances have improved on previous cycloaddition routes to tetrahydrofurans and have shown that this could be a synthetically useful route to oxacyclic scaffolds.

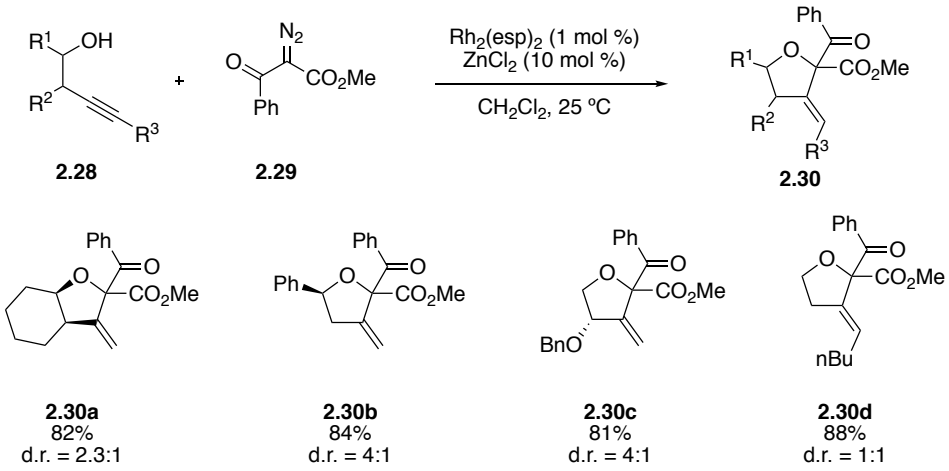
Johnson and coworkers demonstrated a dynamic kinetic resolution/[3+2]-cycloaddition of malonate-derived cyclopropane **2.26** and aryl aldehydes to construct enantioenriched tetrahydrofurans using Lewis acid catalysis. Using these conditions, they were able to forge two new bonds with high levels of stereoselectivity and diastereoselectivity to afford substituted tetrahydrofuran **2.27** (Scheme 2.10).[68] Waser and coworkers also extended this method to chiral copper-catalyzed systems to enable the construction of trisubstituted tetrahydrofurans in enantiomeric excesses up to 92%,

however the authors reported that the reaction only proceeded with polarized push-pull cyclopropanes.[69]



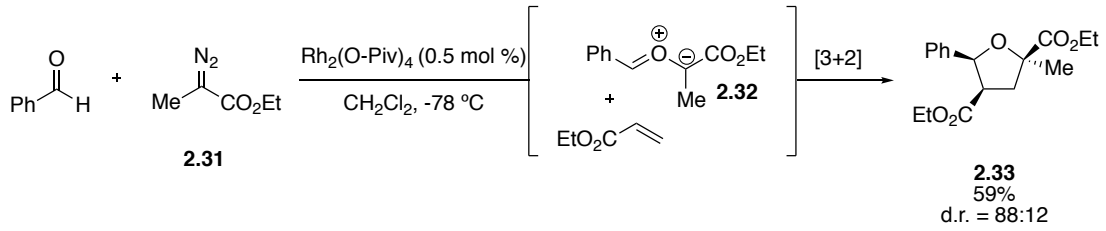
Scheme 2.10 Strained cyclopropanes as 1,3-dipoles for tetrahydrofurans[68]

Another cycloaddition strategy that has been used to construct tetrahydrofurans is the use of rhodium-catalyzed [4+1]-cycloaddition of diazo compounds and homopropargylic alcohols developed by Hatekeyama and coworkers (Scheme 2.11).[70] This method proceeds via C–O bond formation between alcohol **2.28** and diazocarbonyl **2.29**, which then undergoes Lewis acid catalyzed cyclization to afford exocyclic 3-methylene tetrahydrofurans **2.30** in excellent yield and moderate diastereoselectivity. As shown by **2.30a** – **2.30d,** both primary and secondary alcohols were shown to be efficient reaction partners and internal or terminal alkynes were well-tolerated.



Scheme 2.11 Rhodium-catalyzed annulation of homopropargylic alcohols

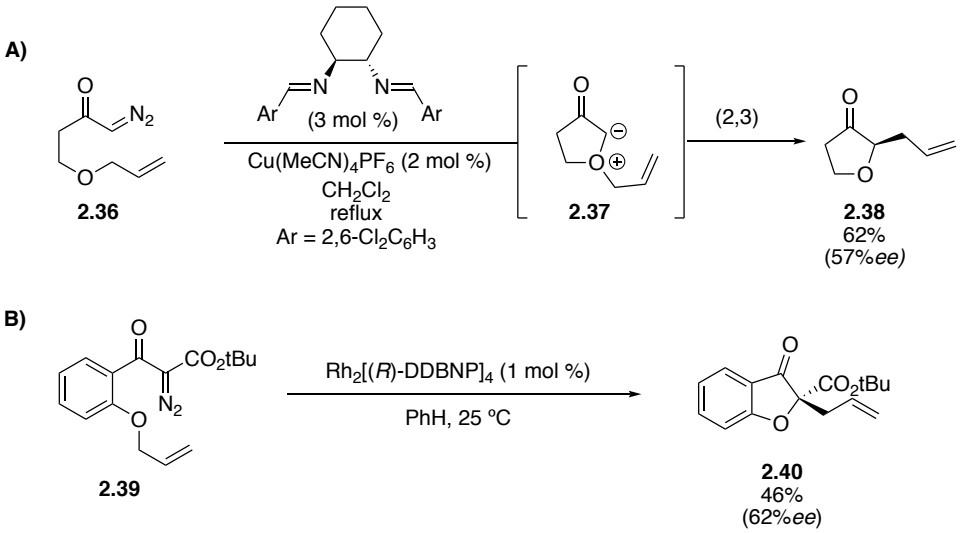
Through a combination of rhodium catalysis and [3+2]-cycloaddition, Fox and coworkers showed that oxocarbenium ylide **2.32** generated from diazo compound **2.31** and benzaldehyde in the presence of $Rh_2(O\text{-}Piv)_4$ could undergo regioselective cycloaddition with alkenes and alkynes to generate highly-substituted tetrahydrofurans such as **2.33** with excellent diastereoselectivity (Scheme 2.12).[71] This complements the state of the art of carbonyl cycloaddition established by Padwa and coworkers, yet does not address the lack of modularity or stability of the required starting materials in this transformation.



Scheme 2.12 [3+2]-cycloaddition of oxocarbenium ylides

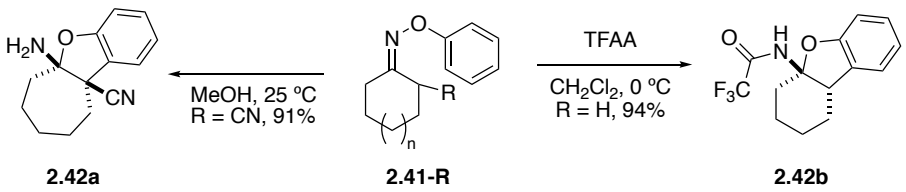
2.1.6 Sigmatropic Rearrangements for the Construction of Tetrahydrofurans

An undervalued strategy for tetrahydrofuran synthesis is the use of sigmatropic rearrangements to forge new C–C bonds in order to furnish these valuable scaffolds. Two examples of this strategy were developed by the groups of Hodgson[72] and Clark[73] through the initiation of a [2,3]-sigmatropic rearrangement of *O*-allyl oxonium ylides **2.37** generated from α-diazo carbonyl **2.36** or **2.39** and a copper catalyst[72] (Scheme 2.13A) or rhodium carbene transfer catalyst[73] (Scheme 2.13B). In these reports, the authors showed that 3-oxo tetrahydrofuran **2.38** or benzofuran **2.40** were accessible in high yield and with moderate levels of stereoselectivity using sigmatropic rearrangement strategies.



Scheme 2.13 [2,3]-Sigmatropic rearrangement of oxocarbenium ylides

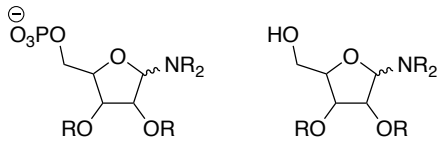
Takeda and coworkers described the use of [3,3']-sigmatropic rearrangements for the preparation of 2-amino dihydrobenzofuran **2.42a** from *O*-aryl oxime ethers **2.41-CN** in a highly diastereoselective fashion (Scheme 2.14).[74] The authors reported that this transformation was accelerated by hydrogen bonding interactions of the imine and was limited to α-cyano ketooximes, whereas β-ketoester and unactivated ketones were unreactive. Previously, the Takeda group described a similar transformation of *O*-aryl oxime ethers **2.41-H**. Activation of **2.41-H** with TFAA induced isomerization to the enamine, which then was poised to undergo spontaneous [3,3']-sigmatropic rearrangement to afford *N*-protected 2-amino dihydrobenzofuran **2.42b** (Scheme 2.14).[75] It is known that tetrahydrofuran and dihydrobenzofuran scaffolds bearing an amino group at the 2-position exhibit high levels of biological activity and makes this an intriguing entry to these scaffolds, which resemble nucleoside analogues.



Scheme 2.14 [3,3']-sigmatropic rearrangement of *O*-aryl oxime ethers

2.1.7 Pharmaceutical Applications of Nucleoside Analogues

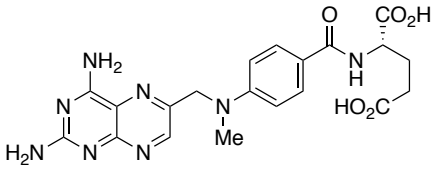
Decorated tetrahydrofuran scaffolds with nucleobases and phosphate groups, known as nucleotides **A** are the structural units that make up DNA and RNA and direct the production of proteins. Their counterparts with phosphate groups removed are known as nucleosides **B** (Scheme 2.15). Nucleobases have been used as therapeutics since the early 1950's when the xanthine-derived molecule dyphylline was found to treat respiratory disorders and 5-fluorouracil was synthesized as an antibiotic and later as cancer chemotherapy.[76] After the discovery of diseases caused by retroviruses in humans, a renaissance of nucleobase therapeutics was realized. Since then, therapeutics derived from pyrimidine and purine nucleobases such as methotrexate **2.43a** (cancer chemotherapy), theophylline **2.43b** (COPD), and trimethoprim **2.43c** (antibiotic) have been used to treat ailments ranging from cancer to diarrhea. Drug candidates derived from nucleobase-decorated tetrahydrofurans have shown more valuable activity for the prevention and treatment of viral diseases such as HIV, hepatitis B and C, herpes simplex, ebola, and for cancers like leukemia. These diseases effect as many as 500 million people today and cost more than $100 billion to treat.[77]



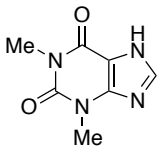
Scheme 2.15 Generic nucleotide and nucleoside

Selected nucleobase-decorated tetrahydrofuran anti-retroviral drugs include azidothymidine (AZT) **2.43d**, emtricitabine **2.43e**, cytarabine **2.43f**, and didanosine **2.43g**

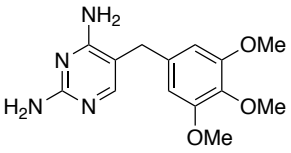
(Scheme 2.16). These drugs typically serve as reverse-transcriptase inhibitors, which act upon the virus' cellular enzymes used to make copies of itself after entering a healthy host cell. By blocking this duplication process, the virus is unable to reproduce and spread. This inhibition can be very efficient under normal conditions, however the development of antiviral resistance can rapidly form from just a single mutation in the virus' RNA. Because of this resistance, new retroviral therapeutic targets must be constantly pursued. New divergent strategies for the rapid construction of these privileged heterocycles are currently in high demand, as it would allow medicinal chemists and fragment-based drug discovery chemists to screen a diverse range of substrates for viral inhibition. An appealing route to access diverse nucleoside drug candidates would improve on the limitations of traditional syntheses of nucleoside analogues.



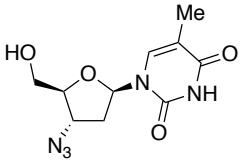
2.43a
methotrexate



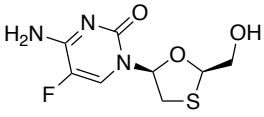
2.43b
theophylline



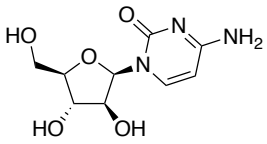
2.43c
trimethoprim



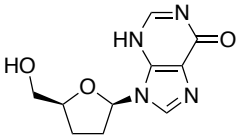
2.43d
azidothymidine
(AZT)



2.43e
emtricitabine



2.43f
cytarabine



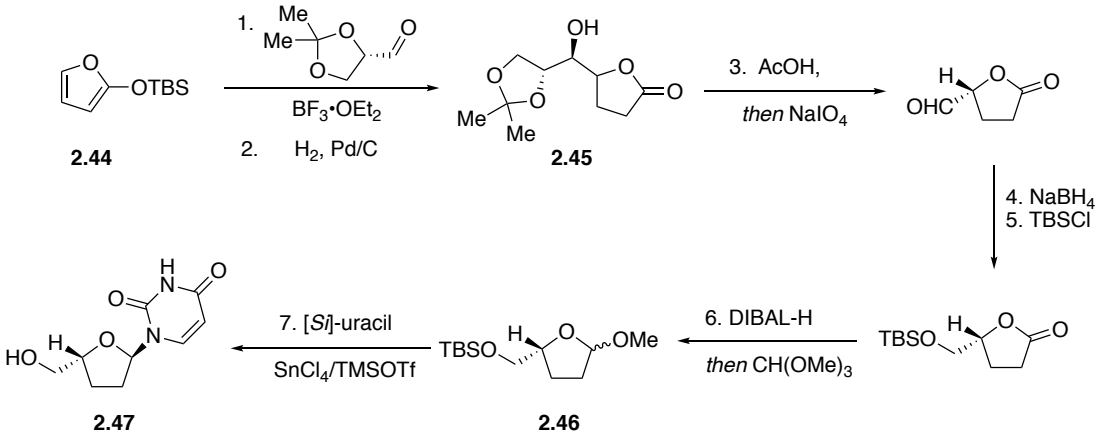
2.43g
didanosine

Scheme 2.16 Common nucleobase therapeutics and 2-amino furanose drugs

2.1.8 Previous Strategies for Nucleoside Analogue Construction

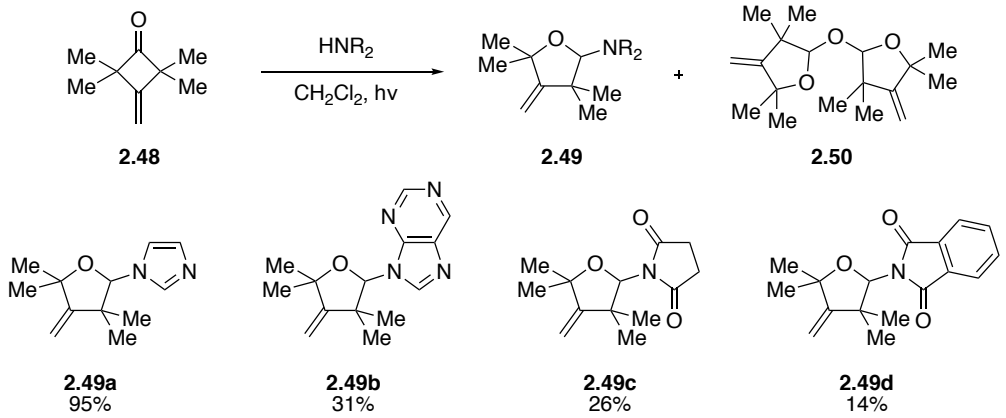
While several different approaches to access tetrahydrofuran scaffolds in a stereoselective manner have been established and described above, methods to access their 2-amino tetrahydrofuran counterparts have received less attention. Traditional methods for the preparation of tetrahydrofuran-containing nucleoside analogues require decoration of previously constructed furan scaffolds in order to install the desired functionality needed for drug activity. To highlight these limitations, selected examples will be discussed.

As shown in Scheme 2.17, Casiraghi and coworkers utilized 2-silyloxy furan **2.44** to perform a Lewis acid promoted aldol reaction to introduce the chirality they desired.[78] Then through a number of oxidation and reduction steps, these researchers were able to access methoxy furanose **2.46**. The authors used silylated uracil in the presence of stoichiometric $SnCl_4$ to install the uracil side-chain in a stereoselective fashion to afford nucleobase-decorated tetrahydrofuran **2.47**. This showed a viable option toward nucleoside analogue construction through first tetrahydrofuran construction and then decoration with amino groups to afford 2-aminotetrahydrofurans.



Scheme 2.17 Furanose modification for nucleoside analogues[78]

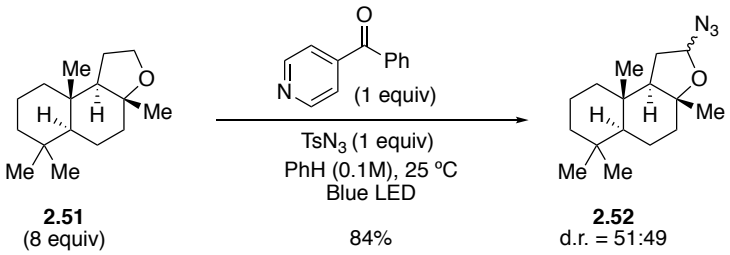
Lee-Ruff and coworkers demonstrated the generation of 2-aminotetrahydrofurans via amination of an oxocarbene generated from ring expansion of cyclobutanone substrates.[79] By subjecting a solution of **2.48** and an amine nucleophile to ultraviolet irradiation, the authors showed that a variety of **2.49** could be accessed by utilizing different amine nucleophiles (Scheme 2.18). In some cases, adventitious water resulted in the formation of bis-acetal **2.50** through the addition of water to the resulting products. While this method did not require pre-formation of the tetrahydrofuran core, it was limited to fully alkylated cyclobutanones and gave little room for diversification of the nucleoside analogues. Furthermore, the use of ultraviolet irradiation in more complex systems could result in unwanted side reactions.



Scheme 2.18 Cyclobutanone ring expansion/amination[79]

The photoinduced C–H functionalization of tetrahydrofurans was reported by Kamijo in 2016.[80] By utilizing a unique 4-benzoylpyridine reagent and *p*-toluenesulfonyl azide as the nitrogen source, they showed that amination of strong C–H bonds was possible by irradiating with blue LED lights. This method was applicable to a broad range of cyclic and acyclic alkanes, however only one example of C–H-amination of tetrahydrofuran **2.51** was shown, providing the azido hemiaminal **2.52** with low levels of

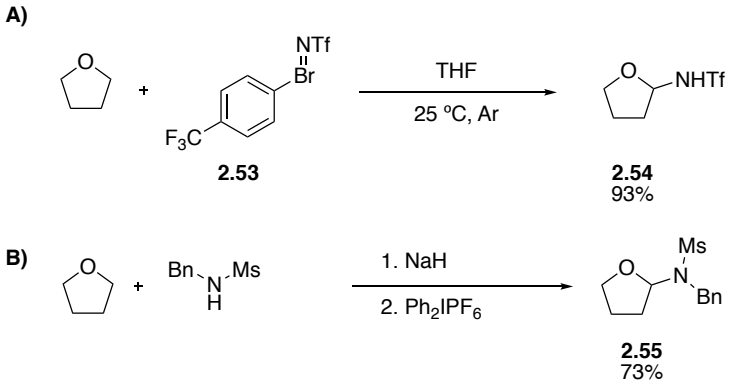
diastereoselectivity (Scheme 2.19). In this report, the valuable tetrahydrofuran substrate was used in large excess, which could be a hindrance to drug discovery efforts. While these conditions were milder than those of Lee-Ruff, the limited substrate scope to provide 2-aminotetrahydrofurans leaves room for improvement.



Scheme 2.19 Photoinduced α-C–H-azidation[80]

An appealing route to 2-aminotetrahydrofurans is the use of hypervalent halogen reagents to install nitrogen functionalities. Ochiai and coworkers showed that sulfonylimino-λ3-bromane **2.53** in excess tetrahydrofuran could afford α-(*N*-triflylamino)tetrahydrofuran **2.54** in excellent yield (Scheme 2.20A).[81] This method was not only limited to tetrahydrofuran but also other cyclic and acyclic ether substrates, however the lack of stereoselectivity makes this strategy less attractive to access stereodefined nucleoside analogues. Hu and coworkers demonstrated that by generating iminoiodane in situ, they were able to access a broader range of 2-aminotetrahydrofuran scaffolds **2.55** with more complex functionality (Scheme 2.20B).[82] This expansion of amino functionality is appealing for the formation of a diverse library of these substrates, however both Ochiai and Hu noted that the use of hypervalent halogen reagents are unselective in the presence of other weak C–H bonds making this strategy inapplicable to complex molecule syntheses. These functionalizations of tetrahydrofurans to access nucleoside analogues are valuable, however a direct route to diverse 2-

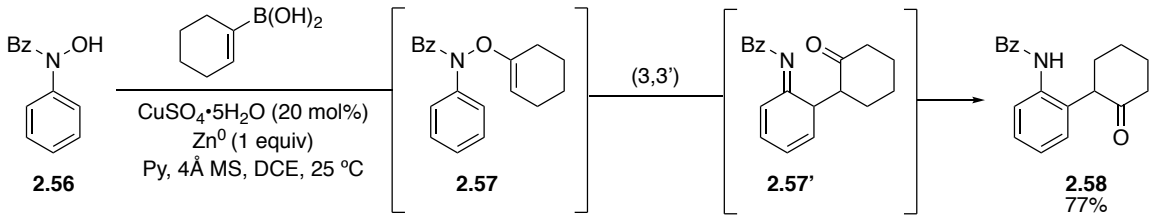
aminotetrahydrofurans would allow for the rapid construction of these molecules without the need for tetrahydrofuran construction prior to decoration.



Scheme 2.20 Metal-free C–H amination of tetrahydrofuran[81,82]

2.2 [3,3']-Sigmatropic Rearrangements of *N,O*-Divinyl Species

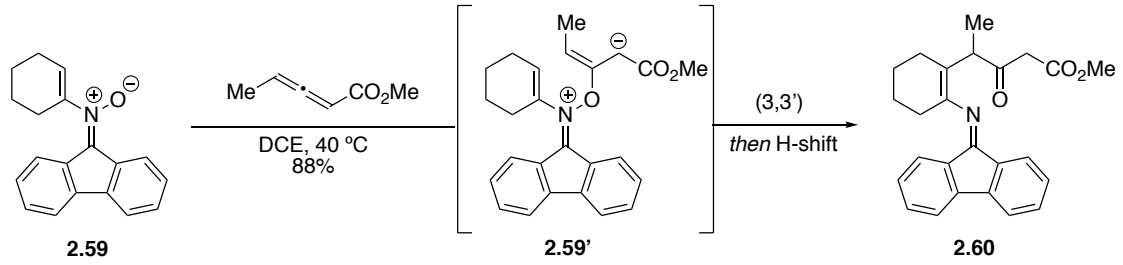
Our lab has previously reported the generation of *N*-aryl-*O*-vinylhydroxylamine **2.57** from *N*-aryl benzhydroxamic acid **2.56** via a copper-mediated Chan-Lam reaction. These reactive intermediates were then shown to spontaneously undergo [3,3']-sigmatropic rearrangement to afford interrupted Fischer-Indole intermediate **2.57'** (Scheme 2.21).[83] After tautomerization, the resulting α-(*o*-anilido)ketone **2.58** could be further functionalized to afford substituted indole products.



Scheme 2.21 Previous work on [3,3']-sigmatropic rearrangements[83]

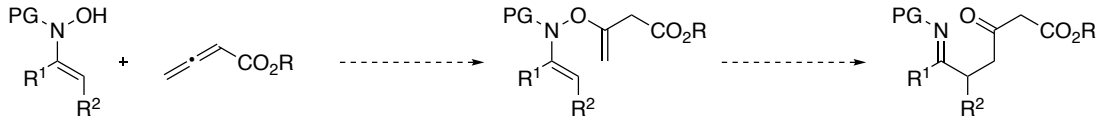
Expanding on this initial work, Anderson and coworkers reported the addition of *N*-vinylnitrone **2.59** to electron-deficient allenoates to trigger a spontaneous [3,3']-sigmatropic rearrangement of **2.59'** resulting in the formation of 1,4-enamino ketone **2.60**

(Scheme 2.22).[84] Interestingly, these products were isolable and no pyrrole formation was observed from the reaction mixture, suggesting that the 9-fluorenone tether of **2.59** stabilizes the reactive enamine under mild conditions. We wondered if it would be possible to utilize other hydroxylamine nucleophiles in a similar manner to access these interrupted rearrangement products.



Scheme 2.22 Nucleophilic addition to electron-deficient allenoates[84]

Taking into account our lab's previous studies of the reactivity of *N*,*O*-divinyl intermediates, it was hypothesized that we may be able to leverage our chemistry to access these privileged structures. Previous studies by Naito and Takeda on the [3,3']-sigmatropic rearrangements of *O*-aryloxime ethers for the formation of 2-amino benzofurans showed that careful development of reaction conditions and substrate design could allow to access functionalized Fisher-Indole intermediates in a modular fashion (Scheme 2.23).

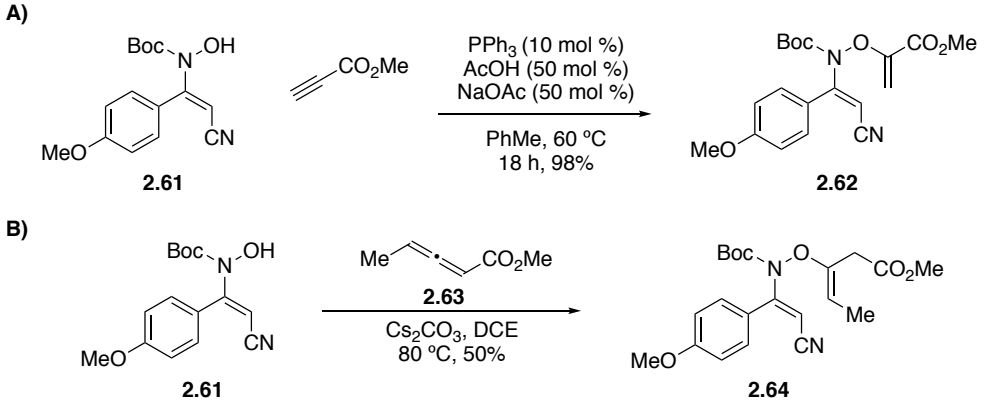


Scheme 2.23 Generation and [3,3']-sigmatropic rearrangement of vinyl hydroxylamines

2.2.1 Development of New Routes to Divinylhydroxylamines

After establishing that in-situ generated *N,O*-divinyl species were viable reactive intermediates for [3,3']-sigmatropic rearrangements, our group postulated that there may

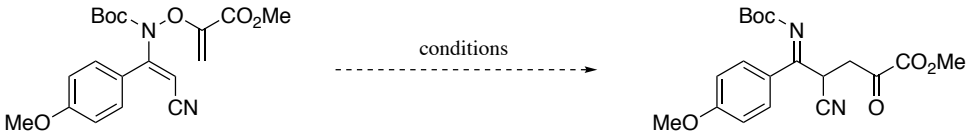
be an opportunity for an entry towards stable intermediates for these transformations. Dr. Jongwoo Son tested a variety of Michael acceptors to determine if a hydroalkoxylation might furnish stable *N*,*O*-divinylhydroxylamine species which could be leveraged for further rearrangement through synthetic manipulation. It was found that protected *N*-vinylhydroxylamine **2.61** could be readily accessed and when subjected to propiolate in the presence of catalytic triphenylphosphine, *O*-vinylation was achieved to give **2.62** (Scheme 2.24A). Furthermore, when **2.61** was added to a solution of electron-deficient allenoate **2.63** in the presence of base, Michael addition product **2.64** could be formed in modest yield (Scheme 2.24B). This proof of principle was highly motivating for further reactivity studies to potentially access a modular synthesis of reactive *N,O*-divinylhydroxylamine species for their sigmatropic rearrangement to functionalized heterocycles.



Scheme 2.24 Initial attempts at *O*-vinylation of *N*-vinylhydroxylamine derivatives

A variety of conditions were screened to determine the propensity for the desired [3,3']-sigmatropic rearrangement of reactive intermediate **2.62** to **2.65**. As shown in Table 2.1, a variety of Lewis acids were tested to determine whether they might trigger the desired rearrangement. At elevated temperature, **2.62** was recovered suggesting that

more forcing conditions were necessary (Table 2.1, entry 1). Lewis acids such as copper(II) and magnesium(II) salts were also inadequate promoters for this transformation (entries 2–3). Palladium and gold complexes, which are known to act as strong π-acids resulted in no reactivity with this substrate (entries 4–6). Stronger Lewis acids such as $Zn(OTf)_2$ and BF_3•OEt_2 resulted in undesirable deprotection of the divinyl moiety, while strong acid selectively removed the Boc protecting group (entries 7–9). It was determined from these findings that this substrate was unfit for the desired transformation. A different approach would be needed that would generate a more reactive *N,O*-divinylhydroxylamine intermediate to be tested in the transformation to functionalized heterocycles.



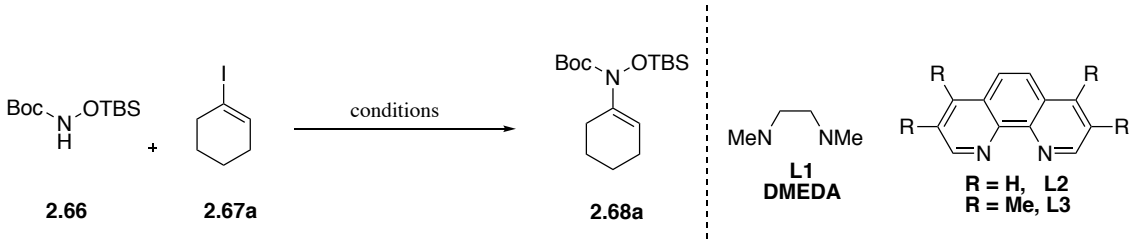
2.62 **2.65**

Entry	Conditions	% Yield[a]
1	150 ºC, PhMe	NR
2	$Cu(OAc)_2$, DCE, 100 ºC	NR
3	$MgBr_2$, DCE, 100 ºC	NR
4	$AuCl_3$, CH_2Cl_2, 25 ºC	NR
5	tBuXPhos Palladacycle, CH_2Cl_2, 25 ºC	NR
6	BrettPhos G3 Pd, CH_2Cl_2, 25 ºC	NR
7	BF_3•OEt_2, CH_2Cl_2, 25 ºC	dec.
8	$Zn(OTf)_2$, DCE, 25 ºC	dec.
9	TFA	dec.

[a] Yield determined by ^1H NMR using CH_2Br_2 as a reference

Table 2.1 Conditions for [3,3']-sigmatropic rearrangement of **2.62**

It was first necessary to develop a method for the selective *N*-vinylation of hydroxylamine derivatives in order to access the required intermediates. Therefore, optimization of the *N*-vinylation of **2.66** with **2.67a** was required using Ullmann coupling conditions to afford **2.68a** (Table 2.2). It was found that efficient C–N bond formation was achieved with 10% CuI as the catalyst and DMEDA as ligand in a 1:1 ratio (Table 2.2, entry 3). Reactions with excess ligand resulted in slightly diminished yields (Entries 2 and 4). Other copper (I) salts were also viable options, albeit requiring higher temperatures and resulting in lower yields (Entries 1,6,7). For these reasons, the ideal conditions were chosen as depicted in Table 2.2, entry 3. Gratifyingly, **2.68a** was found to be stable under these conditions, but could be efficiently deprotected using TBAF in THF to cleanly afford the desired *N*-vinylhydroxylamine **2.69a**. Using the optimal conditions for this two-step sequence, the scope of the vinyl iodide reagent was investigated.



2.66 **2.67a** **2.68a**

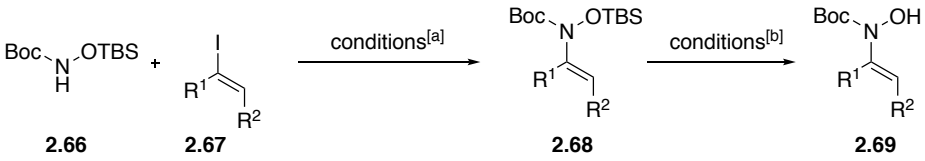
Entry[a]	cat. (mol%)	2.67a (equiv)	Ligand	Solvent	Base (equiv)	Temp	Time	% Yield[b]
1	CuTC 10 %	1.2	L1 20%	PhMe	Cs_2CO_3 (2)	60 ºC	24 h	9
2	CuI 10%	1.2	L1 20%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	55
3	CuI 10%	2.0	L1 10%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	98(95)[c]
4	CuI 20%	2.0	L1 40%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	65
5	CuI 10%	2.0	L1 10%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	95
6	CuCl 10%	2.0	L1 10%	PhMe	Cs_2CO_3 (2)	100 ºC	18 h	65
7	CuBr 10%	2.0	L1 10%	PhMe	Cs_2CO_3 (2)	100 ºC	18 h	38
8	CuI 5%	2.0	L1 5%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	67
9	CuI 5%	2.0	L1 10%	PhMe	Cs_2CO_3 (2)	65 ºC	18 h	31
10	CuI 10%	2.0	L2 10%	PhMe	Cs_2CO_3 (2)	100 ºC	18 h	21

11	CuI 10%	2.0	L3 10%	PhMe	Cs_2CO_3 (2)	100 ºC	18 h	24

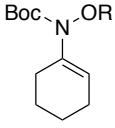
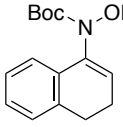
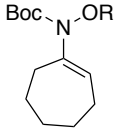
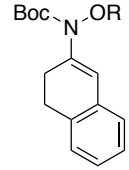
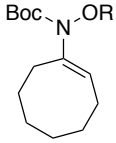
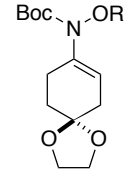
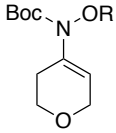
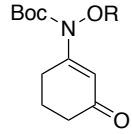
[a] Conditions: **2.66** (1 equiv), **2.67a** (1.2 or 2.0 equiv), 0.1 M in solvent. [b] % Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [c] Isolated yield of **2.68a**.

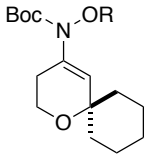
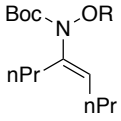
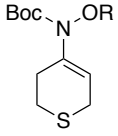
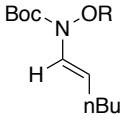
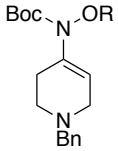
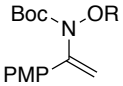
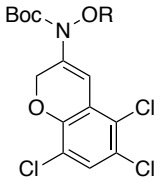
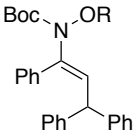
Table 2.2 Optimization of *N*-vinylation of protected hydroxylamine

A variety of functional groups were well-tolerated using these optimal conditions and could be efficiently deprotected to afford desired **2.69** in high yield (Table 2.3). Cyclic alkyl and heterocyclic **2.67a-d,f-g** cleanly afforded the necessary products while spirocyclic ether **2.67e** and acetal **2.67k** were shown to efficiently undergo *N*-vinylation. Fused bicyclic aryl substrates such as **2.67i-j** and phenolic ether **2.67h** were also tolerated. Acylic alkyl **2.67m** and mono-substituted **2.67n-p** gave satisfactory results. All of these intermediates could be deprotected to give the *N*-vinylhydroxylamines in good to excellent yields.



2.66 **2.67** **2.68** **2.69**

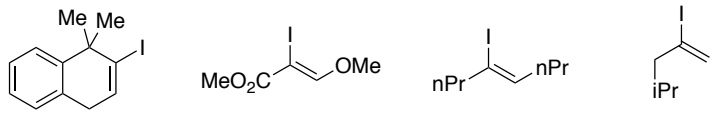
Entry	Product	%Yield[c]	Entry	Product	%Yield[c]
1		**2.68a**, 95 **2.69a**, 70	**9**		**2.68i**, 30 **2.69i**,77
2		**2.68b**, 96 **2.69b**, 54	**10**		**2.68j**, 99 **2.69j**, 88
3		**2.68c,** 98 **2.69c**, 63	**11**		**2.68k**, 83 **2.69k**, 60
4		**2.68d,** 93 **2.69d**, 62	**12**		**2.68l**, 51 **2.69l**, 46

5		**2.68e**, 46 **2.69e**, 83	**13**		**2.68m**, 76 **2.69m**, 79
6		**2.68f**, 52 **2.69f**, 54	**14**		**2.68n**, 86 **2.69n**, 72
7		**2.68g**, 95 **2.69g**, 13	**15**		**2.68o**, 95 **2.69o**, 61
8		**2.68h**, 87 **2.69h**, 80	**16**		**2.68p**, 92 **2.69p**, 95

[a] Conditions: **2.66** (1 equiv), **2.67** (2 equiv), CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (2 equiv), PhMe (0.1 M), 65 ºC, 18 h [b] Deprotection conditions: TBAF (1.1 equiv), THF (0.1 M), 25 ºC, 30 min [c] Isolated yield of **2.68** and **2.69.**

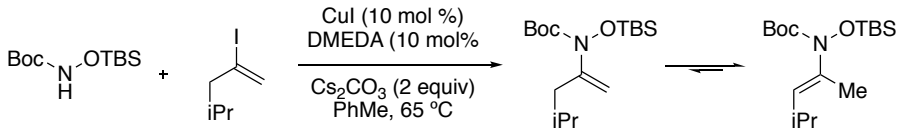
Table 2.3 Tolerance of Ullmann conditions for the preparation of **2.67**

In some cases, vinyl iodides **2.67** were unreactive in the Ullmann reaction with **2.66** (Scheme 2.25). It was hypothesized that the steric environment had a major effect on the reaction outcome. As shown in Scheme 2.23, vinyl iodides that have a quaternary carbon center at the α-position such as **2.67q** were unreactive towards this transformation, presumably due to steric encumbrance during the oxidative addition with copper. Furthermore, while the (*E*)-vinyl iodides shown in Table 2.3 were shown to be well-tolerated for this transformation, the analogous (*Z*)-vinyl iodides (**2.67r-s)** were unreactive. Vinyl iodides such as **2.67t** failed to provide desired *N*-vinylhydroxylamine due to a gradual isomerization of the resulting product **2.68t** to the thermodynamically more stable isomer **2.68t'** via a proposed proton transfer mechanism (Scheme 2.26). These results would allow us to test their reactivity to access divinylhydroxylamines.



2.67q **2.67r** **2.67s** **2.67t**

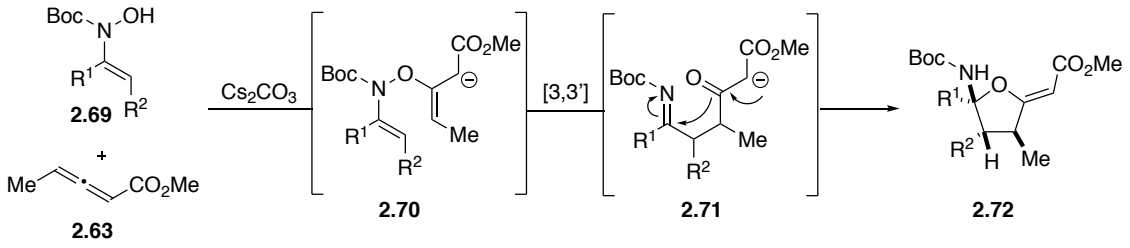
Scheme 2.25 Unproductive substrates for *N*-vinylation of hydroxylamine **2.66**



2.66 **2.67t** **2.68t** **2.68t'**

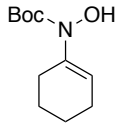
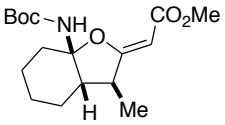
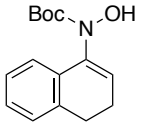
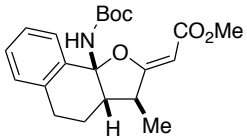
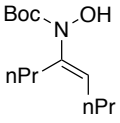
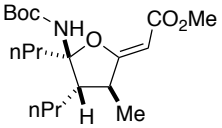
Scheme 2.26 Isomerization of terminal *N*-vinyl hydroxylamines

Three functionally different **2.69** were chosen to test our original hypothesis that we could generate a reactive *N,O*-divinyl intermediate. Because of previous success with **2.63** in our group, it was chosen as the ideal substrate to test our hypothesis. As shown in Table 2.4, when *N*-vinylhydroxylamine **2.69** were treated with **2.63** in the presence of base, the addition of the hydroxylamines to the allene cleanly triggered the generation of intermediate **2.70**, which then underwent spontaneous [3,3']-sigmatropic rearrangement to afford **2.71**. Surprisingly, the resulting cyclization under basic Michael conditions afforded 2-aminotetrahydrofuran **2.72** as opposed to thermodynamically-favored pyrrole formation. This structure was confirmed by XRD analysis by Prof. Donald J. Wink (Figure 2.1). While this proof of principle excited us, further optimization was required before applying this transformation to our library of intermediates.



2.69 **2.63** **2.70** **2.71** **2.72**

Entry	*N*-Vinylhydroxylamine	Conditions	Product	%Yield[a]

1	 **2.69a**	b	 **2.72a**	53 >20:1 d.r.
2	 **2.69i**	b	 **2.72i**	20 >20:1 d.r.
3	 **2.69m**	c	 **2.72m**	25 2:1 d.r.

[a] Isolated yield of **2.72** [b] Cs_2CO_3 (2 equiv), C_6H_6, 25 ºC [c] Cs_2CO_3 (2 equiv), C_6H_6, 0 ºC

Table 2.4 Initial results for the addition of **2.69** to electron-deficient allenoate **2.63**

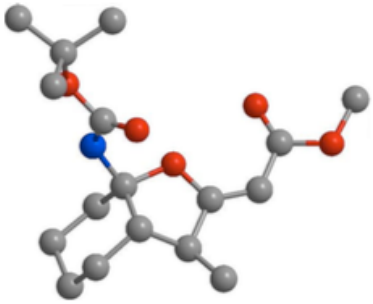
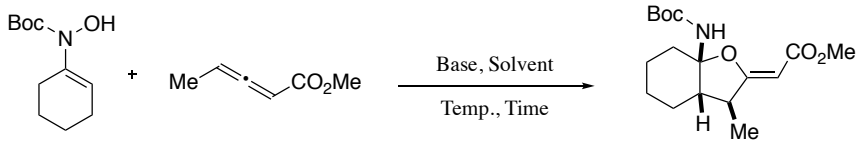


Figure 2.1 X-Ray crystal structure of **2.72a** (CCDC 1814362) – Prof. Donald J. Wink

2.2.2 Development of the Reaction Conditions

After our initial observation of the addition of **2.69a** to **2.63** to give **2.72**, the reaction conditions were optimized. As shown in Table 2.5, Cs_2CO_3 in toluene at ambient temperature gave only a small amount of desired product **2.72a** (Table 2.5, entry 1). Lowering of the temperature to 0 ºC showed significant improvement (entry 2), while solvents such as CH_2Cl_2, DMF, MeCN, and acetone gave attenuated yield (entries 3-6). Swapping the counter-ion from cesium to potassium resulted in higher yield, with CH_2Cl_2 as the solvent after 1 hour (entry 7). Amine bases showed no reactivity (entries 12-14),

and catalytic K_2CO_3 gave the product in high yield (entry 15), but the optimal conditions were chosen to be those in entry 16. It should be noted that at prolonged reaction times in PhMe, the formation of byproduct **2.72a'** was observed via base-promoted ring opening to give the cyclic enamine as the minor product.



2.69a **2.63** **2.72a**

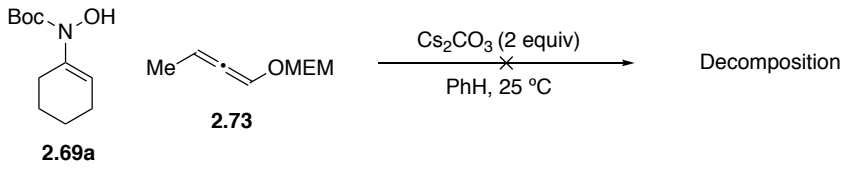
Entry[a]	Base (equiv)	Solvent	Temp.	Time	% Yield[b]
1	Cs_2CO_3 (1)	PhMe	25 ºC	60 min	24
2	Cs_2CO_3 (1)	PhMe	0 ºC	60 min	55
3	Cs_2CO_3 (1)	DMF	0 ºC	60 min	46
4	Cs_2CO_3 (1)	MeCN	0 ºC	60 min	38
5	Cs_2CO_3 (1)	Acetone	0 ºC	60 min	43
6	Cs_2CO_3 (1)	CH_2Cl_2	0 ºC	60 min	57
7	K_2CO_3 (1)	PhMe	0 ºC	120 min	85[d]
8	K_2CO_3 (1)	CH_2Cl_2	0 ºC	60 min	83
9	Na_2CO_3 (1)	CH_2Cl_2	0 ºC	60 min	58
10	Li_2CO_3 (1)	CH_2Cl_2	0 ºC	60 min	54
11	LiOAc (1)	CH_2Cl_2	0 ºC	60 min	N.R.
12	Et_3N (1)	CH_2Cl_2	0 ºC	60 min	N.R.
13	DMAP (1)	CH_2Cl_2	0 ºC	60 min	15
14	DABCO (1)	CH_2Cl_2	0 ºC	60 min	22
15	K_2CO_3 (0.2)	CH_2Cl_2	0 ºC	60 min	69
16	K_2CO_3 (1)	CH_2Cl_2	0 ºC	30 min	93[c]
17	-	CH_2Cl_2	0 ºC	60 min	N.R.

[a] Conditions: **2.69a** (1 equiv), **2.63** (1.2 or 2.0 equiv), 0.1 M in solvent. [b] % Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [c] Isolated yield of **2.72a**. [d] 12% byproduct **2.72a'** isolated. N.R. = No Reaction (Work done by Dr. Jongwoo Son)

Table 2.5 Optimization of generation of *N,O*-divinylhydroxylamine from **2.69a**

Since addition of **2.69a** to electron-deficient allenoate **2.63** was shown to be a potentially useful method for the generation of 2-aminotetrahydrofurans, it was postulated that electron-rich allenes might also be used in this transformation.

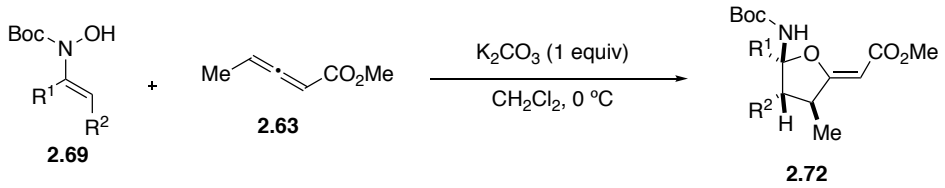
Unfortunately, reaction of **2.69a** and electron-rich allene **2.73** resulted in decomposition and no product was observed, suggesting that an electron-withdrawing group was necessary in order for the desired reactivity (Scheme 2.27).

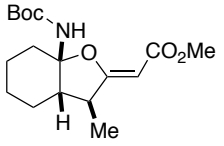
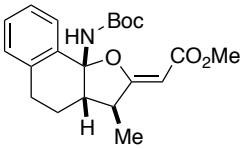
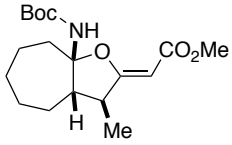
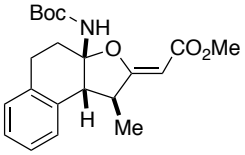
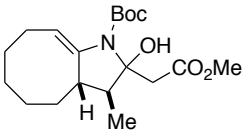
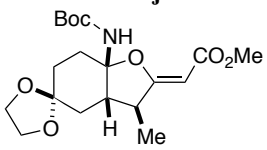
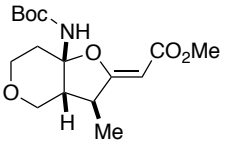
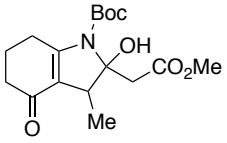
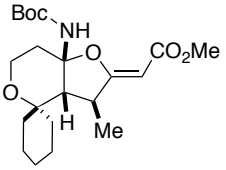
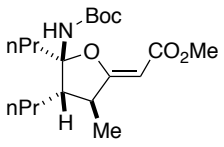
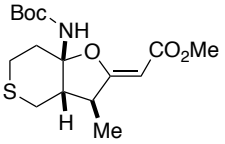
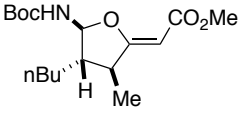
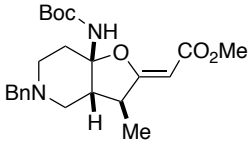
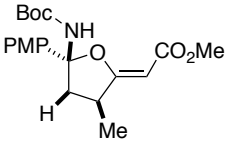
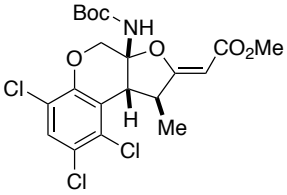
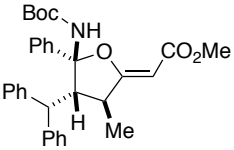


Scheme 2.27 Attempted reaction with electron-rich allene **2.73**

2.2.3 Scope of *N*-Vinylhydroxylamine

Utilizing our library of diverse *N*-vinylhydroxylamines, an array of 2-aminotetrahydrofuran scaffolds were prepared using **2.63** (Table 2.6). Both cyclic and acyclic intermediates were tolerated in this transformation. Cyclooctenyl **2.69c** was found to undergo further reaction to afford pyrrolidine **2.72c'**. Acyclic substrates such as **2.69m** gave diminished diastereoselectivity, while mono-substituted *N*-vinylhydroxylamines were also amenable to this reaction. These mono-substituted substrates were shown to give diminished diastereoselectivity presumably due to an increased freedom of rotation of the pendant side-chains. Important to the outcome of these transformations, it was found that under extended reaction times using the optimal conditions, further rearrangement of **2.72a** to **2.72a'** was observed suggesting that the cyclization could be reversible (Scheme 2.28). Nonetheless, with careful reaction monitoring, it was possible to achieve the desired transformation for a wide range of reactive **2.69** to generate diverse nucleoside analogues **2.72**.

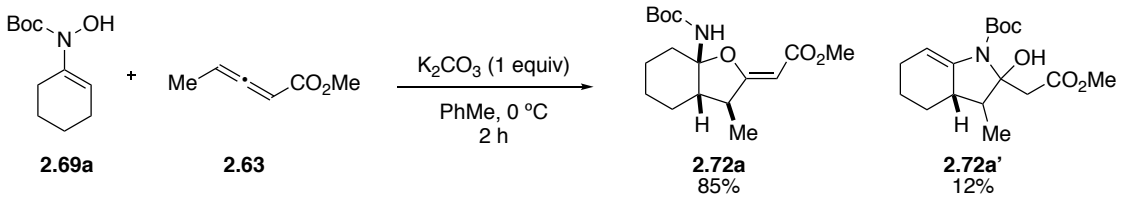


Entry[a]	Product	%Yield[b]	Entry[a]	Product	%Yield[b]
1	 **2.72a**	91 d.r. = >20:1	9	 **2.72i**	83 d.r. = >20:1
2	 **2.72b**	73 d.r. = >20:1	10	 **2.72j**	89 d.r. = 12:1
3	 **2.72c'**	45[c]	11	 **2.72k**	71 d.r. = >20:1
4	 **2.72d**	94 d.r. = >20:1	12	 **2.72l'**	75[d]
5	 **2.72e**	89 d.r. = >20:1	13	 **2.72m**	73 d.r. = 2:1
6	 **2.72f**	78 d.r. = >20:1	14	 **2.72n**	46 d.r. = 8:1
7	 **2.72g**	85 d.r. = >20:1	15	 **2.72o**	61 d.r. = 2:1
8		82 d.r. = >20:1	16	 **2.72p**	68 d.r. = 7:1

2.72h

[a] Conditions: **2.69** (1 equiv), **2.63** (2 equiv), K_2CO_3 (1 equiv), CH_2Cl_2 (0.1 M), 0 ºC. Monitored by TLC every 10 min. [b] Isolated yield of **2.72** [c] Further rearrangement to **2.72c'** was observed. [d] Further rearrangement to **2.72l'** was observed.

Table 2.6 Scope of reaction *N*-vinylhydroxylamine **2.69** with **2.63**

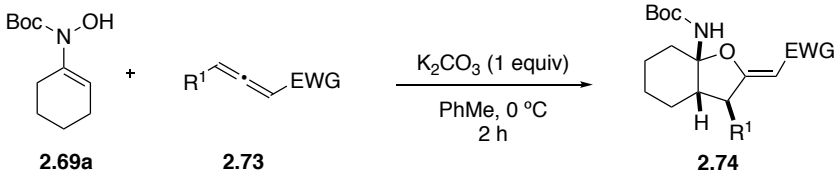


2.69a **2.63** **2.72a** 85% **2.72a'** 12%

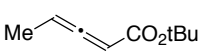
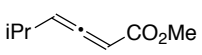
Scheme 2.28 Undesirable side-product formation

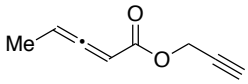
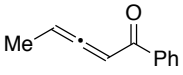
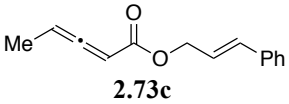
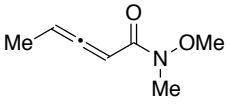
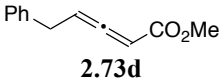
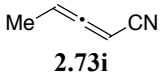
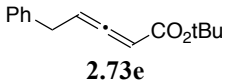
2.2.4 Scope of Allenoate

Having established a robust method for the formation of highly functionalized 2-aminotetrahydrofurans from **2.69** and **2.63**, it was next postulated that other electron-deficient allenes might also facilitate this transformation. A number of functionalized allenes **2.73a–i** were tested for reactivity. As depicted in Table 2.7, the substitution of the ester moiety could be exchanged for bulkier groups or other functional synthetic handles such as **2.73a**, **2.73b**, and **2.73c**. Alternative alkyl groups could also be introduced at the 4-positions as shown in **2.73d**, **2.73e**, and **2.73f** and the electron-withdrawing ester substituent could be exchanged for phenyl ketone **2.73g**, amide **2.73h**, and nitrile **2.73i** (entries 7-9). All of these electron-deficient allenes showed excellent reactivity in the formation of 2-aminotetrahydrofurans **2.74a–i**.



2.69a **2.73** **2.74**

Entry[a]	Allene	%Yield[b]	Entry[a]	Allene	%Yield[b]
1	 **2.73a**	86	**6**	 **2.73f**	34

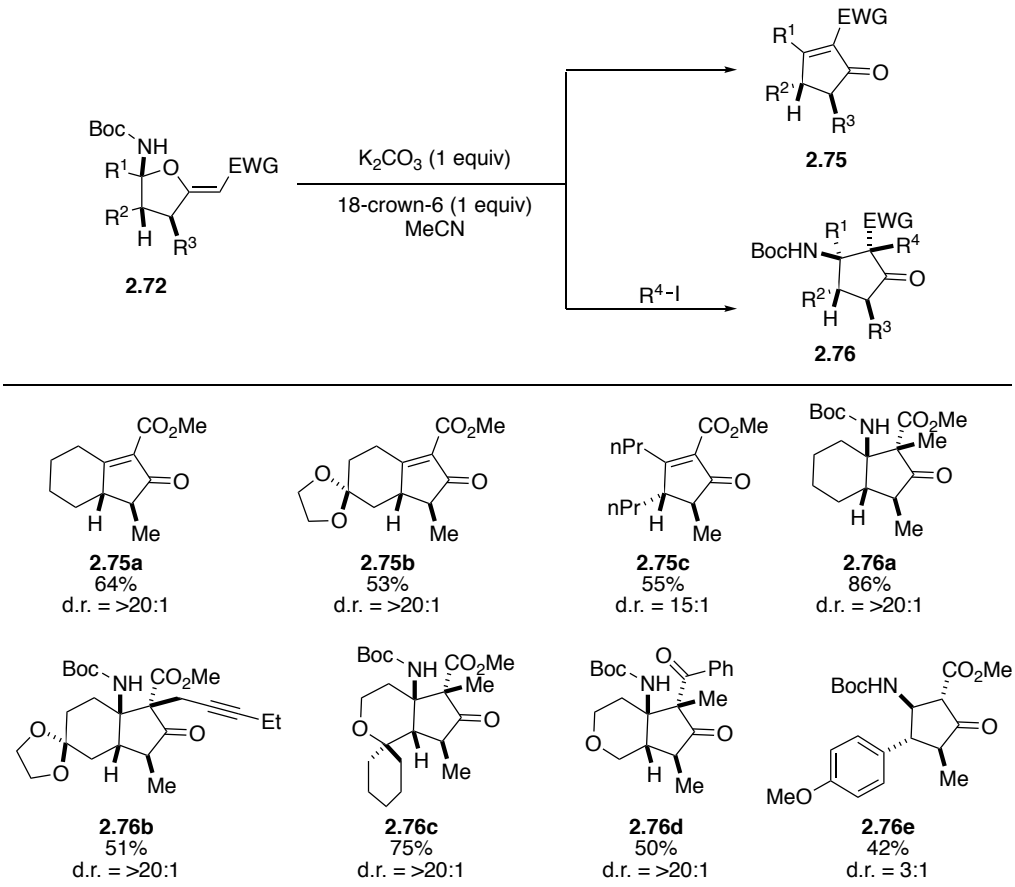
2	 **2.73b**	90	**7**	 **2.73g**	72
3	 **2.73c**	91	**8**	 **2.73h**	73
4	 **2.73d**	81	**9**	 **2.73i**	48
5	 **2.73e**	65			

[a] Conditions: **2.69a** (1 equiv), **2.73** (2 equiv), K_2CO_3 (1 equiv), CH_2Cl_2 (0.1 M), 0 ºC. Monitored by TLC every 10 min. [b] Isolated yield of **2.74a–i**

Table 2.7 Effect of electron-withdrawing group of **2.73** on rearrangement to **2.74**

2.2.5 Use of 2-Aminotetrahydrofurans to Access Modified Cyclic Ketones

With a general method to access densely functionalized 2-aminotetrahydrofuran scaffolds from easily accessible starting materials, we hoped to establish further reactivity to access functionalized scaffolds while still avoiding pyrrole formation. We hoped to leverage the reactivity of these 2-aminotetrahydrofurans to access functionalized cyclic ketones in a modular fashion. Dr. Jongwoo Son subjected **2.72** to basic conditions to facilitate a ring-opening event and afford, after ring closure, either **2.75** from elimination of t-butyl carbamate or **2.76** in the presence of an electrophile (Scheme 2.29). The stereoselectivity of this transformation was confirmed by XRD analysis by Prof. Donald J. Wink to be a *cis*-relationship between the nitrogen and the electrophile. Using this method, a variety of cyclopentenones **2.75a-c** could be accessed with high diastereoselectivity. Further, trapping with alkyl halides furnished β-amino ketones **2.76a-e** with excellent selectivity. This showed that 2-aminotetrahydrofurans could be used as useful synthetic intermediates for the preparation of modified cyclic ketone scaffolds.



Scheme 2.29 Construction of cyclopentenones from 2-aminotetrahydrofurans

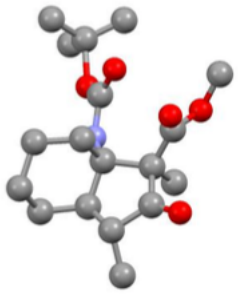


Figure 2.2 X-Ray Crystallography of **2.75a** (CCDC 1814364) – Prof. Donald J. Wink

2.3 Conclusion

Through this work, we have developed a novel method for *N*-vinylation of protected hydroxylamine derivatives for the preparation of *N*-vinylhydroxylamines. Further, these intermediates have been used to add to electron-deficient allenes to trigger a highly diastereoselective [3,3']-sigmatropic rearrangement to afford 2-aminotetrahydrofuran nucleoside analogues. This method demonstrates a modular route to densely substituted 2-aminotetrahydrofuran construction. These intermediates can be further functionalized to access highly-substituted cyclopentenones and cyclopentanone scaffolds in a diastereoselective manner. We hope that this method will find use in both natural product synthesis and drug discovery in the future.

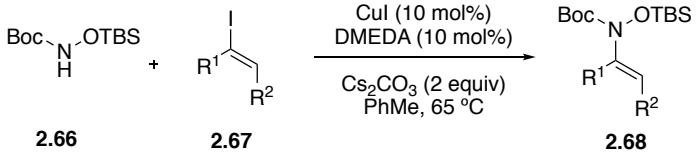
2.4 Supporting Information

2.4.1 General Experimental Information

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed using force flow of the indicated solvent system down columns packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). Unless otherwise noted, all reagents and solvents were obtained from commercial sources and, where appropriate, purified prior to use. Unless otherwise noted, all reactions were performed under N_2 using standard Schlenk techniques. THF, CH_2Cl_2, and toluene were dried by filtration through alumina according to the procedure of Grubbs.[43]. Protected *O*-silylhydroxylamine **2.66**[85] and vinyl iodides **2.67a**[86], **2.67m**[87], **2.67b**[88], **2.67e**[89],

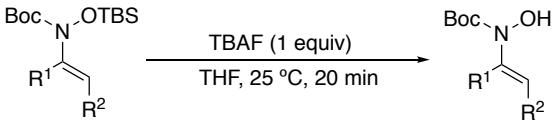
2.67p[90], and **2.67h**[91], were prepared by known methods. Vinyl iodide **2.67n** was purchased from Sigma-Aldrich. A basic workup described for analogous vinyl iodide syntheses was used to maximize yield.[92] Allenes **3.43a**[93], **3.43b**[94], **3.43c** and **3.43e**[84], **3.43g**[95], and **3.43i**[96] were prepared by known methods.

2.4.2 Synthesis and Deprotection of *N*-Siloxyenamines 2.68a – 2.68p (Table 2.3)



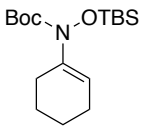
2.66 **2.67** **2.68**

General Procedure A: A conical vial was charged with *N*-Boc-*O*-siloxy hydroxylamine **2.66** (1.0 equiv), CuI (10 mol %), *N*,*N*'-dimethylethylenediamine (DMEDA) (10 mol %), Cs_2CO_3 (2.0 equiv), an vinyl iodide **2.67** (2.0 equiv), and toluene to form a 0.3–1.0 M solution of **2.66**. The reaction vessel was then capped, heated to 65 °C in an oil bath, and stirred for 18 h. The reaction mixture was then filtered through silica gel (8-10 mL), which was then washed with EtOAc (3 x 10.0 mL). The filtrate was concentrated to give the crude product mixture, which was dry-loaded onto celite with CH_2Cl_2 purified by medium pressure chromatography (1-5% EtOAc in hexane) to afford *N*-siloxyenamine **2.68**.



2.68 **2.69**

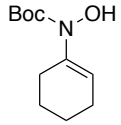
General Procedure B: A round bottom flask was charged with *N*-siloxyenamine **2.68** (1.0 equiv) and diluted with THF to form a 0.1 M solution. TBAF (1.0 M in THF, 1.1 equiv) was then added to the solution of **2.68** via syringe and the reaction mixture was allowed to stir for 20 min at 25 °C. The reaction mixture was then concentrated under vacuum and the residue was dissolved in Et_2O to form a 0.1 M solution and washed with water (3 x 10 mL) and brine (3 x 10 mL). The organic layers were then dried over $MgSO_4$ and concentrated to give the crude product mixture, which was dry-loaded onto celite with CH_2Cl_2 and purified by medium pressure column chromatography to afford *N*-hydroxyenamine **2.69**.



2.68a

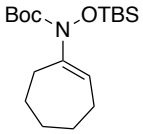
***N*-Siloxyenamine 2.68a:** Compound **2.68a** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 1-iodocyclohexene **2.67a** (0.208 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (10.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **3a** as a clear oil (0.156 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (s, 1H), 2.21 – 2.19 (m, 2H), 2.12 – 2.10 (m, 2H), 1.68 – 1.65 (m, 2H), 1.60 – 1.48 (m, 2H), 1.48 (s, 9H), 0.93 (s, 9H), 0.14 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.4, 139.5, 123.1, 81.2, 28.2, 25.7, 25.2, 24.4, 22.7, 21.9, 17.9, -5.1; IR (thin film) 2961, 2864, 1725, 1701, 1675, 1439, 1416, 1395, 1312, 1199 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{33}NO_3SiNa$ $(M+Na)^+$ 350.2127, found 350.2119.

N*-Siloxyenamine 2.68a (1 mmol scale)*: Compound **2.68a** was prepared on 1 mmol scale as follows: A flame-dried 25 mL round bottom flask with a stir bar was charged with *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.247 g, 1.00 mmol), 1-iodocyclohexene **2.67a** (0.416 g, 2.00 mmol), CuI (0.0190 g, 0.100 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol) and diluted with anhydrous toluene (10.0 mL). The reaction flask was placed under N_2 and flushed with N_2 for 5 min with stirring. DMEDA (0.0088 g, 0.10 mmol) was added via syringe in one portion and the reaction flask was submerged in an oil bath at 65 °C for 18 h. The reaction mixture was the allowed to cool to room temperature and filtered over silica gel (40 mL), which was then washed with EtOAc (3 x 40 mL). The solvent was removed from the filtrate under vacuum, the residue was dry-loaded onto celite with CH_2Cl_2, and purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **2.68a** as a clear oil (0.298 g, 91%).



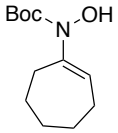
2.69a

***N*-Hydroxyenamine 2.69a:** Compound **2.69a** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68a** (1.16 g, 3.54 mmol), THF (35.0 mL), and TBAF (1.0 M in THF, 3.54 mL, 3.54 mmol). The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:50 EtOAc:hexanes) to afford *N*-hydroxyenamine **2.69a** as a white solid (0.525 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (brs, 1H), 5.75 – 5.74 (m, 1H), 2.22 – 2.16 (m, 2H), 2.12 – 2.08 (m, 2H), 1.70 – 1.65 (m, 2H), 1.59 – 1.53 (m, 2H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.6, 137.4, 122.6, 81.9, 28.3, 25.8, 24.5, 22.7, 21.7; IR (thin film) 3229, 2978, 2931, 2860, 1687, 1477, 1455, 1438, 1391, 1367, 1295 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{19}NO_3Na$ $(M+Na)^+$ 236.1263, found 236.1258; m.p: 46 – 49 °C.



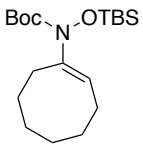
2.68b

***N*-Siloxyenamine 2.68b:** Compound **2.68b** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.247 g, 1.00 mmol) and 1-iodocycloheptene **2.67b** (0.444 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0090 g, 0.10 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **2.68b** as a white solid (0.328 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 – 5.84 (m, 1H), 2.34 – 2.32 (m, 2H), 2.14 – 2.10 (m, 2H), 1.73 – 1.68 (m, 2H), 1.61 – 1.56 (m, 2H), 1.55 – 1.50 (m, 2H), 1.46 (s, 9H), 0.92 (s, 9H), 0.14 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.9, 145.1, 128.0, 81.2, 31.9, 30.5, 28.2, 26.7, 26.6, 26.1, 25.8, 17.9, -5.0; IR (thin film) 2927, 2856, 1738, 1712, 1673, 1472, 1461, 1391, 1366, 1299 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{35}NO_3SiNa$ $(M+Na)^+$ 364.2284, found 364.2274; m.p: 25 – 28 °C.



2.69b

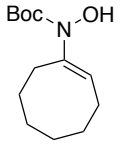
***N*-Hydroxyenamine 2.69b:** Compound **2.69b** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68b** (0.867 g, 2.54 mmol), THF (25.0 mL), and TBAF (1.0 M in THF, 2.54 mL, 2.54 mmol). The crude mixture was purified by medium pressure column chromatography (100% hexanes – 1:25 EtOAc:hexanes) to afford **2.69b** as a white solid (0.312 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (brs, 1H), 5.93 (t, J = 6.5 Hz, 1H), 2.34 – 2.32 (m, 2H), 2.16 – 2.13 (m, 2H), 1.75 – 1.71 (m, 2H), 1.62 – 1.57 (m, 2H), 1.56 – 1.51 (m, 2H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.9, 142.7, 128.8, 82.1, 31.8, 31.2, 28.3, 26.8, 26.5, 26.1; IR (thin film) 3241, 2978, 2925, 2852, 1476, 1454, 1391, 1344, 1264, 1163 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{22}NO_3$ $(M+H)^+$ 228.1594, found 228.1569; m.p: 28 – 33 °C.



2.68c

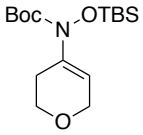
***N*-Siloxyenamine 2.68c:** Compound **2.68c** was prepared using general procedure **A** with the following reagents: *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol, 1.0 equiv), CuI

(0.0190 g, 0.100 mmol, 0.2 equiv), DMEDA (0.0176 g, 0.400 mmol, 0.4 equiv), Cs_2CO_3 (0.326 g, 1.00 mmol, 2.0 equiv), and (*E*)-1-iodocyclooct-1-ene (0.236 g, 1.00 mmol, 2.0 equiv), and toluene (5.0 mL). The reaction mixture was capped and stirred for 18 h at 65 ˚C. The crude mixture was purified by flash chromatography (1:20 EtOAc:hexane) to afford *N*-siloxyenamine **2.68c** as a yellow oil (0.175 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 – 5.55 (m, 1H), 2.30 – 2.24 (m, 2H), 2.11 – 2.05 (m, 2H), 1.55 – 1.46 (m, 8H), 1.40 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 141.2, 127.5, 81.0, 29.2, 28.8, 28.2, 26.4, 26.0, 25.8, 25.7, 25.4, 17.9, -5.1; IR (thin film) 2977, 2915, 2856, 1721, 1705, 1689, 1496, 1479, 1468, 1375 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{37}NO_3SiNa$ $(M+Na)^+$ 378.2440, found 378.2433.



2.69c

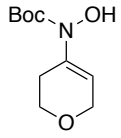
***N*-Hydroxyenamine 2.69c:** Compound **2.69c** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68c** (0.265 g, 0.745 mmol), THF (7.4 mL), and TBAF (1.0 M in THF, 0.745 mL, 0.745 mmol, 1.0 equiv). The crude mixture was purified by column chromatography (1:20; EtOAc:hexane) to afford **2.69c** as a white solid (0.113 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (brs, 1H), 5.64 (t, J = 8.5 Hz, 1H), 2.41 – 2.28 (m, 2H), 2.20 – 2.07 (m, 2H), 1.64 – 1.50 (m, 8H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 138.9, 126.6, 81.9, 29.5, 28.5, 28.3, 26.6, 26.2, 25.9, 25.6; IR (thin film) 3263, 2927, 2858, 1698, 1448, 1392, 1367, 1348, 1279, 1252 cm^{-1}.



2.68d

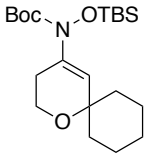
***N*-Siloxyenamine 2.68d:** Compound **2.68d** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 4-iodo-3,6-dihydro-2*H*-pyran **2.67d** (0.210 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **2.68d** as a clear oil (0.153 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 – 5.49 (m, 1H), 4.12 – 4.03 (m, 2H), 3.68 – 3.61 (m, 2H), 2.32 – 2.23 (m, 2H), 1.35 (s, 9H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.4, 137.2, 116.6, 81.6, 64.6, 64.2, 28.0, 26.9, 25.6, 17.8,

-5.3; IR (thin film) 2972, 2856, 1739, 1713, 1607, 1461, 1391, 1366, 1319, 1290 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{31}NO_4SiNa$ $(M+Na)^+$ 352.1920, found 352.1911.



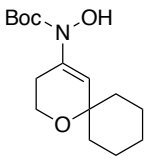
2.69d

***N*-Hydroxyenamine 2.69d:** Compound **2.69d** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68d** (0.150 g, 0.455 mmol), THF (4.6 mL), and TBAF (1.0 M in THF, 0.455 mL, 0.455 mmol). The crude mixture was purified by medium pressure chromatography (1:6 EtOAc:hexanes) to afford **2.69d** as a white solid (0.0607 g, 62%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (brs, 1H), 5.67 – 5.63 (m, 1H), 4.26 – 4.24 (m, 2H), 3.82 – 3.79 (m, 2H), 2.45 – 2.39 (m, 2H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.4, 134.4, 113.6, 82.8, 64.7, 64.2, 28.2, 27.1; IR (thin film) 3269, 2977, 2933, 1693, 1663, 1477, 1456, 1427, 1392, 1368 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{17}NO_4Na$ $(M+Na)^+$ 238.1055, found 238.1053; m.p: 48 – 52 °C.



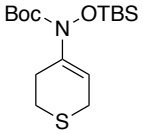
2.68e

***N*-Siloxyenamine 2.68e:** Compound **2.68e** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 4-iodo-1-oxaspiro[5.5]undec-4-ene **2.67e** (0.278 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1:99; EtOAc:hexanes) to afford *N*-siloxyenamine **2.68e** as a clear oil (0.0915 g, 46%). ^1H NMR (500 MHz, $CDCl_3$): δ 5.61 (s, 1H), 3.79 (t, J = 5.5 Hz, 2H), 2.35-2.33 (m, 2H), 1.70-1.65 (m, 2H), 1.64-1.58 (m, 2H), 1.56-1.52 (m, 1H), 1.47 (s, 9H), 1.45-1.39 (m, 3H), 1.32-1.24 (m, 2H), 0.94 (s, 9H), 0.14 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.6, 136.8, 124.9, 81.7, 72.7, 59.0, 35.6, 28.2, 27.1, 25.7, 25.5, 21.6, 17.9, -5.1; IR (thin film) 2930, 2857, 1737, 1714, 1681, 1472, 1462, 1391, 1367, 1250 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{39}NO_4SiNa$ $(M+Na)^+$ 420.2546, found 420.2540.



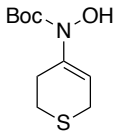
2.69e

***N*-Hydroxyenamine 2.69e:** Compound **2.69e** was prepared using general procedure A with the following reagents: *N*-siloxyenamine **2.68e** (0.199 g, 0.500 mmol), THF (5.0 mL), and TBAF (1.0 M in THF, 0.5 mL, 0.500 mmol). The crude mixture was purified by medium pressure chromatography (1:9; EtOAc:hexanes) to afford **2.69e** as a white solid (0.118 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (brs, 1H), 5.59 (s, 1H), 3.79 – 3.77 (m, 2H), 2.34 – 2.32 (m, 2H), 1.68 – 1.65 (m, 2H), 1.61 – 1.57 (m, 2H), 1.53 – 1.51 (m, 1H), 1.44 (s, 9H), 1.41 – 1.38 (m, 4H), 1.28 – 1.23 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.7, 133.8, 123.2, 82.5, 72.8, 58.9, 35.7, 28.2, 27.0, 25.4, 21.6; IR (thin film) 3260, 2930, 2857, 1710, 1608, 1472, 1462, 1391, 1366, 1320 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{18}NO_2$ $(M\text{-Boc} + 2H)^+$ 184.1332, found 184.1337; m.p: 68 – 72 °C.



2.68f

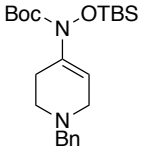
***N*-Siloxyenamine 2.68f:** Compound **2.68f** was prepared by general procedure A. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 4-iodo-3,6-dihydro-2*H*-thiopyran **2.67f** (0.226 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% Et_2O in hexanes) to afford *N*-siloxyenamine **2.68f** as a light yellow oil (0.0898 g, 52%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 – 5.85 (m, 1H), 3.25 – 3.21 (m, 2H), 2.76 – 2.71 (m, 2H), 2.52 – 2.45 (m, 2H), 1.45 (s, 9H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.3, 140.8, 119.9, 81.7, 28.2, 26.9, 25.8, 25.3, 25.1, 17.9, -5.1; IR (thin film) 2957, 2929, 2895, 1710, 1472, 1462, 1423, 1391, 1367, 1321, 1278 cm^{-1}; HRMS (ESI) *m/z* calcd. for C16H31NO3SSiNa $(M+Na)^+$ 368.1692, found 368.1685.



2.69f

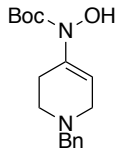
***N*-Hydroxyenamine 2.69f:** Compound **2.69f** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68f** (0.540 g, 1.56 mmol), THF (16.0 mL), and TBAF (1.0 M in THF, 1.56 mL, 1.56 mmol). The crude mixture was purified by medium pressure chromatography (1:5; EtOAc:hexanes) to afford **2.69f** as a pale-brown solid (0.196 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (br, 1H), 5.94 – 5.90 (m, 1H), 3.26 – 3.23 (m, 2H), 2.79 – 2.74

(m, 2H), 2.52 – 2.47 (m, 2H), 1.45 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 155.4, 138.5, 119.5, 82.5, 28.2, 27.2, 25.2, 25.1; IR (thin film) 3240, 2976, 1693, 1477, 1455, 1421, 1391, 1366, 1349, 1300 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{18}NO_3S$ $(M+H)^+$ 232.1002, found 232.0982; m.p: 48 – 52 °C.



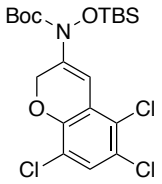
2.68g

***N*-Siloxyenamine 2.68g**: Compound **2.68g** was prepared using general procedure **A** with the following reagents: *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.010 g, 0.050 mmol, 0.1 equiv), DMEDA (0.004 g, 0.050 mmol, 0.1 equiv), Cs_2CO_3 (0.326 g, 1.00 mmol, 2.0 equiv), and 1-benzyl- 4-iodo-1,2,3,6-tetrahydropyridine **2.67g** (0.299 g, 1.00 mmol, 2.0 equiv), and toluene (5.0 mL). The reaction mixture was capped and stirred for 18 h at 65 ˚C. The crude mixture was purified by flash chromatography (1:20; EtOAc:hexane) to afford *N*-siloxyenamine **2.68g** as a yellow oil (0.199 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2H), 7.31 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 5.66 – 5.62 (m, 1H), 3.60 (s, 2H), 3.10 – 3.09 (m, 2H), 2.64 – 2.62 (m, 2H), 2.43 – 2.42 (m, 2H), 1.50 (s, 9H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 138.5, 138.0, 128.9, 128.2, 127.0, 117.3, 81.6, 62.0, 51.7, 49.8, 28.3, 27.1, 25.9, 18.0, -5.1.



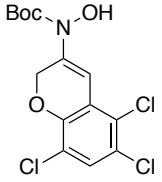
2.69g

***N*-Hydroxyenamine 2.69g:** Compound **2.69g** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68g** (0.446 g, 1.07 mmol), THF (10.0 mL), and TBAF (1.0 M in THF, 1.07 mL, 1.07 mmol, 1.0 equiv). The crude mixture was purified by column chromatography (1:50; EtOAc:hexane) to afford **2.69g** as a clear oil (0.043 g, 13%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.29 (m, 1H), 5.58 (s, 1H), 3.62 (s, 2H), 3.11 (s, 2H), 2.59-2.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 137.0, 135.9, 130.1, 128.4, 127.7, 108.6, 81.3, 62.2, 51.9, 48.9, 28.5, 26.7; IR (thin film) 3001, 2973, 2928, 2825, 2774, 2563, 1699, 1668, 1567, 1496 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{25}N_2O_3$ (M+H)+ 305.1860, found 305.1859.



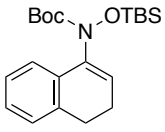
2.68h

***N*-Siloxyenamine 2.68h:** Compound **2.68h** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 5,6,8-trichloro-3-iodo-2*H*-chromene **2.67h** (0.361 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.005 g, 0.05 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1:99; EtOAc:hexanes) to afford *N*-siloxyenamine **2.68h** as a clear oil (0.418 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H), 6.67 – 6.60 (m, 1H), 4.96 (s, 2H), 1.51 (s, 9H), 0.99 (s, 9H), 0.17 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 153.6, 146.7, 137.8, 127.7, 127.1, 125.4, 124.2, 119.6, 103.7, 84.0, 65.8, 28.1, 25.7, 17.9, -5.1; IR (thin film) 3211, 3029, 3015, 2998, 2871, 1715, 1681, 1640, 1581, 1491, 1435, 1391 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C20H28NO_4Cl_3Si$ $(M)^+$ 479.0853, found 479.0853.



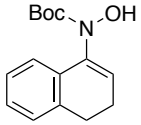
2.69h

***N*-Hydroxyenamine 2.69h:** Compound **2.69h** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68h** (0.866 g, 1.80 mmol), THF (18.0 mL), and TBAF (1.0 M in THF, 1.80 mL, 1.80 mmol). The crude mixture was purified by medium pressure chromatography (1:4; EtOAc:hexanes) to afford **2.69h** as a yellow solid (0.528 g, 80%). ^{1}H NMR (500 MHz, acetone-d_6): δ 9.47 (brs, 1H), 7.32 (s, 1H), 6.62 (s, 1H), 5.12 – 5.10 (m, 2H), 1.52 (s, 9H); $^{13}C\{^1H\}$ NMR (500 MHz, acetone-d_6): δ 152.1, 146.6, 137.9, 126.8, 126.7, 126.1, 124.9, 119.3, 99.3, 83.1, 64.8, 27.4; IR (thin film) 3302, 3119, 3012, 2909, 2865, 1740, 1715, 1659, 1461, 1456, 1389, 1320 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{14}H_{13}NO_4Cl_3$ $(M+H)^+$ 366.0061, found 365.9880; m.p: 88 –91 °C.



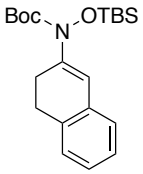
2.68i

***N*-Siloxyenamine 2.68i**: Compound **2.68i** was prepared using general procedure **A** with the following reagents: *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.010 g, 0.050 mmol, 0.1 equiv), DMEDA (0.005 g, 0.050 mmol, 0.1 equiv), Cs_2CO_3 (0.326 g, 1.00 mmol, 2.0 equiv), and α-tetralon-1-yl iodide **2.67i** (0.256 g, 1.00 mmol, 2.0 equiv), and toluene (5.0 mL). The reaction mixture was capped and stirred for 18 h at 65 ˚C. The crude mixture was purified by flash chromatography (1:99; EtOAc:hexane) to afford *N*-siloxyenamine **2.68i** as a yellow oil (0.128 g, 34%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.27 (m, 1H), 7.21 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 6.16 – 6.13 (m, 1H), 2.83 – 2.75 (m, 2H), 2.43 – 2.35 (m, 2H), 1.43 (s, 9H), 0.95 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 140.0, 136.1, 131.5, 127.3, 127.2, 126.2, 124.6, 123.3, 81.4, 28.1, 27.5, 25.8, 22.7, 18.0, -4.9; IR (thin film) 2930, 2866, 2857, 2833, 1736, 1713, 1647, 1486, 1472, 1462 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{33}NO_3SiNa$ $(M+Na)^+$ 398.2127, found 398.2117.



2.69i

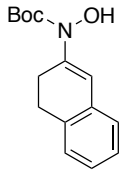
***N*-Hydroxyenamine 2.69i:** Compound **2.69i** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68i** (0.341 g, 0.908 mmol), THF (9.0 mL), and TBAF (1.0 M in THF, 0.9 mL, 0.900 mmol). The crude mixture was purified by medium pressure chromatography (1:50; EtOAc:hexanes) to afford *N*-hydroxyenamine **2.69i** as a clear oil (0.182 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (br, 1H), 7.28- 7.27 (m, 1H), 7.19-7.16 (m, 3H), 6.19-6.18 (m, 1H), 2.84-2.81 (m, 2H), 2.44-2.42 (m, 2H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.6, 138.0, 136.2, 131.5, 127.4, 126.7, 126.3, 122.6, 82.0, 28.1, 27.2, 22.8; IR (thin film) 3225, 3061, 2977, 2934, 2832, 1687, 1644, 1601, 1487, 1476 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{19}NO_3Na$ $(M+Na)^+$ 284.1263, found 284.1259.



2.68j

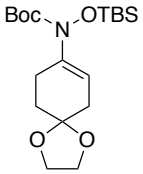
***N*-Siloxyenamine 2.68j:** Compound **2.68j** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and β-tetralon-1-yl **2.67j** (0.256 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.0050 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium

pressure chromatography (2:43; Et_2O:hexanes) to afford *N*-siloxyenamine **2.68j** as a yellow oil (0.372 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 – 7.14 (m, 1H), 7.13 – 7.09 (m, 2H), 7.07 – 7.04 (m, 1H), 6.49 – 6.48 (brs, 1H), 2.93 – 2.88 (m, 2H), 2.70 – 2.64 (m, 2H), 1.54 (s, 9H), 1.03 (s, 9H), 0.22 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.0, 142.3, 134.1, 133.9, 127.1, 126.6, 126.5, 126.2, 116.5, 82.1, 28.7, 28.3, 26.2, 25.9, 18.0, -5.1; IR (thin film) 3061, 2955, 2930, 2885, 1736, 1712, 1638, 1571, 1485, 1425, 1367 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{33}NO_3SiNa$ $(M+Na)^+$ 398.2127, found 398.2114.



2.69j

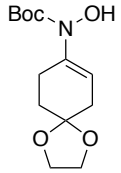
***N*-Hydroxyenamine 2.69j:** Compound **2.69j** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68j** (0.469 g, 1.25 mmol), THF (13.0 mL), and TBAF (1.0 M in THF, 1.25 mL, 1.25 mmol). The crude mixture was purified by medium pressure chromatography (1:50; EtOAc:hexanes) to afford **2.69j** as a white solid (0.287 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (brs, 1H), 7.19 – 7.14 (m, 1H), 7.13 – 7.09 (m, 2H), 7.07 – 7.02 (m, 1H), 6.54 – 6.49 (m, 1H), 2.93 – 2.90 (m, 2H), 2.68 – 2.65 (m, 2H), 1.53 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.4, 139.1, 134.1, 133.5, 127.0, 126.6, 126.5, 126.2, 115.1, 83.3, 28.6, 28.3, 25.8; IR (thin film) 3219, 3064, 2936, 2837, 1687, 1633, 1570, 1485, 1454, 1385, 1353 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{19}NO_3Na$ $(M+Na)^+$ 284.1263, found 284.1255; m.p: 117 – 120 °C.



2.68k

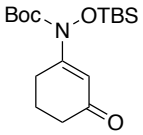
***N*-Siloxyenamine 2.68k:** Compound **2.68k** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 8-iodo-1,4-dioxaspiro[4.5]dec-7-ene **2.67k** (0.266 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1:99; EtOAc:hexanes) to afford *N*-siloxyenamine **2.68k** as a white solid (0.160 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.59 – 5.56 (m, 1H), 3.94 (s, 4H), 2.46 – 2.39 (m, 2H), 2.35 – 2.30 (m, 2H), 1.82 – 1.77 (m, 2H), 1.45 (s, 9H), 0.91 (s, 9H),

0.12 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 156.0, 139.1, 118.7, 107.3, 81.3, 64.3, 34.8, 31.2, 28.2, 25.7, 24.5, 17.9, -5.3; IR (thin film) 2956, 2929, 2884, 1735, 1680, 1472, 1462, 1391, 1367, 1295 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{35}NO_5SiNa$ $(M+Na)^+$ 408.2182, found 408.2178; m.p.: 61 – 63 °C.



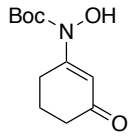
2.69k

***N*-Hydroxyenamine 2.69k:** Compound **2.69k** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **2.68k** (0.460 g, 1.19 mmol), THF (12.0 mL), and TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol). The crude mixture was purified by medium pressure chromatography (1:2 EtOAc:hexanes) to afford **2.69k** as a white solid (0.193 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (brs, 1H), 5.62 (s, 1H), 3.97 (s, 4H), 2.52 – 2.342 (m, 2H), 2.40 – 2.32 (m, 2H), 1.83 – 1.81 (m, 2H), 1.46 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 154.8, 136.5, 116.4, 107.2, 82.4, 64.4, 34.7, 31.1, 28.2, 25.0; IR (thin film) 3307, 2977, 2931, 1693, 1477, 1432, 1367, 1342, 1299, 1253 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{21}NO_5Na$ $(M+Na)^+$ 294.1317, found 293.1316; m.p: 54 – 57 °C.



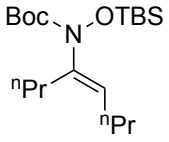
2.68l

***N*-Siloxyenamine 2.68j:** Compound **2.68j** was prepared using general procedure **A** with the following reagents: *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.0190 g, 0.100 mmol, 0.2 equiv), DMEDA (0.0176 g, 0.200 mmol, 0.4 equiv), Cs_2CO_3 (0.326 g, 1.00 mmol, 2.0 equiv), and 3- iodocyclohex-2-en-1-one (0.222 g, 1.00 mmol, 2.0 equiv), and toluene (5.0 mL). The reaction mixture was capped and stirred for 18 h at 65 ˚C. The crude mixture was purified by flash chromatography (1% Et_2O in hexane) to afford *N*-siloxyenamine **3.48j** as a clear oil (0.0870 g, 51%). $_{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.95 – 5.92 (m, 1H), 2.78 – 2.72 (m, 2H), 2.35 – 2.30 (m, 2H), 2.00 – 1.92 (m, 2H), 1.48 (s, 9H), 0.95 (s, 9H), 0.10 (s, 6H); $_{13}C$ NMR (125 MHz, $CDCl_3$): δ 199.0, 161.7, 152.7, 112.2, 84.0, 37.0, 29.1, 28.0, 25.7, 23.4, 17.9, -5.0; IR (thin film) 2954, 2930, 2887, 2859, 1724, 1660, 1599, 1472, 1462, 1428 cm_{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{32}NO_4Si$ $(M+H)_+$ 342.2095, found 342.2089.



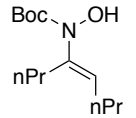
2.69l

***N*-Hydroxyenamine 2.69j:** Compound **2.69j** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68j** (0.524 g, 1.53 mmol), THF (15.0 mL), and TBAF (1.0 M in THF, 1.53 mL, 1.53 mmol). The crude mixture was purified by medium pressure chromatography (1:2; EtOAc:hexane) to afford **2.69j** as a white solid (0.159 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (brs, 1H), 6.06 (s, 1H), 2.85 – 2.82 (m, 2H), 2.29 – 2.27 (m, 2H), 1.96 – 1.93 (m, 2H), 1.48 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 201.2, 161.2, 151.6, 107.6, 84.3, 36.0, 28.0, 27.6, 22.5; IR (thin film) 3150, 2932, 1726, 1615, 1567, 1477, 1455, 1416, 1368, 1342 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{17}NO_4Na$ $(M+Na)^+$ 250.1055, found 250.1050; m.p.: 54 – 57 ºC.



2.68m

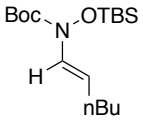
***N*-Siloxyenamine 2.68m:** Compound **2.68m** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.231 g, 1.00 mmol) and *(E)*-4-iodooct-4-ene **2.67m** (0.476 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0082 g, 0.10 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol) in toluene (3.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **2.68m** as a colorless oil (0.272 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.40 (t, J = 8.0 Hz, 1H), 2.20 – 2.17 (m, 2H), 2.01 (q, J = 7.5 Hz, 2H), 1.45 (s, 9H), 1.42 – 1.35 (m, 4H), 0.93 (s, 9H), 0.89 – 0.85 (m, 6H), 0.10 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.8, 139.7, 128.4, 80.6, 29.3, 29.2, 28.2, 25.8, 22.6, 20.7, 17.9, 14.1, 13.8, -5.1; IR (thin film) 3218, 2959, 2930, 2872, 2860, 1713, 1689, 1670, 1390, 1366, 1308, 1250, 1170 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{39}NO_3SiNa$ $(M+Na)^+$ 380.2597, found 350.2590.



2.69m

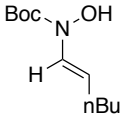
***N*-Hydroxyenamine 2.69m:** Compound **2.69m** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **2.68m** (0.165 g, 0.461 mmol), THF (4.6 mL), and TBAF

(1.0 M in THF, 0.461 mL, 0.461 mmol). The crude mixture was purified by medium pressure chromatography (1:50; EtOAc:hexane) to afford **2.69m** as a colorless oil (0.0889 g, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (brs, 1H), 5.47 – 5.44 (m, 1H), 2.24 – 2.21 (m, 2H), 2.03 (q, *J* = 7.5 Hz, 2H), 1.41 – 1.36 (m, 13H), 0.90 – 0.88 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.0, 137.9, 128.6, 81.4, 29.5, 29.3, 28.2, 22.4, 20.4, 13.7, 13.7; IR (thin film) 3263, 2960, 2932, 2873, 1686, 1456, 1391, 1367, 1167, 1116 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{25}NO_3Na$ $(M+H)^+$ 266.1732, found 266.1731.



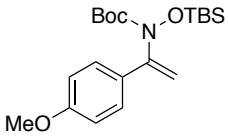
2.68n

***N*-Siloxyenamine 2.68n:** Compound **2.68n** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.231 g, 1.00 mmol) and *trans*-1-iodo-1-hexene **2.67n** (0.420 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0082 g, 0.10 mmol) and Cs_2CO_3 (0.652 g, 2.00 mmol) in toluene (3.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1:99; EtOAc:hexane) to afford *N*-siloxyenamine **2.68n** as a colorless oil (0.285 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (d, *J* = 13.5 Hz, 1H), 5.08 (dt, *J* = 13.5 Hz, 7.5 Hz, 1H), 1.96 (q, *J* = 7.0 Hz, 2H), 1.45 (s, 9H), 1.32 – 1.25 (m, 4H), 0.95 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.11 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.4, 127.0, 109.5, 81.9, 32.4, 29.3, 28.1, 25.7, 22.0, 17.9, 13.8, -4.8; IR (thin film) 2958, 2929, 2858, 1739, 1711, 1667, 1472, 1462, 1391, 1368, 1321 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{35}NO_3SiNa$ $(M+Na)^+$ 352.2284, found 352.2274.



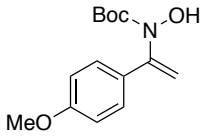
2.69n

***N*-Hydroxyenamine 2.69n:** Compound **2.69n** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68n** (0.0500 g, 0.151 mmol), THF (2.0 mL), and TBAF (1.0 M in THF, 0.16 mL, 0.160 mmol). The crude mixture was purified by flash chromatography (1:20; EtOAc:hexane) to afford **2.69n** as a colorless oil (0.0234 g, 72 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (brs, 1H), 6.62 (d, *J* = 13.5 Hz, 1H), 5.29 – 5.23 (m, 1H), 2.03 (q, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 1.35 – 1.32 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.1, 123.8, 109.2, 82.9, 32.3, 29.4, 28.3, 22.1, 13.9; IR (thin film) 3320, 3055, 3021, 2995, 2957, 1660, 1635, 1596, 1481, 1468, 1339 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{21}NO_3Na$ $(M+Na)^+$ 238.1419, found 238.1419.



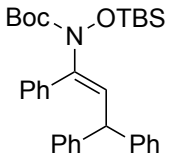
2.68o

***N*-Siloxyenamine 2.68o:** Compound **2.68o** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and 1-(1-iodovinyl)-4-methoxybenzene **2.67o** (0.260 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.005 g, 0.05 mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1:99; EtOAc:hexane) to afford *N*-siloxyenamine **2.68o** as a clear oil (0.180 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.21 (s, 1H), 5.10 (s, 1H), 3.76 (s, 3H), 1.29 (s, 9H), 0.95 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 155.3, 148.5, 130.4, 127.2, 113.5, 104.6, 81.6, 55.2, 27.9, 25.7, 17.9, -5.1; IR (thin film) 2871, 2850, 1725, 1710, 1599, 1489, 1435, 1390, 1352 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{33}NO_4SiNa$ $(M+Na)^+$ 402.2077, found 402.2067.



2.69o

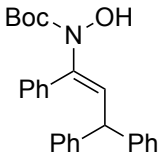
***N*-Hydroxyenamine 2.69o:** Compound **2.69o** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68o** (0.569 g, 1.50 mmol), THF (15.0 mL), and TBAF (1.0 M in THF, 1.50 mL, 1.50 mmol). The crude mixture was purified by medium pressure chromatography (1:6; EtOAc:hexanes) to afford **2.69o** as a yellow oil (0.528 g, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (brs, 1H), 7.36 – 7.34 (m, 2H), 6.85 – 6.84 (m, 2H), 5.25 (s, 1H), 5.14 (s, 1H), 3.80 (s, 3H), 1.26 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.7, 155.4, 146.2, 130.2, 127.4, 113.5, 106.2, 82.5, 55.3, 27.9; IR (thin film) 3319, 3126, 3046, 3019, 2975, 2901, 1735, 1640, 1599, 1491, 1435, 1391 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{14}H_{19}NO_4Na$ $(M+Na)^+$ 288.1212, found 288.1204.



2.68p

***N*-Siloxyenamine 2.68p:** Compound **2.68p** was prepared by general procedure **A**. *N*-Boc-*O*-silyl hydroxylamine **2.66** (0.124 g, 0.500 mmol) and (*E*)-(3-iodoprop-2-ene-1,1,3-triyl)tribenzene **2.67p** (0.396 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.005 g, 0.05

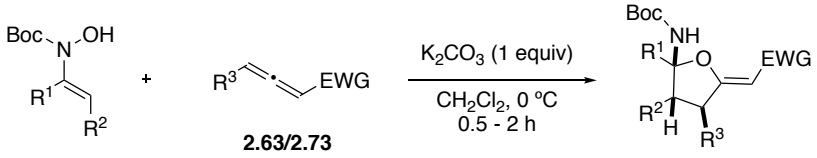
mmol), and Cs_2CO_3 (0.326 g, 1.00 mmol) in toluene (5.0 mL) at 65 °C for 18 h. The crude mixture was purified by medium pressure chromatography (1% EtOAc in hexanes) to afford *N*-siloxyenamine **2.68p** as a yellow oil (0.475 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 9H), 7.23 – 7.19 (m, 2H), 7.18 – 7.15 (m, 4H), 6.26 (d, *J* = 11.1 Hz, 1H), 4.85 (d, *J* = 11.1 Hz, 1H), 1.28 (s, 9H), 0.84 (s, 9H), 0.09 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.9, 144.1, 140.7, 135.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.3, 127.1, 126.4, 81.6, 49.3, 28.0, 25.7, 17.9, -5.1; IR (thin film) 3083, 3059, 2976, 2953, 2894, 1735, 1641, 1596, 1471, 1453, 1391, 1286 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{32}H_{41}NO_3SiNa$ $(M+Na)^+$ 538.2753, found 538.2755; m.p: 75 –78 °C.



2.69p

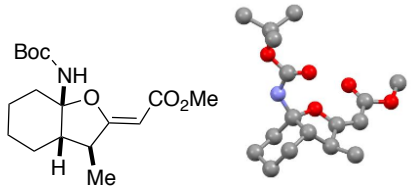
***N*-Hydroxyenamine 2.69p:** Compound **2.69p** was prepared using general procedure **B** with the following reagents: *N*-siloxyenamine **2.68p** (1.03 g, 2.00 mmol), THF (20.0 mL), and TBAF (1.0 M in THF, 2.00 mL, 2.00 mmol). The crude mixture was purified by medium pressure chromatography (1:25; EtOAc:hexane) to afford **2.69p** as a yellow oil (0.763 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (brs, 1H), 7.46 – 7.42 (m, 2H), 7.41 – 7.38 (m, 3H), 7.36 – 7.32 (m, 4H), 7.29 – 7.21 (m, 6H), 6.43 (d, *J* = 11.1 Hz, 1H), 4.94 (d, *J* = 11.1 Hz, 1H), 1.26 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.7, 144.1, 138.9, 135.8, 128.8, 128.6, 128.4, 128.2, 128.0, 127.7, 126.5, 82.4, 49.0, 28.1; IR (thin film) 3221, 3083, 3059, 3025, 2978, 2927, 1684, 1639, 1598, 1492, 1445, 1382 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{26}H_{27}NO_3Na$ $(M+Na)^+$ 424.1889, found 424.1883.

2.4.3 Synthesis of Tetrahydrofurans 2.72a-2.72v, 2.74a-2.74i (Table 2.6)



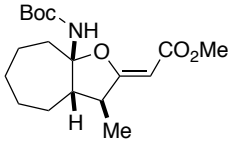
2.69 **2.63/2.73** **2.72**

General Procedure C: A scintillation vial was charged with *N*-hydroxyenamine **2.69** (1.0 equiv) and K_2CO_3 (1.0 equiv). These solids were suspended in CH_2Cl_2 to form a 0.1 M solution, which was cooled to 0 °C in an ice bath for 5 min. At this time, allene **2.63** or **2.73** (2.0 equiv) was added dropwise via syringe and the reaction mixture was allowed to continue to stir at 0 °C. After the complete addition of **2.63**, reaction progress was monitored by TLC for disappearance of **2.69** and appearance of **2.72**. Upon consumption of **2.69**, the reaction mixture was filtered through celite, which was then washed with EtOAc (20.0 mL). The filtrate was then concentrated under vacuum to give the crude product mixture, which was purified by flash chromatography (1:8 – 1:3; EtOAc:hexane) to afford the substituted tetrahydrofuran **2.72**.



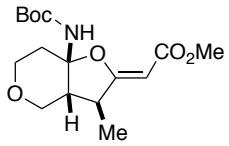
2.72a

Tetrahydrofuran 2.72a: Compound **2.72a** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.63** (0.0224 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **2.69a** & **2.72a** = 0.40 and 0.30). Chromatography (1:6; EtOAc:hexane) afforded **2.72a** as a white solid (0.0296 g, 91%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.25 (brs, 1H), 4.79 (d, J = 1.5 Hz, 1H), 3.64 (s, 3H), 2.96 – 2.88 (m, 1H), 2.85 – 2.77 (m, 1H), 2.17 – 2.14 (m, 1H), 1.76 – 1.63 (m, 3H), 1.62 – 1.52 (m, 2H), 1.42 (s, 9H), 1.40 – 1.29 (m, 2H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.5, 166.3, 153.7, 96.6, 87.6, 80.3, 50.5, 42.7, 39.9, 34.6, 28.3, 23.0, 22.7, 19.9, 15.6; IR (thin film) 3331, 2978, 2934, 2861, 1700, 1640, 1506, 1453, 1436, 1365, 1265; HRMS(ESI) m/z calcd. for $C_{17}H_{27}NO_5Na$ $(M+Na)^+$ 348.1787, observed 348.1780; m.p: 115 – 117 °C.



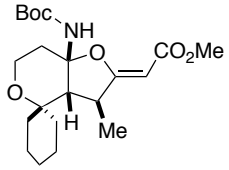
2.72b

Tetrahydrofuran 2.72b: Compound **2.72b** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69b** (0.0455 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **5a** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexane; R_f of **2.69b** & **2.72b** = 0.35 and 0.17). Chromatography (1:6; EtOAc:hexane) afforded **2.72b** as a white solid (0.0498 g, 73%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (brs, 1H), 4.70 (s, 1H), 3.62 (s, 3H), 2.69 – 2.68 (m, 2H), 2.19 – 2.15 (m, 1H), 2.01 – 1.86 (m, 2H), 1.66 – 1.60 (m, 3H), 1.53 – 1.42 (m, 13H), 1.23 – 1.22 (d, J = 5.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 174.5, 166.4, 153.7, 102.0, 85.7, 80.3, 50.4, 49.4, 44.8, 36.6, 30.8, 29.4, 28.2, 24.3, 23.0, 15.8; IR (thin film) 3322, 3055, 2976, 1931, 1497, 1459, 1435, 1390, 1366, 1338.



2.72d

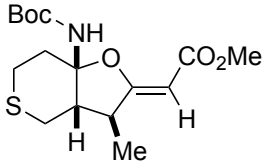
Tetrahydrofuran 2.72d: Compound **2.72d** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69d** (0.0327 g, 0.152 mmol), K_2CO_3 (0.0210 g, 0.152 mmol), CH_2Cl_2 (1.5 mL), and allenoate **2.63** (0.0280 g, 0.152 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8, EtOAc:hexane; R_f of **2.39d** and **2.72d** = 0.50 & 0.40). Chromatography (1:8; EtOAc:hexane) afforded **2.72d** as a white solid (0.0468 g, 94%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (brs, 1H), 4.84 (s, 1H), 3.89 – 3.84 (m, 2H), 3.71 – 3.65 (m, 1H), 3.61 (s, 3H), 3.59 – 3.54 (m, 1H), 3.08 – 3.02 (m, 1H), 2.97 – 2.89 (m, 1H), 2.31 – 2.28 (m, 1H), 1.88 – 1.82 (m, 1H), 1.37 (s, 9H), 1.22 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.5, 166.4, 154.2, 94.3, 87.5, 79.8, 65.2, 63.9, 50.4, 43.0, 38.8, 34.8, 28.3, 15.2; IR (thin film) 3323, 3056, 2973, 2950, 1723, 1699, 1643, 1392, 1366, 1280, 1147; HRMS(ESI) m/z calcd. for $C_{16}H_{25}NO_6Na$ $(M+Na)^+$ 350.1580, observed 350.1575; m.p: 163 – 165 °C.



2.72e

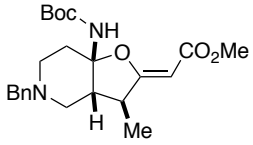
Tetrahydrofuran 2.72e: Compound **2.72e** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69e** (0.0567 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200

mmol), CH_2Cl_2 (2.0 mL), and allenoate **2.63** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:2, EtOAc:hexane; R_f of **2.69e** and **2.72e** = 0.50 & 0.40). Chromatography (1:6; EtOAc:hexane) afforded **2.72e** as a white solid (0.0704 g, 89%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (brs, 1H), 4.87 (s, 1H), 3.82 – 3.80 (m, 1H), 3.67 – 3.64 (m, 1H), 3.61 (s, 3H), 3.09 – 3.02 (m, 2H), 2.42 – 2.40 (m, 1H), 2.16 – 2.13 (m, 1H), 1.78 – 1.72 (m, 1H), 1.67 – 1.57 (m, 3H), 1.52 – 1.43 (m, 4H), 1.38 (s, 9H), 1.34 (d, J = 6.0 Hz, 3H), 1.28 – 1.23 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 174.4, 166.6, 153.9, 94.8, 88.1, 79.6, 73.2, 56.9, 50.3, 47.1, 38.7, 37.4, 34.8, 30.7, 28.3, 25.6, 21.6, 21.1, 20.2; IR (thin film) 3299, 3082, 3057, 2890, 2857, 1719, 1697, 1560, 1447, 1433, 1365, 1332; HRMS(ESI) m/z calcd. for $C_{21}H_{33}NO_6Na$ $(M+Na)^+$ 418.2206, observed 418.2202; m.p: 198 – 202 °C.



2.72f

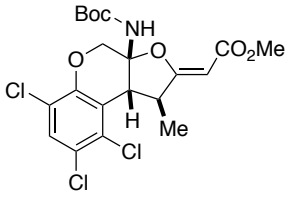
Tetrahydrofuran 2.72f: Compound **2.72f** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **2.69f** (0.0694 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **2.63** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4, EtOAc:hexane; R_f of **2.69f** and **2.72f** = 0.20 & 0.23). Chromatography (1:6; EtOAc:hexane) afforded **2.72f** as a white solid (0.0804 g, 78%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (brs, 1H), 4.86 (s, 1H), 3.62 (s, 3H), 3.35 – 3.34 (m, 2H), 3.16 – 3.13 (m, 1H), 2.90 – 2.85 (m, 1H), 2.58 – 2.51 (m, 2H), 2.46 – 2.43 (m, 1H), 1.86 – 1.80 (m, 1H), 1.37 (s, 9H), 1.19 (d, J = 5.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.7, 166.3, 154.0, 95.8, 87.6, 79.8, 50.5, 41.4, 38.1, 35.2, 28.3, 26.1, 25.5, 15.1; IR (thin film) 3316, 2974, 1721, 1699, 1551, 1450, 1435, 1366, 1341, 1266, 1249, 1231; HRMS(ESI) m/z calcd. for $C_{16}H_{25}NO_5SNa$ $(M+Na)^+$ 366.1351, observed 366.1344; m.p: 163 – 166 °C.



2.72g

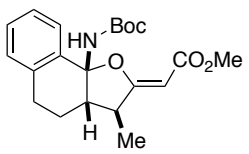
Tetrahydrofuran 2.72g: Compound **2.72g** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69g** (0.0212 g, 0.0696 mmol), K_2CO_3 (0.00962 g, 0.0696 mmol), CH_2Cl_2 (0.7 mL), and allenoate **2.63** (0.0156 g, 0.139 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of

2.69g and **2.72g** = 0.50 & 0.40). Chromatography (1:8; EtOAc:hexane) afforded **2.72g** as a white solid (0.0246 g, 85%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 5H), 5.53 (brs, 1H), 4.81 (s, 1H), 3.67 (s, 3H), 3.56 (d, *J* =13.5 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.27 – 3.23 (m, 1H), 2.96 – 2.86 (m 1H), 2.79 – 2.74 (m, 2H), 2.29 – 2.26 (m, 1H), 2.18 – 2.11 (m 2H), 1.99 – 1.93 (m, 1H), 1.41 (s, 9H), 1.11 (d, *J* = 6.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.7, 166.2, 153.7, 138.5, 128.5, 128.3, 127.1, 94.9, 87.5, 80.3, 62.0, 50.5, 50.3, 49.8, 44.0, 39.6, 35.4, 28.3, 15.2; IR (thin film) 3322, 2971, 2944, 2814, 2783, 1731, 1698, 1637, 1552, 1494 cm^{-1}; HRMS(ESI) m/z calcd. for $C_{16}H_{25}NO_6Na$ $(M+H)^+$ 417.2384, observed 417.2389; m.p.: 163 – 165 ºC.



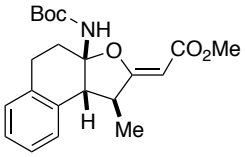
2.72h

Tetrahydrofuran 2.72h: Compound **2.72h** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **2.69h** (0.100 g, 0.273 mmol), K_2CO_3 (0.0377 g, 0.273 mmol), CH_2Cl_2 (2.7 mL), and allenoate **2.63** (0.0612 g, 0.545 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:6, EtOAc:hexane; R_f of **2.69h** and **2.72h** = 0.40 & 0.25). Chromatography (1:6; EtOAc:hexane) afforded **2.72h** as a white solid (0.107 g, 82%, *dr* = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.39 (s, 1H), 5.98 (brs, 1H), 4.83 (s, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.63 (s, 3H), 2.90 – 2.82 (m, 1H), 1.57 (d, *J* = 6.5 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 173.0, 165.7, 153.4, 149.6, 131.0, 129.5, 129.3, 126.4, 122.1, 96.0, 89.8, 81.2, 69.7, 50.9, 47.8, 41.5, 28.2, 18.1; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 7.44 (s, 1H), 6.54 (brs, 1H), 4.90 (s, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 3.93 (d, *J* = 11.6 Hz, 1H), 3.63 (s, 3H), 1.42 (s, 9H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 173.5, 165.8, 153.8, 149.9, 131.8, 128.4, 126.6, 125.9, 121.7, 89.4, 69.5, 50.8, 46.2, 36.7, 28.3, 20.8; IR (thin film) 3295, 2963, 2933, 2873, 1721, 1697, 1642, 1546, 1504, 1450; HRMS(ESI) m/z calcd. for $C_{20}H_{22}NO_6Cl_3Na$ $(M+Na)^+$ 500.0410, observed 500.0406; m.p: 195 – 196 °C.



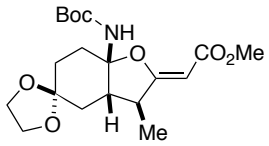
2.72i

Tetrahydrofuran 2.72i: Compound **2.72i** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69i** (0.0584 g, 0.223 mmol), K_2CO_3 (0.0308 g, 0.223 mmol), CH_2Cl_2 (2.2 mL), and allenoate **2.63** (0.0500 g, 0.446 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2; EtOAc:hexane; R_f of **2.69i** and **2.72i** = 0.20 & 0.25). Chromatography (1:6; EtOAc:hexane) afforded **2.72i** as a white solid (0.0691 g, 83%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 7.5 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 5.26 (brs, 1H), 4.73 (d, J = 1.0 Hz, 1H), 3.64 (s, 3H), 3.43 – 3.28 (m, 1H), 2.82 – 2.71 (m, 2H), 2.64 – 2.58 (m, 1H), 2.17 – 2.10 (m, 1H), 1.85 – 1.79 (m, 1H), 1.41 (s, 9H), 1.25 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.1, 166.1, 153.0, 152.9, 135.7, 128.9, 128.3, 127.5, 127.0, 95.4, 87.2, 80.7, 50.5, 42.8, 40.6, 28.2, 24.3, 21.2, 15.5; IR (thin film) 3316, 2974, 2932, 1712, 1650, 1488, 1453, 1435, 1366, 1352 cm^{-1}; HRMS(ESI) m/z calcd. for $C_{21}H_{27}NO_5Na$ $(M+Na)^+$ 396.1787, observed 396.1781; m.p.: 132 – 134 ºC.



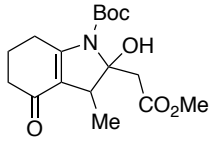
2.72j

Tetrahydrofuran 2.72j: Compound **2.72j** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69j** (0.131 g, 0.500 mmol), K_2CO_3 (0.0691 g, 0.500 mmol), CH_2Cl_2 (5.0 mL), and allenoate **2.63** (0.112 g, 1.000 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexane; R_f of **2.69j** and **2.72j** = 0.20 & 0.10). Chromatography (1:3; EtOAc:hexane) afforded **2.72j** as a white solid (0.332 g, 89%, d.r. = 12:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.22 – 7.14 (m, 4H), 6.02 (brs, 1H), 4.80 (d, J = 1.0 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.64 (s, 3H), 3.00 – 2.92 (m, 1H), 2.85 – 2.77 (m, 1H), 2.76 – 2.71 (m, 1H), 2.31 – 2.25 (m, 1H), 2.21 – 2.15 (m, 1H), 1.44 (d, J = 6.5 Hz, 3H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 173.6, 166.3, 153.9, 135.7, 135.4, 129.3, 128.6, 126.9, 126.4, 97.5, 86.7, 80.1, 50.6, 48.6, 47.4, 32.7, 28.3, 26.8, 16.3; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 7.13 – 7.10 (m, 2H), 7.07 – 7.05 (m, 1H), 6.08 (brs, 1H), 4.72 (d, J = 1.0 Hz, 1H), 4.37 – 4.34 (m, 1H), 3.63 (s, 3H), 1.41 (s, 9H), 0.76 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 137.4, 130.7, 128.1, 126.5, 126.1, 99.3, 86.4, 45.6, 42.7, 35.1, 30.4, 29.7, 26.1; IR (thin film) 3316, 2974, 2947, 1721, 1702, 1646, 1545, 1494, 1455, 1435; HRMS(ESI) m/z calcd. for $C_{21}H_{27}NO_5Na$ $(M+Na)^+$ 396.1787, observed 396.1779; m.p: 145 – 148 °C.



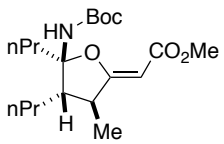
2.72k

Tetrahydrofuran 2.72k: Compound **2.72k** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69k** (0.0542 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **2.63** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:2; EtOAc:hexane; R_f of **2.69k** and **2.72k** = 0.15 & 0.13). Chromatography (1:2; EtOAc:hexane) afforded **2.72k** as a white solid (0.0544 g, 71%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.44 (brs, 1H), 4.77 (s, 1H), 3.93 – 3.89 (m, 4H), 3.64 (s, 3H), 3.29 – 3.25 (m, 1H), 3.10 – 3.00 (m, 1H), 2.04 – 1.92 (m, 2H), 1.79 – 1.65 (m, 4H), 1.42 (s, 9H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.7, 166.2, 153.7, 107.6, 95.7, 87.3, 80.4, 64.6, 63.9, 50.5, 43.3, 40.6, 31.8, 31.1, 31.0, 28.2, 15.3; IR (thin film) 3323, 2971, 2949, 2874, 1699, 1643, 1545, 1456, 1389, 1334; HRMS(ESI) m/z calcd. for $C_{19}H_{29}NO_7Na$ $(M+Na)^+$ 406.1842, observed 406.1835; m.p: 203 – 205 °C.



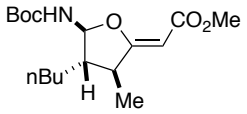
2.72l'

Pyrrole 2.72l': Compound **2.72l'** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69l** (0.0798 g, 0.328 mmol), K_2CO_3 (0.0453 g, 0.328 mmol), CH_2Cl_2 (3.2 mL), and allenoate **2.63** (0.0736 g, 0.328 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.69l** and **2.72l'** = 0.05 & 0.15). Chromatography (1:10; EtOAc:hexane) afforded **2.72l'** as a white solid (0.0851 g, 73%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (brs, 1H), 3.57 (s, 3H), 3.15 (q, J = 6.5 Hz, 1H), 2.91 (d, J = 13.5 Hz, 1H), 2.83 (d, J = 13.5 Hz, 1H), 2.79 – 2.74 (m, 1H), 2.65 – 2.59 (m, 1H), 2.29 – 2.22 (m, 2H), 1.99 – 1.89 (m, 2H), 1.49 (s, 9H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.2, 169.4, 156.8, 152.0, 121.1, 93.9, 83.9, 51.8, 44.3, 42.2, 36.6, 28.2, 25.5, 22.4, 12.7; IR (thin film) 3469, 2927, 2853, 1739, 1649, 1608, 1455, 1426, 1369, 1346; HRMS(ESI) m/z calcd. for $C_{17}H_{26}NO_6$ $(M+H)^+$ 340.1755, observed 340.1752; m.p: 89 – 92 °C.



2.72m

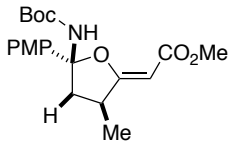
Tetrahydrofuran 2.72m: Compound **2.72m** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69m** (0.0798 g, 0.328 mmol), K_2CO_3 (0.0453 g, 0.328 mmol), CH_2Cl_2 (3.2 mL), and allenoate **2.63** (0.0736 g, 0.328 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.69m** and **2.72m** = 0.40 & 0.25). Chromatography (1:10; EtOAc:hexane) afforded **2.72m** as a white solid (0.0851 g, 73%, dr = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 5.00 (brs, 1H), 4.72 (s, 1H), 3.63 (s, 3H), 3.26 – 3.10 (m, 1H), 2.00 – 1.94 (m, 1H), 1.77 – 1.39 (m, 17H), 1.15 (d, J = 6.5 Hz, 3H), 0.96 – 0.90 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 176.0, 166.4, 153.6, 98.9, 85.9, 79.9, 50.3, 46.5, 43.5, 36.6, 31.7, 28.1, 21.7, 17.9, 16.6, 14.4, 13.9; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 5.10 (brs, 1H), 4.72 (s, 1H), 3.63 (s, 3H), 2.97 – 2.85 (m, 1H), 2.54 – 2.49 (m, 1H), 1.77 – 1.39 (m, 17H), 1.22 (d, J = 6.5 Hz, 3H), 0.96 – 0.90 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (minor diastereomer): δ 173.5, 166.2, 153.4, 99.3, 86.7, 80.2, 51.0, 46.5, 44.4, 36.6, 30.5, 28.2, 20.7, 17.9, 15.9, 14.2, 14.1. IR (thin film) 3321, 2961, 2933, 2873, 1722, 1703, 1643, 1503, 1457, 1435, 1367; HRMS(ESI) m/z calcd. for $C_{19}H_{33}NO_5Na$ $(M+Na)^+$ 378.2256, observed 378.2251; m.p: 124 – 128 °C.



2.72n

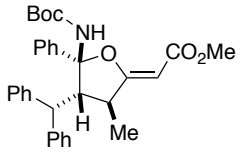
Tetrahydrofuran 2.72n: Compound **2.72n** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69n** (0.0431 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **2.63** (0.0449 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8; EtOAc:hexane; R_f of **2.69n** and **2.72n** = 0.20 & 0.12). The crude product mixture was dissolved in a minimum amount of Et_2O (~ 0.5 mL), layered with hexane(s) and placed in a -40 °C freezer for 48 h. During this time, white crystals collected on the sides of the vial. The solvent was decanted and the residual solvent mixture was removed under vacuum to give **2.72n** as a white solid (0.0301 g, 46%, d.r. = 8:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 5.73 – 5.60 (m, 1H), 5.16 (brs, 1H), 4.77 (s, 1H), 3.67 (s, 3H), 2.60 – 2.54 (m, 1H), 1.61 – 1.49 (m, 2H), 1.46 (s, 9H), 1.39 – 1.29 (m, 5H), 1.17 (d, J = 7.0 Hz, 3H), 0.89 – 0.86 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 173.1, 166.4, 154.0, 91.0, 87.3, 80.8, 50.7, 49.2, 43.5, 29.6, 29.0, 28.2, 22.9, 15.5, 13.8; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 6.16 – 6.12 (m, 1H), 5.10 (brs, 1H), 4.79 (s, 1H), 3.66 (s, 3H), 2.49 – 2.46 (m, 1H), 1.61 – 1.49 (m, 2H), 1.45 (s, 9H), 1.39 – 1.29

(m, 5H), 1.17 (d, J = 7.0 Hz, 3H), 0.89 – 0.86 (m, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 173.5, 166.2, 88.3, 50.8, 46.1, 31.2, 29.4, 27.4, 22.7; IR (thin film) 3322, 3057, 2932, 2861, 1708, 1651, 1525, 1457, 1436, 1392, 1367, 1342; HRMS(ESI) m/z calcd. for $C_{17}H_{29}NO_5Na$ $(M+Na)^+$ 350.1943, observed 350.1939; m.p: 93 – 95 °C.



2.72o

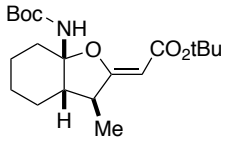
Tetrahydrofuran 2.72o: Compound **2.72o** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69o** (0.0265 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allene **2.63** (0.0224 g, 0.200 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:1; EtOAc:hexane; R_f of **2.72o** = 0.13). Chromatography (1:2; EtOAc:hexane) afforded **2.72o** as a white solid (0.0230 g, 61%, d.r. = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.50 – 7.48 (m, 2H), 6.90 – 6.88 (m, 2H), 5.88 (brs, 1H), 4.86 (s, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.66 – 3.52 (m, 1H), 3.41 – 3.27 (m, 1H), 1.93 – 1.88 (m, 1H), 1.40 (s, 9H), 1.12 (d, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 166.5, 159.6, 153.3, 136.0, 133.9, 126.1, 113.9, 97.9, 87.3, 80.5, 55.3, 50.7, 42.6, 38.3, 28.3, 18.2; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 7.40 – 7.38 (m, 2H), 6.87 – 6.86 (m, 2H), 5.32 (brs, 1H), 4.83 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.08 – 2.92 (m, 1H), 2.78 – 2.67 (m, 1H), 2.41 – 2.37 (m, 1H), 1.41 (s, 9H), 1.23 (d, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 166.3, 159.8, 153.5, 126.0, 113.8, 87.1, 80.4, 37.2, 16.3; IR (thin film) 3235, 3021, 2953, 2771, 2111, 2012, 1999, 1992, 1735, 1658, 1491; HRMS(ESI) m/z calcd. for $C_{20}H_{27}NO_6Na$ $(M+Na)^+$ 400.1736, observed 400.1732; m.p: 99 – 102 °C.



2.72p

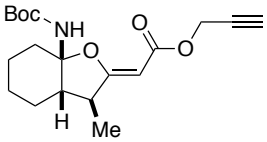
Tetrahydrofuran 2.72p: Compound **2.72p** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69p** (0.121 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **2.63** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.69p** and **2.72p** = 0.20 & 0.25). Chromatography (1:10; EtOAc:hexane) afforded **2.72p** as a white solid (0.105 g, 68

%, dr = 7:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.35 – 7.30 (m, 1H), 7.25 – 7.24 (m , 5H), 7.19 – 7.12 (m, 4H), 7.11 – 7.10 (m, 1H), 7.02 – 7.01 (m, 2H), 6.85 – 6.84 (m, 2H), 5.44 (br, 1H), 4.83 (s, 1H), 4.67 – 4.40 (m, 1H), 3.66 (s, 3H), 3.08 (d, J = 11.5 Hz, 1H), 2.79 – 2.77 (m, 1H), 1.51 (s, 9H), 0.52 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 174.3, 166.2, 153.9, 143.0, 141.6, 139.1, 128.9, 128.7, 128.6, 128.5, 128.15, 128.12, 126.7, 126.6, 125.9, 101.4, 86.5, 80.6, 54.3, 50.5, 48.6, 43.0, 28.3, 17.8; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 5.52 (brs, 1H), 4.80 (s, 1H), 4.36 – 4.34 (m, 1H), 3.66 (s, 3H), 2.93 – 2.89 (m, 1H), 1.51 (s, 9H), 0.56 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 128.8, 128.3, 126.9, 124.5, 58.9, 52.8, 44.1, 28.2, 20.0; IR (thin film) 3411, 3278, 3061, 3027, 2977, 2931, 1717, 1692, 1645, 1599, 1584; HRMS(ESI) m/z calcd. for $C_{32}H_{35}NO_5Na$ $(M+Na)^+$ 536.2413, observed 536.2415; m.p.: 130 – 133 ºC.



2.74a

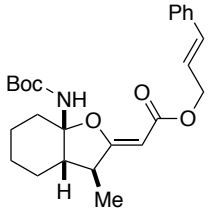
Tetrahydrofuran 2.74a: Compound **2.74a** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.73a** (0.0308 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8; EtOAc:hexane; R_f of **2.69a** and **2.74a** = 0.20 & 0.15). Chromatography (1:8; EtOAc:hexane) afforded **2.74a** as a white solid (0.0316 g, 86%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (brs, 1H), 4.72 (s, 1H), 2.95 – 2.88 (m, 1H), 2.81 – 2.73 (m, 1H), 2.15 – 2.12 (m, 1H), 1.72 – 1.64 (m, 3H), 1.62 – 1.51 (m, 2H), 1.45 (s, 9H), 1.42 (s, 9H), 1.39 – 1.25 (m, 2H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 165.4, 153.7, 96.3, 89.6, 80.2, 78.7, 42.6, 39.9, 34.7, 28.4, 28.3, 23.1, 22.7, 20.0, 15.7; IR (thin film) 3317, 2975, 2931, 1727, 1696, 1556, 1454, 1365, 1331, 1312; HRMS(ESI) m/z calcd. for $C_{20}H_{33}NO_5Na$ $(M+Na)^+$ 390.2256, observed 390.2248; m.p: 142 – 144 °C.



2.74b

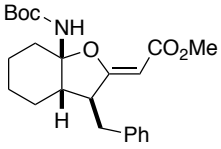
Tetrahydrofuran 2.74b: Compound **2.74b** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.73b** (0.0272 g, 0.200 mmol). The reaction mixture was

stirred at 0 °C and monitored by TLC (TLC eluent = 1:8; EtOAc:hexane; R_f of **2.69a** and **2.74b** = 0.20 & 0.15). Chromatography (1:8; EtOAc:hexanes) afforded **2.74b** as a white solid (0.0314 g, 90%, dr = ≥20:1). Major diastereomer was assigned in analogy to **2.72a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.32 (brs, 1H), 4.85 (d, J = 1.5 Hz, 1H), 4.70 – 4.63 (m, 2H), 3.02 – 2.92 (m, 1H), 2.86 – 2.78 (m, 1H), 2.41 – 2.40 (m, 1H), 2.16 – 2.13 (m, 1H), 1.75 – 1.62 (m, 3H), 1.60 – 1.51 (m, 2H), 1.42 (s, 9H), 1.40 – 1.29 (m, 2H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0, 164.6, 153.7, 97.1, 86.7, 80.4, 78.7, 74.0, 50.7, 42.5, 40.0, 34.7, 28.3, 22.9, 22.7, 19.8, 15.5; IR (thin film) 3331, 2971, 2865, 1707, 1640, 1551, 1455, 1366, 1332, 1289; HRMS(ESI) m/z calcd. for $C_{19}H_{27}NO_5Na$ $(M+Na)^+$ 372.1787, observed 372.1780; m.p: 115 – 118 °C.



2.74c

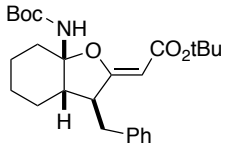
Tetrahydrofuran 2.74c: Compound **2.74c** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K2CO3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.73c** (0.0429 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8; EtOAc:hexane; *Rf* of **2.69a** and **2.74c** = 0.20 & 0.15). Chromatography (1:8; EtOAc:hexane) afforded **2.74c** as a white solid (0.0389 g, 91%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.37 (m, 2H), 7.31 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 6.66 (d, J = 16.0 Hz, 1H), 6.31 (dt, J = 15.5 Hz, 6.5 Hz, 1H), 5.36 – 5.22 (m, 1H), 4.85 (d, J = 1.0 Hz, 1H), 4.77 – 4.69 (m, 2H), 3.01 – 2.92 (m, 1H), 2.87 – 2.79 (m, 1H), 2.18 – 2.15 (m, 1H), 1.75 – 1.52 (m, 5H), 1.41 (s, 9H), 1.39 – 1.28 (m, 2H), 1.19 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 165.5, 153.7, 136.7, 133.2, 128.5, 127.7, 126.6, 124.5, 96.8, 87.6, 80.3, 63.8, 42.6, 40.0, 34.7, 28.3, 22.9, 22.7, 19.9, 15.6.



2.74d

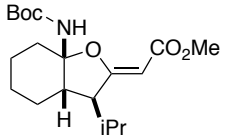
Tetrahydrofuran 2.74d: Compound **2.74d** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.73d** (0.0376 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8; EtOAc:hexane; R_f of **2.69a** and **2.74d** =

0.25 & 0.15). Chromatography (1:5; EtOAc:hexane) afforded **2.74d** as a white solid (0.0325 g, 81%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 2H), 7.24 – 7.20 (m, 3H), 5.09 (brs, 1H), 4.88 (s, 1H), 3.64 (s, 3H), 3.07 – 2.98 (m, 3H), 2.92 – 2.84 (m, 1H), 2.20 – 2.13 (m, 1H), 1.75 – 1.66 (m, 1H), 1.61 – 1.48 (m, 2H), 1.45 (s, 9H), 1.42 – 1.24 (m, 3H), 1.14 – 1.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 166.1, 153.5, 138.9, 128.8, 128.7, 126.6, 96.9, 89.5, 80.3, 50.6, 47.8, 41.4, 39.2, 34.0, 28.3, 25.1, 22.2, 20.4; IR (thin film) 3322, 3028, 2975, 2945, 1702, 1638, 1603, 1549, 1496, 1454, 1389; HRMS(ESI) m/z calcd. for $C_{23}H_{31}NO_5Na$ $(M+Na)^+$ 424.2100, observed 424.2095; m.p: 163 – 166 °C.



2.74e

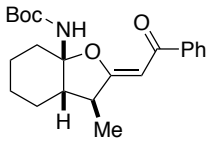
Tetrahydrofuran 2.74e: Compound **2.74e** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **2.73e** (0.0461 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2; EtOAc:hexane; R_f of **2.69a** and **2.74e** = 0.50 & 0.60). Chromatography (1:5; EtOAc:hexane) afforded **2.74e** as a white solid (0.0288 g, 65%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.23 – 7.19 (m, 3H), 5.15 (brs, 1H), 4.85 (s, 1H), 3.07 – 3.04 (m, 1H), 2.97 – 2.95 (m, 2H), 2.87 – 2.82 (m, 1H), 2.17 – 2.14 (m, 1H), 1.77 – 1.71 (m, 2H), 1.45 (s, 9H), 1.44 (s, 9H), 1.33 – 1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 165.2, 153.5, 139.1, 128.7, 128.6, 126.5, 96.8, 91.6, 80.1, 78.9, 48.3, 41.1, 39.6, 33.9, 28.39, 28.36, 25.5, 22.1, 20.5.



2.74f

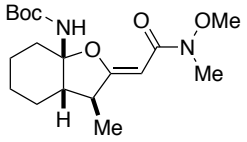
Tetrahydrofuran 2.74f: Compound **2.74f** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allene **2.73f** (0.0280 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8;EtOAc:hexane; R_f of **2.69a** and **2.74f** = 0.20 & 0.10). Chromatography (1:6; EtOAc:hexanes) afforded **2.74f** as a white solid (0.0120 g, 34%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.00 (brs, 1H), 4.89 (d, J = 1.0 Hz, 1H), 3.65 (s, 3H), 3.19 – 3.10 (m, 1H), 2.57 – 2.54 (m, 1H), 2.19 – 2.13 (m, 1H), 2.08 – 2.00 (m, 1H), 1.76 – 1.68 (m, 2H), 1.66 (s, 1H), 1.59 – 1.52 (m, 2H), 1.50 – 1.44 (m, 2H), 1.43 (s, 9H), 1.05 (d, J = 7.0

Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 166.1, 153.3, 96.8, 90.4, 80.1, 53.6, 50.6, 37.7, 34.0, 29.8, 28.3, 26.6, 22.2, 20.9, 20.6, 19.6; IR (thin film) 3299, 3079, 2973, 2857, 2222, 2176, 2035, 2001, 1992, 1974, 1723, 1652, 1589; HRMS(ESI) m/z calcd. for $C_{19}H_{31}NO_5Na$ $(M+Na)^+$ 376.2100, observed 376.2094; m.p: 130 – 133 °C.



2.74g

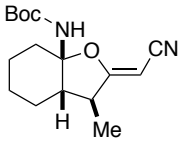
Tetrahydrofuran 2.74g: Compound **2.74g** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allene **2.73g** (0.0316 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.69a** and **2.74g** = 0.25 & 0.13). Chromatography (1:8; EtOAc:hexane) afforded **2.74g** as a bright yellow solid (0.0267 g, 72%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 – 7.86 (m, 2H), 7.47 – 7.43 (m, 1H), 7.41 – 7.37 (m, 2H), 5.98 (brs, 1H), 5.88 (d, J = 1.0 Hz, 1H), 3.20 – 3.07 (m, 1H), 3.01 – 2.90 (m, 1H), 2.27 – 2.24 (m, 1H), 1.80 – 1.72 (m, 2H), 1.71 – 1.65 (m, 1H), 1.62 – 1.50 (m, 3H), 1.48 – 1.42 (m, 1H), 1.38 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 174.6, 153.9, 140.4, 131.3, 128.1, 127.8, 97.8, 93.6, 80.0, 41.9, 40.5, 34.7, 28.3, 22.9, 22.7, 19.9, 15.8; IR (thin film) 3329, 2974, 2935, 2865, 2212, 1704, 1639, 1529, 1454, 1367, 1285; HRMS(ESI) m/z calcd. for $C_{22}H_{29}NO_4Na$ $(M+Na)^+$ 394.1994, observed 394.1984; m.p: 88 – 93 °C.



2.74h

Tetrahydrofuran 2.74h: Compound **2.74h** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **2.69a** (0.0640 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allene **2.73h** (0.0847 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:1; EtOAc:hexane; R_f of **2.69a** and **2.74h** = 0.75 & 0.10). Chromatography (1:2; EtOAc:hexane) afforded **2.74h** as a white solid (0.0776 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (brs, 1H), 5.25 (s, 1H), 3.64 (s, 3H), 3.13 (s, 3H), 3.01 – 2.92 (m, 1H), 2.84 – 2.77 (m, 1H), 2.18 – 2.15 (m, 1H), 1.72 – 1.65 (m, 2H), 1.63 – 1.41 (m, 4H), 1.38 (s, 9H), 1.34 – 1.27 (m, 1H), 1.19 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 167.3, 153.8, 96.5, 86.0, 79.8, 61.1, 42.3, 40.1, 34.5, 32.5, 28.3, 23.2, 22.7, 20.0, 16.1; IR

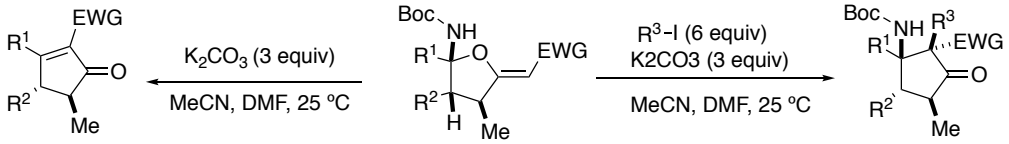
(thin film) 3328, 2980, 2859, 2160, 1736, 1706, 1641, 1519, 1436, 1365, 1246; HRMS(ESI) m/z calcd. for $C_{18}H_{30}N_2O_5Na$ $(M+Na)^+$ 377.2052, observed 377.2045; m.p: 123 – 125 °C.



2.74i

Tetrahydrofuran 2.74i: Compound **2.74i** was prepared using general procedure **C** with the following reagents: *N*-hydroxyenamine **2.69a** (0.0640 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **2.73i** (0.0474 g, 0.600 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.69a** and **2.74i** = 0.25 & 0.15). Chromatography (1:6; EtOAc:hexane) afforded **2.74i** as a white solid (0.0421 g, 48%, dr = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11 (brs, 1H), 4.16 (d, J = 1.0 Hz, 1H), 3.05 – 2.91 (m, 1H), 2.88 – 2.75 (m, 1H), 2.08 – 2.05 (m, 1H), 1.75 – 1.64 (m, 3H), 1.61 – 1.51 (m, 2H), 1.44 (s, 9H), 1.38 – 1.24 (m, 2H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 153.6, 116.9, 96.8, 80.9, 65.2, 43.3, 39.1, 34.8, 28.3, 22.7, 22.5, 19.8, 15.1; IR (thin film) 3283, 3074, 2936, 2868, 1655, 1558, 1455, 1417, 1318, 1270; HRMS(ESI) m/z calcd. for $C_{16}H_{24}N_2O_3Na$ $(M+Na)^+$ 315.1685, observed 315.1681; m.p: 140 – 143 °C.

2.4.4 Aza-Petasis-Ferrier Rearrangements of 2.72 and 2.74

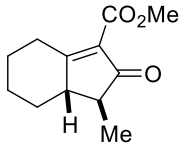


2.75 **2.72/2.74** **2.76**

General Procedure D: A scintillation vial was charged with tetrahydrofuran **2.72** or **2.74** (1.0 equiv), an alkyl halide (6.0 equiv), 18-crown-6 (3.0 equiv), and K_2CO_3 (3.0 equiv). These reagents were diluted with MeCN to form a 0.1 M solution of **2.72** or **1.74** and DMF (0.2 mL) was added. The vial was then sealed with a cap and stirred at 25 °C. Reaction progress was monitored by TLC for the disappearance of **2.72**. Once **2.72** had been consumed, the reaction mixture was filtered through celite, and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (1:15 – 1:3; EtOAc:hexane) to afford β-amino acid derivative **2.76**.

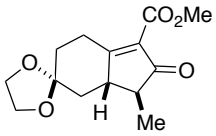
General Procedure E: A scintillation vial was charged with tetrahydrofuran **2.72** or **2.74** (1.0 equiv) and K_2CO_3 (3.0 equiv). These reagents were diluted with MeCN to form a 0.1 M solution

of **2.72** and DMF (0.2 mL) was added via pipet. The vial was then sealed with a Teflon cap and stirred at 25 °C. Reaction progress was monitored by TLC for the disappearance of **2.72**. Once **2.72** had been consumed, the reaction mixture was filtered through celite, and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (1:15 – 1:3; EtOAc:hexane) to afford cyclopentenone **2.75**.



2.75a

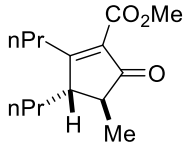
Cyclopentenone derivative 2.75a: Compound **2.75a** was synthesized using general procedure **E** with the following reagents: tetrahydrofuran **2.72a** (0.0980 g, 0.301 mmol), 18-crown-6 (0.239 g, 0.903 mmol), K_2CO_3 (0.125 g, 0.903 mmol), MeCN (3.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane, *Rf* of **2.72a** and **2.75a** = 0.10 & 0.20). Chromatography (1:6; EtOAc:hexane) afforded **2.75a** as a colorless oil (0.0401 g, 64%, d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.55 – 3.52 (m, 1H), 2.29 – 2.16 (m, 3H), 2.04 – 2.00 (m, 2H), 1.88 – 1.86 (m, 1H), 1.54 – 1.44 (m, 2H), 1.24 – 1.20 (m, 1H), 1.17 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 188.2, 163.8, 128.3, 51.7, 49.7, 47.7, 33.9, 29.8, 26.6, 25.0, 14.8; IR (thin film) 3381, 3055, 2936, 1748, 1713, 1495, 1448, 1366, 1264, 1159; HRMS(ESI) m/z calcd. for $C_{12}H_{16}O_3Na$ $(M+Na)^+$ 231.0997, observed 231.0995.



2.75b

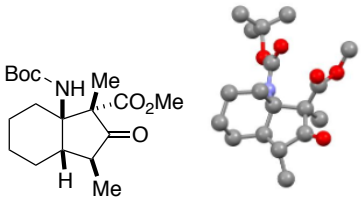
Cyclopentenone 2.75b: Compound **2.75b** was synthesized using general procedure **E** with the following reagents: tetrahydrofuran **2.72k** (0.115 g, 0.300 mmol), 18-crown-6 (0.238 g, 0.900 mmol), K_2CO_3 (0.124 g, 0.900 mmol), MeCN (3.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored on TLC (TLC eluent = 1:2; EtOAc:hexane, R*f* of **2.72k** and **2.75b** = 0.25 & 0.50). Chromatography (1:8; EtOAc:hexane) afforded **2.75b** as a colorless oil (0.0423 g, 53%, d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.10 – 4.01 (m, 4H), 3.83 (s, 3H), 3.56 – 3.54 (m, 1H), 2.64 – 2.56 (m, 2H), 2.26 – 2.23 (m, 1H), 2.03 – 1.99 (m, 2H), 1.75 – 1.70 (m, 1H), 1.51 – 1.41 (m, 1H), 1.18 (d, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 204.3, 185.2, 163.5, 129.0, 107.3, 64.7, 51.8, 47.6, 46.8, 40.8, 33.6, 26.3, 14.4; IR (thin film) 3108, 3025, 2993, 2864, 1713, 1706, 1625, 1494, 1463, 1447; HRMS(ESI) m/z calcd. for

$C_{14}H_{18}O_5Na$ $(M+Na)^+$ 289.1052, observed 289.1052.



2.75c

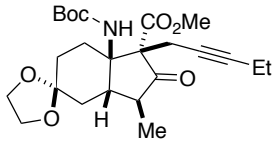
Cyclopentenone derivative 2.75c: Compound **2.75c** was synthesized using general procedure **E** with the following reagents: tetrahydrofuran **2.72m** (0.0735 g, 0.207 mmol), 18-crown-6 (0.164 g, 0.621 mmol), K_2CO_3 (0.0858 g, 0.621 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored on TLC (TLC eluent = 1:4; EtOAc:hexane, *Rf* of **2.72m** and **2.75c** = 0.50 & 0.60). Chromatography (1:10; EtOAc:hexane) afforded **2.75c** as a yellow oil (0.0272 g, 55%, d.r. = 15:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 3.81 (s, 3H), 2.97 – 2.92 (m, 1H), 2.46 – 2.41 (m, 2H), 2.12 (q, J = 7.5 Hz, 1H, 1.79 – 1.73 (m, 1H), 1.64 – 1.58 (m, 1H), 1.53 – 1.46 (m, 1H), 1.41 – 1.34 (m, 2H), 1.32 – 1.23 (m, 1H), 1.17 (d, J =7.5 Hz, 3H), 1.01 – 0.93 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 205.6, 189.2, 164.1, 131.1, 51.8, 50.0, 46.6, 34.6, 31.7, 21.2, 20.5, 16.9,14.2, 14.1, ^{1}HNMR (500 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 3.66 (s, 3H), 2.46 – 2.41 (m, 1H),1.13 (d, J = 7.0 Hz, 3H), 0.90 – 0.88 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 188.9, 45.0, 32.2, 30.3, 29.6, 20.7, 10.9; IR (thin film) 3379, 2971, 2932, 2857, 1745, 1705, 1668, 1596, 1579, 1499; HRMS(ESI) m/z calcd. for $C_{14}H_{22}O_3Na$ $(M+Na)^+$ 261.1461, observed 261.1466.



2.76a

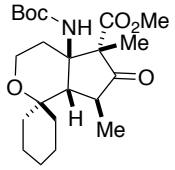
β-Amino acid derivative 2.76a: Compound **2.76a** was synthesized using general procedure **D** with the following reagents: tetrahydrofuran **2.72a** (0.0650 g, 0.200 mmol), MeI (0.170 g, 1.20 mmol), 18-crown-6 (0.159 g, 0.600 mmol), K_2CO_3 (0.0828 g, 0.600 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored on TLC (TLC eluent = 1:4; EtOAc:hexane, *Rf* of **2.76a** = 0.25). Chromatography (1:10; EtOAc:hexane) afforded **2.76a** as a white solid (0.0584 g, 86%.d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.45 (brs, 1H), 3.66 (s, 3H), 2.68 – 2.55 (m, 1H), 2.52 – 2.48 (m, 1H), 1.84 – 1.77 (m, 1H), 1.73 – 1.70 (m, 2H), 1.62 – 1.47 (m, 4H), 1.40 (s, 9H), 1.33 – 1.30 (m, 1H), 1.26 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.0, 171.3, 154.5, 79.2, 65.6, 62.0, 51.9, 43.1, 42.1, 30.0, 28.2,

21.8, 21.5, 19.1, 17.2, 13.4; IR (thin film) 3055, 2933, 2862, 1719, 1499, 1453, 1366, 1264, 1161, 1102; HRMS(ESI) m/z calcd. for $C_{18}H_{29}NO_5Na$ $(M+Na)^+$ 362.1943, observed 362.1933; m.p: 142 – 144 °C.



2.76b

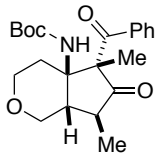
β-Amino acid derivative 2.76b: Compound **2.76b** was synthesized using general procedure **E** with the following reagents: tetrahydrofuran **2.72k** (0.115 g, 0.300 mmol), 18-crown-6 (0.238 g, 0.900 mmol), K_2CO_3 (0.124 g, 0.900 mmol), 1-bromo-2-pentyne (0.184 mL, 1.80 mmol), MeCN (3.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored by TLC (TLC eluent = 1:2; EtOAc:hexane, *Rf* of **2.72k** and **2.76b** = 0.25 & 0.50). Chromatography (1:8; EtOAc:hexane) afforded **2.76b** as a colorless oil (0.0701 g, 51%, d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.71 (brs, 1H), 3.93 – 3.88 (m, 4H), 3.67 (s, 3H), 3.03 – 2.97 (m, 1H), 2.81 – 2.66 (m, 2H), 2.60 – 2.54 (m, 1H), 2.42 – 2.40 (m, 1H), 2.10 – 1.97 (m, 4H). 1.81 – 1.75 (m, 2H), 1.62 – 1.59 (m, 1H), 1.43 (s, 9H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl^3$): δ 212.6, 170.4, 154.5, 107.5, 84.5, 75.5, 67.0, 64.6, 63.8, 61.7, 59.7, 52.2, 46.3, 44.9, 30.3, 30.1, 28.2, 26.6, 22.2, 13.8, 12.3, 11.7; IR (thin film) 3307, 3216, 3135, 2989, 2863, 2107, 1729, 1707, 1698, 1652; HRMS(ESI) m/z calcd. for $C_{24}H_{35}NO_7Na(M+Na)^+$ 472.2311, observed 472.2311.



2.76c

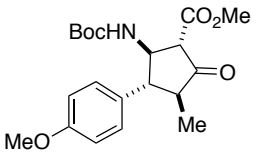
β-Amino acid derivative 2.76c: Compound **2.76c** was synthesized using general procedure D with the following reagents: tetrahydrofuran **2.72e** (0.0791 g, 0.200 mmol), MeI (0.170 g, 1.20 mmol), 18-crown-6 (0.159 g, 0.600 mmol), K_2CO_3 (0.0828 g, 0.600 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C and monitored by TLC (TLC eluent = 1:2; EtOAc:hexane, *Rf* of **2.72e** and **2.76c** = 0.25 & 0.6). Chromatography (1:8; EtOAc:hexane) afforded **2.76c** as a colorless oil (0.0609 g, 75%, d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 (br, 1H), 3.75 – 3.72 (m, 1H), 3.68 (s, 3H), 3.59 – 3.57 (m, 1H), 2.60 – 2.52 (m, 2H), 1.80 – 1.75 (m, 1H), 1.64 – 1.58 (m, 3H), 1.50 – 1.45 (m, 3H), 1.40 (s, 9H), 1.35 – 1.28 (m, 8H), 1.22 – 1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.9, 170.4, 154.6, 79.7, 73.0, 66.4, 61.0, 56.1,

52.0, 42.3, 37.6, 31.5, 28.2, 28.0, 25.5, 21.5, 21.3, 20.3, 17.1; IR (thin film) 3054, 2980, 2937, 1749, 1716, 1495, 1455, 1366, 1264, 1159; HRMS(ESI) m/z calcd. for $C_{22}H_{35}NO_6Na$ $(M+Na)^+$ 432.2362, observed 432.2362.



2.76d

β-Amino acid derivative 2.76d: Compound **2.76d** was synthesized using general procedure **D** with the following reagents: tetrahydrofuran **2.72d** (0.0747 g, 0.200 mmol), MeI (0.170 g, 1.20 mmol), 18-crown-6 (0.159 g, 0.600 mmol), K_2CO_3 (0.0828 g, 0.600 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane, *Rf* of **2.72d** and **2.76d** = 0.10 & 0.25). Chromatography (1:6; EtOAc:hexanes) afforded **2.76d** as a colorless oil (0.0387 g, 50%, d.r. = ≥20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.47 (m, 1H), 7.40 – 7.37 (m, 2H), 4.79 (brs, 1H), 3.89 (dd, *J* = 30.5 Hz, 12.5 Hz, 2H), 3.81 – 3.78 (m, 1H), 3.63 (t, *J* = 12.0 Hz, 1H), 3.00 – 2.91 (m, 2H), 2.05 – 1.99 (m, 1H), 1.55 – 1.52 (m, 1H), 1.47 – 1.40 (m, 12H), 1.22 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.8, 202.7, 155.0, 138.5, 131.9, 128.6, 128.0, 79.8, 70.5, 63.9, 63.9, 60.9, 43.5, 41.5, 33.1, 28.3, 19.9, 13.4; IR (thin film) 3358, 3286, 2972, 2931, 2861, 1741, 1709, 1690, 1643, 1512; HRMS(ESI) m/z calcd. for $C_{22}H_{29}NO_5Na$ $(M+Na)^+$ 410.1943, observed 410.1933.

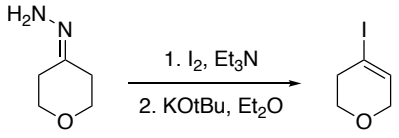


2.76e

β-Amino acid derivative 2.76x: Compound **2.76e** was prepared using general procedure **E** with the following reagents: *N*-hydroxyenamine **2.72q** (0.0796 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **2.63** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4; EtOAc:hexane; R_f of **2.72q** and **2.76e** = 0.25 & 0.20). Chromatography (1:6; EtOAc:hexane) afforded **2.76e** as a white solid (0.0476 g, 42%, d.r. = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.20 – 7.28 (d, *J* = 8.5 Hz, 2H), 6.91 – 6.90 (m, 2H), 4.72 (brs, *J* = 6.0 Hz, 1H), 4.38 – 4.24 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 – 3.65 (m, 1H), 3.01 – 2.95 (m, 1H), 2.51 – 2.49 (m, 1H), 1.25 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (major diastereomer): δ 208.0, 168.9,

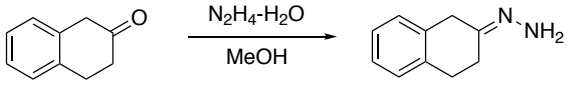
159.1, 155.0, 129.9, 128.7, 114.3, 79.8, 60.0, 57.7, 55.3, 54.1, 52.7, 51.5, 28.2, 11.7; ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 7.20 – 7.28 (d, *J* = 8.5 Hz, 2H), 6.91 – 6.90 (m, 2H), 4.99 (brd, *J* = 6.0 Hz, 1H), 4.60 – 4.55 (m, 1H), 3.96 – 3.89 (m, 1H), 3.12 – 3.07 (m, 1H), 2.44 – 2.39 (m, 1H), 1.31 (s, 9H), 1.07 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (minor diastereomer, diagnostic peaks): δ 209.1, 168.8, 159.0, 129.8, 128.6, 114.3, 79.9, 57.4, 54.0, 52.5, 51.8, 12.1; IR (thin film) 3251, 3012, 2896, 2756, 1708, 1701, 1632, 1603, 1587, 1503; HRMS(ESI) m/z calcd. for $C_{21}H_{27}NO_5Na$ $(M+Na)^+$ 396.1787, observed 396.1779; m.p: 93 – 95 °C.

2.4.5 Preparation of Vinyl Iodides

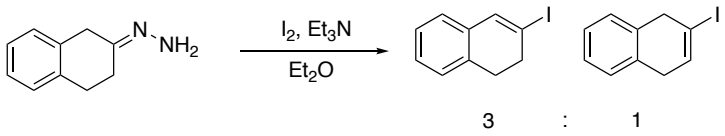


86%

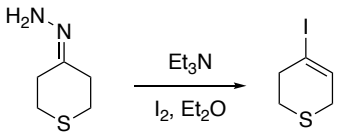
Preparation of 4-pyran vinyl iodide: The previously prepared[98] (tetrahydro-4*H*-pyran-4-ylidene)hydrazine (11.415 g, 100.0 mmol, 1.0 equiv) was dissolved in Et_2O (250.0 mL) and Et_3N (139.4 mL, 1000.0 mmol, 10.0 equiv) was added in one portion. This mixture was stirred at room temperature and a solution of I_2 (45.7 g, 180.0 mmol, 1.8 equiv) in Et_2O (200.0 mL) was added dropwise over 30 min and stirred 1 h at room temperature. The reaction was quenched by the addition of sat. $NaS_2O_{3(aq)}$ (100.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed well with sat. $NH_4Cl_{(aq)}$ to remove all the Et_3N salts and dried over Na_2SO_4 and concentrated to yield a crude sample which was redissolved in Et_2O (200.0 mL) and placed in an ice bath. While vigorously stirring, solid KOtBu (22.4 g, 200.0 mmol, 2.0 equiv) was added in one portion. The dark brown reaction mixture was then allowed to warm to room temperature over 1 h. The reaction was quenched with H_2O (100 mL), extracted with Et_2O (3 x 100 mL), and dried over Na_2SO_4. Concentration under vacuum yield the pure vinyl iodide as a light brown oil (18.1g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 – 6.32 (m, 1H), 4.12 – 4.11 (m, 2H), 3.78 – 3.76 (m, 2H), 2.57 – 2.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 90.5, 67.9, 65.8, 38.8; IR (thin film) 2920, 2846, 1735, 1435, 1391, 1276, 1133, 1096; The data match those reported previously.



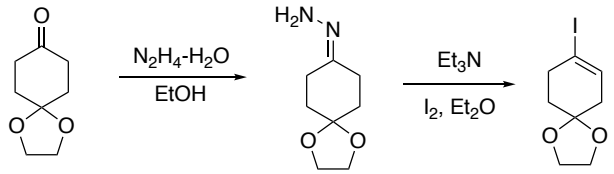
General Procedure: A flame dried 250-mL round bottom flask was charged with β-tetralone (10.0 g, 68.4 mmol, 1.0 equiv) and diluted with methanol (140 mL). Hydrazine hydrate (20.0 mL, 410.4 mmol, 6.0 equiv) was added dropwise over 10 min then refluxed at 65 °C for 2 h. The reaction as cooled to room temperature and the methanol was removed under vacuum. Dichloromethane (100.0 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50.0 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent afforded (3,4-dihydronaphthalen-2(1*H*)-ylidene)hydrazine as a clear oil (10.9 g, >95%) which was used without further purification.



The previously prepared hydrazine was dissolved in Et_2O (200.0 mL) and Et_3N (95.4 mL, 684.0 mmol, 10.0 equiv) was added in one portion. This mixture was stirred at room temperature and a solution of I_2 (31.2 g, 123.1 mmol, 1.8 equiv) in Et_2O (200.0 mL) was added dropwise over 30 min and stirred 1h at root temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$(aq) (100.0 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield a crude sample which was purified by column chromatography (hexane) to yield an inseparable mixture of regioisomeric (3:1) vinyl iodides as a yellow oil (15.7 g, 90%). This mixture was used in the subsequent reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) (3-iodo-1,2-dihydronaphthalene): δ 7.26 – 7.18 (m, 3H), 7.14 – 7.11 (m, 1H), 7.01 – 6.95 (m, 1H), 2.95 – 2.90 (m, 2H), 2.89 – 2.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 134.9, 134.7, 133.3, 127.6, 126.7, 125.4, 97.2, 37.9, 29.6; ^{1}H NMR (500 MHz, $CDCl_3$) (2-iodo-1,4-dihydronaphthalene): δ 7.26 – 7.18 (m, 3H), 7.06 – 7.01 (m, 1H), 6.60 – 6.56 (m, 1H), 3.90 – 3.85 (m, 2H), 3.53 – 3.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.0, 131.5, 128.5, 127.7, 127.5, 126.6, 126.4, 92.6, 43.1, 33.5; IR (thin film) 2945, 2930, 2872, 2715, 1605, 1571, 1501, 1491, 1151 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{10}H_9I$ (M)+ 255.9749, found 255.9760.



Preparation of 4-Thiopyran vinyl iodide: Previously prepared[97] (tetrahydro-4*H*-thiopyran-4-ylidene)hydrazine (6.5 g, 50.0 mmol, 1.0 equiv) was dissolved in Et_2O (150.0 mL) and Et_3N (69.7 mL, 500.0 mmol, 10.0 equiv) was added in one portion. This mixture was stirred at room temperature and a solution of I_2 (22.9 g, 90.0 mmol, 1.8 equiv) in Et_2O (100.0 mL) was added dropwise over 30 min and stirred 1 h at room temperature. The reaction was quenched by the addition of sat. $NaS_2O_{3(aq)}$ (75.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed well with sat. $NH_4Cl_{(aq)}$ to remove all the Et_3N salts and dried over Na_2SO_4 and concentrated to yield a crude sample which was redissolved in Et_2O (200.0 mL) and 1,1,3,3-Tetramethylguanidine (10.0 mL, 79.7 mmol, 1.6 equiv) was added in one portion. The mixture was refluxed at 80 °C over 2 h, cooled to room temperature, and quenched with sat. $NH_4Cl_{(aq)}$ (50.0 mL). The crude reaction mixture was diluted with Et_2O (100.0 mL) and the aqueous layer was extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with sat. $NH_4Cl_{(aq)}$, water, brine, and dried over $MgSO_4$. Purification on SiO_2 (hexane) afforded the pure vinyl iodide as a light yellow oil (11.3, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 – 6.49 (m, 1H), 3.16 – 3.09 (m, 2H), 2.76 – 2.72 (m, 2H), 2.71 – 2.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.7, 98.0, 39.7, 28.9, 27.4; IR (thin film) 2967, 2812, 1605, 1421, 1381, 1361, 1112, 1087, 973; HRMS(ESI) m/z calcd. for C_5H_7SI $(M)^+$ 225.9313, observed 225.9321.



General Procedure: A flame dried 250-mL round bottom flask was charged with 1,4-Cyclohexanedione monoethylene acetal (15.6 g, 100.0 mmol, 1.0 equiv) and diluted with methanol (100 mL). Hydrazine hydrate (7.60 mL, 156.0 mmol, 10.0 equiv) was added dropwise over 10 min then stirred at room temperature for 18 h. The methanol was removed under vacuum. Dichloromethane (150.0 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50.0 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent afforded (1,4-dioxaspiro[4.5]decan-8-ylidene)hydrazine as a clear oil (16.5 g, >95%) which was used without further purification.

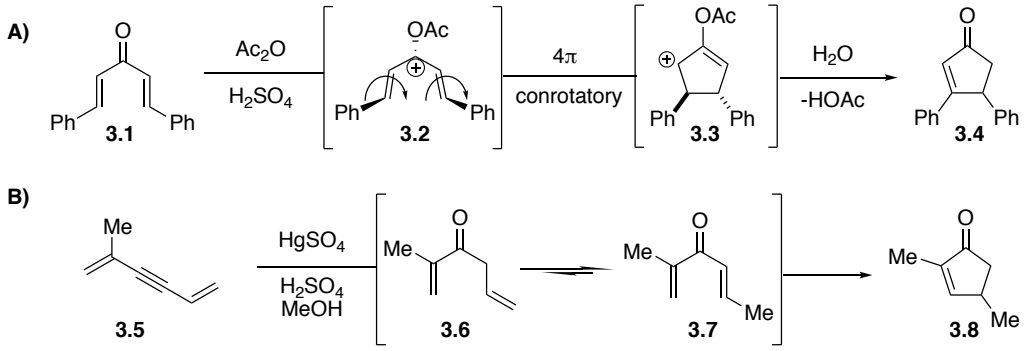
The previously prepared hydrazone (16.5 g, 96.9 mmol, 1.0 equiv) was dissolved in Et_2O (200.0 mL) and Et_3N (135.1 mL, 969.0 mmol, 10.0 equiv) was added in one portion. This mixture was stirred at room temperature and a solution of I_2 (44.3 g, 174.4 mmol, 1.8 equiv) in Et_2O (100.0

mL) was added dropwise over 30 min and stirred 1 h at room temperature. The reaction was quenched by the addition of sat. $NaS_2O_{3(aq)}$ (100.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed well with sat. $NH_4Cl_{(aq)}$ to remove all the Et_3N salts and dried over Na_2SO_4 and concentrated to yield a crude sample which was redissolved in Et_2O (200.0 mL) and placed in an ice bath. While vigorously stirring, solid KOtBu (21.7 g, 193.8 mmol, 2.0 equiv) was added in one portion. The dark brown reaction mixture was then allowed to warm to room temperature over 1 h. The reaction was quenched with H_2O (100 mL), extracted with Et_2O (3 x 100 mL), and dried over Na_2SO_4. Concentration under vacuum yielded pure vinyl iodide as a clear oil (17.0 g, 66%). The spectra matched previously reported values[99]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 – 6.18, m, 1H), 3.99 (s, 4H), 2.76 – 2.69 (m, 2H), 2.35 – 2.30 (m, 2H), 1.85 – 1.80 (m, 2H).

Chapter 3: Towards the Asymmetric 4π-Electrocyclization of *N*-Vinylnitrones

3.1 Introduction

The 4π-electrocyclization of dienyl cations dates back to the early 20th century when Prof. David Vorlander unknowingly performed the first of these transformations (Scheme 3.1A). A mixture of dibenzylideneacetone **3.1**, Ac_2O, and H_2SO_4 resulted in the formation of a new product, which was later identified as cyclopentanone **3.4**.[100] The *trans*/*trans* relationship of the two alkenes in **3.1** resulted in a *trans* relationship of the two phenyl substituents because of the conrotatory motion during cyclization. More famously, Igor Nazarov discovered during his investigations into the mercury salt and acid-catalyzed hydration of 1,2-divinylacetylene **3.5**, the spontaneous formation of a new product identified as cyclopentenone **3.8** (Scheme 3.1B).[101] This cyclization was postulated to proceed through first hydration to form allyl vinylketone **3.6**, followed by tautomerization to divinylketone **3.7**. Acid then triggers a 4π-electrocyclization to afford the cyclopentenone **3.8**. The driving force of these formations is the thermodynamic favorability to form cyclic conjugated ketone instead of acyclic divinyl substrates.

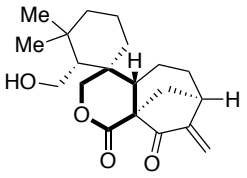


Scheme 3.1 Discovery of Nazarov cyclization by Vorlander and Nazarov

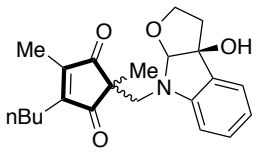
A variety of Nazarov cyclizations have been developed in recent years utilizing Lewis acid, Brønsted acid, transition metal, and tertiary amine catalysis. Asymmetric variants of this transformation have gained increasing attention because of the potential to access stereodefined cyclic ketones in a single step from divinylketone intermediates such as **3.7**; however the analogous transformation of a nitrogen-containing divinyl system known as the aza-Nazarov is less established. Our previous report of the 4π-electrocyclization of *N*-vinylnitrones led to the proposal that we might be able to access stereodefined unsaturated azetidine *N*-oxides through asymmetric catalysis and further functionalization of these enantioenriched heterocycles would give diastereoselective products. Herein, examples of both Nazarov and aza-Nazarov cyclizations will be discussed to highlight their importance as well as some limitations associated with these methods in hopes of translating them to our system.

3.1.1 Nazarov Cyclization Characteristics and Asymmetric Developments

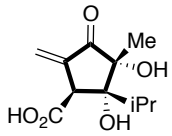
Nazarov-type cyclizations have gained attention in recent years from the groups of Frontier[102], Tius[103], Thomson[104], Denmark[105], Aggarwal[106], and Shindo[107] (Scheme 3.2). These groups have taken advantage of the efficient reactivity and facial selectivity of Nazarov cyclizations to access natural products with high levels of diastereoselectivity.



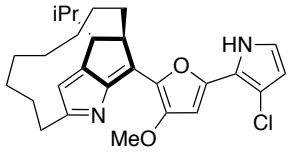
3.9 (±)-sculponeatin N
Thomson, 2014



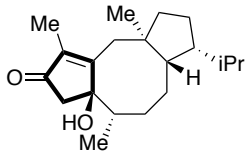
3.10 madindoline A/B
Tius, 2007



3.11 (±)-xanthocidin
Shindo, 2010



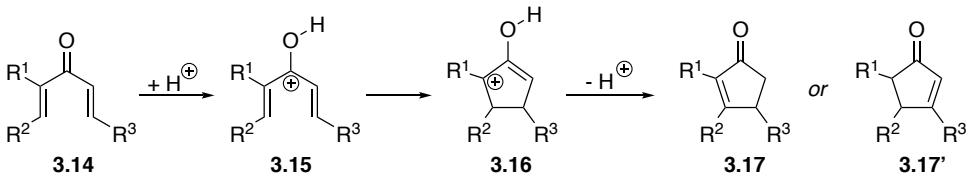
3.12 (+)-roseophilin
Flynn, 2012



3.13 (+)-fusicoauritone
Williams, 2007

Scheme 3.2 Natural products recently accessed using Nazarov cyclization

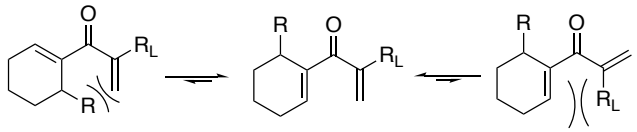
The Nazarov cyclization proceeds through generation of pentadienyl cation **3.15** via protonation of divinyl ketone **3.14** (Scheme 3.3). Ketones **3.14** can contain either cyclic or acyclic alkenes substituted with a variety of functional groups. These alkenes can be mono, di, tri, or in some cases, tetra-substituted. The alkenes of the dienylketone can also be replaced with allenes or arenes. Cyclization of **3.15** affords oxyallyl cation **3.16**, which is then deprotonated to give either **3.17** or **3.17'**. This elimination can be problematic in some cases in which competition between the two sites of deprotonation sites leads to a mixture of products. Further challenges can occur if the resulting pentadienyl cation **3.15** is stabilized or if the two vinyl moieties cannot come into proximity to allow cyclization. A variety of strategies have been demonstrated to circumvent these issues and will be discussed in further detail.



3.14 **3.15** **3.16** **3.17** **3.17'**

Scheme 3.3 General mechanism of Nazarov cyclization

In order for the Nazarov cyclization to occur, the two vinyl moieties must be free to rotate into close proximity. It is known that divinyl ketones with small or no substituent at the α-position are sluggish in the Nazarov cyclization. This can be attributed to the most stable isomer being populated by *s-cis*/*s*-t*rans*-configuration **3.19** instead of *s-trans*/*s*-t*rans*-configuration **3.20** (Scheme 3.4). By placing a substituent at the α-position, steric interactions force the two alkenes toward a more favorable orientation for cyclization in **3.20** and lower the energy required for bond rotation to the more favorable orientation for cyclization. A successful strategy to favor the *s-trans* conformation is to utilize larger substituents at the α-position to accelerate the rate of cyclization or to use cyclic unsaturated ketones, which can only exist as the *s-trans* isomer. Changing the electronics of these positions also can accelerate the rate of cyclization by stabilizing the ground state and transition state of this transformation.

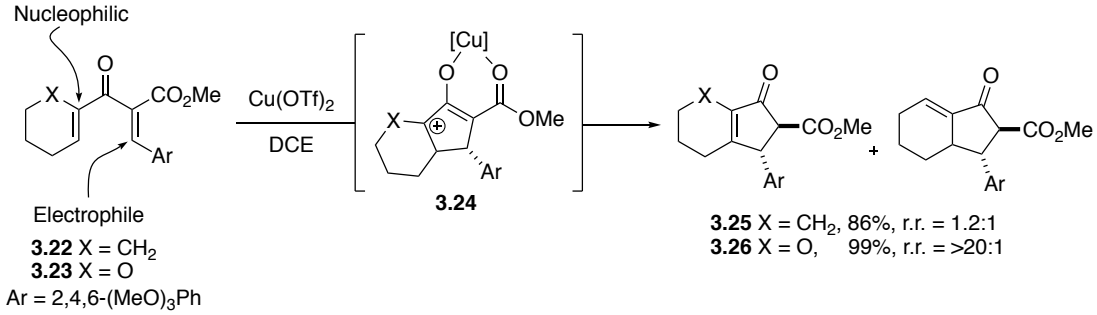


Scheme 3.4 Steric conformational preference for divinyl ketones

One limitation of the Nazarov reaction can be identified by the substitution pattern of the divinyl ketone. Electron-donating substituent at the α-position of pentadienyl ketone systems have been shown to stabilize the oxyallyl cation intermediate to favor the formation of a new C–C bond. Frontier and coworkers popularized this stabilization by utilizing polarized divinyl ketone **3.23** to favor the formation of oxyallyl cation **3.24** in the presence of a copper Lewis acid catalyst (Scheme 3.5).[102] With this this polarization, a number of electron-rich aryl rings at the acrylate β-position were

shown to favor cyclization. With regard to the nucleophilic alkene, their scope was limited to dihydropyran-containing substrates and they were limited to acrylates as the electrophilic alkene in their polarized system. Even more satisfying, the elimination step was shown to be completely selective with their polarized substrate to give **3.26** in stark contrast to their analogous methylene substrate **3.25**. This proof of principle was highly impactful for their future asymmetric endeavors and proved that polarization paired with two-point binding could give highly selective catalytic Nazarov reaction. The same stabilization effect used by Frontier can also be achieved using β-directing groups, which have been shown to accelerate the Nazarov cyclization to selectively give cyclopentenones.

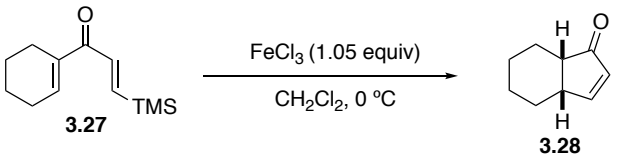
3.1.2 Examples of Catalytic Nazarov Reactions



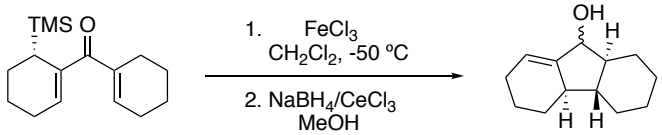
Scheme 3.5 Polarized Nazarov 5-atom-4π-electrocyclization

Denmark and coworkers reported that divinyl ketone **3.27** with a β-silyl substituent also has the ability to accelerate the rate of cyclization through inductive stabilization via the β-silicon effect.[105] This substituent effect allowed the selective formation of cyclopentenones such as **3.28** in high yield from unactivated divinyl ketones (Scheme 3.6). This strategy also allowed for highly regioselective elimination to form the kinetic unsaturated ketone as the only product. Later work by the Denmark group showed excellent substrate control by utilizing chiral silicon-containing stereocenters on

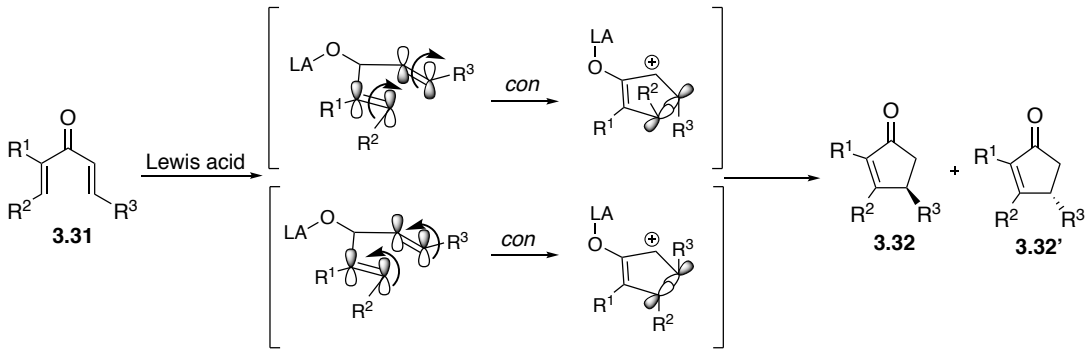
divinyl ketone **3.29** to transfer chirality while also directing the elimination to afford enantioenriched cyclopentenone **3.30** (Scheme 3.7).[110] The chiral center was proposed to direct torquoselective conrotatory rotation of **3.31** by favoring one direction of conrotatory rotation over the other to form either **3.32** or **3.32'** (Scheme 3.8). Using this concept, a number of other groups have investigated substrate-controlled torquoselectivity using Lewis acid promoters.



Scheme 3.6 Traceless silicon directing group for Nazarov cyclization[105]



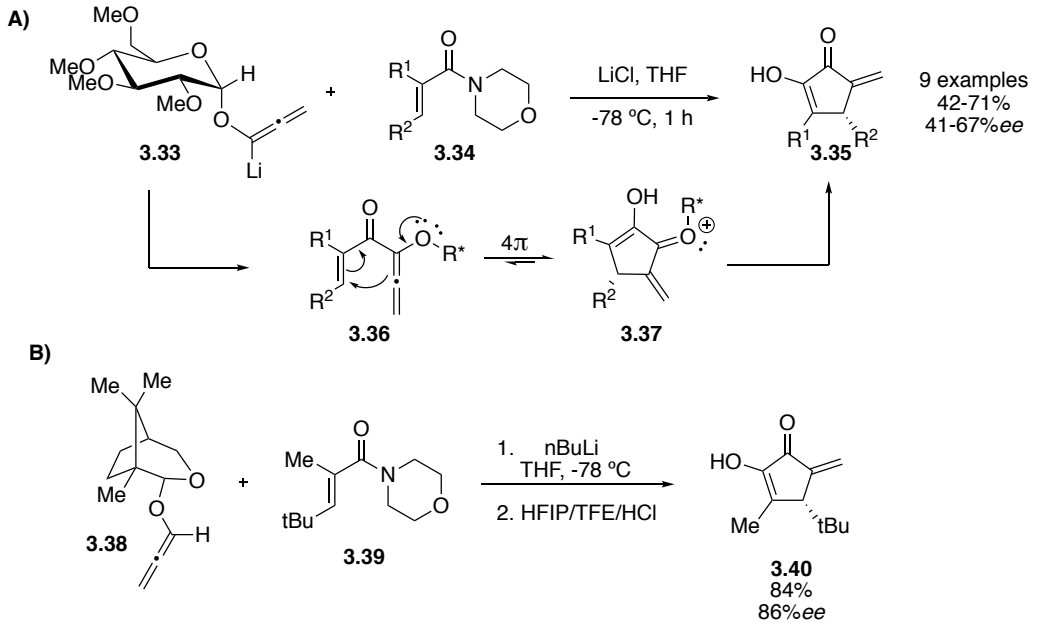
Scheme 3.7 Stereospecific Nazarov using enantioenriched silyl directing group[110]



Scheme 3.8 General torquoselectivity of conrotatory motion

Tius initially demonstrated substrate-controlled torquoselectivity in the Nazarov reaction through the addition of lithiated **3.33** to **3.34**, generating reactive allenyl vinylketone **3.36** which was shown to favor cyclization directed by the chiral sugar

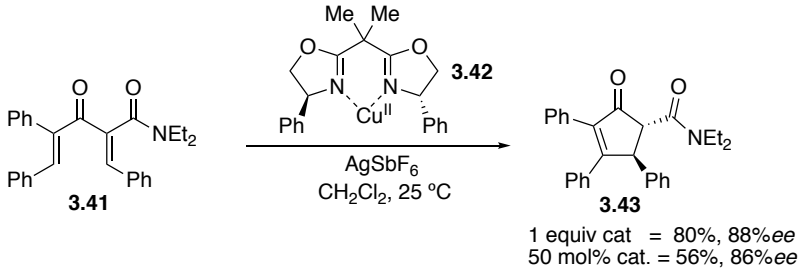
(Scheme 3.9A).[111] The chiral sugar of this intermediate was shown to control the facial selectivity of conrotatory cyclization to afford **3.37**. After loss of the sugar auxiliary, cyclopentenone **3.35** was obtained with moderate levels of enantioselectivity, but suffered from low yields and lack of scalability. The authors improved on these limitations by utilizing the addition of lithiated allene **3.38** derived from camphor auxiliaries to enamide **3.39** (Scheme 3.9B).[112] The resulting divinyl species then underwent torquoselective Nazarov cyclization to forge cyclopentenone **3.40** with enantiomeric excess of 73%. While this showed that substrate-control of cyclization was possible, a more general approach would be needed to be applicable to a broad scope for this transformation. The most efficient and general method to achieve an asymmetric Nazarov cyclizations is through the use of chiral Lewis acid catalysis.



Scheme 3.9 Torquoselectivity using chiral auxiliaries – Tius, 2000 & 2002[111, 112]

Aggarwal and coworkers first reported chiral Lewis acid catalysis for asymmetric 5-atom-4π-electrocyclization in 2003 using chiral copper/bis-oxazoline complex **3.42** (Scheme 3.10).[113] Their report utilized two-point binding of β-ketoamide divinyl ketone

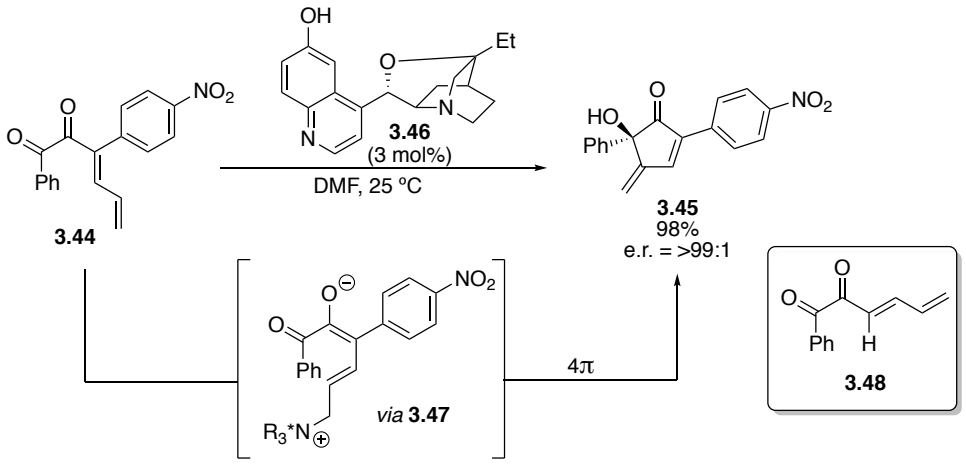
3.41, which can selectively coordinate to the chiral metal center enforcing the required *s-trans* conformation. Due to the C2-symmetry at the metal center, conrotatory motion favors the direction that avoids steric clash with the phenyl substituents to form **3.43** with high levels of stereoselectivity. The use of stoichiometric **3.42** to mediate the transformation shown in Scheme 3.10 gave the desired product in high yield; however catalytic amounts of the catalyst complex resulted in diminished yield with retention of enantioselectivity. This control of torquoselectivity was a major advancement on previous methods as it allowed a broad range of substrates to participate in the Nazarov cyclization to form enantioenriched cyclopentenones; however a truly catalytic method was still desired.



Scheme 3.10 First catalytic asymmetric 4π-electrocyclization using a chiral Lewis acid[113]

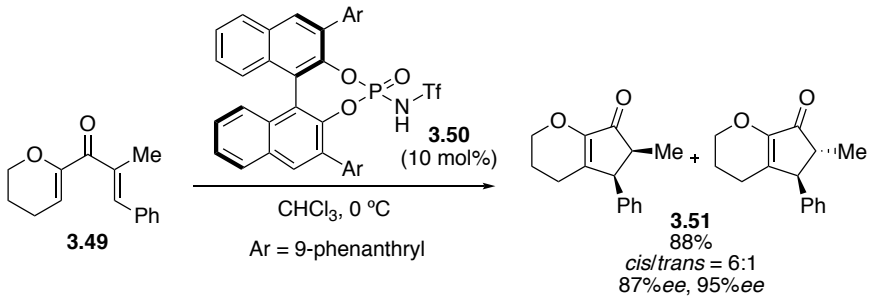
The use of chiral amine catalysts for the Nazarov cyclization was reported in 2015 by Frontier (Scheme 3.11).[114] Using unactivated unsaturated 1,2-dione **3.44**, cinchona alkaloid **3.46** could be used to access ammonium enolate **3.47**, which then was shown to readily participate in 5-atom-4π-electrocyclization to afford enantiodefined 5-hydroxy γ-methylene cyclopentenone **3.45** with excellent enantioselectivity. This method relied on inherent substrate preference for forming the *s-trans* configuration of the divinyl ketone, which presented limitations in substrate design. The substituents at the α-position had to be large enough to perturb the divinyl ketone to adopt the required conformation for 4π-

electrocyclization. Substrates such as **3.48** were unreactive in this transformation because the most favorable conformation places the smaller proton substituent near the benzoyl group disfavoring the required orientation for cyclization. Further perturbation is required for substrates such as these and other organocatalysts have been used to achieve this reactivity.



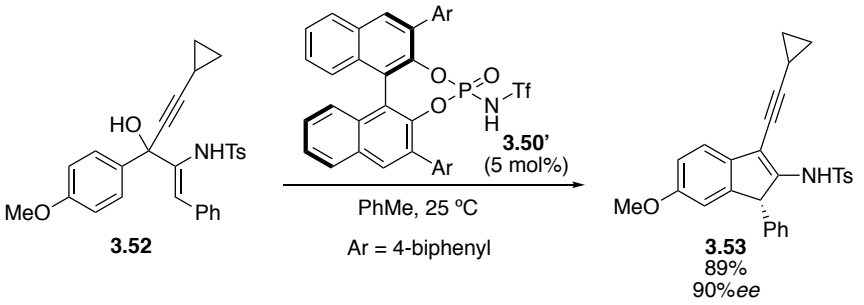
Scheme 3.11 Conjugate addition symmetric Nazarov cyclization[114]

The first use of a chiral Brønsted acid to catalyze an asymmetric Nazarov reaction was demonstrated by Rueping in 2007 (Scheme 3.12).[115] Using chiral phosphoramide **3.50**, the authors were able to expand on previously demonstrated 4π-electrocyclizations of divinyl ketones. This strategy was applicable to the same dihydropyran-containing divinyl ketones used by Frontier (see Scheme 3.6), but did not require an electron withdrawing group to polarize these substrates toward C–C bond formation because Lewis acid catalysis lowered the activation barrier to allow cyclization. To that end, Rueping and coworkers were able to access a variety of chiral cyclopentenone scaffolds **3.51** with high levels of enantioselectivity.



Scheme 3.12 Chiral Brønsted acid catalyzed Nazarov cyclization – Rueping, 2007

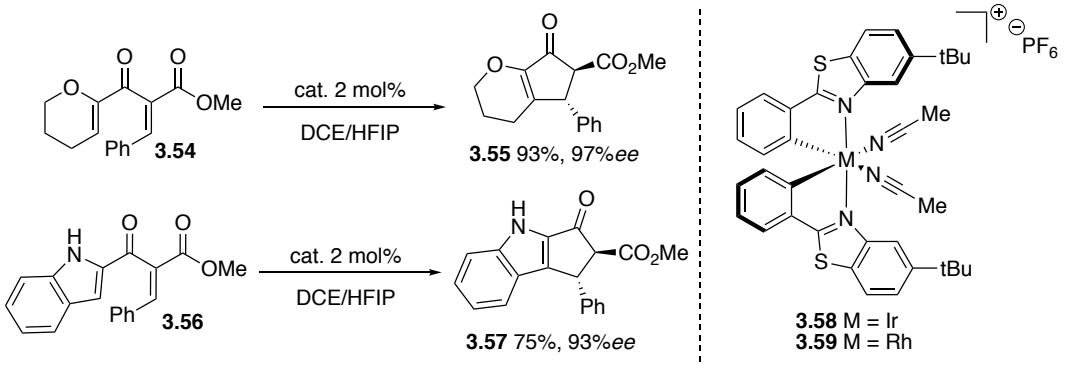
Ariaford and Chan recently reported the use of the same class of chiral Brønsted acid to achieve dehydrative Nazarov cyclization to access carbocyclic enamines such as **3.53** (Scheme 3.13).[116] Using benzylic alcohol **3.52** bearing an enamide, chiral *N*-triflyl phosphoramide **3.50'** was shown to catalyze the generation of a phenonium ion intermediate, which was rapidly trapped by the enamide. Through a lengthy mechanistic investigation, it was found that this novel dehydrative Nazarov cyclization was made possible because of the tight chiral ion-pair generated from **3.52** and **3.50'**. Their conclusion from these investigations were that the observed enantioselectivities arise from the more stable conformation of the substrate cation and that the ensuing ion-pair acted as a thermodynamic sink to prevent interconversion of the other conformer. The enamide substituent of **3.52** was crucial, as it acted as a polarizing group and nucleophile to accelerate the Nazarov cyclization. Other reports of amine polarization have been reported in recent years.



Scheme 3.13 Organocatalytic asymmetric 4π-electrocyclization of all-carbon systems

3.1.3 Examples of Aza-Nazarov 4π-electrocyclization

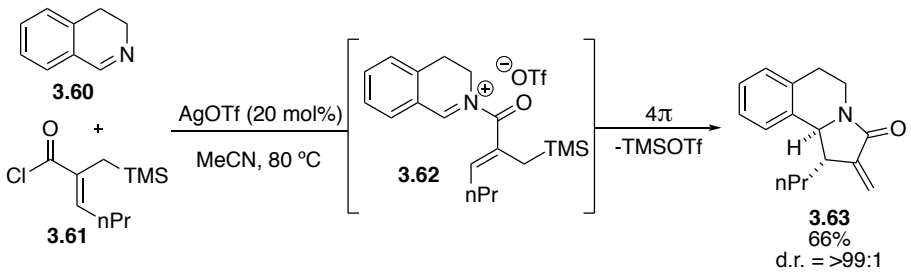
Meggers and coworkers demonstrated polarization by using chiral iridium **3.58** and rhodium **3.59** catalysts to efficiently activate polarized divinyl ketones **3.54** and **3.56** with excellent levels of enantioselectivity (Scheme 3.14).[117] Through the careful design of these catalysts, high levels of enantioselectivity were achieved. The authors used diydropyran- and indole-containing unsaturated β-ketoesters as polarized ketones in the same manner as Frontier to acess **3.55** and **3.57**. Their advancement was the use of novel catalysts to achieve torquoselectivity in this transformation. In the case of indole-substituted divinyl ketone **3.56**, the proposed intermediate after cyclization is the generation of an aza-allyl cation which is effective in imparting chirality in the resulting C–C bond forming event. This aza-allyl cation intermediate has also been documented in previous reports to facilitate asymmetric Nazarov cyclization.



Scheme 3.14 Chiral iridium and rhodium catalyzed 4π-electrocyclization[117]

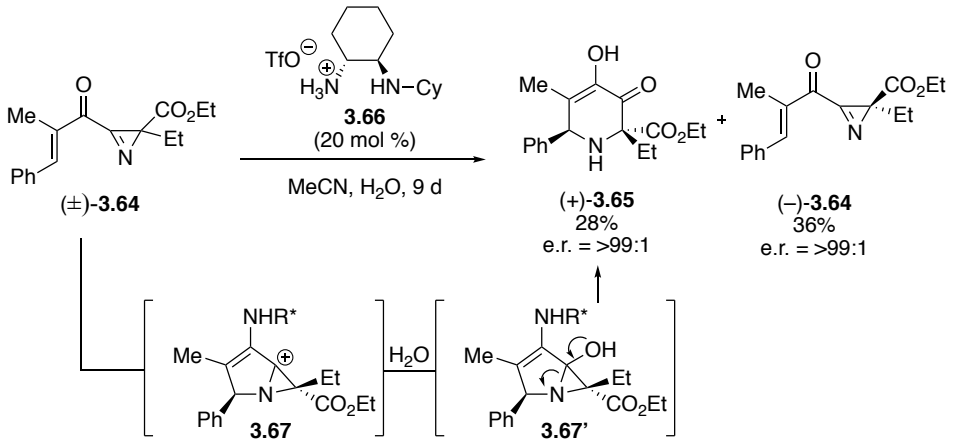
Turkmen and Bozkaya recently disclosed an iminium-aza-Nazarov cyclization by taking advantage of the previously discussed β-silicon stabilization effect to efficiently generate enantiodefined tetrahydroisoquinolines **3.63** (Scheme 3.15).[118] The authors reported that acylation of dihydroisoquinoline **3.60** affords iminium vinyl ketone **3.62**,

which bears a trimethylsilyl group to stabilize the buildup of positive charge during electrocyclization. This silyl substitution was computationally shown to lower the reaction barrier by almost 10 kcal/mol. After desilylation, exocyclic methylene γ-lactams **3.63** could be obtained as a single diastereomer.



Scheme 3.15 Iminium aza-Nazarov cyclization via β-silicon stabilization[118]

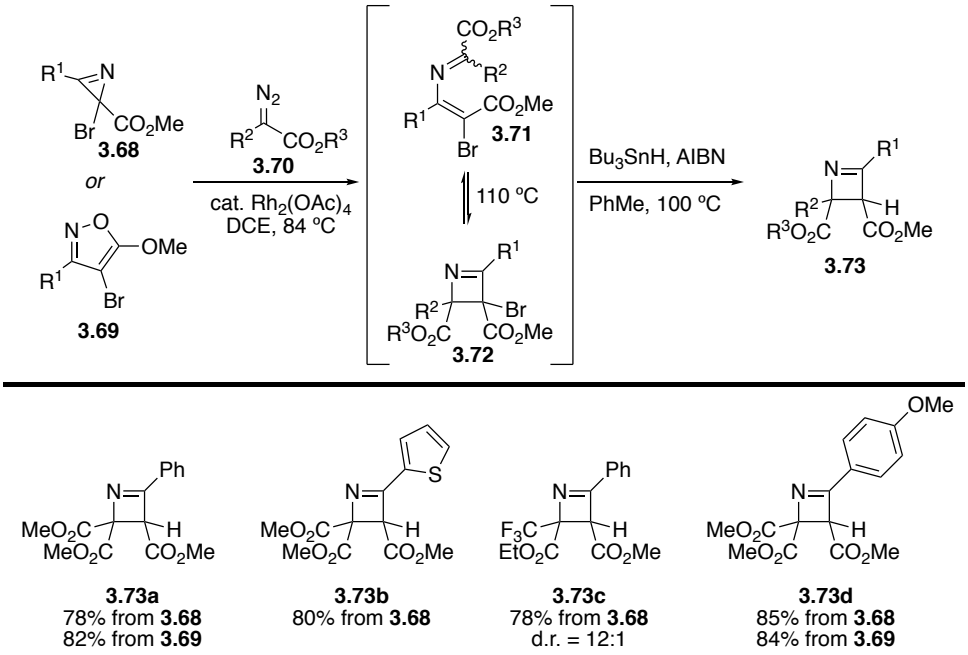
In an example of enantioselective aza-Nazarov cyclization, Tius and coworkers first described the use of racemic strained azirines to afford enantioenriched azacyles in 2010 (Scheme 3.16).[103a] Utilizing azirine **3.64** in the presence of catalytic chiral diamine **3.66**, ring-expansion and cyclization afforded tetrahydropyridine **3.65** with >99%*ee*. This transformation is thought to proceed via iminium ion formation of azirine **3.64** followed by cyclization to access bicyclic cation **3.67**, which is then trapped by water. Ketone formation facilitates aziridine ring-opening and after chiral auxiliary hydrolysis the product is formed in low yield with recovery of enantioenriched **3.64**, suggesting that this process is a combination of kinetic resolution and enantioselective catalysis. The novel use of these strained azirines in asymmetric aza-Nazarov cyclizations shows that alternative reactive intermediates are also applicable to analogous reaction pathways.



Scheme 3.16 Asymmetric aza-Nazarov cyclization of strained azirines[103a]

3.1.4 Four-atom 4π-Electrocyclization of 2-Azadienes

As previously described, Novikov and coworkers have developed the 4π-electrocyclization of 2-azadienes accessed via rhodium carbene insertion to azirines for the formation of dihydroazetes. This strategy was limited by the instability of the resulting products under thermal conditions, which led to reversible ring-opening to revert back to the 2-azadiene. In an attempt to access more stable dihydroazetes, the same group found that use of electron-deficient diazo compounds **3.70** and azirine **3.68** or isoxazole **3.69** could lead to the formation of a stable isolable dihydroazete in moderate yield (Scheme 3.17).[119] Their strategy was realized by first forming halogenated dihydroazete **3.72** via 4π-electrocyclization of 2-azadiene **3.71**. Dehalogenation with tributyltin hydride afford a variety of stable dihydroazetes **3.73a-d**. This 2-azadiene 4π-electrocyclization differs from previously reported aza-Nazarov cyclizations in that it is a 4-atom system which leads to the formation of azetidine precursors instead of lactams. The greater stabilization of azadienes might lead to the development of reactivity studies of 2-azadiene derivatives for the 4π-electrocyclization of these systems.



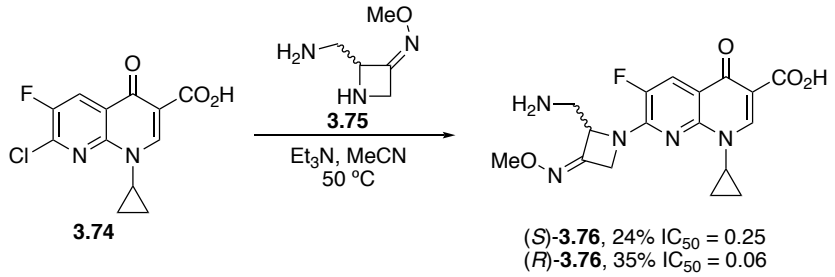
Scheme 3.17 4π-Electrocyclization of 2-azadienes – Novikov, 2016[119]

3.2 Previous Strategies for Stereoselective Azetidine Synthesis

3.2.1 Functionalization of Minimally Substituted Azetidines

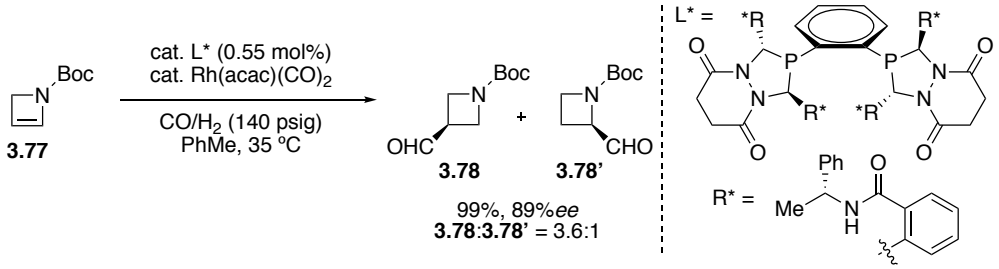
As previously described, azetidine heterocycles are a valuable pharmacophore and mild stereoselective methods for their preparation are in high demand. The ability to selectively install functional groups to increase drug efficacy as well as potency would allow medicinal chemists to access a broad new array of drug candidates. As demonstrated in 2012, Liu and coworkers showed that by substituting the (*R*)-enantiomer of azetidinone **3.75**, a noticeable difference in the IC_{50} against S. aureus was obtained in contrast to the (*S*)-enantiomer of **3.76** (Scheme 3.18).[120] The ability to access chiral functionalized azetidine scaffolds would allow for the advancement of antibiotics, drug discovery, and natural product synthesis for azetidine-containing scaffolds. Unfortunately, current methods for the stereoselective synthesis of azetidine analogues

require the post-synthetic modification of minimally substituted saturated and unsaturated azetidines, azetes, and dihydroazetes.



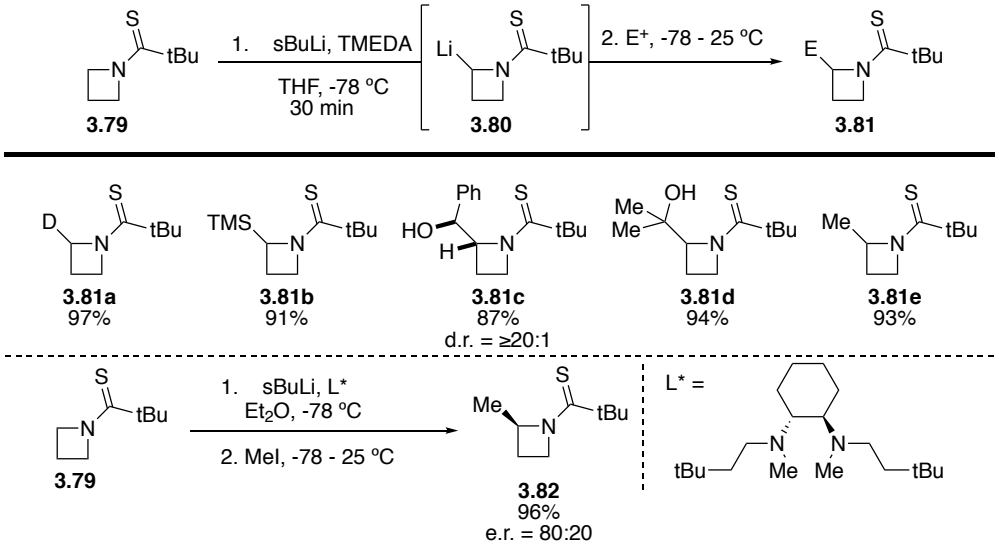
Scheme 3.18 Difference in inhibition of *S. aureus* from two azetidinone enantiomers[120]

Some methods for accessing stereodefined azetidines use unsaturated azetidines to selectively install desirable functionalities. Landis and Stahl demonstrated an asymmetric hydroformylation of dihydroazete **3.77** to afford a regioisomeric mixture of **3.78** and **3.78'**, which favors 3-substituted azetidine **3.78** (Scheme 3.19).[121] The regioisomeric mixture is thought to be obtained because of a lack of steric control due to the unsubstituted dihydroazete. This report established the utility of unsaturated azetidine precursors as viable intermediates for stereodefined functionalized azetidines, however it was limited to only a single example of chiral azetidine formation. The resulting formyl azetidine substrates lack diversity due to the harsh conditions and a method that would tolerate more functionality is desirable.



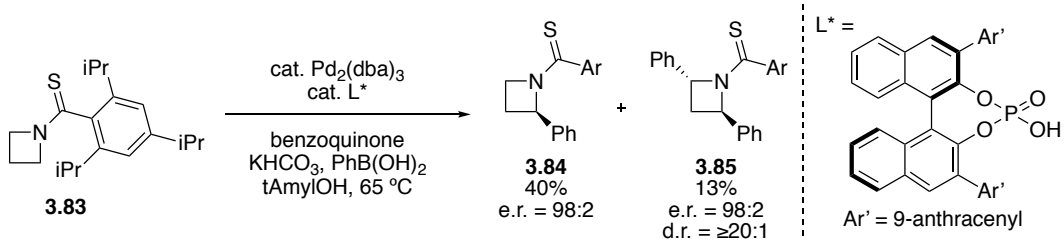
Scheme 3.19 Enantioselective hydroformylation of dihydroazete – Landis and Stahl[121]

The functionalization of azetidines by α-lithiation and electrophilic trapping has gained momentum as an active and expanding area for the divergent functionalization of azetidines. The use of protecting groups as directing groups for saturated azetidine functionalization was first established by Hodgson and coworkers. They showed that directing groups could allow azetidines to participate in similar α-lithiation/trapping reactions that have been used with pyrrolidines, piperidines, and aziridines. Common *N*-protecting groups such as Boc, t-butylsulfinyl, and t-butylsulfonyl were used to lithiate saturated azetidine scaffolds in the presence of LDA or alkyl lithium reagents, but these groups showed no reactivity. Substituting *N*-thiopivaloyl as the azetidine protecting group in **3.79**, treatment with *s*-BuLi and quenching with MeOD afforded α-deuterated azetidine **3.81a** in high yield. Investigation into the scope of the electrophile in this transformation showed that silyl halide, aldehyde, ketone, and alkyl halides were an efficient quench of lithiated azetidine **3.80** to give **3.81a** – **3.80e** (Scheme 3.20).[122] When a chiral diamine was added to the reaction, enantioenriched azetidine **3.82** was obtained, showing that stereoselective trapping of lithiated azetidines was a viable route to chiral azetidines. This report showed that functionalization of saturated azetidines could be used to access enantiodefined azetidine scaffolds.



Scheme 3.20 Directed lithiation for functionalized azetidines[122]

Yu and coworkers showed an example of directed C–H α-arylation of thioamide azetidine **3.83** using palladium/phosphoric acid catalysis (Scheme 3.21).[123] The authors obtained the 2-substituted azetidine **3.84** as the major product with a small amount of 2,4-disubstituted **3.85** after purification. While these products were obtained with almost perfect enantiocontrol, their method was mostly applicable to acyclic and 5- and 6-membered azacycle functionalization and only one example of azetidine functionalization was reported. Furthermore, the resulting azetidine scaffolds would be hard to functionalize due to the steric environment and lack of synthetic handles for post-synthetic modification. A more general method would be highly valuable to enantioselectively access unsaturated azetidine precursors.



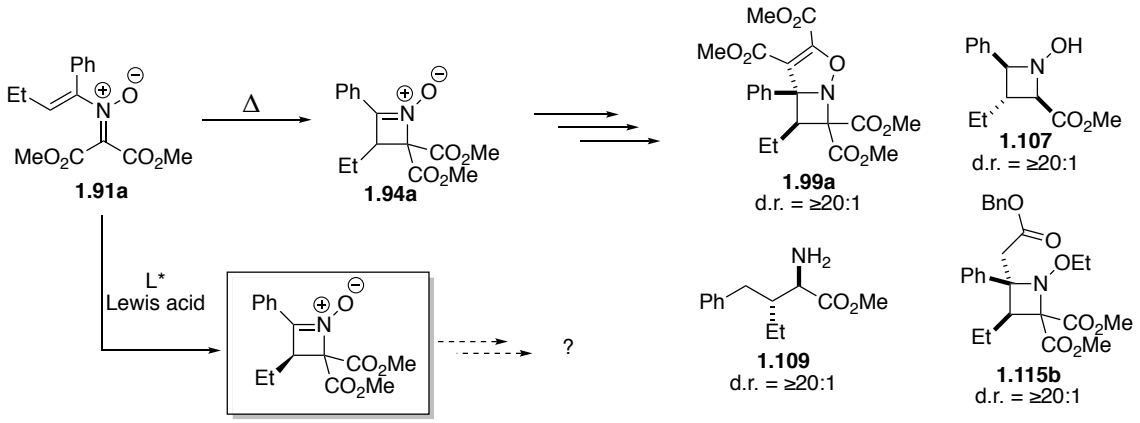
Scheme 3.21 Enantioselective directed α-C–H-arylation for chiral azetidine[123]

These selected examples of enantioselective azetidine functionalization are shown to be limited to a narrow mode of reactivity and lack modularity due to very specific substrate control. The use of *N*-protecting groups to direct lithiation and allow stereoselective trapping with various electrophiles has been explored; however these strategies require the use of minimally substituted azetidines to avoid unwanted side-reactions under these conditions. Enantioselective hydroelementation processes could offer an entry into densely functionalized chiral azetidines from dihydroazetes, but these methods have proven difficult to control regioselectively, giving a mixture of different azetidine products. These limitations of modularity, synthetic utility, and regiocontrol make the current technology for accessing stereodefined azetidine scaffolds less attractive for both medicinal and synthetic chemists. A more general and modular route to enantioenriched azetidine precursors, which contain synthetic handles and participate in diastereoselective functionalization would be a drastic improvement on previous methods and would allow for the rapid stereoselective construction of azetidine-containing drug targets.

3.2.2 Diastereoselective Functionalization of Azetidine Nitrones

In our initial dissemination of the 4π-electrocyclization of *N*-vinylnitrones for the formation of azetidine nitrones, we also extensively studied various functionalizations of these strained heterocycles. Through reduction, cycloaddition, and electrophilic activation/nucleophilic trapping (Chapter 1, Sections 1.2.3 – 1.2.5) it was found that the resulting hydroxylamines, isoxazolidines, and nucleophilic addition products were obtained as single diastereomers in most cases (Scheme 3.22). This suggests that a single stereocenter bearing an alkyl group has the ability to differentiate the facial selectivity of

these functionalizations and that minimal substitution is required to achieve selectivity. With this knowledge in hand, we wondered if the same strategies used in the enantioselective 4π-electrocyclization of all-carbon-5-atom and aza-Nazarov cyclizations could be leveraged in our system to access stereodefined azetidine nitrones. These products would then be highly valuable for use in functionalizations to access densely substituted enantioenriched azetidines. As previously discussed, chiral azetidines have the potential to act as powerful antibiotics, cancer therapeutics, and disease treatments so this is an area that is of utmost importance for further advancement.

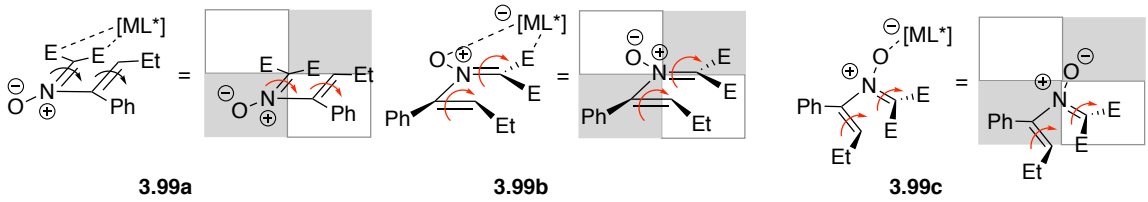


Scheme 3.22 Goal: Diastereoselective functionalization of chiral azetidine nitrones

3.3 Hypothesis

When comparing known asymmetric catalysts for enantioselective electrocyclizations and cycloadditions, a common theme is the utilization of two-point binding to coordinate a chiral Lewis or Brønsted acid catalyst. We postulated that this binding could be applied to our system and would destabilize these *N*-vinylnitrones to lower the transition state energy, making the iminium carbon more electrophilic and allowing the catalytic 4π-electrocyclization to proceed with high levels of enantioselectivity under mild conditions. The two-point binding of chiral catalysts

should favor the lower energy diastereomeric transition state to favor a single enantiomer of the product. Three potential binding modes of our substrates were envisioned: coordination to the two esters of the malonate portion of our nitrone **3.99a**, coordination of the nitrone oxygen and one ester **3.99b**, or mono-coordination of only the nitrone oxygen **3.99c** (Scheme 3.23). These three coordination modes could result in torquoselectivity in the 4π-electrocyclization. It was also postulated that with enantioenriched azetidines in hand, application of our cycloaddition, reduction, and activation/trapping reactions should give functionalized azetidine scaffolds with diastereoselective conservation of enantiocenters.



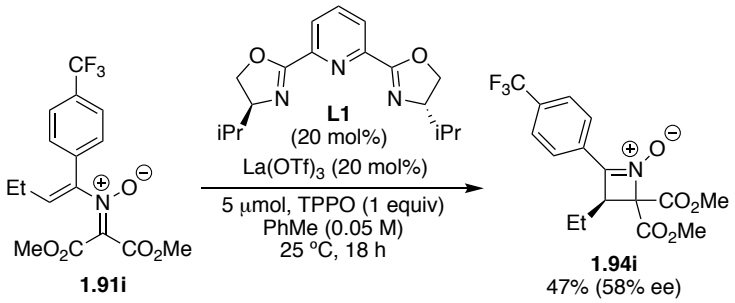
3.99a **3.99b** **3.99c**

Scheme 3.23 Hypothesized two-point binding of our model substrates

3.3.1 Initial HTE Screening

Mike Shevlin, an associate principle scientist at Merck, performed the initial high-throughput experimentation (HTE) utilizing nitrone **1.91i** due to its ease of access and easily crystallizable nature. Screening with a series of lanthanides and chiral PyBox, Box, and Mox ligands, he was able to determine the optimal conditions for preliminary hits to give moderate levels of enantioselectivity as measured by SFC/MS. It was found that the addition of 1 equivalent of triphenylphosphine oxide with respect to substrate had a drastic effect on the enantiomeric excess. This is in line with previous studies on the oligomeric nature of chiral lanthanide complexes.[124] Inanaga found that addition of a monodentate triphenylphosphine oxide helps to break up the oligomer into monomers as

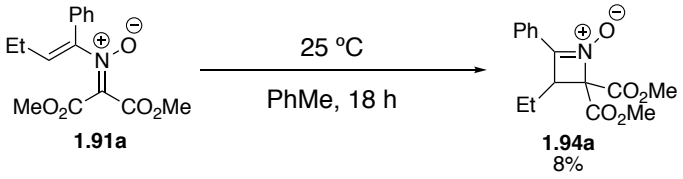
well as maintaining a 1:1 ratio of ligand to metal to ensure proper stoichiometry in the asymmetric epoxidation of α,β-unsaturated ketones. Under these conditions, initial hits yielded the corresponding azetidine nitrone in 48% yield and with 58%*ee* (Scheme 3.24). These results excited us and provided a novel entry into the asymmetric 4π-electrocyclization of *N*-vinylnitrones for the preparation of chiral azetidine nitrones.



Scheme 3.24 Initial hit for enantioselective 4π-electrocyclization of *N*-vinylnitrones

3.3.2 Our Results

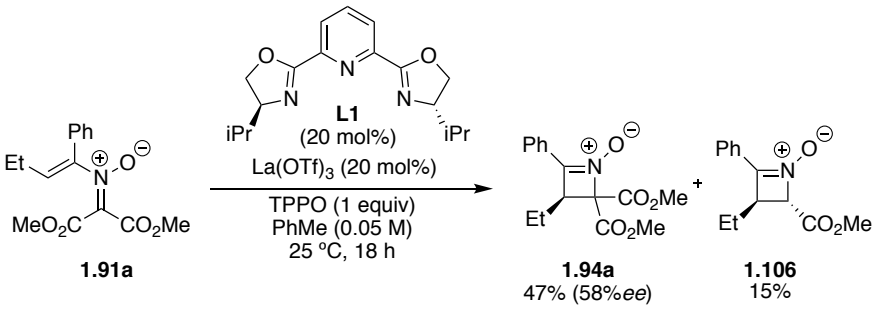
Before testing this transformation, it was necessary to determine the rate of the thermal background reaction. It was found that azetidine nitrone **1.94a** was slowly formed from *N*-vinylnitrone **1.91a** in PhMe at ambient temperature (Scheme 3.25). After 18 hours, less than 10% conversion was observed, suggesting that background reactivity should not interfere with this reaction.



Scheme 3.25 Ambient thermal background reaction of **1.91a**

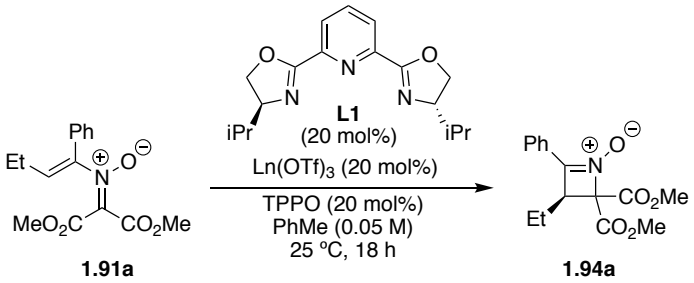
Reproducing Mr. Shevlin's HTE hits came with some challenges. Under optimal conditions, it was found that a full equivalent of triphenylphosphine oxide (TPPO) resulted in dealkoxycarbonylation of the resulting azetidine nitrone to give **1.106** as a side

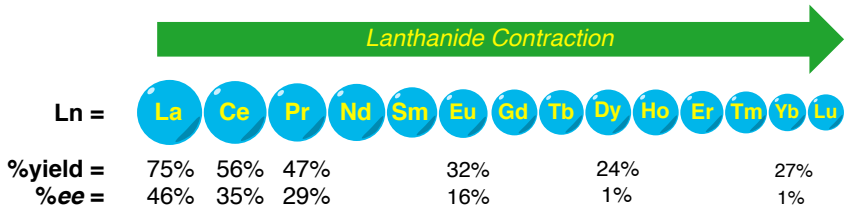
product (Scheme 3.26). This is assumed to be due to the relatively nucleophilic nature of TPPO and the destabilization of the malonate moiety of the product when ligated to a Lewis acid. By decreasing this equivalency to 20 mol%, this side product formation was reduced or eliminated and allowed further screening of other Lewis acid catalysts.



Scheme 3.26 Side product formation in presence of excess TPPO

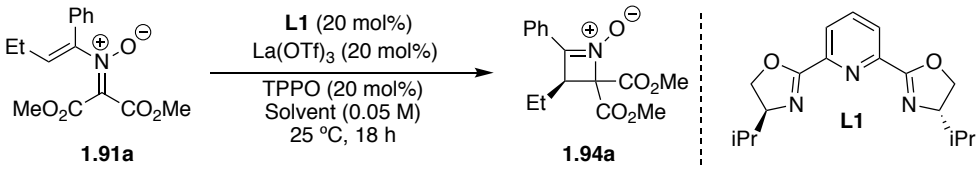
Our attention next turned to screening a variety of lanthanide triflate salts to determine if atomic radius had an effect on this transformation. Screening across the series of lanthanides, it was found that the larger radii lanthanides created a better binding pocket for our malonate nitrone substrates and resulted in higher enantioselectivities (Scheme 3.27). Screening of the "heavy lanthanides" such as europium, dysprosium, and ytterbium gave diminished enantioselectivity. Lanthanides with lower atomic mass but larger atomic radius such as lanthanum, cerium, and praseodymium gave moderate levels of enantioselectivity and higher yields, suggesting that these metal salts would be better suited for further screening of ligands for this transformation.





Scheme 3.27 Effect of lanthanide radius on enantioselectivity

The solvent used in this transformation was postulated to have an effect on the enantioselectivity of the reaction, so a variety of solvents were screened to determine this effect Table 3.1). Using the optimal catalytic combination of $La(OTf)_3$ and PyBox-**L1** in the presence of TPPO, it was found that aromatic solvents such as PhMe, $PhCF_3$, PhH, *o*-Xylene, $1,3\text{-}(CF_3)_2C_6H_4$, $1,4\text{-}(CF_3)_2C_6H_4$, and PhCl gave the highest levels of enantioselectivity with moderate yields (Table 3.1, entries 1-4,7,9,10). Higher dielectric constant solvents like MeCN and CH_2Cl_2 gave higher yields, but resulted in attenuated levels of enantioselectivity (entries 5,8). In THF, a complex mixture of products was observed and in ethanol, the major product was dealkoxycarbonylated **1.106**, which was further trans-esterified to the ethyl ester (Entries 6,11). These investigations led us to conclude that toluene was the optimal solvent for the $La(OTf)_3$-catalyzed electrocyclization of *N*-vinylnitrones.



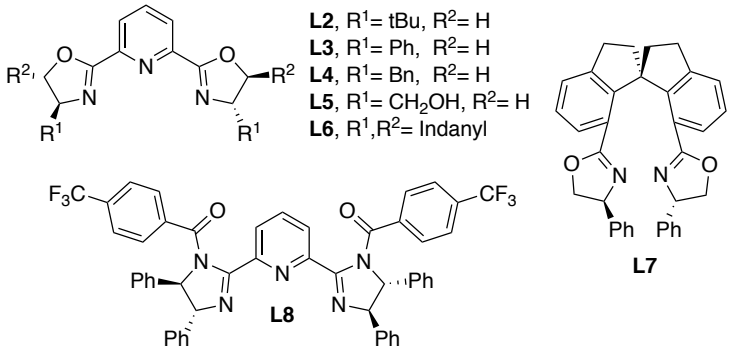
	Metal	Ligand	Solvent	%[a]	%*ee*[b]
1	$La(OTf)_3$	L1	PhMe	75	46
2	$La(OTf)_3$	L1	$PhCF_3$	61	45
3	$La(OTf)_3$	L1	PhCl	54	33
4	$La(OTf)_3$	L1	PhH	47	33
5	$La(OTf)_3$	L1	MeCN	71	27
6	$La(OTf)_3$	L1	THF	46	27
7	$La(OTf)_3$	L1	*o*-xylene	39	24
8	$La(OTf)_3$	L1	CH_2Cl_2	56	21

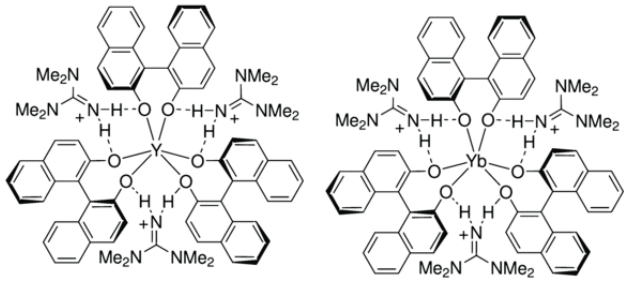
9	$La(OTf)_3$	L1	$1,3\text{-}(CF_3)_2C_6H_4$,	46	8
10	$La(OTf)_3$	L1	$1,4\text{-}(CF_3)_2C_6H_4$	38	8
11	$La(OTf)_3$	L1	EtOH	nd	nd

[a] %Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [b] Enantiomeric excess determined using chiral HPLC: Daicel Chiralpak IA-3 column, 30% THF in hexane, column temperature: 45 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 9.07 min, t_{major} = 10.94 min.

Table 3.1 Solvent effect on enantioselective 4π-electrocyclization

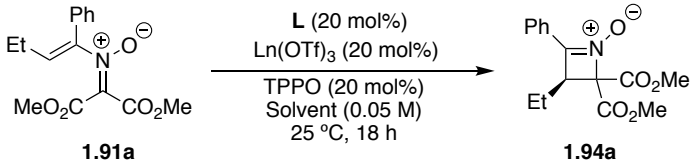
It was next postulated that by changing the substituents on the chiral ligand, the enantiomeric excess of azetidine nitrone formation might be increased by perturbation of the sterics of the C2-symmetric Lewis acid catalyst. A number of bulky chiral ligands were synthesized and screened using the optimal conditions with either $La(OTf)_3$ or $Ce(OTf)_3$. As depicted in Table 3.2 and Scheme 3.28, increasing the size of the R^1 group to tBu (**L2**) resulted in a decrease in both yield and enantioselectivity. Phenyl (**L3)**, benzyl (**L4)**, hydroxymethyl (**L5)**, indanyl PyBox (**L6)** gave diminished levels of enantioselectivity. SpiroBox (**L7**) and PyBim (**L8**) gave diminished selectivity. Finally, Shibasaki-Yb and Shibasaki-Y catalysts (Strem 70-0130 and 39-5850) were tested and showed no reactivity.





Y-Shibasaki and Yb-Shibasaki

Scheme 3.28 Ligands used for screening in **Table 3.2**



1.91a **1.94a**

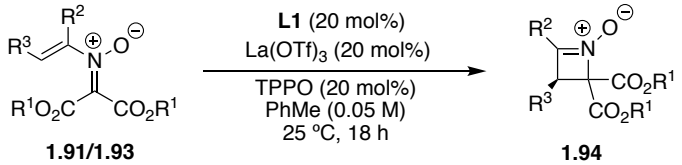
	Metal	Ligand	Solvent	%[a]	%*ee*[b]
1	$La(OTf)_3$	L2	PhMe	44	4
2	$La(OTf)_3$	L3	PhMe	32	1
3	$La(OTf)_3$	L3	MeCN	70	3
4	$Ce(OTf)_3$	L3	PhMe	25	0
5	$Ce(OTf)_3$	L3	MeCN	79	2
3	$La(OTf)_3$	L4	PhMe	52	25[c]
4	$La(OTf)_3$	L4	MeCN	64	7[c]
5	$Ce(OTf)_3$	L4	PhMe	48	21[c]
6	$Ce(OTf)_3$	L4	MeCN	72	24[c]
7	$La(OTf)_3$	L5	PhMe	33	0
8	$La(OTf)_3$	L6	PhMe	39	7
9	$La(OTf)_3$	L7	PhMe	41	5
10	$La(OTf)_3$	L8	PhMe	44	10
11	$La(OTf)_3$	L8	MeCN	74	0
12	$Ce(OTf)_3$	L8	PhMe	45	10
13	$Ce(OTf)_3$	L8	MeCN	85	1
14	Shib-Yb[d]	-	PhMe	22	1
15	Shib-Y[e]	-	PhMe	22	3

[a] %Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [b] Enantiomeric excess determined using chiral HPLC: Daicel Chiralpak IA-3 column, 30% THF in hexane, column temperature: 45 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 9.07 min, t_{major} = 10.94 min. [c] t_{major}= 10.94 min, t_{minor} = 9.07 min. [d] Shib-Yb CAS# = 1611526-75-0. [e] Shib-Y CAS# = 1611526-73-8

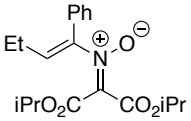
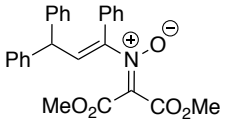
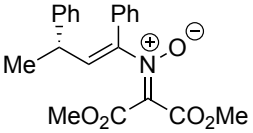
Table 3.2 Ligand effect on enantioselectivity

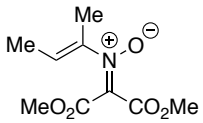
With some success using **1.91a** in the enantioselective formation of azetidine nitrone **1.94a**, it was wondered if modifying the structure of the *N*-vinylnitrone might result in an increase in enantioselectivity (Table 3.3). Making the ester more sterically

hindered in **1.91m** resulted in a slight decrease in both yield and %*ee*. Increasing the sterics at the β-position of the vinyl group was postulated to have an effect on the %*ee* as this center is close to the C–C bond forming center and is likely to participate in the stereoselective gearing of the conrotatory electrocyclization. Benzhydrol substituted nitrone **1.93s** gave diminished reactivity, but enantioselectivity was improved presumably due to a more sterically hindered vinyl group. In the same manner, it was hoped that a chiral center at this position might control the direction of conrotatory motion. When nitrone **1.93r** was tested under these conditions, 60%*ee* was observed, suggesting that a match/mismatch relationship might be possible. Dimethyl vinylnitrone **1.93a** gave no reactivity, suggesting that the α-aryl substituent is necessary in order for the *s-trans* configuration to be favorable. This led us to hypothesize that alternative binding modes might lead to an increase enantioselectivity by forcing this conformation and controlling the direction of rotation of the aryl substituent.



1.91/1.93 **1.94**

	Nitrone	% [a]	%*ee*
1	 **1.91m**	61	45 [b]
2	 **1.93s**	12	65 [c]
3	 **1.93r**	20	60 [d]

4	 **1.93a**	-	-

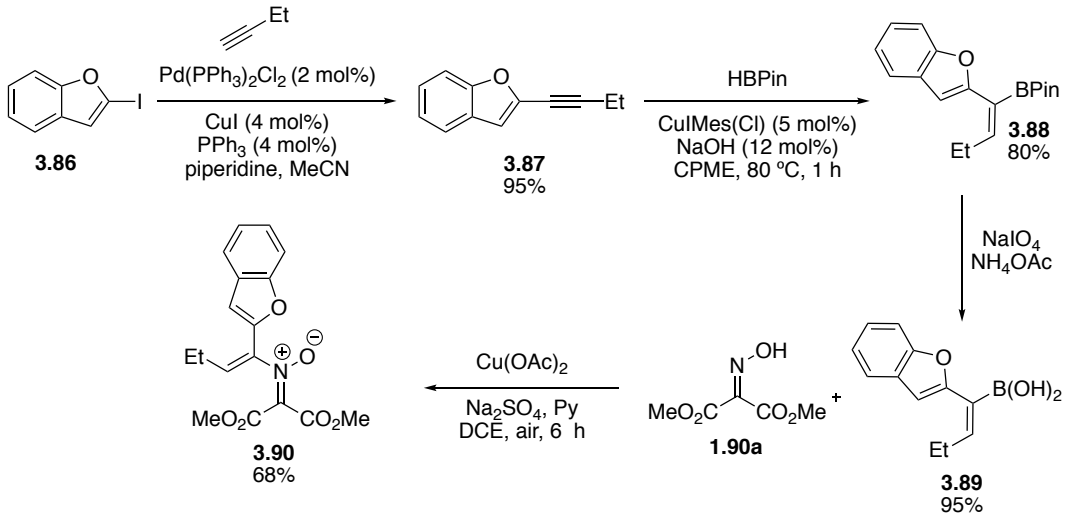
[a] %Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference. [b] Enantiomeric excess determined using chiral HPLC: Daicel Chiralpak IA-3 column, 1% MeOH in hexane, column temperature: 35 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 7.07 min, t_{major} = 7.79 min. [c] Daicel Chiralpak IA-3 column, 30% THF in hexane, column temperature: 35 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 7.57 min, t_{major} = 12.56 min. [d] Daicel Chiralpak IA-3 column, 30% THF in hexane, column temperature: 35 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 9.13 min, t_{major} = 12.31 min.

Table 3.3 Modified *N*-vinylnitrones tested in catalytic asymmetric 4π-electrocyclization

3.3.3 Designing Nitrones for Alternative Two-Point Binding

After observing the lack of reactivity of **1.93a**, it was postulated that the aryl ring helps to stabilize the transition state of the 4π-electrocyclization of **1.91a** and by raising the ground state energy of **1.91a** making this transformation thermodynamically downhill. This is evidenced by the aryl ring being orthogonal to the vinyl group in the crystal structure of *N*-vinylnitrone **1.91a**, but being in plane in azetidine nitrone **1.94a**. With the aryl ring in-plane with the π-system of the nitrone, orbital overlap makes the azetidine nitrone lower in energy than the analogous alkyl-substituted azetidine **1.93a**. By using coordination catalysis, these barriers could be further lowered. For this reason, it was hypothesized that the introduction of a coordinating group on the aryl ring might allow coordination to a Lewis acid to favor the two central atoms of the 4-atom electrocyclization substrate to bring the axis of the conrotatory motion as close to the C2 symmetry center of the Lewis acid catalyst and thus, direct the direction of rotation of this aryl ring during the 4π-electrocyclization event. This would allow the formation of azetidine nitrones with enantiocontrol. To achieve this goal, designing of a vinylboronic acid bearing a coordinating group was needed (Scheme 3.29). After iodination of benzofuran **3.86**, Sonagashira coupling with 1-butyne was efficiently performed to afford

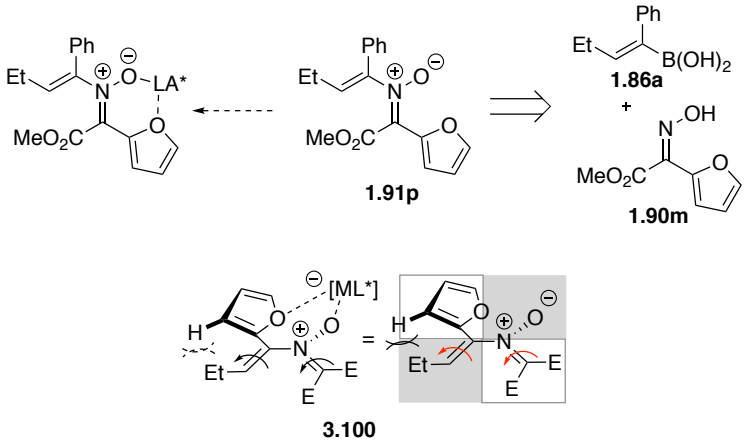
alkyne **3.87**. Copper-catalyzed borylation was then possible giving vinyl pinacol borate **3.88**, which was hydrolyzed to boronic acid **3.89** using our oxidative cleavage conditions. It was found that the subsequent Chan-Lam coupling of this boronic acid was very sensitive to both time and substrate. Overnight, only trace amount of the *N*-vinylnitrone was observed. Careful monitoring of reaction progress resulted in the isolation of *N*-vinylnitrone **3.90** in 68% yield. This substrate will be tested in the future to determine if enantiocontrol is possible via this binding mode.



Scheme 3.29 Design of coordinating vinyl substituent for Lewis acid catalysis

Hoping to reach high levels of enantioselectivity for the 4π-electrocyclization of *N*-vinylnitrones to access stereodefined azetidine nitrones, it was postulated that alternative binding modes that did not have competitive binding sites might allow for better stereocontrol (Scheme 3.30). This would require designing new nitrones with specific substitution patterns that favor coordination to the oxygen and a second coordinating group on the oxime portion of the molecule without competition between a competing second oxime substituent. *N*-vinylnitrone **1.91p** bearing a furan in lieu of an ester was designed because of the coordinating ability of furan to Lewis acids. Chan-

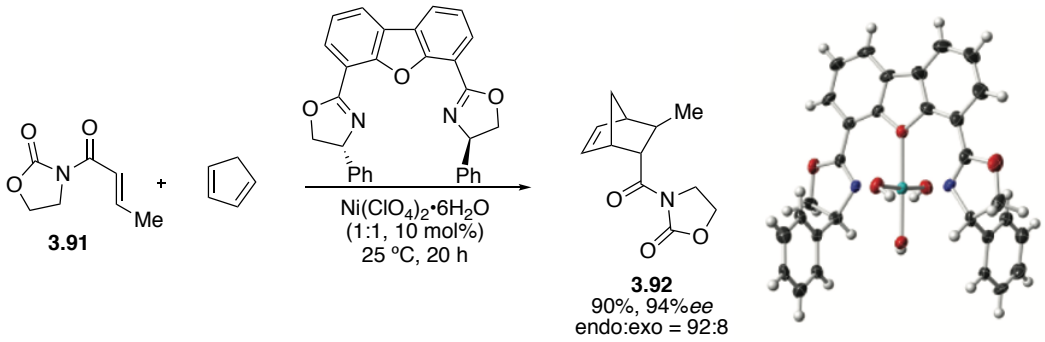
Lam coupling of furan-containing ester **1.90m** and vinylboronic acid **1.86a** provided the desired isomer of *N*-vinylnitrone **1.91p** to test this hypothesis. It was hoped that coordination of the *N*-vinylnitrone oxygen and the furan oxygen would adopt a favorable 6-membered transition state. This binding mode could selectively coordinate to catalyze the 4π-electrocyclization to form azetidine nitrone **1.94p** with high levels of enantioselectivity. Transition state model **3.100** indicates how this type of coordination mode could be used to control torquoselectivity.



Scheme 3.30 Alternative binding mode utilizing oxime **1.90m**

3.3.4 Nickel/Zinc/Copper/Silver Catalysis

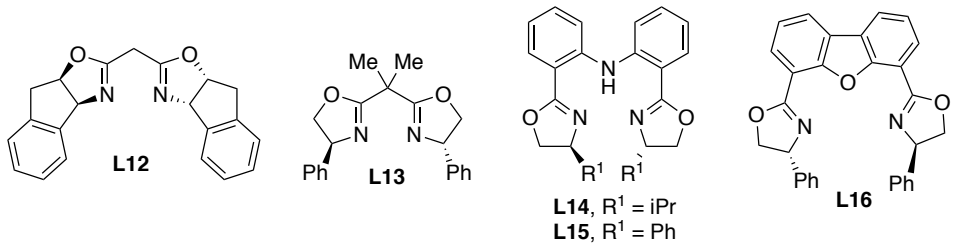
Further exploration of alternative binding modes led to the exploration of nickel catalysis. Previously, Kanemasa and coworkers have utilized $Ni(ClO_4)_2 \cdot 6H_2O$ and chiral DB-FOX ligands to catalyze the asymmetric Diels-Alder reaction of oxazolidinone **3.91** and cyclopentadiene to afford bicyclic product **3.92** with high enantioselectivity of the endo product (Scheme 3.31).[125] It was proposed that this two-point binding was quite efficient because of the large bond-angle of the DB-FOX ligand to nickel (174.2º, Scheme 3.31). High levels of enantioselectivity were achieved because of the rigid octahedral geometry, which created a tight chiral pocket with the oxazolidinone substrate.



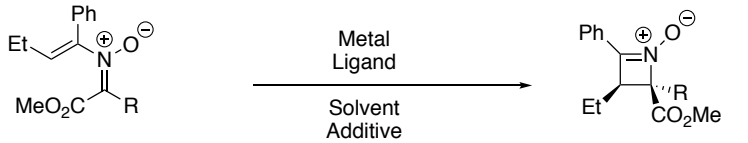
Scheme 3.31 Asymmetric Diels-Alder reaction with chiral Ni/DB-FOX[125]

Using this logic, we thought our *N*-vinylnitrones might also coordinate in a similar manner. After synthesizing Ph_2-DB-FOX using Kanemasa's reported method, our nitrones were tested. Utilizing *N*-vinylnitrone **1.91a**, a variety of conditions were tested (Scheme 3.32 and Table 3.4). Nickel, copper, and zinc were screened with Box ligands **L12** and **L13,** AmidoBox ligands **L14** and **L15**, and Ph_2DB-FOX **L16**. It was found that the addition of silver salts to these metal/ligand complexes resulted in a substantial increase in yield, presumably due to the salt metathesis and formation of nickel salts with weakly-coordinating counterions (Table 3.4, entry 2). When the nickel and zinc salts were removed and $AgSbF_6$ was used as the catalyst, high yields were achieved but the enantioselectivity of the process decreased (entry 11). It might be possible that the silver and nickel complexes have competing coordination abilities at different coordination sites of the substrate. Further investigation of these coordination preferences is currently underway in our lab. Utilization of designed *N*-vinylnitrone **1.91p** under these conditions with Ni/DB-FOX/Ag and Zn/DB-FOX/Ag catalyst systems yielded promising results when compared to those without either $AgSbF_6$ or a Lewis acid (entries 19,20 vs. entry 21). Clearly, this alternative binding-mode is plausible for enantioselective 4π-electrocyclization; however further investigations into the nitrone

substitution and correct ligand/metal combination will need to be addressed in order to determine if it is the optimal binding mode for enantioselective azetidine nitrone formation.



Scheme 3.32 Ligands used with nickel, copper and zinc catalysts



1.91a R = CO_2Me
1.91p R = 2-furanyl

1.94a R = CO_2Me
1.94p R = 2-furanyl

	Metal	Additive	Ligand	Solvent	%[a]	%*ee*[b]
1	$Ni(ClO_4)_2•6H_2O$	-	L16	CH_2Cl_2	42	7
2	$NiCl_2•6H_2O$	$AgSbF_6$	L16	CH_2Cl_2	82	43
3	$Cu(ClO_4)_2$	-	L16	CH_2Cl_2	44	5
4	$ZnBr_2$	$AgSbF_6$	L16	CH_2Cl_2	85	21
5	$ZnBr_2$	$AgPF_6$	L1	CH_2Cl_2	43	0
6	$ZnBr_2$	$AgSbF_6$	L2	CH_2Cl_2	91	2
7	$ZnBr_2$	$AgClO_4$	L16	CH_2Cl_2	95	0
8	$ZnBr_2$	$AgBF_4$	L16	CH_2Cl_2	85	8
9	$La(OTf)_3$	$AgSbF_6$	L1	CH_2Cl_2	73	0
10	$CuBr_2$	$AgSbF_6$	L16	CH_2Cl_2	100	10
11	-	$AgSbF_6$	L16	CH_2Cl_2	87	17
12	$ZnBr_2$	-	L16	CH_2Cl_2	96	0
13	$CuBr_2$	$AgSbF_6$	L1	CH_2Cl_2	91	0
14	$CuBr_2$	-	L16	CH_2Cl_2	43	0
15	-	$AgNTf_2$	L16	CH_2Cl_2	46	2
16	-	$AgSbF_6$	L13	CH_2Cl_2	65	5
17	$Ni(ClO_4)_2•6H_2O$	$AgSbF_6$	L15	CH_2Cl_2	10	7
18	$Ni(ClO_4)_2•6H_2O$	$AgSbF_6$	L14	CH_2Cl_2	15	3
19	$NiCl_2•6H_2O$	$AgSbF_6$	L16	CH_2Cl_2	39[d]	0
20	$CuBr_2$	$AgSbF_6$	L16	CH_2Cl_2	44[d]	22
21	-	$AgSbF_6$	L16	CH_2Cl_2	10[d[	7

[a] Reactions run for 18 h. %Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [b] Enantiomeric excess determined using chiral HPLC: Daicel Chiralpak IA-3 column, 30% THF in hexane, column temperature: 25 °C, flow rate: 1.0 mL/min, λ = 254 nm, t_{minor}= 14.55 min, t_{major} = 16.79 min. [d] Nitrone **1.91p** was used: Enantiomeric excess determined using chiral HPLC: Daicel Chiralpak IA-3 column, 1% MeOH in hexane, column temperature: 25 °C, flow rate: 1.0 mL/min, λ = 280 nm, t_{minor}= 11.15 min, t_{major} = 18.96 min).

Table 3.4 Nickel, copper, zinc, and silver catalysis of 4π-electrocyclization

3.4 Conclusion

These initial investigations into the asymmetric 4π-electrocyclization of *N*-vinylnitrones have elucidated key mechanistic details toward controlling this transformation. The use of wider bite-angle DB-FOX as a chiral ligand with either nickel, zinc, or copper has shown promising results. Alternative coordinating modes either with a furan-containing oxime or a benzofuran-containing vinylboronic acid might lend further improvement on these initial results. Furthermore, the addition of silver salts to these reactions leads to significant increases in yields, which will provide valuable azetidine nitrones in the future. Our group will continue to investigate this catalytic asymmetric 4π-electrocyclization and we hypothesize that it will lead to the generation of enantioenriched functionalized azetidines scaffolds.

3.5 Supporting Information

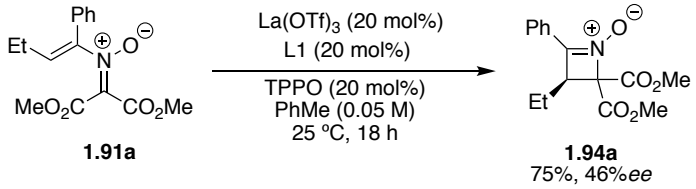
3.5.1 General Experimental Information

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded at ambient temperature using ATR sampling. High-resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed using force flow of the indicated solvent system down columns packed with 60 Å (40 – 60 μm) mesh silica gel (SiO_2). Samples purified by medium pressure liquid chromatography were dry-loaded onto celite. Unless otherwise noted, all reagents and solvents were obtained from commercial sources and,

where appropriate, purified prior to use. Unless otherwise noted, all reactions were performed under N_2 using standard Schlenk techniques. CH_2Cl_2, toluene, and THF were dried by filtration through alumina according to the procedure of Grubbs.[43] Oxime **1.90m** was prepared by known methods.[126]

3.5.2 Experimental Procedures and Characterization Data

3.5.3 HPLC Traces



1.91a **1.94a**
75%, 46%*ee*

Racemic:

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Sample Name: PhEtRac
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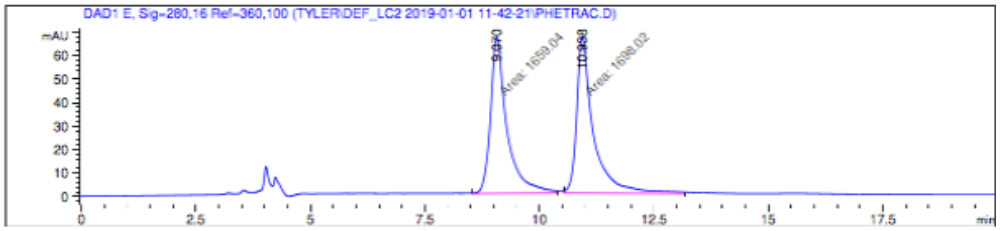


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Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.070 MM    0.4149 1659.04492   66.65149  49.4194
   2  10.938 MM    0.4236 1698.02405   66.80360  50.5806

Totals :                  3357.06897  133.45509

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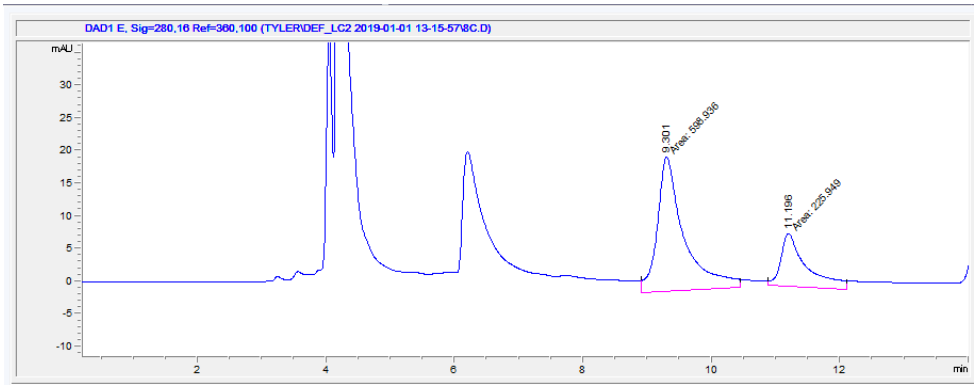
Chiral run: 20%La(OTf)$_3$, 20%L1, 20%TPPO, PhMe 0.05M, 18 h: 75%, 46%*ee*



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.301	MM	0.4824	598.93604	20.69384	72.6084
2	11.196	MM	0.4636	225.94934	8.12276	27.3916
Totals :				824.88538	28.81660	

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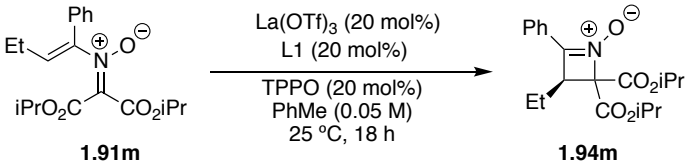

1.91m

1.94m
61%, 45%*ee*

Racemic:

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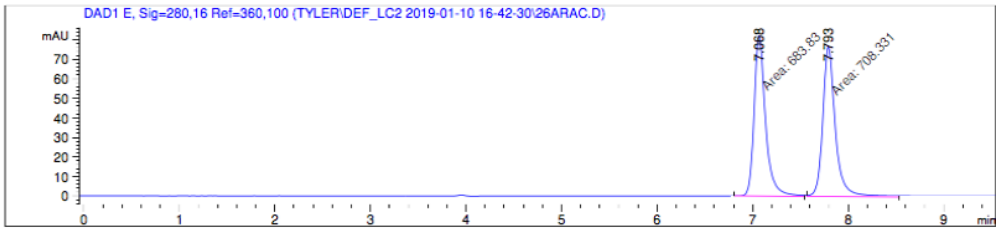
Sample Name: 26Arac

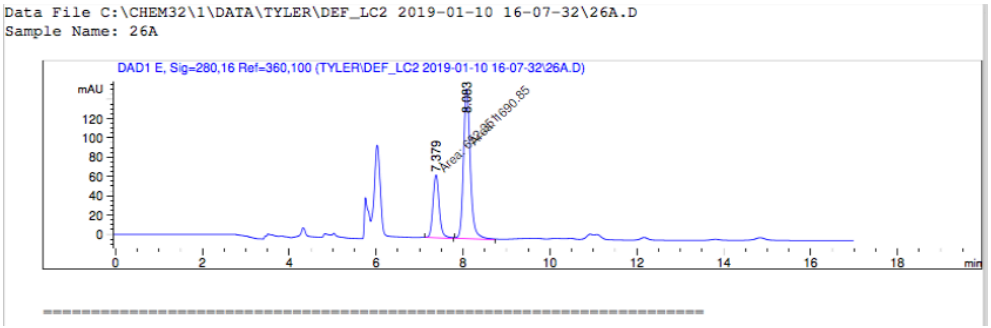


Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.068	MM	0.1382	683.82965	82.47274	49.1200
2	7.793	MM	0.1537	708.33105	76.78935	50.8800
Totals :				1392.16071	159.26209	

*** End of Report ***

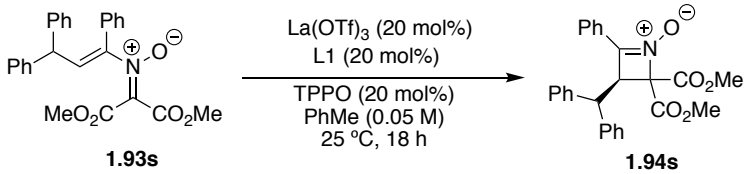
Chiral run: 20%La(OTf)$_3$, 20%L1, 20%TPPO, PhMe 0.05M, 18 h: 61%, 45%*ee*



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.379	MM	0.1669	652.35059	65.13729	27.8401
2	8.083	MM	0.1815	1690.85425	155.28000	72.1599
Totals :				2343.20483	220.41729	

*** End of Report ***



1.93s

1.94s
12%, 65%*ee*

Racemic:

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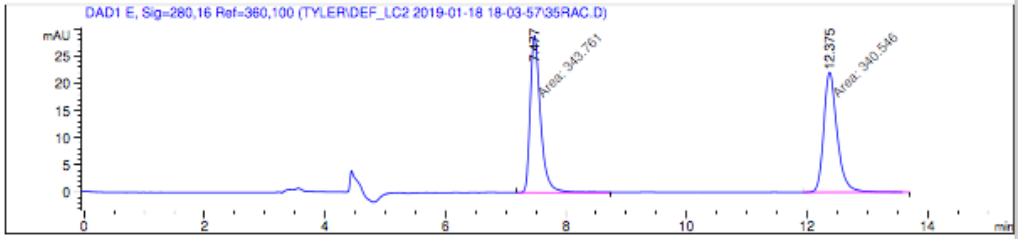
Sample Name: 35Rac

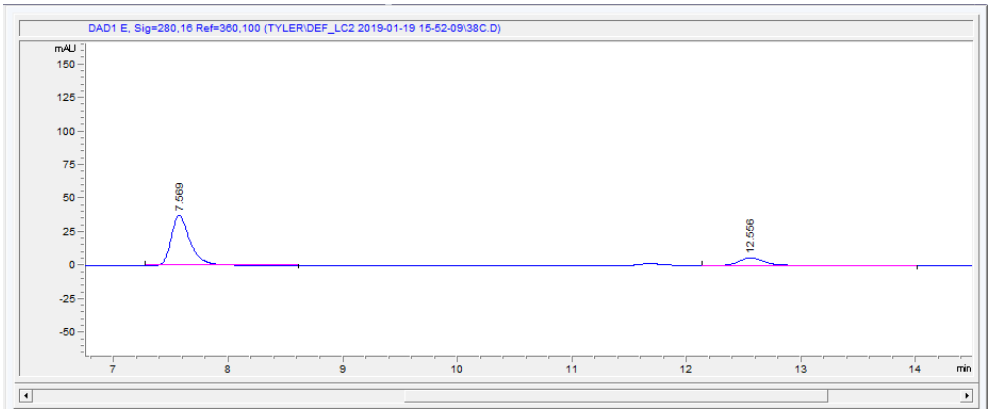


Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.477	MM	0.1988	343.76111	28.81394	50.2349
2	12.375	MM	0.2576	340.54636	22.03342	49.7651
Totals :				684.30746	50.84736	

*** End of Report ***

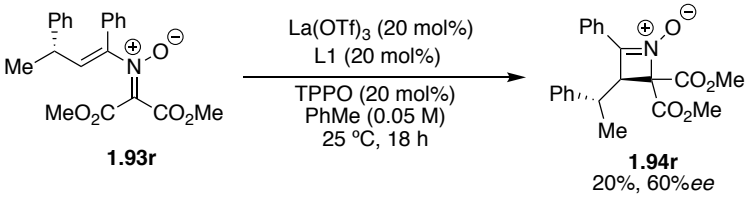
Chiral run: 20%La(OTf)$_3$, 20%L1, 20%TPPO, PhMe 0.05M, 18 h: 61%, 45%*ee*



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

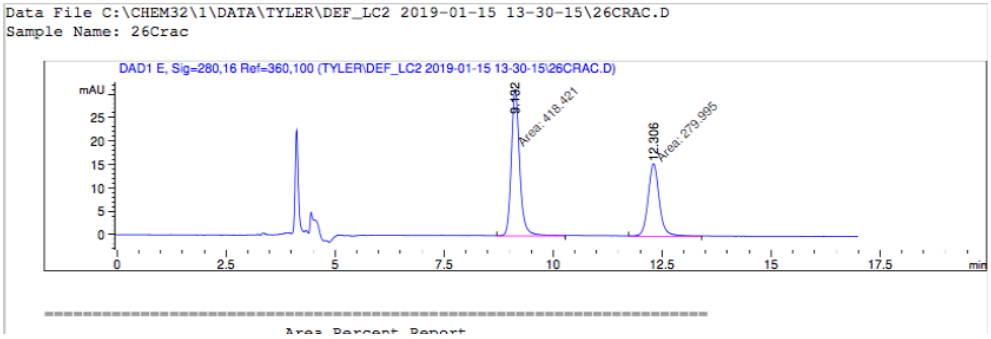
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.569	BB	0.1748	433.21918	37.49533	81.9286
2	12.556	VB	0.2444	95.55726	5.85543	18.0714
Totals :				528.77644	43.35077	

*** End of Report ***



1.93r → **1.94r**
20%, 60%*ee*

Racemic:



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.132	MM	0.2232	418.42056	31.24904	59.9099
2	12.306	MM	0.3009	279.99548	15.50941	40.0901
Totals :				698.41605	46.75845	

*** End of Report ***

Chiral run: 20%La(OTf)$_3$, 20%L1, 20%TPPO, PhMe 0.05M, 18 h: 61%, 45%*ee*

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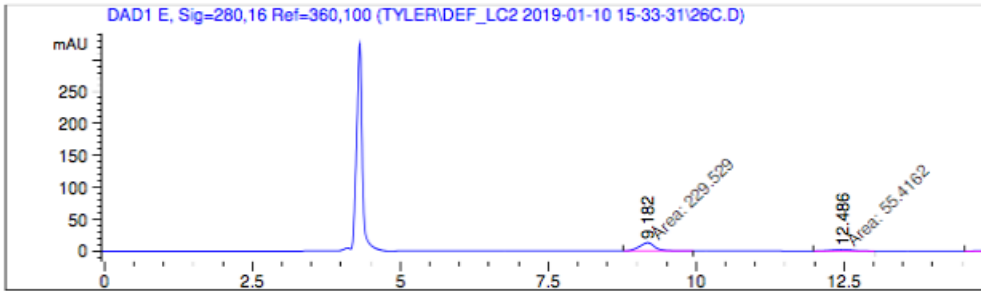

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.182	MM	0.2961	229.52896	12.91863	53.5658
2	12.486	MM	0.4076	55.41625	2.26571	12.9326
3	15.105	MM	0.5477	39.52887	1.20280	9.2250
4	15.985	MM	0.5454	104.02505	3.17862	24.2766
Totals :				428.49913	19.56575	

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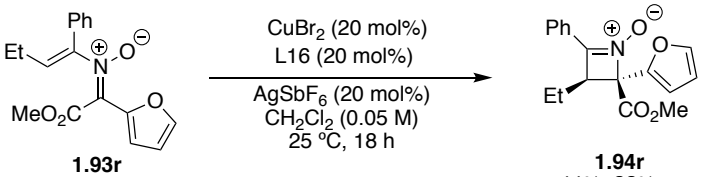

1.93r

1.94r
44%, 22%*ee*

Racemic:

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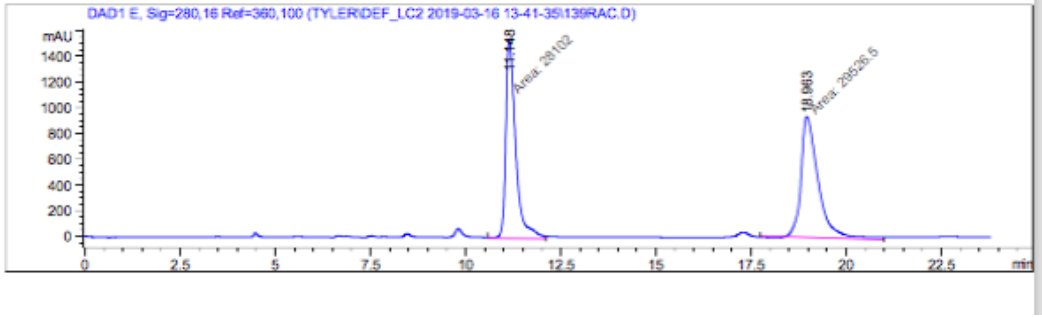
Sample Name: 139Rac



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Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.148	MM	0.3019	2.81020e4	1551.25720	48.7641
2	18.963	MM	0.5254	2.95265e4	936.66193	51.2359
Totals :				5.76285e4	2487.91913	

*** End of Report ***

Chiral run: 20% $CuBr_2$, 20% L16, 20%$AgSbF_6$, CH_2Cl_2 0.05M, 18 h: 44%, 22%*ee*

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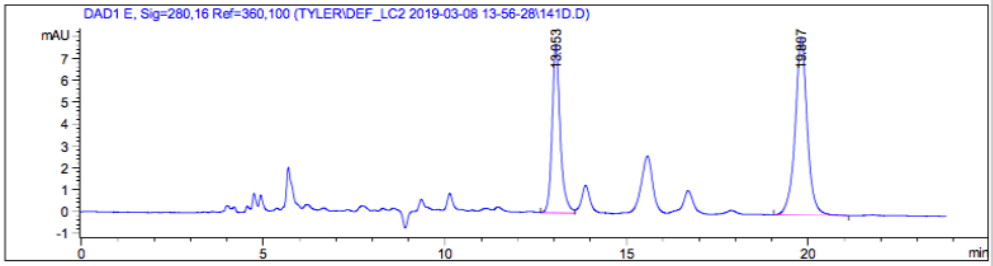


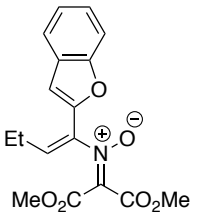
Area Percent Report

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.053	BV	0.2328	118.97919	7.67672	38.6245
2	19.807	BB	0.3479	189.06194	8.11096	61.3755
Totals :				308.04113	15.78768	

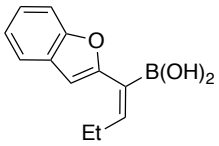
*** End of Report ***

3.5.4 Synthesis of *N*-vinylnitrone 3.90



3.90

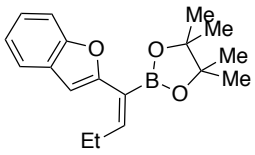
General Procedure A: A scintillation vial was charged with oxime **1.90m** (0.161 g, 1.0 mmol, 1.0 equiv), (1-(benzofuran-2-yl)but-1-en-1-yl)boronic acid **3.89** (0.756 g, 3.5 mmol, 3.5 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol, 1.0 equiv), and Na_2SO_4 (1.14 g, 8.0 mmol, 8.0 equiv). These solids were diluted with 10.0 mL DCE to form a 0.1 M solution of **1.90m** and pyridine (0.237 g, 3.0 mmol, 3.0 equiv) was added with vigorous stirring. The reaction was stirred at 25 ºC open to air and monitored by TLC for 3-6 h until complete disappearance of oxime **1.90m**. The reaction mixture was then filtered through a plug of silica gel covered with a layer of celite and washed with EtOAc (3 x 10 mL). The filtrate was concentrated under vacuum to give the crude product mixture that was dry-loaded using EtOAc onto celite and purified by medium pressure column chromatography (1:9; EtOAc:hexane) to afford nitrone **3.90** as a light-yellow oil (0.225 g, 68%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.56 – 7.54 (m, 1H), 7.49 – 7.48 (m, 1H), 7.32 – 7.29 (m, 1H), 7.24 – 7.21 (m, 1H), 6.82 (s, 1H), 6.02 (t, J = 7.5 Hz, 1H), 3.96 (s, 3H), 3.71 (s, 3H), 2.71 – 2.62 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.5, 154.9, 148.2, 137.9, 132.8, 127.4, 125.5, 123.4, 121.5, 111.5, 107.0, 103.1, 53.4, 53.0, 21.4, 13.2.



3.89

Preparation of Vinylboronic Acid 3.89: To a solution of vinyl pinacolborane **3.88** (0.596 g, 2.0 mmol, 1 equiv) in acetone (25.0 mL) and water (25.0 mL) were added NH_4OAc (0.500 g, 6.0 mmol, 3.0 equiv) and $NaIO_4$ (1.29 g, 6.0 mmol, 3.0 equiv), and stirred for 2 d at 25 °C. The mixture was then concentrated to remove acetone and

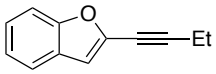
extracted with Et_2O (3 x 40 mL). The organic extracts were combined, dried with Na_2SO_4, and concentrated under vacuum. The crude white solid **3.89** (0.372 g, 86%) was used without further purification. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.57 – 7.55 (m, 1H), 7.47 – 7.45 (m, 1H), 7.29 – 7.21 (m, 2H), 6.85 (t, *J* = 7.0 Hz, 1H), 6.64 (s, 1H), 5.48 (brs, 2H), 2.53 – 2.51 (m, 2H), 1.16 (t, 3H).



3.88

Preparation of Vinylboronic Acid Pinacol Ester 3.88[127]

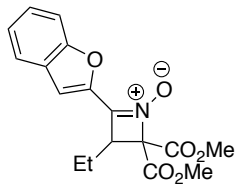
A flame-dried 25mL round bottom flask was charged with CuIMesCl (0.048 g, 118.0 mg 2 mol%), NaOH (28.2 mg, 12 mol%), alkyne **3.87** (1.0 g, 5.88 mmol, 1.0 equiv), and CPME (7.4 m, 0.8 M). The mixture was stirred open to air for 5 min at 25 ºC, then cooled to −40 °C. Pinacolborane (1.13 g, 8.81 mmol, 1.5 equiv) was added dropwise. The vial was sealed with a screw cap, and placed in a preheated oil bath at 80 °C. After TLC indicated complete consumption of the alkyne, the reaction was cooled, filtered through celite, and concentrated in vacuo. The crude mixture was purified by medium pressure column chromatography (1:99; EtOAc:hexane) to afford **3.88** as a light-yellow oil (1.40 g, 80%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.56 – 7.54 (m, 1H), 7.46 – 7.44 (m, 1H), 7.26 – 7.17 (m, 2H), 6.97 (s, 1H), 6.36 (t, *J* = 7.0 Hz, 1H), 2.79 – 2.73 (m, 2H), 1.35 (s, 12H), 1.17 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 154.4, 152.1, 129.0, 123.7, 122.4, 120.8, 110.9, 106.3, 83.8, 24.9, 24.8, 13.9 (*C*–B too broad to be observed).



3.87

Preparation of Alkyne 3.87: A 50-mL flame-dried round bottom flask was cooled to 25 °C under N_2 and charged with 2-iodobenzofuran **3.86** (6.10 g, 25.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.220 g, 0.313 mmol, 0.01 equiv), CuI (0.119 g, 0.626 mmol, 0.02 equiv),

PPh_3 (0.164 g, 0.626 mmol, 0.02 equiv), piperidine (6.39 g, 75.0 mmol, 3.0 equiv), and diluted with MeCN (50.0 mL). A balloon was fitted and 1-butyne (2.70 g, 50.0 mmol, 2.0 equiv) was added to the reaction flask. The reaction mixture was stirred for 2 h under an atmosphere of 1-butyne and then concentrated extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with sat. $NH_4Cl_{(aq)}$ (3 x 25 mL), brine, and dried with $MgSO_4$. After evaporation, the crude reaction mixture was purified directly by medium pressure chromatography (hexane) to afford **3.87** as a light yellow liquid (4.04 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.53 – 7.52 (m, 1H), 7.44 – 7.42 (m, 1H), 7.32 – 7.28 (m, 1H), 7.23 – 7.20 (m, 1H), 6.82 (s, 1H), 2.53 – 2.49 (m, 2H), 1.28 (t, 3H).



Azetidine from 3.90

Azetidine Nitrone: Azetidine nitrone was prepared by general procedure **B** using nitrone **3.90** (0.0331 g, 0.10 mmol) in MeOH (1.0 mL) and heating for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded azetidine from **3.90** as a yellow oil (0.0315 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.74 (s, 1H), 7.62 – 7.61 (m, 1H), 7.47 – 7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.26 – 7.23 (m, 1H), 7.47 – 7.46 (m, 1H), 3.89 (s, 6H), 3.86 (dd, J = 10.0, 4.0 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.85 – 1.76 (m, 1H), 1.15 (dd, J = 10.0, 5.5 Hz, 1H).

Chapter 4: Cycloaddition/Rearrangement Cascade of *N*-Vinylnitrones and Alkynes

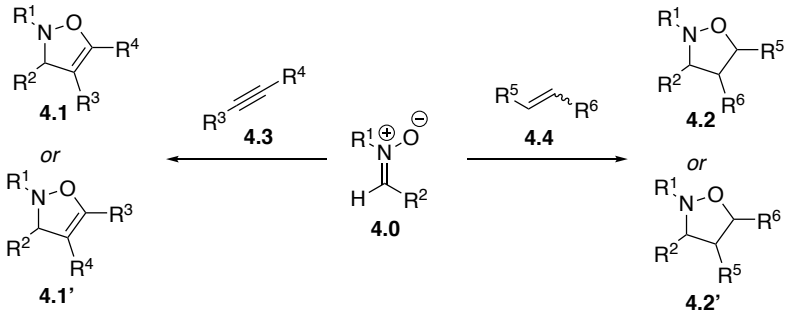
4.1 Introduction

A novel cascade reaction involving a [3+2]-cycloaddition followed by a [3,3']-sigmatropic rearrangement has been discovered in our lab. This transformation utilizes stable *N*-vinylnitrones and benzyne or cyclic alkyne intermediates generated in situ to trigger the initial [3+2]-cycloaddition and proceeds with high levels of diastereoselectivity to afford densely substituted 4-acyl-1-pyrroline scaffolds. The optimization and scope of the method will be discussed in addition to initial efforts to

towards the design of a catalytic asymmetric analogue. The work in this chapter is unpublished and future goals for different sections of this project have been added to the appropriate sections below.

4.1.1 Synthetic Utility of Nitrone Cycloaddition

Nitrones represent a valuable class of synthetic tools for heterocycle construction. The most widely used transformation utilizing these reactive intermediates is the [3+2]-cycloaddition of nitrones with alkenes, alkynes, or allenes. Generally, aldo-nitrones are most widely used due to their ease of access through condensation, oxidation, or elimination reactions. This substitution pattern is also preferable due to the decrease of reactivity prohibitive steric interactions at the imine reaction center and the fact that aldehyde-derived nitrones selectively form as single (*Z*)-isomers. In a normal-demand [3+2]-dipolar cycloaddition of **4.0** with **4.3** or **4.4**, the reaction outcome is dictated by the interaction between $HOMO_{nitrone} - LUMO_{alkyne}$ (Figure 4.1, left). This typically provides only one regioisomer of the product, while inverse-demand 1,3-dipolar cycloaddition between nitrones **4.0** and dipolarophiles **4.3** or **4.4** affords the opposite regioisomer. Inverse-demand cycloadditions rely on the opposite orbital interaction: overlap of $HOMO_{alkyne} - LUMO_{nitrone}$ (Figure 4.1, right). In ambiguous cases, a mixture of two regioisomers **4.1**/**4.1'** or **4.2**/**4.2'** can be obtained, reducing the efficiency of these reactions (Scheme 4.1). This could be a potential limitation in natural product syntheses.



Scheme 4.1 Traditional [3+2]-cycloadditions of nitrones with alkenes and alkynes

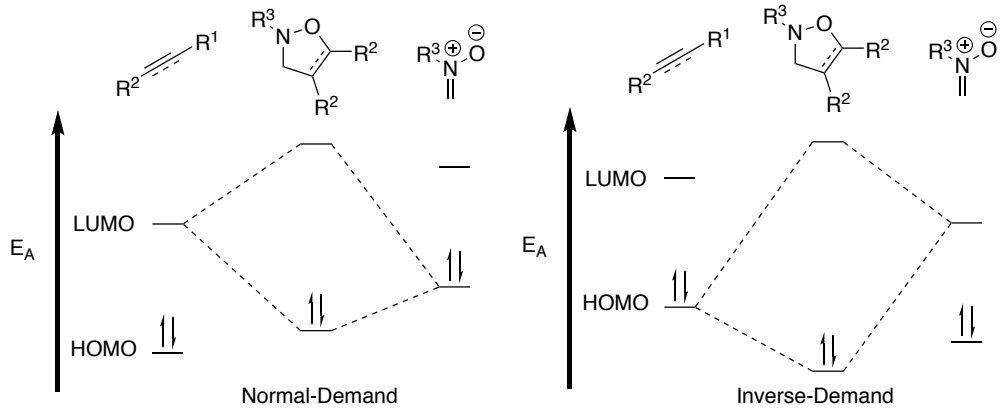
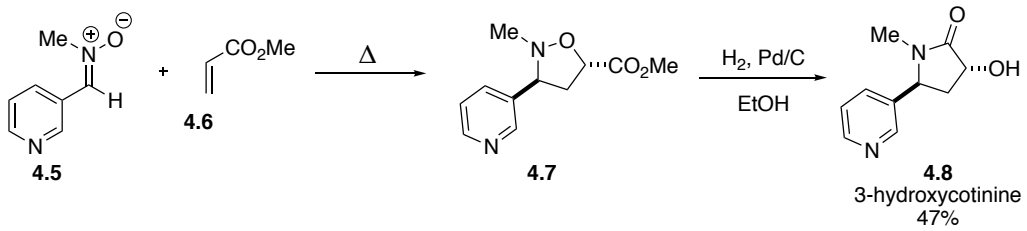


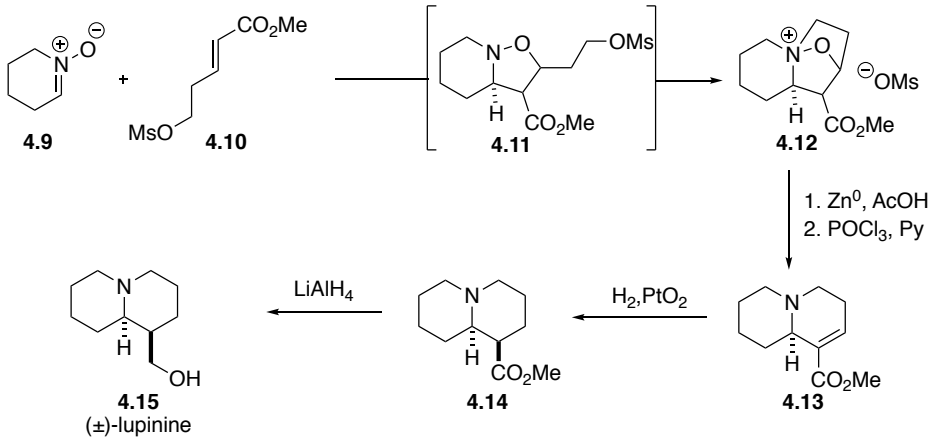
Figure 4.1 FMO theory of [3+2] of dipolarophiles and nitrones

The relative stereochemistry of natural products containing isoxazoldines has been solved through the use of nitrone cycloaddition. When investigating the major pathway for nicotine metabolism in humans, Castagnoli used the [3+2]-cycloaddition of 3-pyridyl nitrone **4.5** with methyl acrylate to generate isoxazolidine **4.7** (Scheme 4.2).[128] This intermediate was then hydrogenated and spontaneously cyclized to form both enantiomers of 3-hydroxycotinine **4.8**. The authors were able to separate these isomers using preparative TLC. Using mass spectroscopy and melting point analysis, the naturally occurring isomer was determined to be the (3*R*,5*S*)-configuration. Castagnoli successfully established a natural product synthesis from nitrone cycloaddition and showed that other natural products could also be accessed using this strategy.



Scheme 4.2 Elucidation of natural 3-hydroxycotinine using nitrone [3+2]-cycloaddition[128]

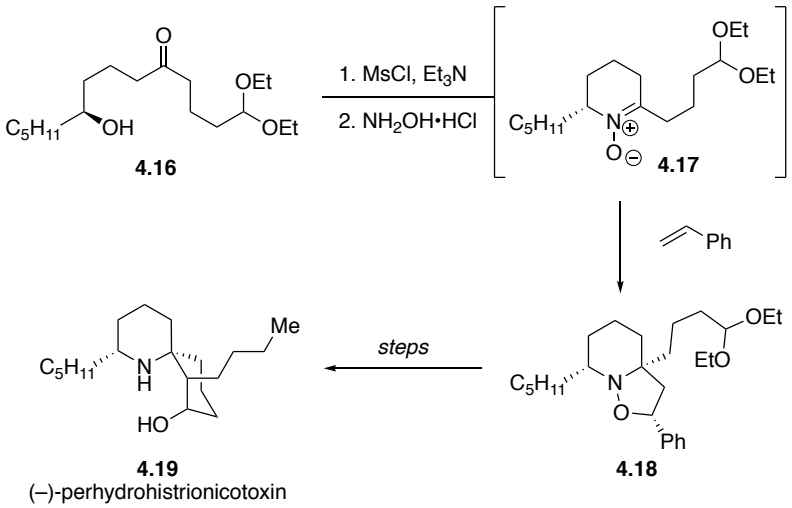
Tufariello and coworkers demonstrated the synthetic utility of [3+2]-cycloaddition of nitrone and alkene in the total synthesis of the natural product (±)-lupinine **4.15**. (Scheme 4.3). [129] Exposure of cyclic nitrone **4.9** to **4.10** generated isoxazolidine **4.11** in situ, which then underwent S_N2 elimination to afford ammonium salt **4.12**. Reduction of the N–O bond and dehydration led to the formation of unsaturated ester **4.13**. This compound was hydrogenated and the ester reduced to give the (±)-lupinine. This synthesis was limited by the cycloaddition step, as it led to a racemic mixture of the natural product. The cycloaddition in the initial step ultimately determined the stereochemical outcome of the target and demonstrated the utility of nitrone cycloaddition in natural product synthesis.



Scheme 4.3 Utilization of nitrone [3+2]-cycloaddition in the synthesis of (±)-lupinine[129]

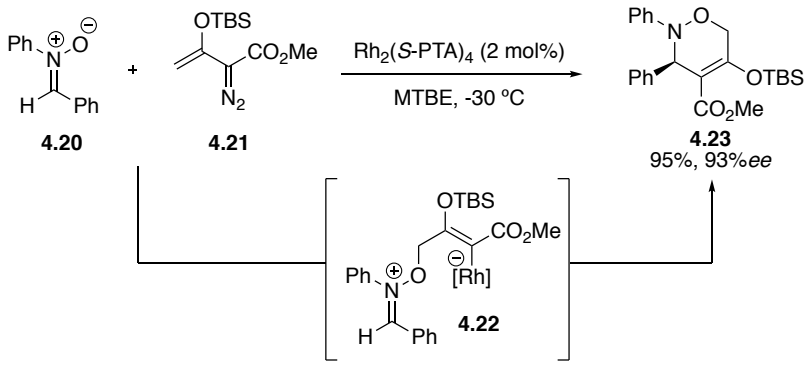
Ryan and coworkers demonstrated the gram-scale flow-synthesis of the poison-arrow frog histrionicotoxin alkaloid (–)-perhydrohistrionicotoxin **4.9** via nitrone [3+2]-cycloaddition (Scheme 4.4).[130] After mesylation of alcohol **4.16**, hydroxylamine condensation and nucleophilic substitution efficiently generated cyclic nitrone **17** in situ. Stereospecific cycloaddition of this nitrone with styrene afforded isoxazolidine **4.18** as a mixture of endo and exo diastereomers. After a number of steps, spirocyclic azacycle

4.19 was furnished on gram scale in enantiomerically pure form. This process demonstrated the potential for in-flow cycloadditions between nitrones and alkenes as a viable synthetic strategy toward natural product synthesis.



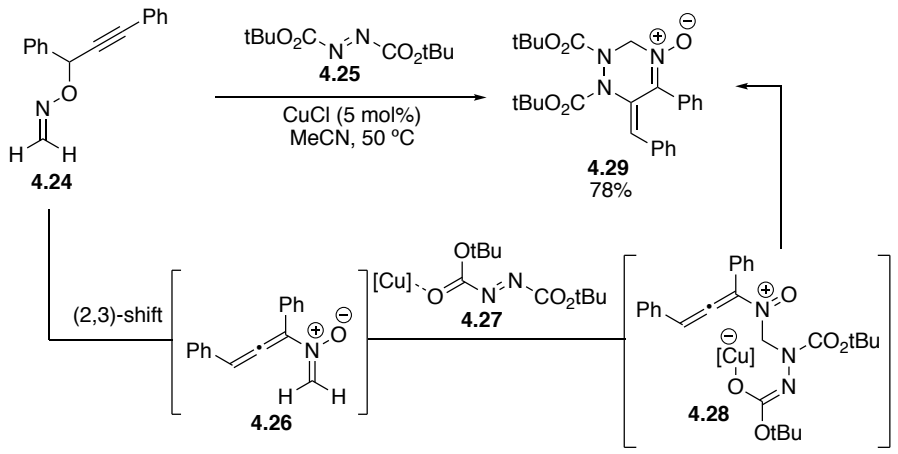
Scheme 4.4 Gram-scale synthesis of **4.19** through nitrone [3+2]-cycloaddition[130]

Another synthetic strategy toward *N*-heterocycles involves the [3+3]-cycloaddition of aldo-nitrones and electrophilic vinyl carbenes. Doyle and coworkers demonstrated the enantioselective [3+3]-cycloaddition of **4.20** and rhodium carbene **4.22** generated from diazo silyl enol ether **4.21** (Scheme 4.5).[131] This method generates functionalized 1,2-oxazines with excellent levels of enantioselectivity under relatively mild conditions. Doyle found that the TBS-silyl enol ether was crucial for the success of this reaction, as it allowed the capture of 1,3-dipoles in a stepwise process that is a formal [3+3]-cycloaddition. This allowed for expansion of the nitrone cycloaddition toolbox and presented the possibility for further exploration into more diverse cycloaddition reactions.



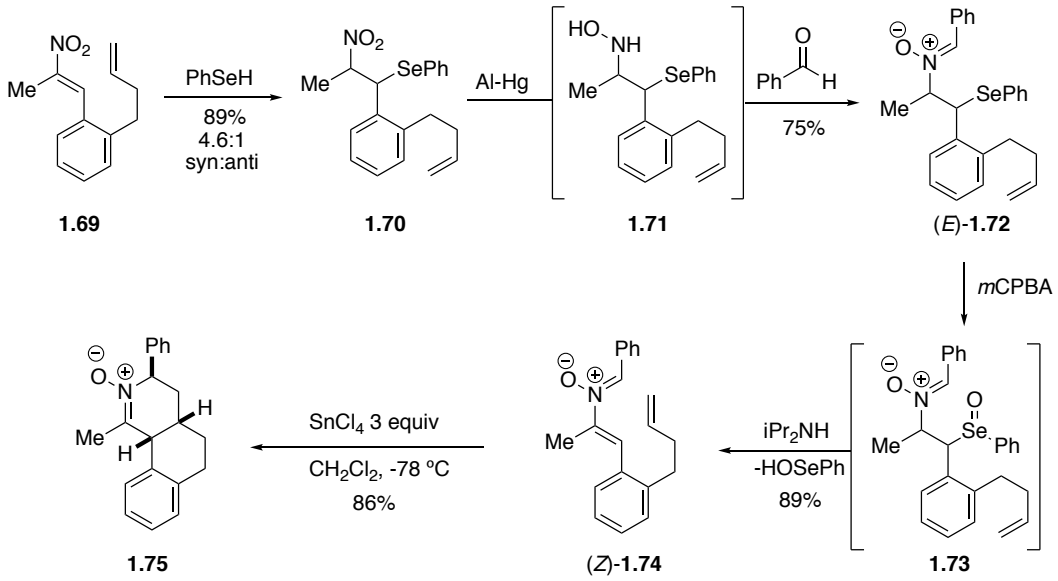
Scheme 4.5 Formal [3+3]-cycloaddition of nitrones and diazo-enol ether – Doyle[131]

The [4+2]-cycloaddition of nitrones has long been a desirable transformation for the generation of heterocycles. Nakamura and Terada showed that *N*-allenyl nitrone **4.26** could be generated in situ via a 2,3-rearrangement of **4.24** in the presence of a catalytic amount of copper (Scheme 4.6).[132] These intermediates were then shown to participate in an inverse-demand cycloaddition with copper-coordinated azodicarboxylate **4.27** to achieve a formal [4+2]-cycloaddition, affording 1,2,4-triazine *N*-oxide **4.29** in high yield. This transformation was shown to be tolerant of a variety of substituents on the propargyl group, but was limited in the imine substitution as 4π-electrocyclization was observed as a competitive pathway. This report presents a stepwise mechanism that is complementary to the initial reports of an intramolecular [4+2]-cycloaddition of nitrones by Denmark.



Scheme 4.6 Formal [4+2]-cycloaddition of *N*-allenyl nitrones[132]

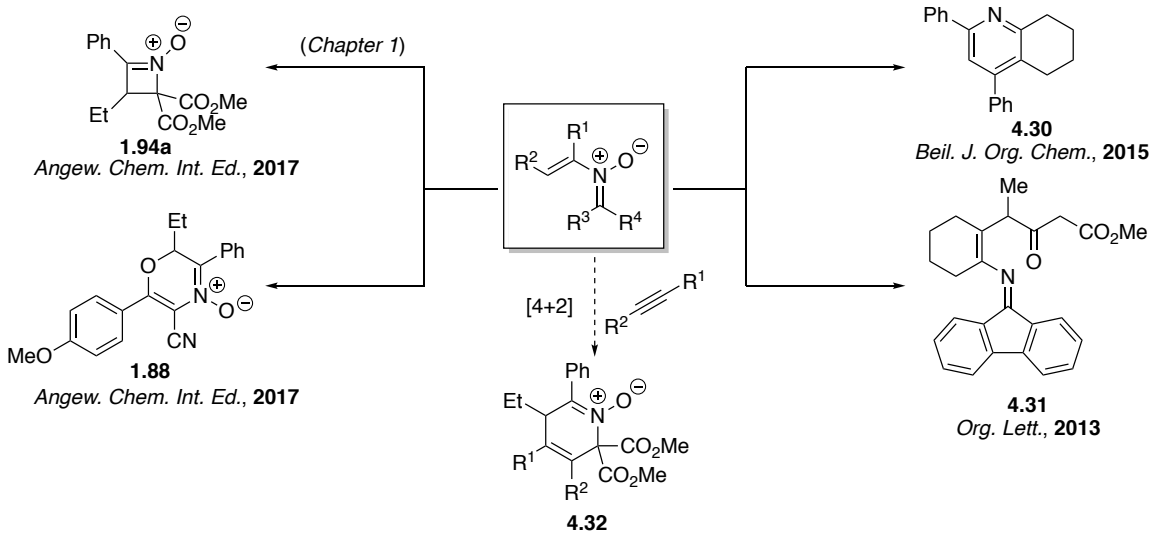
As previously discussed, Denmark and coworkers demonstrated the synthetic utility of *N*-vinylnitrones through a lengthy synthesis of these reactive intermediates from nitro alkenes.[33] Using this method, the authors were able to access *N*-vinylnitrone **1.74** in a modular fashion from **1.69**, but were limited to aldo-nitrones because of the condensation step required for these syntheses. In a single example, they showed that the tethered alkene in **1.74** could be exposed to super-stoichiometric $SnCl_4$ to afford [4+2]-cycloadduct **1.75** in high yield and as a single diastereomer. While this report showed that *N*-vinylnitrones could be viable synthetic intermediates in cycloaddition processes, we wondered if there might be some opportunity to expand on this report. Our mild and extremely modular route to *N*-vinylnitrones made this transformation an appealing target for our future works.



Scheme 4.7 Denmark's [4+2]-cycloaddition of an *N*-vinylnitrone[33]

4.1.2 The [4+2]-Cycloaddition of *N*-Vinylnitrones

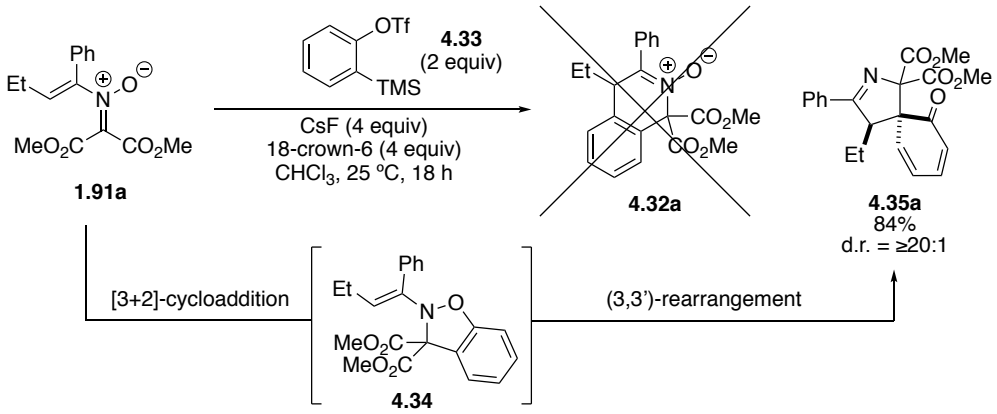
In Chapter 1, the 4π-electrocyclization of *N*-vinylnitrones for the generation of azetidine nitrone **1.94a** was discussed. The resulting unsaturation in these products allowed for myriad diastereoselective functionalization to afford densely substituted azetidine scaffolds in high yield and selectivity. Previously, our lab has also reported the utilization of *N*-vinylnitrones to access morpholine *N*-oxides such as **1.88** and pyridines such as **4.30** via a 6π-electrocyclization process. We have also shown that these intermediates can undergo a Michael addition with electron-deficient allenoates and trigger a [3,3']-sigmatropic rearrangement to access 1,4-enamino ketones **4.31** (Scheme 4.8). Considering Denmark's previous report of an intramolecular [4+2]-cycloaddition of *N*-vinylnitrone (*Z*)-**1.74** and our modular route to these reactive intermediates, we postulated that a similar reaction pathway might be possible to access cyclic nitrone **4.32**.



Scheme 4.8 Synthetic utility of *N*-vinylnitrones; Goal: [4+2]-cycloaddition

4.1.3 Initial Attempts at [4+2]-Cycloaddition of *N*-Vinylnitrones

Our goal of achieving [4+2]-cycloadditions of *N*-vinylnitrones was initially tested using *N*-vinylnitrone **1.91a** with benzyne precursors **4.33** under benzyne generation conditions. Using 4 equivalents of cesium fluoride as a base and an equal amount of 18-crown-6, benzyne precursor **4.33** was efficiently generated and trapped with our nitrone substrate. Surprisingly, the expected [4+2]-cycloadduct **4.32a** was not obtained, but rather an interesting dearomatized spirocyclic pyrroline **4.35a** was isolated in high yield and diastereoselectivity. The mechanism is proposed to proceed through a [3+2]-cycloaddition of benzyne and **1.91a** to generate *N*-vinyl benzisoxazoline **4.34**, followed by a facile [3,3']-sigmatropic rearrangement to yield the spirocyclic heterocycle. This structure was confirmed by both NMR and XRD analyses. Further investigation into the mechanism was needed to confirm our proposed pathway.



Scheme 4.9 Initial results – Abdullah Alshreimi

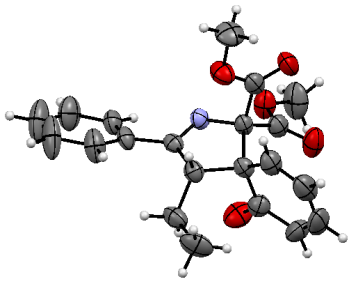
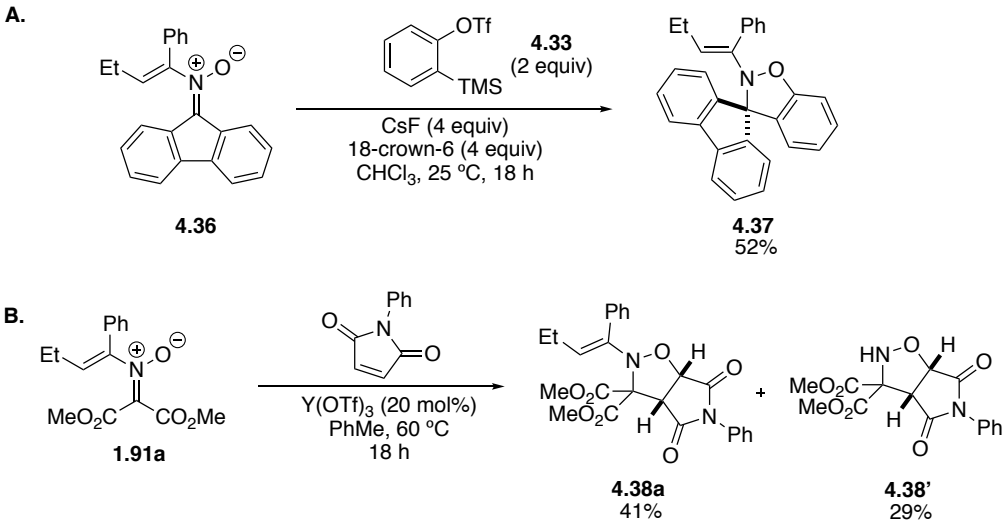


Figure 4.2 X-Ray Crystallography of **4.35a** – Prof. Donald J. Wink

Hoping to elucidate mechanistic details of this cycloaddition/rearrangement cascade, other nitrones were tested to determine if the same outcome could be observed. When fluorenone *N*-vinylnitrone[45b] **4.36** was applied to the same reaction conditions, the [3+2]-cycloadduct was obtained in modest yield (Scheme 4.10A). It is hypothesized that the sterics and electronics of this *N*-vinyl benzisoxazoline hinder the desired [3,3']-rearrangement and allow for isolation of the corresponding cycloaddition intermediate. To provide further evidence that this process does proceed through a [3+2]-cycloadduct, **1.91a** and *N*-phenylmaleimide were subjected to Lewis acid catalyzed cycloaddition conditions used previously in our lab (Scheme 4.10). After [3+2]-cycloaddition, the resulting *N*-vinyl isoxazolidine **4.38a** is unable to proceed through the [3,3']-sigmatropic rearrangement and was isolated as a mixture with the corresponding hydrolyzed

isoxazolidine **4.38'** in modest yield (Scheme 4.10B). With some evidence to support our proposed mechanism, we decided to turn our studies towards looking at the steric and electronic substrate tolerance of this interesting cascade process.



Scheme 4.10 Mechanistic evidence supporting [3+2]-cycloaddition pathway

4.1.4 [3,3']-Sigmatropic Rearrangements of *N,O*-Divinyl Intermediates

Our group has previously reported the generation and [3,3']-sigmatropic rearrangement of *N*,*O*-divinyl hydroxylamine derivatives for the construction of *N*-heterocycles. In 2010, early investigations into these reactive intermediates showed that when benzoylnitrile derived *O*-allyl oxime ether **4.39** was exposed to an Ir(I) hydride catalyst, isomerization gave Paal-Knorr intermediate **4.40**, tautomerization gave *N,O*-divinyl hydroxylamine **4.40'** and spontaneous [3,3']-rearrangement gave pyrroles **4.41** in high yield (Scheme 4.11).[133] This transformation inspired our group to further investigate the potential of *N,O*-divinyl intermediates as useful synthetic tools for heterocycle construction.

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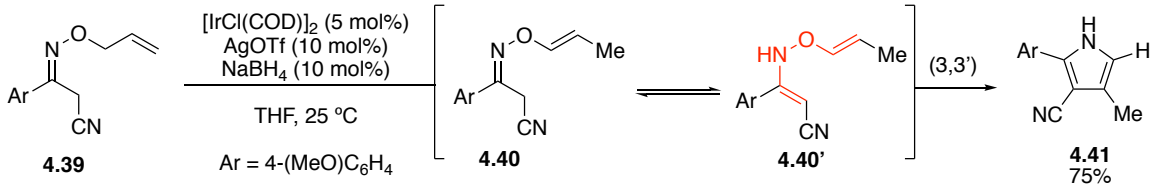
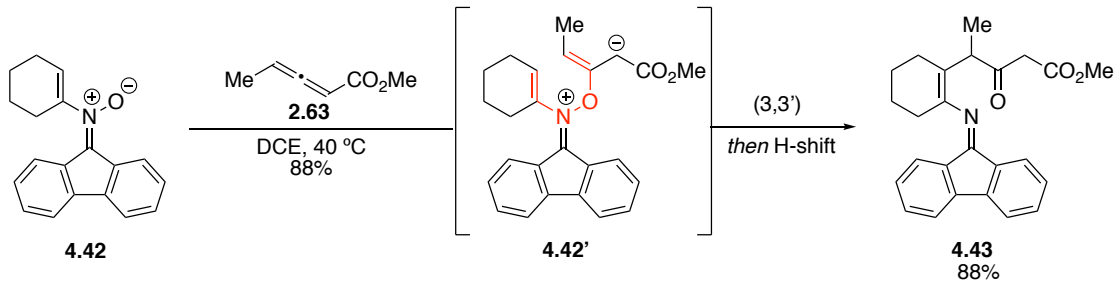


Scheme 4.11 Pyrrole construction via [3,3']-rearrangement of *O*-vinyl oxime ether[133]

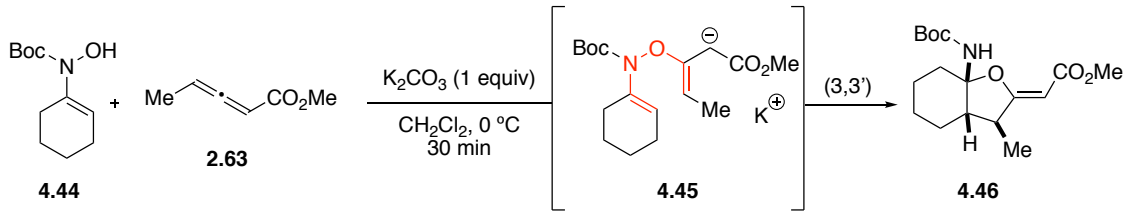
In 2014, Anderson and coworkers showed that *N*-vinylnitrones were valuable starting materials to access *N,O*-divinyl intermediates and initiate [3,3']-sigmatropic rearrangements to give interrupted Paal-Knorr reaction products (Scheme 4.12).[84] Addition of fluorenone nitrone **4.42** to electron-deficient allenoate **2.63** smoothly generated the divinyl iminium zwitterion **4.42'** which then proceeded through a [3,3']-rearrangement and tautomerization to afford fluorenone imine-protected 1,4-diketone surrogate **4.43** in excellent yield. These products are particularly interesting because they show that under mild conditions, Paal-Knorr intermediates can be accessed before thermodynamic pyrrole formation. This report led us to postulate whether allenoates and *N*-vinyl hydroxylamines could be utilized in the same type of transformation to expand our [3,3']-rearrangement reactivity studies of *N,O*-divinylhydroxylamines.



Scheme 4.12 Synthesis of 1,4-enamino ketones via [3,3']-rearrangement[84]

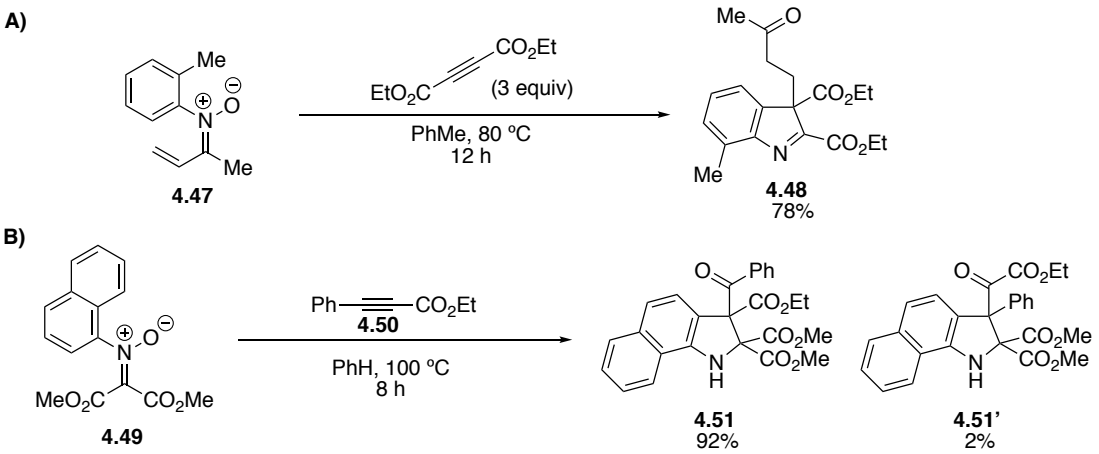
As discussed in Chapter 2, our latest publication involved the addition of *N*-vinyl hydroxylamine **4.44** to electron-deficient allenoates **2.63** to generate transient *N,O*-divinyl hydroxylamine intermediate **4.45** (Scheme 4.13).[134] Like previous works, this

intermediate was shown to undergo facile [3,3']-rearrangement to afford, after *O*-cyclization, 2-amino tetrahydrofurans **4.46**. This transformation was highly diastereoselective and allowed for the isolation of 1,4-dicarbonyl surrogates without the formation of pyrrole under mild basic conditions. Furthermore, **4.46** can be used as an intermediate for the aza-Petasis-Ferrier rearrangement to access diastereoselective cyclopentenones and cyclic amino acid derivatives.



Scheme 4.13 Generation and [3,3']-rearrangement of *N,O*-divinylhydroxylamines[134]

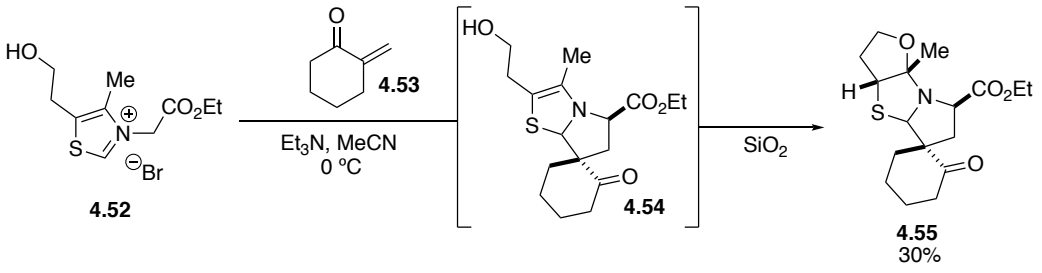
Yang and coworkers demonstrated a [3+2]-cycloaddition/[3,3']-rearrangement cascade from unsaturated keto-nitrone **4.47** and diethyl acetylene dicarboxylate (DEAD) to afford C3-quaternary indolenines **4.48** (Scheme 4.14A).[135] The authors proposed that this reaction proceeds through a stepwise Michael addition and hydrolysis to afford an *N,O*-divinyl intermediate, which then undergoes [3,3']-rearrangement to afford the product. Similarly, Tomioka and coworkers used unsymmetrical alkyne **4.50** in a [3+2]-cycloaddition with malonate-derived *N*-arylnitrone **4.49** (Scheme 4.14B).[136] After [3,3']-rearrangement, the major product of this reaction was indoline **4.51** with a minor amount of the opposite [3+2]-regioisomer product **4.51'**. These two examples demonstrate the synthetic utility of nitrones in cascade reactions to afford densely functionalized heterocycles and excited us to continue to explore the recently discovered transformation of our *N*-vinylnitrones and benzyne intermediates to construct spirocyclic pyrrolines.



Scheme 4.14 Previous [3+2]/[3,3']-cascade reactions of nitrones[135,136]

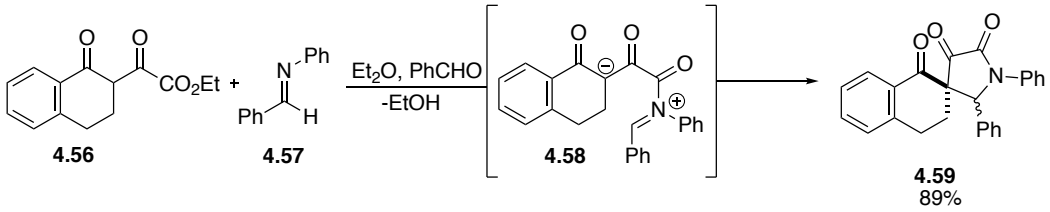
4.1.5 Previous Strategies for the Construction of Spirocyclic *N*-Heterocycles

Spirocyclic heterocycles represent a challenging and valuable biomimetic scaffold in drug discovery. While carbon and oxygen containing spirocyclic compounds are well know, their *N*-heterocyclic counterparts are not as thoroughly studied due to limited examples of their preparation. Traditionally, spirocyclic pyrrolines related to **4.35a** are made via [3+2]-cycloaddition of azomethine ylides with exocyclic α,β-unsaturated ketones. Kraus and Nagy displayed this strategy to construct spirocyclic 2-amino-3-thio tetrahydrofuran **4.55** from cycloaddition of an azomethine ylide generated from thiazolium salt **4.52** and vinyl ketone **4.53** (Scheme 4.15).[137] The alcohol in **4.54** then spontaneously cyclized with the thiazole fragment to afford the tricyclic core of this interesting scaffold. Using this strategy, the authors went on to successfully synthesize (±)-α-allokainic acid, a marine algae natural product with anti-epilepsy and anti-Alzheimer's properties. This shows the importance of spirocyclic *N*-heterocycles in disease treatment and prompted more investigation into these privileged structures.



Scheme 4.15 Thiazolium azomethine ylide [3+2]-cycloaddition for *N*-spirocycles[137]

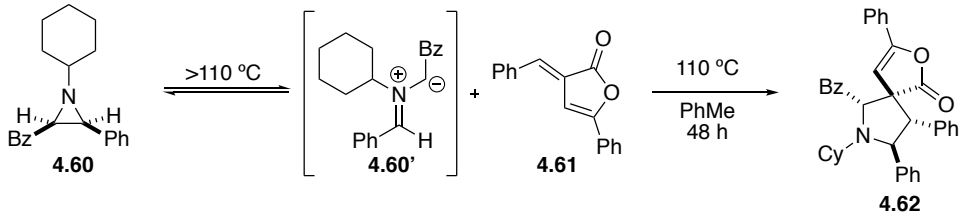
Another opportunity for the construction of spirocyclic pyrrolidines is through an acyl-iminium Mannich cyclization as reported by Emerson and Titus (Scheme 4.16).[138] Esters of glyoxylic acids are known to readily undergo condensation with imines to access highly reactive *N*-acyl-iminium ions. The authors subjected **4.56** and imine **4.57** to reaction conditions to generate acyl-iminium zwitterion **4.58** which then underwent a Mannich cyclization to afford **4.59** in high yield but with low diastereoselectivity. These spirocyclic azacycles were then screened and showed desirable inhibition against mold and as antibiotics. Other spirocyclic azacycles have also shown high biological activity and justified further exploration into our transformation.



Scheme 4.16 Spirocyclic pyrrolidine-2,3-dione via acyl-iminium Mannich cyclization[138]

Raghunathan and coworkers showed that aziridines could also be used as synthetic intermediates for the construction of spirocyclic *N*-heterocycles. By heating electron-deficient aziridine **4.60** to high temperature, strain-release ring-opening gave azomethine ylide **4.60'**, which then formed **4.62** via [3+2]-cycloaddition with arylidine-5-butenolide **4.61** (Scheme 4.17).[139] These compounds were screened against a variety of

bacteria for inhibition and the authors found "good inhibition" of S. dysenteriae, salmonella, S. aureus, and E. coli. The biological activity of the spirocyclic compounds in these selected examples highlight the potential for these scaffolds in drug discovery and natural product synthesis. This potential excited us and encouraged us to perform more exploration of our method.



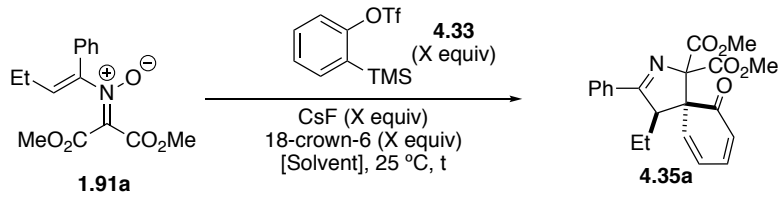
Scheme 4.17 Aziridines as azomethine ylide precursors for spirocycle construction[139]

4.2 Cycloaddition/Rearrangement Cascade for Spirocyclic 1-Pyrrolines

4.2.1 Optimization of Cycloaddition/Rearrangement Cascade

With our hypothesis that a diverse library of spirocyclic pyrrolines could be accessed using our method, optimization studies were first performed to determine the ideal reaction conditions. Using *N*-vinylnitrone **1.91a** as our model substrate, the stoichiometry, solvent, and time was investigated (Table 4.1). It was found that the reaction was complete in just 2 hours instead of overnight (entry 2). All solvents screened gave satisfactory results; however, it was found that 18-crown-6 ether was challenging to separate from the pyrroline product via column chromatography. The low solubility of 18-crown-6 in PhMe and iPrOAc made removal of the majority of the 18-crown-6 from the crude product mixture possible by filtering through celite without any reduction in yield. The reaction stoichiometry of the benzyne precursor could be reduced to 1.5 equivalents without a loss of yield and reduction of the equivalents of CsF and 18-crown-6 also gave satisfactory yields and simplified purification. The optimal conditions

were determine to be use of iPrOAc as the reaction solvent with blank equivalents of blank and blank for the generation of the benzyne intermediate (entry 14).



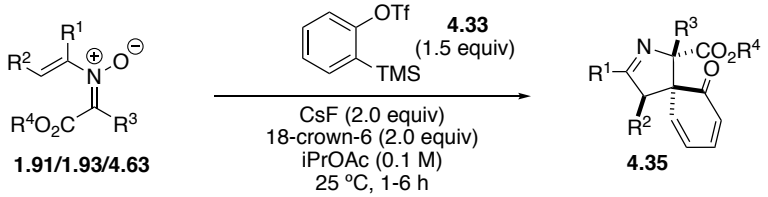
Entry	4.33	Eq CsF	Eq 18-c-6	Solvent	[M]	time (h)	% Yield[a]	d.r.
1	2.0	4.0	4.0	$CHCl_3$	0.1	18	84	≥20:1
2	1.5	4.0	4.0	$CHCl_3$	0.1	2	75	19:1
3	1.5	4.0	4.0	DCE	0.1	2	>95	≥20:1
4	1.5	4.0	4.0	Acetone	0.1	2	73	≥20:1
3	1.5	4.0	4.0	MeCN	0.1	2	68	≥20:1
4	1.5	4.0	4.0	PhMe	0.1	2	90	≥20:1
5	1.5	4.0	4.0	iPrOAc	0.1	2	72	≥20:1
6	1.5	4.0	4.0	THF	0.1	2	77	≥20:1
7	1.5	4.0	4.0	CF_3Ph	0.1	2	64	≥20:1
8	1.5	4.0	4.0	PhMe	0.05	2	96	≥20:1
9	1.5	4.0	4.0	PhMe	0.25	2	52	≥20:1
10	1.5	4.0	4.0	DCE	0.05	2	97	≥20:1
11	1.5	4.0	4.0	DCE	0.25	2	98	≥20:1
12	3.0	4.0	4.0	PhMe	0.1	2	71	≥20:1
13	3.0	4.0	4.0	iPrOAc	0.05	2	72	17:1
14	1.5	2.0	2.0	iPrOAc	0.1	2	96 (95)[b]	≥20:1
15	1.5	2.0	2.0	iPrOAc	0.1	1	85	≥20:1

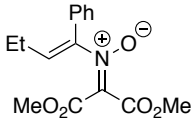
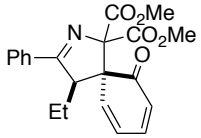
[a] % Yield determined by ^1H NMR using CH_2Br_2 as a reference. [b] Isolated yield of **4.35a**

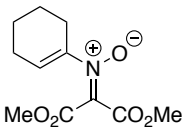
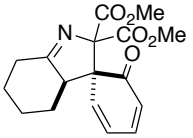
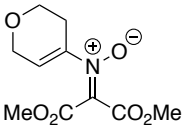
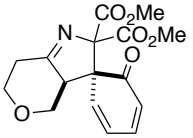
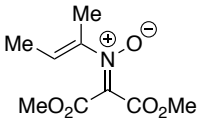
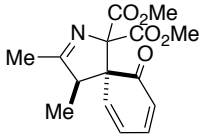
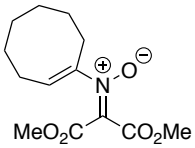
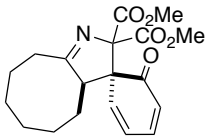
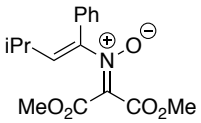
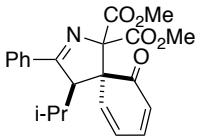
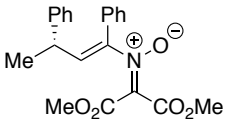
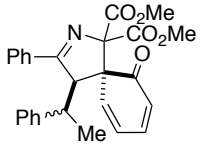
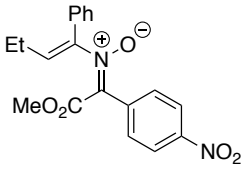
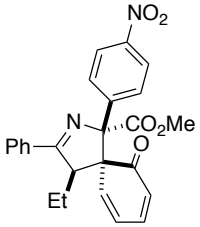
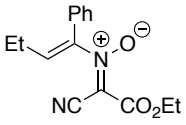
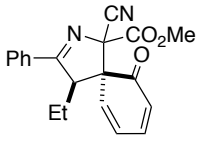
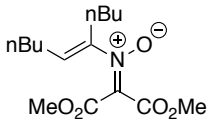
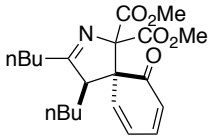
Table 4.1 Optimization of solvent, time, and stoichiometry

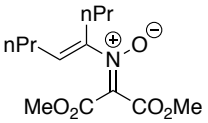
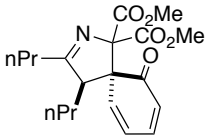
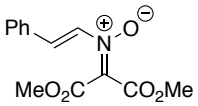
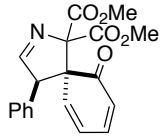
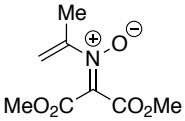
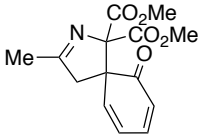
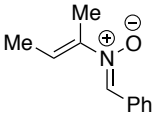
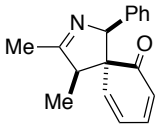
With optimal conditions in hand, we set out to test the scope of the transformation with respect to *N*-vinylnitrone substitution patterns. A variety of nitrones formed from a-styrenyl and alkenyl boronic acids that we have previously used for electrocyclization studies (**1.91** and **1.93**, see Chapters 1 and 3) were evaluated under the optimal reaction conditions. In addition, substrates such as **4.63** and **4.93** were tested for the formation of

4.35 to see if less complicated substitution patterns were also tolerated (Table 4.2). Aryl-substituted **1.91**, **1.93**, and **4.63** showed excellent reactivity for this reaction and afforded spirocyclic pyrrolines in high yield and excellent diastereoselectivity. Nitrones **1.93a,e,f,** and **4.63a** with alkyl-substituted *N*-vinyl substituents gave the desired product as a single diastereomer; however, *N*-cyclooctenyl **1.93b** and *N*-5-decenyl **1.93c** gave diminished selectivity. Monosubstituted *N*-vinyl substituents gave no product (entries 12 and 13). It is postulated that aryl-substituted nitrones give higher yields and more stable products because the imine of **4.35** is in conjugation with the aryl ring. Substrates without this conjugation such as **4.35j-l** are not stabilized and result in low selectivity or are not formed. Nitrone **4.36h**, prepared by a procedure reported by the Sammakia group[140] involving 1,4-elimination of an α-halo ketonitrone, decomposed under the cascade reaction conditions and suggested that specific nitrone substitution patterns are required to obtain the appropriate electronic requirements for pyrroline formation to occur. In the case of unsymmetrical nitrone **1.91o**, a single diastereomer of **4.35** was formed suggesting that the [3,3']-sigmatropic rearrangement portion of the cascade process is facial-selective and should allow for asymmetric manipulation in the future



Entry	Nitrone	Product	%Yield[a]
1	 1.91a	 4.35a	95 d.r. = ≥20:1

2	 **1.93e**	 **4.35b**	95 d.r. = ≥20:1
3	 **1.93f**	 **4.35c**	70 d.r. = ≥20:1
4	 **1.93a**	 **4.35d**	90 d.r. = ≥20:1
5	 **4.63a**	 **4.35e**	69 d.r. = ≥20:1
6	 **4.63b**	 **4.35f**	86 d.r. = ≥20:1
7	 **1.93r**	 **4.35g**	72 d.r. = 2:1
8	 **1.91o**	 **4.35h**	74 d.r. = ≥20:1
9	 **4.63c**	 **4.35i**	40 d.r. = 2:1
10	 **1.93b**	 **4.35j**	91 d.r. = 2:1

11	 **1.93c**	 **4.35k**	86 d.r. = 3:1
12	 **1.93i**	 **4.35l**	-
13	 **4.93j**	 **4.35m**	-
14	 **4.36h**	 **4.35n**	-

[a] Isolated yield of **4.35a – 4.35k**

Table 4.2 Scope of nitrones for the formation of **4.35**

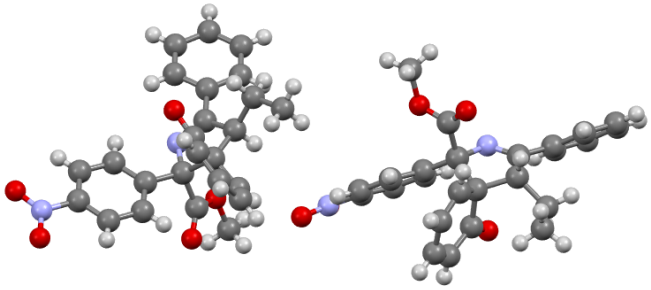
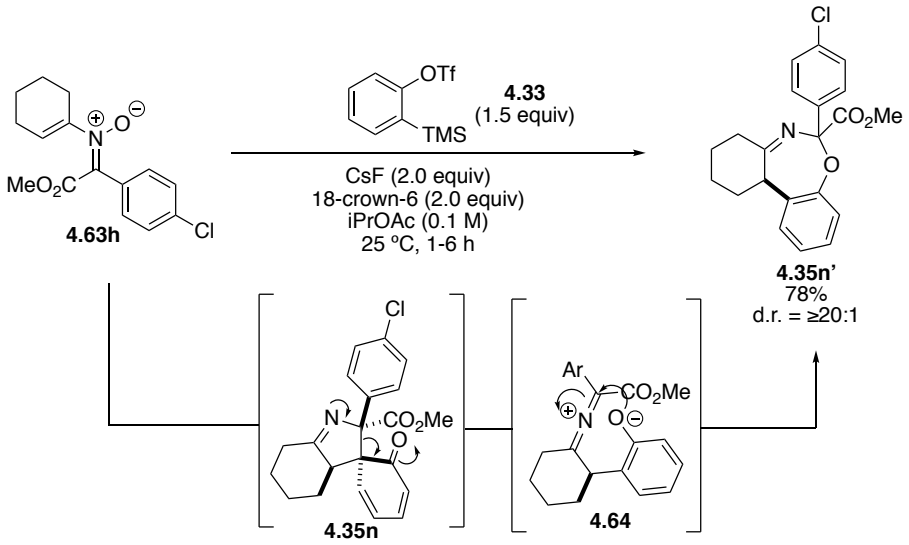


Figure 4.3 X-Ray Crystallography of **4.35h** – Prof. Donald J. Wink

When methyl benzoylformate derived nitrone **4.63h** was treated with benzyne under the optimal cycloaddition and rearrangement cascade reaction conditions, the corresponding spirocyclic pyrroline product was not observed and an alternative rearranged product was obtained. We propose that after facile cascade formation of desired product **4.35n**, a retro-Mannich reaction to form iminium-phenoxide **4.64** occurs followed by cyclization to give unusual 1,3-benzoxazepine hemiaminal **4.35n'** in high

yield. We proposed that this type of pyrroline ring-opening reactivity might be more likely for substrates bearing an aryl group due to a more stabilized aza-allenium intermediate.



Scheme 4.18 Further rearrangement from non-stabilized pyrrolines

Observation of rearomatization of these spirocyclic pyrrolines in some cases prompted us to investigate further. Single-crystal X-ray analysis of two related products revealed that **4.35a** and **4.35b** differed in bond lengths by a small amount. This suggests that the electronics of these substrates lead to a slightly higher propensity of **4.35a** to undergo further rearrangement to afford the 1,3-benzoxazepine products. The mechanism and limitations of this pathway are currently under investigation in our lab.

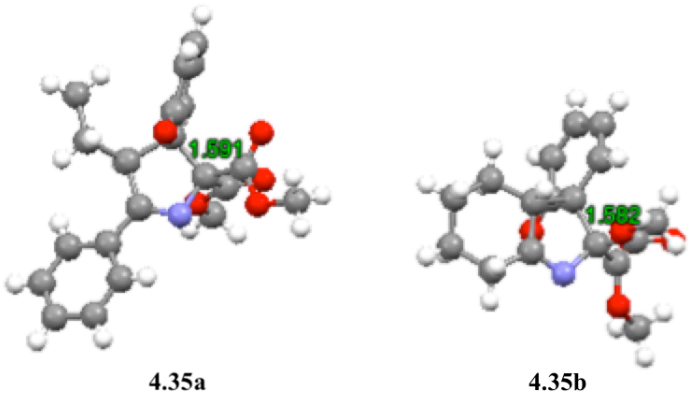
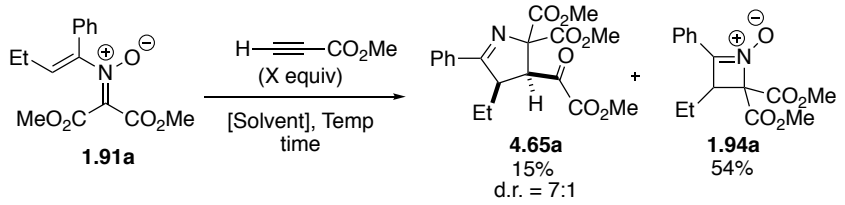


Figure 4.6 Slightly longer bond length in **4.35a** when compared to **4.35b**

4.2.2 Cascade Reaction of *N*-Vinylnitrones with Acyclic Alkynes

We next turned our attention to alkynes other than benzyne to determine the scope of dipolarophiles in the cycloaddition and rearrangement cascade reaction. Initially, we decided to test propiolate due to its activity in related cycloaddition processes. As depicted in Table **4.3**, optimization was performed with **1.91a** and the corresponding 4-acyl-1-pyrroline was obtained in high yield. At room temperature, modest yields of the desired product **4.65a** were observed in most solvents. Increasing the reaction time gave a slight increase in yield (entries 10 and 11). Increasing the temperature to 40 ºC led to an increase in the yield of pyrroline; however, competitive 4π-electrocyclization was also observed (entries 12 and 13). Our previous optimization studies of 4π-electrocyclizations of *N*-vinylnitrones provided insight into the best solvents to deter competitive formation of **1.94a**. Pyrroline **4.65a** was produced in high yield when *N*-vinylnitrone **1.91a** was treated with methyl propiolate at 40 ºC in iPrOAc. We wondered if *N*-vinylnitrones that are unable to undergo 4π-electrocyclization might also give higher yields.



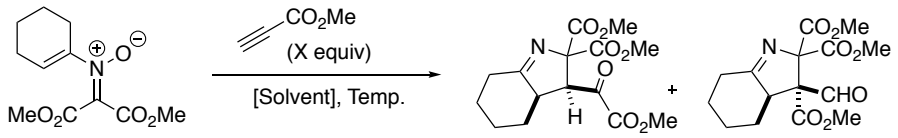
Entry	Alkyne	Solvent	[M]	Temp. ºC	time (h)	% Yield[a]	d.r.	1.94a
1	1.5	$CHCl_3$	0.1	25	18	50	15:1	17
2	1.5	PhMe	0.1	25	18	58	≥20:1	6
3	1.5	$PhCF_3$	0.1	25	18	69	≥20:1	13
4	1.5	THF	0.1	25	18	38	2:1	26
5	1.5	iPrOAc	0.1	25	18	40	≥20:1	13
6	1.5	TFE	0.1	25	18	15	2:1	80
7	1.5	MeOH	0.1	25	18	31	2:1	58
8	1.5	DMSO	0.1	25	18	27	3:1	27
9	1.5	C_6F_5H	0.1	25	18	58	≥20:1	19
10	1.5	$PhCF_3$	0.1	25	24	71	≥20:1	15
11	1.5	PhMe	0.1	25	36	71	≥20:1	13
12	1.5	iPrOAc	0.1	40	18	72	≥20:1	15
13	1.5	MeOH	0.1	40	18	20	1:1	67
14	1.5	$CHCl_3$	0.1	40	18	55	≥20:1	34
15	3.0	iPrOAc	0.1	40	18	59	≥20:1	14
16	0.5	iPrOAc	0.1	40	18	39	≥20:1	45
17	1.5	iPrOAc	0.25	40	18	73	≥20:1	14

[a] % Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference.

Table 4.3 Optimization of cascade reaction of **1.91a** with methyl propiolate

When cyclohexenyl nitrone **1.93e** was used in lieu of **1.91a**, a cycloaddition and rearrangement cascade reaction was observed to give 4-acyl-1-pyrroline **4.66a** (Table 4.4). Side product formation via 4π-electrocyclization was not observed since **1.93e** does not participate in this type of potentially competitive reactivity. Across a variety of reaction conditions, the major product of the transformation was the unexpected inverse-demand [3+2]-cycloaddition product generated from oxygen attack at C2-position of the propiolate. A trace amount of the normal-demand product was also observed by NMR.

Once again, iPrOAc was chosen as the optimal solvent since this reaction medium gave a high yield of **4.66a** as a single diastereomer. It was then hoped that other unactivated terminal or internal alkynes might also participate in this reaction to proved diverse 4-acyl-1-pyrroline derivatives.



1.93e **4.66a** **4.66a'**

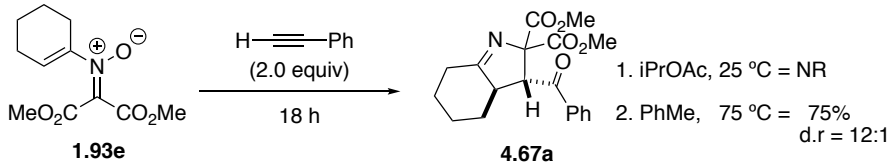
Entry	Alkyne	Solvent	[M]	Temp. ºC	time (h)	% Yield[a]	d.r.	4.66a'
1	1.5	$CHCl_3$	0.1	25	18	51	≥20:1	6
2	1.5	PhMe	0.1	25	18	53	1:1	5
3	1.5	$PhCF_3$	0.1	25	18	82	10:1	1
4	1.5	THF	0.1	25	18	52	3:1	2
5	1.5	iPrOAc	0.1	25	18	53	≥20:1	1
6	1.5	TFE	0.1	25	18	63	1:1	5
7	1.5	MeOH	0.1	25	18	64	≥20:1	5
8	1.5	DMSO	0.1	25	18	49	1:1	4
9	1.5	C_6F_5H	0.1	25	18	76	4:1	5
10	1.5	PhMe	0.1	25	36	80	14:1	2
11	1.5	$PhCF_3$	0.1	40	18	90	≥20:1	6
12	1.5	iPrOAc	0.1	40	18	90	≥20:1	5
13	1.5	MeOH	0.1	40	18	80	≥20:1	0
14	1.5	$CHCl_3$	0.1	40	18	79	≥20:1	9
15	3.0	iPrOAc	0.1	40	18	91	≥20:1	8
16	0.5	iPrOAc	0.1	40	18	55	≥20:1	4
17	1.5	iPrOAc	0.25	40	18	93	≥20:1	7

[a] % Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference.

Table 4.3 Optimization of cascade reaction of **1.93e** with methyl propiolate

Initial reactivity of **1.93e** with phenylacetylene was investigated by Robert Zhang. Subjecting these reagents in iPrOAc at room temperature gave no reactivity (Scheme 4.19). Increasing the temperature led to a small amount of formation of **4.67a**, and by

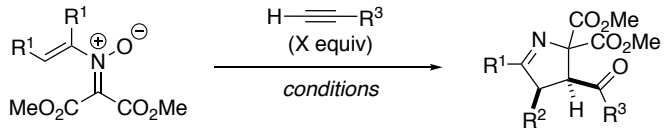
switching to PhMe and heating at 75 ºC, the desired product was obtained in satisfactory yield and selectivity, but as the opposite *trans*-diastereomer compared to **4.66a**. This assignment is based on extensive ^{1}H nOe NMR analysis. This selectivity will be explored in the future and is postulated to be due to isomerization of the *cis*-pyrroline to *trans*-**4.66a.**



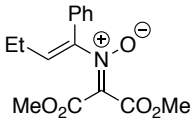
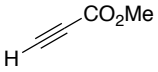
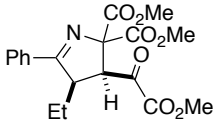
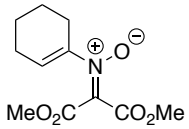
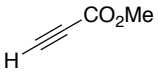
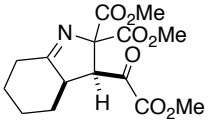
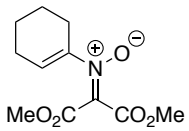
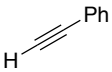
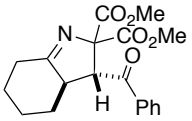
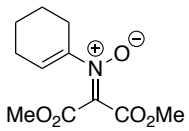
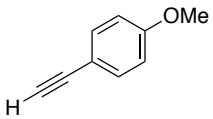
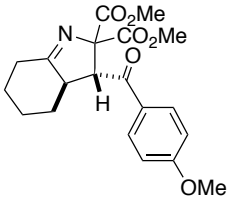
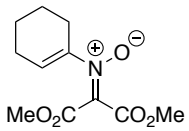
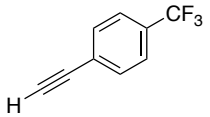
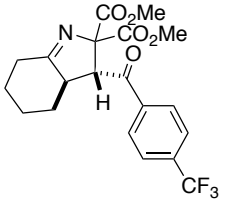
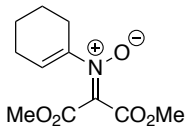
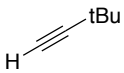
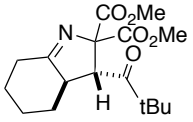
Scheme 4.19 Cycloaddition cascade with unactivated alkynes – Robert Zhang

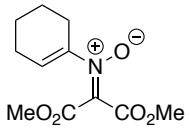
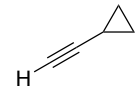
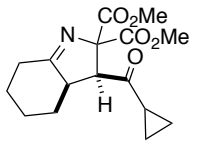
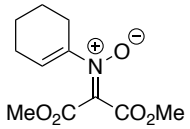
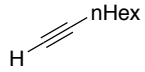
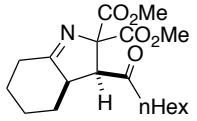
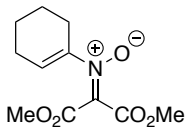
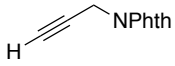
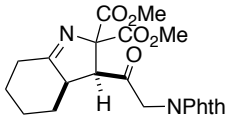
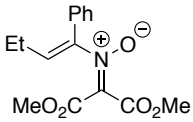
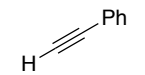
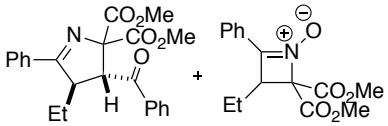
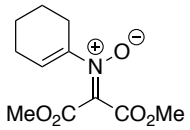
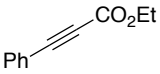
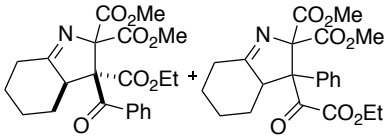
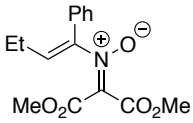
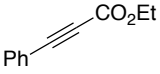
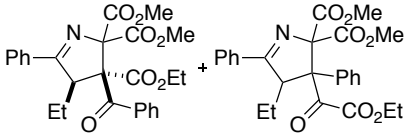
The scope of our cascade reaction of *N*-vinylnitrones with acyclic alkynes was then explored. In addition to propiolate adducts **4.66a** and **4.66b**, a variety of unactivated aryl-acetylenes and terminal aliphatic alkynes showed reactivity with **1.93e** (Table 4.4). Due to the high temperature required for unactivated alkynes to participate, only **1.93e** was a viable option. When **1.91a** was utilized, only a minor amount of **4.67h** was observed along with **1.94a** (entry 10). In the case of internal alkyne such as ethyl phenylpropiolate, high temperatures were required, resulting in a modest mixture of two regioisomeric pyrrolines in the case of **4.67i** and **4.67i'**. With **1.91a**, only trace amount of the desired product was observed with the majority of the reaction being azetidine nitrone **1.94a**. We wondered if there may be some opportunity for Lewis acid activation to perturb the [3+2]-cycloaddition of our *N*-vinylnitrones with internal alkynes to expand the used of all of our nitrone intermediates without the use of elevated temperatures. In this way, 4π-electrocyclization could be avoided giving an expanded library of 4-acyl-1-pyrrolines scaffolds. We also hoped to merge our benzyne cascade chemistry with our

acyclic alkyne chemistry to access cyclic alkyne precursors to form spirocyclic pyrrolines that are more stable and might exhibit different pharmacological properties.



1.91/1.93 **4.66/4.67**

Entry	Nitrone	Alkyne	Products	%Yield[a]
1	 **1.91a**	 **1.5 equiv**	 **4.66a**	72[b] d.r. = ≥20:1
2	 **1.93e**	 **1.5 equiv**	 **4.66b**	90[b] d.r. = ≥20:1
3*	 **1.93e**	 **2.0 equiv**	 **4.67a**	75[c] d.r. = 12:1
4*	 **1.93e**	 **2.0 equiv**	 **4.67b**	88[c] d.r. = 12:1
5*	 **1.93e**	 **2.0 equiv**	 **4.67c**	84[c] d.r. = 17:1
6*	 **1.93e**	 **2.0 equiv**	 **4.67d**	54[c] d.r. = 10:1

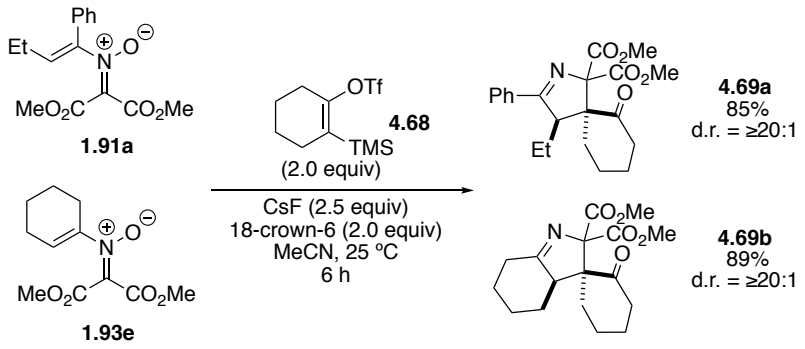
7*	 **1.93e**	 **2.0 equiv**	 **4.67e**	71[c] d.r. = 17:1
8*	 **1.93e**	 **2.0 equiv**	 **4.67f**	78[c] d.r. = ≥20:1
9*	 **1.93e**	 **2.0 equiv**	 **4.67g**	74[c] d.r. = ≥20:1
10*	 **1.91a**	 **2.0 equiv**	 **4.67h** **1.94a**	**4.67h** 15%, 7:1[c] **1.94a** 54%[c]
11	 **1.93e**	 **1.5 equiv**	 **4.67i** **4.67i'**	**4.67i** 56%, ≥20:1[c] **4.67i'** 22%, 1:1[c]
12	 **1.91a**	 **1.5 equiv**	 **4.67j** **4.67j'**	**4.67j** 10%, ≥20:1[c] **4.67j'** 10%, 2:1[c] **1.94a** 70%[c]

[a] Isolated yield**.** [b] iPrOAc (0.1 M), 40 ºC, 18 h. [c] PhMe (0.1 M), 75 ºC, 18 h. *Robert Zhang performed the optimization and scope depicted in entries 3 – 10.

Table 4.4 Acyclic alkyne scope in cascade reaction with **1.91a** and **1.93e**

4.2.3 Cyclic Alkyne Precursors in Novel Cascade Reaction of *N*-Vinylnitrones

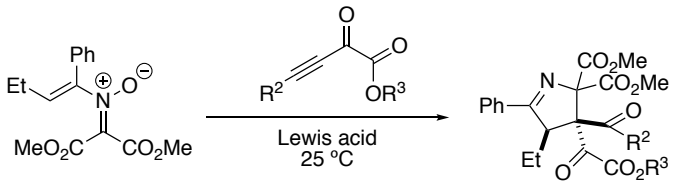
Initial investigations into the [3+2]-cycloaddition/[3,3']-sigmatropic rearrangement cascade of **1.91a** and **1.93e** with cyclohexyne precursor **4.68** have shown promising results (Scheme 4.20). Robert Zhang has again elucidated the optimal conditions for this transformation and these results will be expanded on in the future.



Scheme 4.20 Cyclic alkyne [3+2]/[3,3']-cascade – Preliminary data – Robert Zhang

4.2.4 Lewis Acid Catalyzed Cycloaddition Cascade

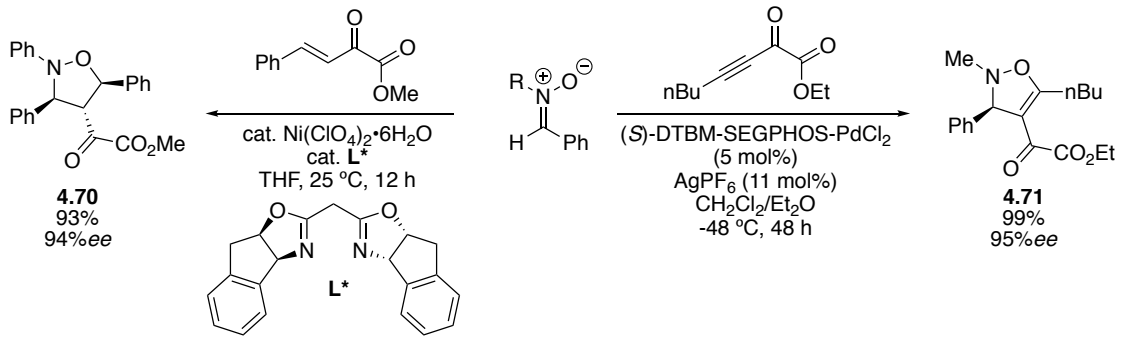
It is well known that Lewis acid coordination to dipolarophiles sufficiently lowers $LUMO_{alkyne}$ to allow orbital overlap with $HOMO_{nitrone}$. With regards to applying internal alkynes in this transformation, it was wondered if activation of the dipolarophile would provide enough lowering of the $LUMO_{alkyne}$ to allow mild conditions to be used to access 4-acyl-1-pyrrolines without the risk of byproduct azetidine nitrone formation. Furthermore, chiral ligands used with these Lewis acids may be able to direct the [3,3']-rearrangement to afford enantiopure products (Scheme 4.21).



Scheme 4.21 Goal: mild Lewis acid activation for cascade reaction

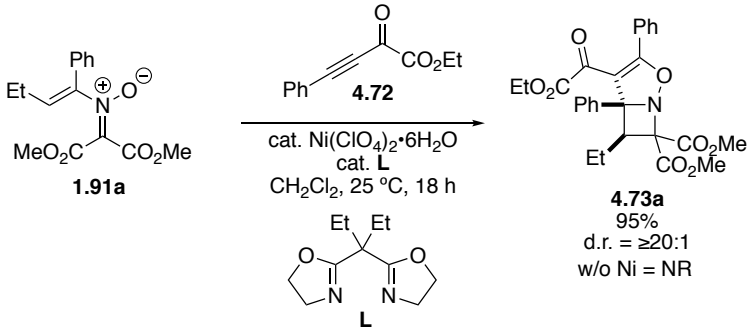
Lewis acid activation of a dipolarophile in the [3+2]-cycloaddition with nitrones has been demonstrated recently by the groups of Mikami and Fu.[141,142] Fu and coworkers applied chiral nickel catalysis to α,β-unsaturated acylcarboxylates, lowering the $LUMO_{alkene}$ to achieve highly selective [3+2]-cycloaddition with high yield and stereoselectivity for **4.70** (Scheme 4.22 left). Mikami and Honda used similar activation

of glyoxylate alkynes in the presence of a chiral palladium complex to afford isoxazoline **4.71** quantitatively and with excellent enantioselectivity. It was hoped that this type of dipolarophile activation might be applicable to our system to not only afford 4-acyl-1-pyrrolines under mild conditions, but also as enantiopure products.



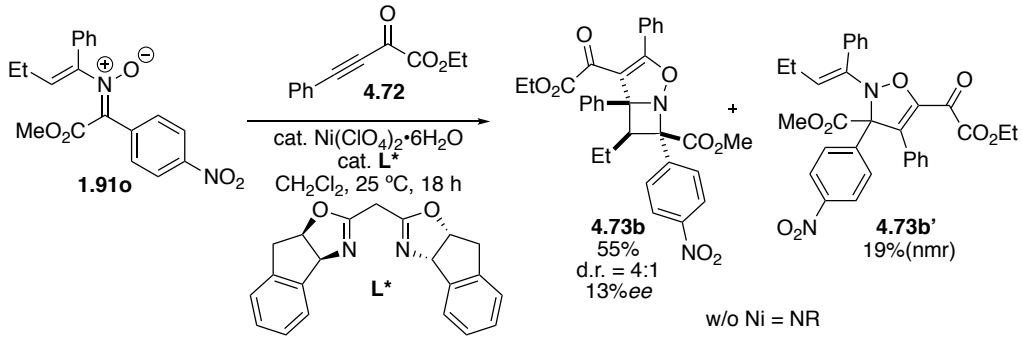
Scheme 4.22 Lewis acid activation of alkene/alkyne for mild [3+2]-cycloaddition[141,142]

Our first attempts at this activation of glyoxylate alkyne **4.72** in the presence of **1.91a** gave unsurprising results (Scheme 4.23). Rather than [3+2]-cycloaddition, facile 4π-electrocyclization followed by trapping with activate alkyne led to the formation of isoxazoline **4.73a** in near quantitative yield. In the absence of nickel, no product was formed, providing encouragement that this system was in fact activating the glyoxylate alkyne towards [3+2]-cycloaddition under mild conditions. We hopes that perhaps a nitrone that is less likely to undergo 4π-electrocyclization would give the desired reactivity, instead.



Scheme 4.23 Attempted activated Lewis acid catalyzed [3+2]/[3,3']-cascade

Electron-deficient nitrone **1.91o** was applied under this catalytic activation mode and again, the major product was the formation of 4π-cycloadduct **4.73b** in enantiomeric excess of 13% (Scheme 4.24). However, the reduced likelihood of nitrone **1.91o** to undergo 4π-electrocyclization led to the formation of a minor amount of *N*-vinyl isoxazoline **4.73b'**. This excited us further and we hoped other nitrones might give this as the major product to further perturb the [3,3']-sigmatropic rearrangement to afford enantiopure cascade products. Again, without nickel, no formation of either of these products was observed.



Scheme 4.24 Initial attempts at chiral Lewis acid catalyzed [3+2]/[3,3']-cascade

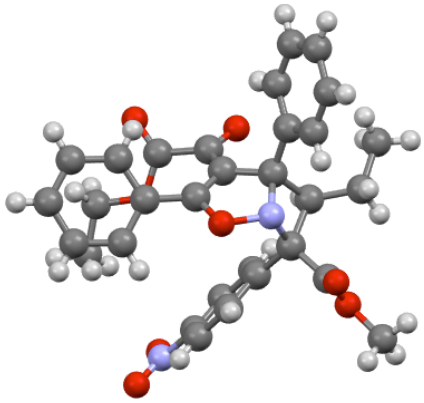
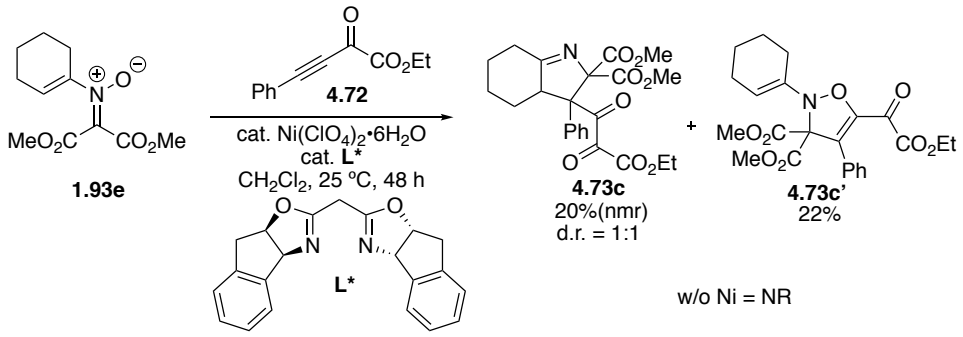


Figure 4.4 X-Ray Crystallography of **4.73b** – Prof. Donald J. Wink

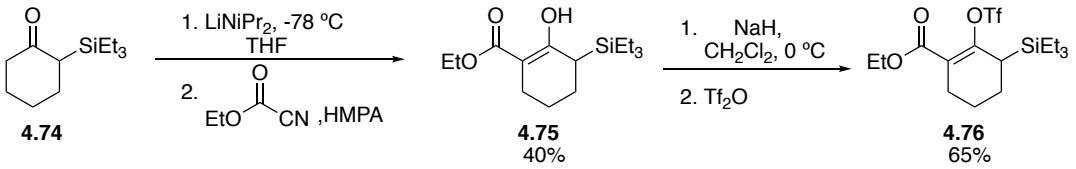
When nitrone **1.93e** was subjected to these conditions, the desired product **4.73c** was observed by NMR while the [3+2]-cycloadduct **4.73'** was isolated in 22% yield (Scheme 4.25). These promising results show that with the right electronics, the desired reactivity can be achieved. These investigations will be continued in the near future.



Scheme 4.25 Asymmetric [3+2]/[3,3']-cascade with **1.93e**

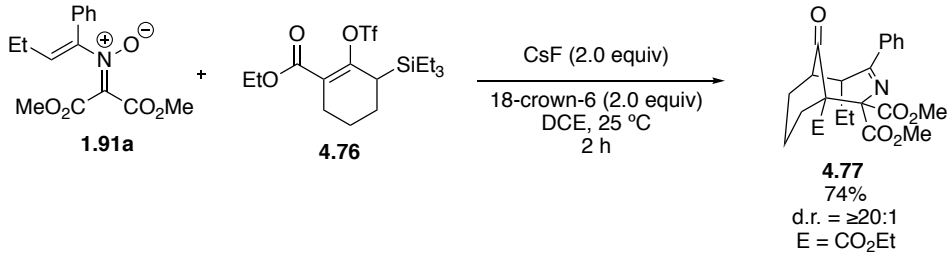
4.2.5 Cascade Reaction of *N*-Vinylnitrones and a Cyclic Allenoate Precursor

Encouraged by the work of Garg[143], we were interested to see if our nitrones would exhibit similar regioselective [3+2]-cycloaddition with cyclic allenoates. Our previous work with electron-deficient allenoates (Chapter 2) and our current work previously described in this chapter led us to hypothesize that our substrates would selectively add to the central allene carbon, generating an *N*,*O*-divinyl intermediate. This reactive intermediate would then be poised to undergo diastereoselective [3,3']-rearrangement to afford, in this case, a bicyclic imine. We hypothesized that this bicyclic compound could then be hydrolyzed to afford 1,4-diketone products and a library of these scaffolds could quickly be produced to test for biological activity. Using an adapted procedure, the cyclic allenoate was first prepared in 2 steps from known 2-silyl cyclohexanone **4.74** (Scheme 4.26).



Scheme 4.26 Construction of cyclic allenoate precursor **4.76**

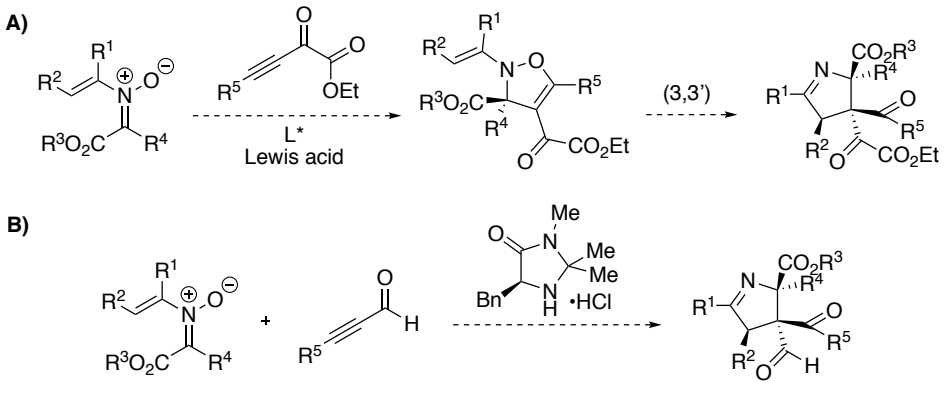
Subjecting *N*-vinylnitrone **1.91a** to standard reaction conditions in the presence of **4.76**, desired bicyclic imine **4.77** was isolated in high yield as a single diastereomer (Scheme 4.27). With this success, more investigation into the scope, selectivity, and functionalizations will be disclosed in the future.



Scheme 4.27 Cyclic allenoate [3+2]/[3,3']-cascade – Preliminary data

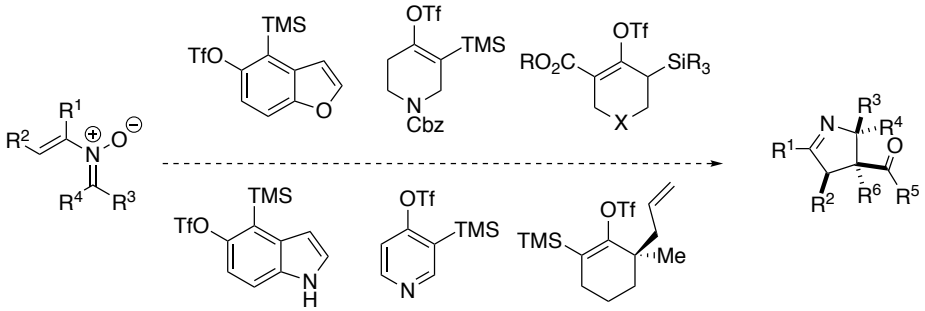
4.3 Future Directions

After my time here in the Anderson lab, it is plausible that enantioselective variants of this cycloaddition cascade might be realized. Initial results have shown that Lewis acid coordination of glyoxylate alkynes sufficiently activated these substrates toward [3+2]-cycloaddition and should lead to the formation of our cascade products. Further, it has been postulated that organocatalytic activation of ynals popularized by MacMillan[144] could be applied to this system. In fact, there have been limited reports of such an activation for the [3+2]-cycloaddition of ynals with nitrones. It is expected that with the right catalysts, this goal will be realized (Scheme 4.28).



Scheme 4.28 Future enantioselective endeavors

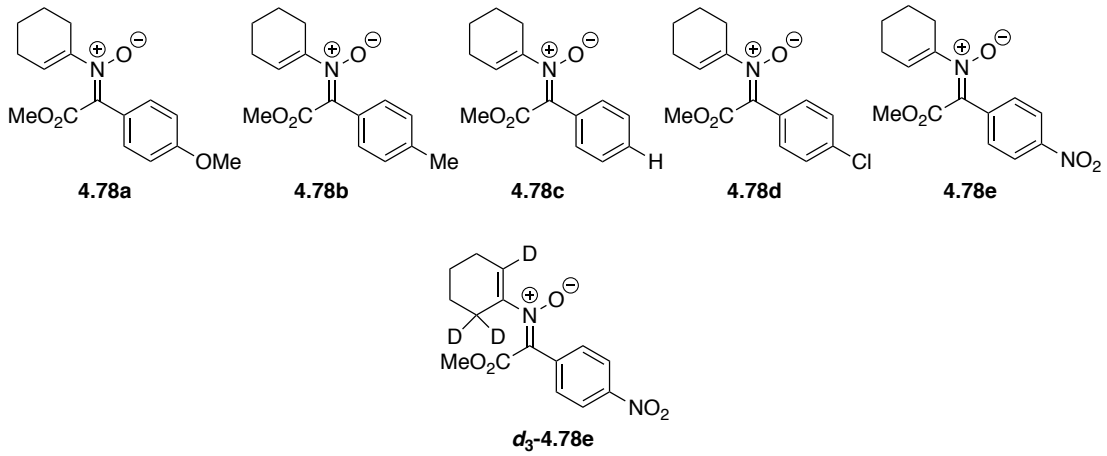
Furthermore, members of our lab are currently working to expand the scope of this transformation by synthesizing a variety of heterocyclic alkynes, heteroarynes, and enantiodefined cyclic alkynes to use for the preparation of 4-acyl-1-pyrrolines (Scheme 4.29).



Scheme 4.29 Future expansion of [3+2]/[3,3']-cascade reaction of *N*-vinylnitrones

Lastly, both Robert Zhang and I are working towards performing kinetic studies as well as labeling studies to determine the mechanistic parameters of this reaction. I have synthesized a number of para-substituted aryl glyoxalate cyclohexenyl nitrones to use in a competition study to determine the electronic effect at the imine carbon. We expect electron-rich aryl rings to accelerate the rate of reaction while electron-poor aryl rings to slow it down. Robert has successfully synthesized ***d*$_3$-4.78e** and will determine if

there is a secondary KIE effect using this substrate. These experiments will elucidate some of the important mechanistic details and allow for further expansion of this project.



Scheme 4.30 Mechanistic studies for cycloaddition cascade

4.4 Conclusion

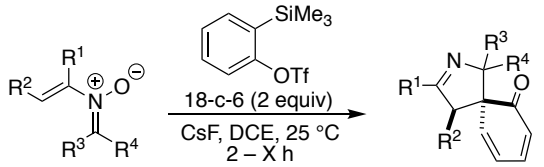
A novel [3+2]-cycloaddition/[3,3']-sigmatropic rearrangement cascade has been realized starting from stable *N*-vinylnitrones and benzyne, cycloalkyne, cyclic allenoate, and acyclic alkynes to afford a variety of highly functionalized pyrroline scaffolds. Initial Lewis acid catalysis has laid the foundation for further exploration into asymmetric methods for their preparation. A novel bicyclic imine scaffold is accessible in high yield from a cyclic allenoate precursor and nitrones. These results have further solidified the Anderson group's *N*-vinylnitrone substrate class as a highly valuable synthetic tool for the diastereoselective construction of *N*-heterocycles.

4.5 Supplementary Information

4.5.1 General Experimental Information

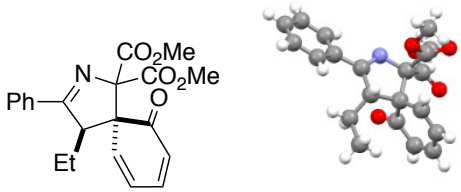
^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded at ambient temperature using ATR sampling. High resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed using force flow of the indicated solvent system down columns packed with 60 Å (40 – 60 μm) mesh silica gel (SiO_2). Samples purified by medium pressure liquid chromatography were dry-loaded onto celite. Unless otherwise noted, all reagents and solvents were obtained from commercial sources and, where appropriate, purified prior to use. Unless otherwise noted, all reactions were performed under N_2 using standard Schlenk techniques. CH_2Cl_2, toluene, and THF were dried by filtration through alumina according to the procedure of Grubbs. MeOH was dried by filtration through a column loaded with activated 4 Å molecular sieves. Oximes **4.100a-e** was prepared by modification to a known method. Vinyl boronic acids **4.200a,b** were prepared by modifications to a known method.

4.5.2 Synthesis of Spirocyclic Pyrrolines 4.35a – 4.35k from Benzyne Intermediate



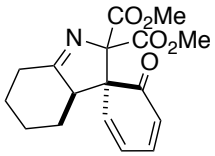
General Procedure A: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91** (0.50 mmol, 1.0 equiv), 18-crown-6 (1.0 mmol, 2 equiv), CsF (1.0 mmol, 2.0 equiv), and diluted with 2.5 mL of iPrOAc. Then, a solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.75 mmol, 1.5 equiv) in 2.5 mL of iPrOAc was added in one portion to form a 0.1 M solution and the vial was sealed with a Teflon screw cap. The solution was stirred at 25 ºC for 1–4 h and monitored by TLC. Once the nitrone was completely consumed, the reaction mixture was filtered through a pad of Celite to remove the 18-crown-6/CsF adduct and the filter cake was washed with

EtOAc (3 x 5.0 mL), concentrated, and analyzed by NMR using either MeCN-*d*3 or MeOH-*d*4. This crude mixture was then dry-loaded onto Celite with EtOAc and purified on basified SiO_2 by medium pressure chromatography (1:5 – 4:1, EtOAc: hexanes with 1% Et_3N) to afford spirocyclic pyrrolines **4.35**.



4.35a

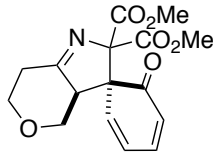
Pyrroline 4.35a: Pyrroline **4.35a** was prepared by general procedure **A** using nitrone **1.91a** (0.146 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 2 h. Chromatography (1:2, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35a** as a yellow solid (0.175 g, 95%). ^{1}H NMR (500 MHz; MeOH-d_4): δ 7.65 – 7.58 (m, 2H), 7.52 – 7.44 (m, 3H), 7.20 – 7.14 (m, 1H), 6.52 – 6.44 (m, 2H), 6.07 (d, J = 9.8 Hz, 1H), 3.88 (dd, J = 10.0, 4.0 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 1.77 – 1.67 (m, 1H), 1.44 – 1.33 (m, 1H), 0.77 (dd, J = 10.0, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, MeOH-d_4): δ 201.2, 182.0, 168.3, 166.8, 141.4, 140.8, 133.8, 130.4, 128.2, 127.6, 126.5, 123.7, 93.2, 64.9, 62.8, 52.6, 51.8, 21.4, 11.1; IR (thin film) 3725, 3709, 2953, 2341, 1736, 1710, 1660, 1560, 1434, 1306 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1498, found 368.1489; m.p.: 139 – 141 °C. Purified **4.35a** was further dissolved in a minimal amount of EtOAc, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



4.35b

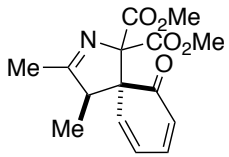
Pyrroline 4.35b: Pyrroline **4.35b** was prepared by general procedure **A** using nitrone **1.93e** (0.121 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 2 h. Chromatography (1:2,

EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35b** as a yellow solid (0.085 g, 95%). ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.11 – 7.04 (m, 1H), 6.44 – 6.37 (m, 1H), 6.32 – 6.26 (m, 1H), 5.89 – 5.81 (m, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.21 – 3.14 (m, 1H), 2.74 – 2.66 (m, 1H), 2.32 – 2.18 (m, 2H), 1.94 – 1.87 (m, 1H), 1.80 – 1.74 (m, 1H), 1.71 – 1.63 (m, 1H), 1.35 – 1.27 (m, 1H), 1.18 – 1.10 (m, 1H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 201.3, 179.9, 169.1, 167.7, 141.4, 140.0, 125.6, 123.6, 93.5, 65.7, 59.5, 53.0, 51.8, 31.1, 26.4, 24.2, 23.9; IR (thin film) 2949, 2863, 2359, 2341, 1733, 1710, 1659, 1561, 1434, 1161 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}NO_5$ $(M+H)^+$ 318.1341, found 318.1337; m.p.: 135 – 137 °C.



4.35c

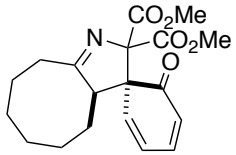
Pyrroline 4.35c: Pyrroline **4.35c** was prepared by general procedure **A** using nitrone **1.93f** (0.122 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 2 h. Chromatography (3:1, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35c** as a white solid (0.123 g, 77%). ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.15 – 7.07 (m, 1H), 6.47 – 6.39 (m, 1H), 6.36 – 6.28 (m, 1H), 5.92 – 5.54 (m, 1H), 4.09 – 4.06 (m, 1H), 3.85 – 3.79 (m, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.42 – 3.35 (m, 1H), 3.32 – 3.25 (m, 1H), 3.16 – 3.11 (m, 1H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 200.0, 176.4, 168.7, 167.3, 141.9, 139.6, 125.3, 123.8, 94.0, 67.2, 66.0, 63.7, 58.2, 53.2, 52.0, 32.4; IR (thin film) 2955, 2359, 1733, 1710, 1659, 1631, 1561, 1434, 1364, 1220 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{18}NO_6$ $(M+H)^+$ 320.1134, found 320.1131; m.p.: 134 – 137 °C.



4.35d

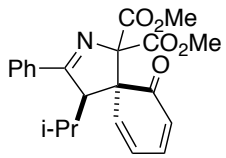
Pyrroline 4.35d: Pyrroline **4d** was prepared by general procedure **A** using nitrone **1.93a** (0.108 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-

(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. Chromatography (1:4, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35d** as a yellow solid (0.131 g, 90%). ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.12 – 7.03 (m, 1H), 6.47 – 6.39 (m, 1H), 6.26 – 6.25 (m, 1H), 5.86 – 5.84 (m, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.29 (q, *J* = 7.5 Hz, 1H), 2.01 (s, 3H), 0.90 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 201.0, 179.8, 169.0, 167.5, 141.2, 139.7, 126.0, 124.0, 92.9, 66.2, 56.6, 53.0, 51.9, 17.4, 10.2; IR (thin film) 3726, 3627, 2359, 2341, 1732, 1659, 1630, 1562, 1433, 1309 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}NO_5$ $(M+H)^+$ 292.1185, found 292.1179; m.p.: 135 – 138 °C.



4.35e

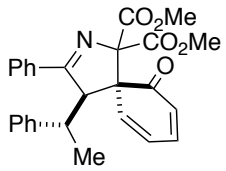
Pyrroline 4.35e: Pyrroline **4.35e** was prepared by general procedure **A** using nitrone **4.63a** (0.135 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. Chromatography (1:4, Acetone:hexanes with 1% Et_3N) afforded pyrroline **4.35e** as a white solid (0.119 g, 69%). ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.07 – 7.00 (m, 1H), 6.46 – 6.38 (m, 1H), 6.26 – 6.21 (m, 1H), 5.87 – 5.85 (m, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.36 (dd, *J* = 9.6, 2.6 Hz, 1H), 2.68 – 2.53 (m, 2H), 1.87 – 1.63 (m, 5H) 1.43 – 1.24 (m, 5H): ^{13}C NMR (125 MHz, MeCN-*d*3): δ 201.0, 183.6, 169.0, 167.2, 141.0, 139.7, 126.5, 124.3, 92.2, 67.3, 62.5, 53.1, 52.0, 29.7, 29.6, 25.5, 25.4, 25.0, 24.7; IR (thin film) 2927, 2855, 2360, 2341, 1733, 1661, 1629, 1564, 1435, 1285 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{24}NO_5$ $(M+H)^+$ 346.1654, found 346.1649; m.p.: 131 – 133 °C.



4.35f

Pyrroline 4.35f: Pyrroline **4.35f** was prepared by general procedure **A** using nitrone **4.63b** (0.153 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-

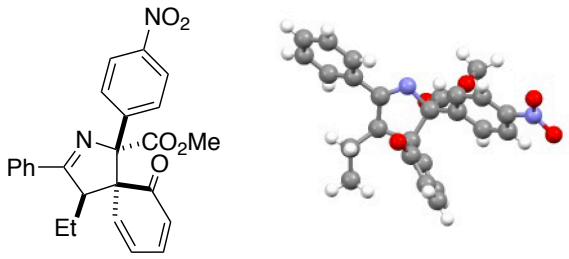
(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. Chromatography (1:2, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35f** as a yellow solid (0.159 g, 86%). ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.68 – 7.66 (m, 2H), 7.53 – 7.42 (m, 3H), 7.14 – 7.08 (m, 1H), 6.39 – 6.32 (m, 1H), 6.31 – 6.27 (m, 1H), 6.14 – 6.12 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.66 (d, *J* = 6.5 Hz, 1H), 2.25 – 2.15 (m, 1H), 0.71 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 199.4, 179.8, 168.3, 167.6, 142.1, 140.8, 136.3, 130.3, 128.4, 127.7, 127.2, 122.4, 92.2, 66.6, 66.0, 52.8, 52.4, 26.9, 22.2, 20.3; IR (thin film) 2955, 2359, 2341, 1661, 1633, 1445, 1434, 1362, 1267, 1221 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{24}NO_5$ $(M+H)^+$ 382.1654, found 382.1645; m.p.: 141 – 145 °C.



4.35g

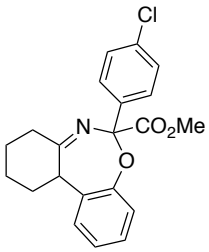
Pyrroline 4.35g: Pyrroline **4.35g** was prepared by general procedure **A** using nitrone **1.93r** (95%*ee*, 0.184 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. Chromatography (1:6, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35g** as a white solid (0.160 g, 72%, d.r. = 2:1). Major diastereomer ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.20 – 7.18 (m, 2H), 7.14 – 7.02 (m, 4H), 6.98 – 6.91 (m, 4H), 6.90 – 6.89 (m, 1H), 6.40 – 6.34 (m, 1H), 6.31 – 6.25 (m, 1H), 6.19 – 6.12 (m, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.18 – 3.25 (m, 1H), 0.99 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 199.7, 181.4, 168.1, 167.1, 143.8, 141.6, 140.6, 139.1, 135.9, 128.6, 127.9, 127.8, 127.5, 127.0, 126.0, 123.1, 92.9, 67.1, 66.4, 63.1, 52.5, 38.1, 19.6; Minor diastereomer ^{1}H NMR (500 MHz; MeCN-*d*3): δ 7.75 – 7.70 (m, 2H), 7.55 – 7.47 (m, 3H), 7.14 – 7.02 (m, 3H), 6.98 – 6.91 (m, 2H), 6.60 – 6.53 (m, 1H), 6.19 – 6.12 (m, 1H), 6.02 – 5.99 (m, 1H), 5.53 – 5.51 (m, 1H), 4.11 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.32 – 3.27 (m, 1H), 0.80 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 198.8, 179.7, 168.2, 167.7, 145.3, 141.4, 136.8, 130.4, 128.7, 128.5, 127.9, 127.7, 127.4, 127.1, 126.5, 121.5, 91.5, 66.1,

65.4, 52.7, 52.6, 38.5, 22.1; IR (thin film) 3725, 3628, 2953, 2341, 1737, 1710, 1660, 1560, 1434, 1267 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{27}H_{26}NO_5$ $(M+H)^+$ 444.1811, found 444.1811; m.p.: 138 – 140 °C.



4.35h

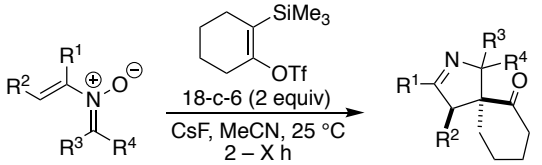
Pyrroline 4.35h: Pyrroline **4.35h** was prepared by general procedure **A** using nitrone **1.91o** (0.177 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.75 mmol, 1.5 equiv), CsF (0.152 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. Chromatography (1:4, EtOAc:hexanes with 1% Et_3N) afforded pyrroline **4.35h** as a yellow solid (0.159 g, 74%). ^1H NMR (500 MHz; MeCN-*d*3): δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.76 – 7.68 (m, 2H), 7.56 – 7.49 (m, 3H), 7.03 – 6.95 (m, 1H), 6.84 – 6.77 (m, 1H), 6.58 – 6.50 (m, 1H), 5.55 (d, *J* = 9.7 Hz, 1H), 4.19 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.72 (s, 3H), 1.92 – 1.83 (m, 1H), 1.39 – 1.29 (m, 1H), 0.72 (dd, *J* = 15.0, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 199.3, 181.1, 169.0, 147.8, 147.3, 143.2, 141.0, 134.8, 130.3, 129.0, 128.5,127.9, 127.2, 124.3, 122.4 89.4, 68.8, 63.0, 53.0, 21.6, 10.8; IR (thin film) 3726, 3709, 2965, 2341, 1737, 1712, 1657, 1600, 1491, 1481, 1347 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{23}N_2O_5$ $(M+H)^+$ 431.1607, found 431.1604; m.p.: 145 – 148 °C. Purified **4.35h** was further dissolved in a minimal amount of EtOAc, layered with hexane, and placed in a -40 °C freezer. After 3 d, X-ray quality crystals had formed.



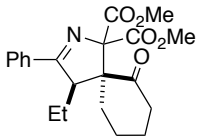
Hemiaminal 4.35n': Hemiaminal **4.35n'** was prepared by general procedure **A** using nitrone **4.78d** (0.147 g, 0.500 mmol), 18-crown-6 (0.264 g, 1.00 mmol, 2.0 equiv), 2-

(trimethylsilyl)phenyl trifluoromethanesulfonate (0.224 g, 0.750 mmol, 1.5 equiv), CsF (0.152 g, 1.00 mmol, 2.0 equiv) in 5.0 mL of iPrOAc for 1 h. The reaction mixture was stirred at 25 °C and monitored by TLC for ~ 1 h (TLC eluent = 20% EtOAc:hexanes with 1% Et_3N; R_f of **4.78d** = 0.50 and R_f of **4.35n'** = 0.79; $KMnO_4$). Chromatography (5% EtOAc:hexanes with 1% Et_3N) afforded benzoxazepine **4.35n'** as an orange oil (90%). ^1H NMR (500 MHz, MeCN-*d*3): δ 7.67 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.17 – 7.12 (m, 2H), 6.92 – 6.89 (m, 1H), 6.76 – 6.74 (m, 1H), 3.90 (s, 3H), 3.45 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.13 – 2.04 (m, 1H), 2.03 – 1.92 (m, 2H), 1.77 – 1.69 (m, 1H), 1.65 – 1.56 (m, 1H), 1.55 – 1.48 (m, 2H), 1.46 – 1.39 (m, 1H); ^{13}C NMR (125 MHz, MeCN-*d*3): δ 167.4, 157.1, 153.2, 137.0, 133.0, 131.4, 128.9, 128.8, 127.9, 123.7, 121.4, 110.4, 102.8, 52.1, 47.5, 32.2, 27.6, 20.5, 20.4; IR (thin film) 3726, 2933, 2341, 1735, 1637, 1592, 1489, 1402, 1293, 1209 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}NO_3Cl$ $(M+H)^+$ 370.1210, found 370.1202.

4.5.3 Synthesis of Spirocyclic Pyrrolines 4.69a and 4.69b from Cyclohexyne

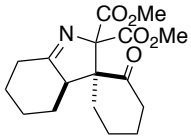


General Procedure B: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91** (0.50 mmol, 1.0 equiv), 18-crown-6 (1.0 mmol, 2 equiv), 2-(triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (1.0 mmol, 2.0 equiv), and 5.0 mL of MeCN. The MeCN solution was stirred at 25 ºC until homogeneity (usually within 3 min). Solid CsF (1.3 mmol, 2.5 equiv) was added to the solution in one portion and the vial was sealed with a Teflon screw cap. The solution was stirred at 25 ºC for 1 - 8 h and monitored by TLC. Once the nitrone was completely consumed, the reaction mixture was filtered through a pad of SiO_2 which was rinsed with 3 x 10 mL EtOAc, concentrated, and wet-loaded onto silica gel with 5 mL acetone and purified on basified SiO_2 by medium pressure chromatography (1:5 – 4:1, EtOAc: hexanes with 1% Et_3N) to afford spirocyclic pyrrolines **4.69a** and **4.69b**.



4.69a

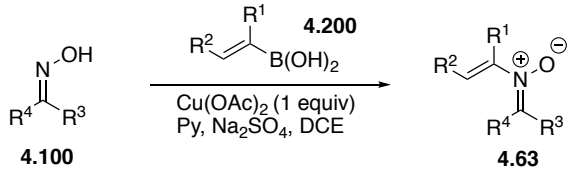
Pyrroline 4.69a: Pyrroline **4.69a** was prepared by general procedure **B** using nitrone **1.91a** (0.145 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (0.344 g, 1.0 mmol, 2.0 equiv), CsF (0.190 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of MeCN for 6 h. Chromatography (3:1, EtOAc:hexanes) afforded pyrroline **4.69a** as a yellow solid (0.175 g, 95%). ^{1}H NMR (500 MHz; CD_3CN): δ 7.74 (d, J = 7.0 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 3.73 (s, 3H), 3.68 (s, 3H), 3.54 (dd, J = 6.0, 4.8 Hz, 1H), 2.49 (d, J = 15.6 Hz, 1H), 2.38 (ddd, J = 15.6, 12.8, 6.4 Hz, 1H), 2.04 (ddt, J = 12.7, 6.2, 3.0 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.94 – 1.88 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.63 (m, 3H), 1.53 (dtt, J = 15.2, 7.6, 3.8 Hz, 1H), 0.91 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ 209.6, 180.4, 170.2, 169.6, 135.7, 131.8, 129.4, 129.1, 127.9, 91.9, 67.2, 60.4, 53.1, 52.9, 42.6, 36.5, 26.2, 24.0, 22.3, 15.1.



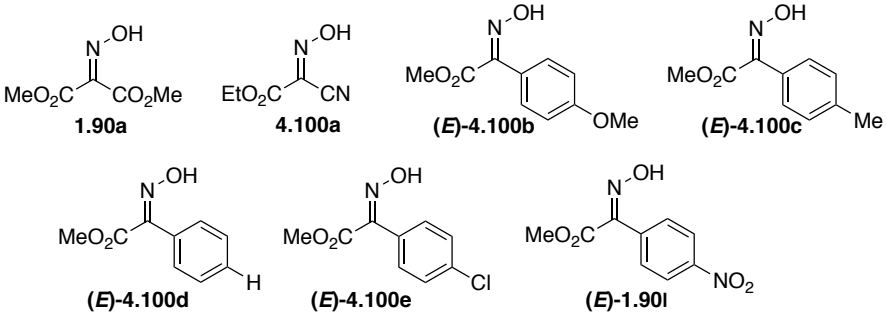
4.69b

Pyrroline 4.69b: Pyrroline **4.69b** was prepared by general procedure **B** using nitrone **1.93e** (0.121 g, 0.50 mmol), 18-crown-6 (0.264 g, 1.0 mmol, 2.0 equiv), 2-(triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (0.344 g, 1.0 mmol, 2.0 equiv), CsF (0.190 g, 1.0 mmol, 2.0 equiv) in 5.0 mL of MeCN for 6 h. Chromatography (1:1, EtOAc:hexanes) afforded pyrroline **4.69b** as a yellow solid (0.175 g, 95%). ^{1}H NMR (500 MHz; CD_3OD): δ 3.73 (s, 3H), 3.72 (s, 3H), 3.01 (dd, J = 12.9, 6.4 Hz, 1H), 2.70 (d, J = 16.0 Hz, 1H), 2.52 (ddt, J = 17.5, 4.7, 2.2 Hz, 1H), 2.32 – 2.16 (m, 4H), 2.02 – 1.88 (m, 5H) 1.79 – 1.64 (m, 2H), 1.51 (qt, J = 13.2, 3.1 Hz, 1H), 1.34 – 1.24 (m, 1H), 1.12 (qd, J = 12.8, 3.3 Hz, 1H); ^{13}C NMR (125 MHz, MeOH-d_4): δ 210.6, 182.7, 170.0, 167.9, 90.4, 64.0, 58.7, 52.3, 51.3, 41.9, 34.0, 34.0, 31.1, 30.2, 30.1, 24.2, 24.1, 24.1, 23.3, 22.0.

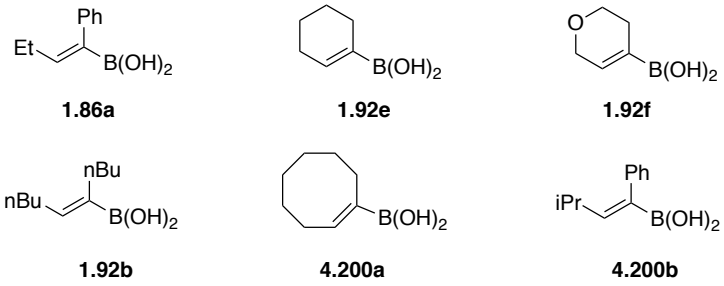
4.5.4 Synthesis of *N*-Vinylnitrones



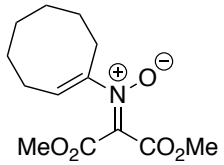
Oximes:



Vinylboronic Acids:

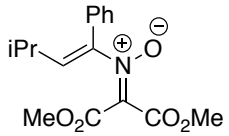


General Procedure C: A scintillation vial was charged with oxime substrate **4.100** (0.50 mmol, 1.0 equiv), alkenylboronic acid **4.200** (3 – 5 equiv), $Cu(OAc)_2$ (1.0 equiv), and anhydrous Na_2SO_4 (8.0 equiv). These solids were diluted with 1,2-dichloroethane (DCE) to form a 0.1 M solution of oxime **4.100**. Pyridine (3.0 equiv) was then added to the resulting slurry via syringe. The scintillation vial was capped with a septum, pierced with a ventilation needle, and the reaction mixture was allowed to stir at 25 °C for 2 – 18 h. The reaction mixture was then filtered through a plug of silica gel covered with a layer of celite and washed with EtOAc (3 x 10 mL). The filtrate was then concentrated under vacuum to give the crude product mixture that was dry-loaded using EtOAc or Et_2O onto celite and purified by medium pressure column chromatography (1:20 – 1:3, EtOAc: hexanes) to afford nitrone **4.63** as a white solid or light-yellow oil.



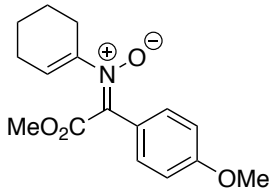
4.63a

Nitrone 4.63a: Nitrone **4.63a** was prepared by general procedure **C**. Oxime **1.90a** (0.806 g, 5.00 mmol, 1.0 equiv) was treated with cyclooct-1-en-1-ylboronic acid **4.200a** (2.31 g, 15.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.908 g, 5.0 mmol, 1.0 equiv), Na_2SO_4 (5.68 g, 40.0 mmol, 8.0 equiv), and pyridine (1.19 g, 15.0 mmol, 3.0 equiv) in 50.0 mL DCE and stirred for 18 h. Chromatography (1:5, Et_2O: hexanes) afforded **4.63a** as a yellow oil (1.21 g, 90%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.83 (t, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.52 – 2.49 (m, 2H), 2.21 – 2.15 (m, 2H), 1.78 – 1.70 (m, 2H), 1.65 – 1.56 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 159.8, 148.2, 131.2, 126.9, 53.0, 52.9, 29.1, 28.8, 28.6, 25.7, 25.7, 25.4; IR (thin film) 3726, 2929, 2853, 2360, 1733, 1615, 1513, 1435, 1214, 1154 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{20}NO_5$ $(M+H)^+$ 270.1341, found 270.1339.



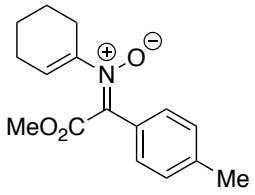
4.63b

Nitrone 4.63b: Nitrone **4.63b** was prepared by general procedure **C**. Oxime **1.90a** (0.0806 g, 0.50 mmol, 1.0 equiv) was treated with (3-methyl-1-phenylbut-1-en-1-yl)boronic acid **4.200b** (0.475 g, 2.50 mmol, 5.0 equiv), $Cu(OAc)_2$ (0.0908 g, 0.50 mmol, 1.0 equiv), Na_2SO_4 (0.568 g, 4.0 mmol, 8.0 equiv), and pyridine (0.119 g, 1.50 mmol, 3.0 equiv) in 5.0 mL DCE and stirred for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **4.63b** as a yellow solid (0.0962 g, 63%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.52 – 7.48 (m, 2H), 7.41 – 7.35 (m, 3H), 5.76 (d, *J* = 10.8 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 2.63 –2.53 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 159.2, 144.4, 136.1, 132.2, 131.4, 129.3, 129.2, 128.4, 53.1, 52.9, 27.4, 22.1; IR (thin film) 3725, 3627, 2359, 2341, 1722, 1487, 1437, 1384, 1349, 1291 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_5$ $(M+H)^+$ 306.1341, found 306.1337; m.p: 95 – 97 °C.



4.78a

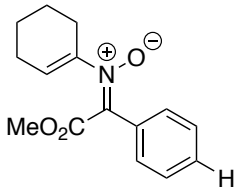
Nitrone 4.78a: Nitrone **4.78a** was prepared by general procedure **C**. Oxime **(*E*)-4.100b** (1.05 g, 5.0 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (1.89 g, 15.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.908 g, 5.0 mmol, 1.0 equiv), Na_2SO_4 (5.68 g, 40.0 mmol, 8.0 equiv), and pyridine (1.19 g, 15.0 mmol, 3.0 equiv) in 50.0 mL DCE and stirred for 6 h. Chromatography (1:4, EtOAc: hexanes) afforded **4.78a** as a yellow solid (1.14 g, 79%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.09 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.88 – 5.81 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.54 – 2.46 (m, 2H), 2.10 – 2.04 (m, 2H), 1.76 – 1.68 (m, 2H), 1.60 – 1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 161.1, 147.3, 138.9, 130.4, 123.2, 121.4, 113.7, 55.3, 52.9, 25.4, 24.2, 22.1, 21.3; IR (thin film) 2937, 2839, 2341, 1728, 1602, 1567, 1435, 1289, 1202, 1174 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_4$ $(M+H)^+$ 290.1392, found 290.1392; m.p: 116 – 118 °C.



4.78b

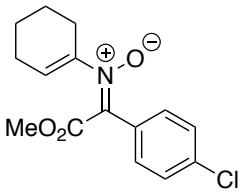
Nitrone 4.78b: Nitrone **4.78b** was prepared by general procedure **C**. Oxime **(*E*)-4.100c** (0.773 g, 4.0 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (1.51 g, 12.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.727 g, 4.0 mmol, 1.0 equiv), Na_2SO_4 (4.54 g, 32.0 mmol, 8.0 equiv), and pyridine (0.949 g, 12.0 mmol, 3.0 equiv) in 40.0 mL DCE and stirred for 8 h. Chromatography (1:5, Et_2O: hexanes) afforded **4.78b** as a white crystalline solid (0.951 g, 87%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 5.85 – 5.80 (m, 1H), 3.75 (s, 3H), 2.51 – 2.43 (m, 2H), 2.28 (s, 3H), 2.08 – 1.99 (m, 2H), 1.72 – 1.66 (m, 2H), 1.56 – 1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 147.5, 141.1, 139.1, 129.0, 128.4, 126.0, 123.1, 52.8, 25.4, 24.1, 22.0, 21.6, 21.2; IR (thin film) 2933, 2858, 1723, 1608, 1518, 1504, 1447, 1435, 1362, 1272, 1182 cm^{-1};

HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_3$ $(M+H)^+$ 274.1443, found 274.1441; m.p: 112 – 117 °C.



4.78c

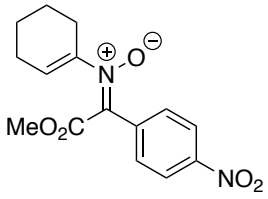
Nitrone 4.78c: Nitrone **4.78c** was prepared by general procedure **C**. Oxime **(*E*)-4.100d** (0.717 g, 4.0 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (1.51 g, 12.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.727 g, 4.0 mmol, 1.0 equiv), Na_2SO_4 (4.54 g, 32.0 mmol, 8.0 equiv), and pyridine (0.949 g, 12.0 mmol, 3.0 equiv) in 40.0 mL DCE and stirred for 6 h. Chromatography (1:6, Et_2O: hexanes) afforded **4.78c** as a white solid (0.830 g, 80%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.04 – 7.98 (m, 2H), 7.36 – 7.30 (m, 3H), 5.86 – 5.82 (m, 1H), 3.75 (s, 3H), 2.51 – 2.44 (m, 2H), 2.07 – 2.00 (m, 2H), 1.73 – 1.66 (m, 2H), 1.57 – 1.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 147.5, 139.0, 130.6, 128.8, 128.4, 128.3, 123.2, 52.9, 25.4, 24.1, 22.0, 21.2; IR (thin film) 2941, 2861, 2341, 1726, 1570, 1520, 1495, 1349, 1305, 1264, 1114 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}NO_3$ $(M+H)^+$ 260.1287, found 260.1283; m.p: 117 – 121 °C.



4.78d

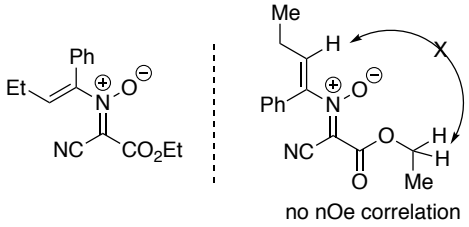
Nitrone 4.78d: Nitrone **4.78d** was prepared by general procedure **C**. Oxime **(*E*)-4.100e** (0.855 g, 4.0 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (1.51 g, 12.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.727 g, 4.0 mmol, 1.0 equiv), Na_2SO_4 (4.54 g, 32.0 mmol, 8.0 equiv), and pyridine (0.949 g, 12.0 mmol, 3.0 equiv) in 40.0 mL DCE and stirred for 4 h. Chromatography (1:20, EtOAc: hexanes) afforded **4.78d** as a white solid (1.01 g, 73%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.04 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 5.93 – 5.88 (m, 1H), 3.85 (s, 3H), 2.58 – 2.51 (m, 2H), 2.17 – 2.10 (m, 2H), 1.82 – 1.74

(m, 2H), 1.65 – 1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 147.7, 138.1, 136.2, 129.8, 128.6, 127.3, 123.4, 53.0, 25.5, 24.2, 22.1, 21.2; IR (thin film) 3726, 2941, 2861, 1728, 1587, 1486, 1435, 1339, 1299, 1201 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}NO_3Cl$ $(M+H)^+$ 294.0897, found 294.0892; m.p: 115 – 119 °C.



4.78e

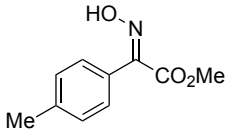
Nitrone 4.78e: Nitrone **4.78e** was prepared by general procedure **C**. Oxime **(*E*)-1.90l** (0.897 g, 4.0 mmol) was treated with cyclohex-1-en-1-ylboronic acid **1.92e** (1.51 g, 12.0 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.727 g, 4.0 mmol, 1.0 equiv), Na_2SO_4 (4.54 g, 32.0 mmol, 8.0 equiv), and pyridine (0.949 g, 12.0 mmol, 3.0 equiv) in 40.0 mL DCE and stirred for 10 h. Chromatography (1:4, Et_2O: hexanes) afforded **4.78e** as a yellow solid (1.13 g, 93%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.25 – 8.20 (m, 4H), 5.95 – 5.93 (m, 1H), 3.87 (s, 3H), 2.53 – 2.51 (m, 2H), 2.16 – 2.14 (m, 2H), 1.80 – 1.76 (m, 2H), 1.65 – 1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 148.0, 147.8, 137.3, 134.8, 129.3, 123.9, 123.4, 53.3, 25.5, 24.2, 22.0, 21.1; IR (thin film) 3725, 2941, 2360, 1725, 1599, 1489, 1434, 1343, 1270, 1123 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}N_2O_5$ $(M+H)^+$ 305.1137, found 305.1135; m.p: 109 – 112 °C.



(*Z*)-4.63c

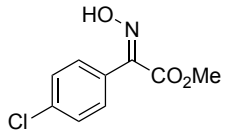
Nitrone (*Z*)-4.63c: Nitrone **(*Z*)-4.63c** was prepared by general procedure **C**. Oxime **4.100a** (0.142 g, 1.0 mmol, 1.0 equiv) was treated with ((1-phenylbut-1-en-1-yl)boronic acid **1.86a** (0.880 g, 5.0 mmol, 5.0 equiv), $Cu(OAc)_2$ (0.182 g, 1.0 mmol, 1.0 equiv), Na_2SO_4 (1.14 g, 8.0 mmol, 8.0 equiv), and pyridine (0.237 g, 3.0 mmol, 3.0 equiv) in 10.0 mL DCE and stirred for 48 h. Chromatography (1:7, Et_2O: hexanes) afforded **3q** as a yellow oil (0.163 g, 60%, *E*:*Z* = 1:6). This mixture was then triturated with 5.0 mL

hexane and 1 drop of EtOAc to obtain **(*Z*)-4.63c** as a yellow solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 – 7.33 (m, 5H), 5.98 (t, *J* = 15.0, 7.5 Hz, 1H), 4.23 – 4.19 (m, 2H), 2.22 – 2.07 (m, 2H), 1.26 (t, *J* = 14.0, 7.0 Hz, 3H), 1.10 (t, *J* = 15.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 146.9, 132.2, 129.3, 128.9, 127.6, 125.1, 118.1, 111.4, 63.1, 21.4, 13.9, 13.2; IR (thin film) 2973, 2937, 2359, 2341, 1739, 1716, 1474, 1446, 1375, 1291 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}N_2O_3$ $(M+H)^+$ 273.1239, found 273.1234; m.p: 101 – 103 °C.



(*E*)-4.100c

General Procedure: A flame-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with methyl 2-oxo-2-(*p*-tolyl)acetate (1.78 g, 10.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.5 equiv), NaOAc (1.64 g, 20.0 mmol, 2.0 equiv), and MeOH (50 mL). The mixture was stirred under reflux for 2 h, then diluted with H_2O (10 mL) and concentrated under reduced pressure to remove MeOH. The crude residue was dissolved in EtOAc and the organic phase was washed with water (50 mL) and brine (50 mL), and then dried over MgSO4, filtered, and concentrated in *vacuo*. The crude product was purified by flash column chromatography (TLC = 20% EtOAc:hexane, Rf **(*Z*)-4.100c**: 0.55, Rf **(*E*)-4.100c**: 0.42; FCC with 10% EtOAc:hexane) to provide (*E*)-oxime as a white solid in 45% yield (0.869 g). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.44 – 7.43 (d, 2H), 7.19 – 7.18 (d, 2H), 3.96 (s, 3H); IR (thin film) 3389, 3341, 2953, 2359, 2341, 1741, 1708, 1606, 1512, 1413 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{12}NO_3$ $(M+H)^+$ 194.0817, found 194.0813; m.p: 81 – 84 °C.

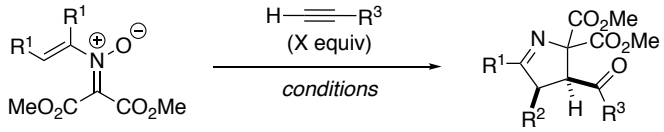


4.100e

A flame-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with methyl 2-(4-chlorophenyl)-2-oxoacetate (1.99 g, 10.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.5 equiv), NaOAc (1.64 g, 20.0 mmol, 2.0 equiv), and MeOH (50 mL). The mixture was stirred under reflux for 2 h, then

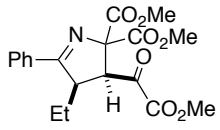
diluted with H_2O (10 mL) and concentrated under reduced pressure to remove MeOH. The crude residue was dissolved in EtOAc and the organic phase was washed with water (50 mL) and brine (50 mL), and then dried over MgSO4, filtered, and concentrated in *vacuo*. The crude product was purified by flash column chromatography (TLC = 20% EtOAc:hexane, Rf **(*Z*)-4.100e**: 0.59, Rf **(*E*)-4.100e**: 0.48; FCC with 10% EtOAc:hexane) to provide (*E*)-oxime as a white solid in 50% yield (1.07 g). ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.11 (brs, 1H), 7.46 – 7.44 (d, 2H), 7.42 – 7.40 (d, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 148.1, 135.7, 130.8, 128.3, 127.1, 53.0; IR (thin film) 2955, 2837, 2360, 2341, 1741, 1594, 1489, 1439, 1397, 1220 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_9H_9NO_3Cl$ $(M+H)^+$ 213.0318, found 213.0313; m.p: 84 – 87 °C.

4.5.5 Cascade Reaction of Acyclic Alkynes with *N*-Vinylnitrones



1.91/1.93 **4.66/4.67**

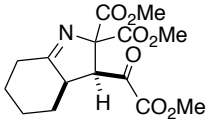
General Procedure D: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91** (0.50 mmol, 1.0 equiv), alkyne (1.5 or 2.0 equiv), and diluted with 5.0 mL of iPrOAc or DCE and the vial was sealed with a Teflon screw cap. The solution was stirred at 40 ºC for 18 h. The reaction mixture was concentrated and analyzed by NMR. This crude mixture was then wet-loaded with acetone and purified on SiO_2 by medium pressure chromatography (1:5 – 1:1, EtOAc: hexane) to afford pyrrolines **4.66a** and **4.67b.**



4.66a

Pyrroline 4.66a: Pyrroline **4.66a** was prepared by general procedure **D** using nitrone **1.91a** (0.0291 g, 0.10 mmol), methyl propiolate (0.0168 g, 0.20 mmol) in 1.0 mL of iPrOAc for 18 h. Chromatography (1:2, EtOAc:hexane) afforded pyrroline **4.66a** as a yellow oil (0.0518 g, 69%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.79 – 7.77 (m, 2H), 7.49 –

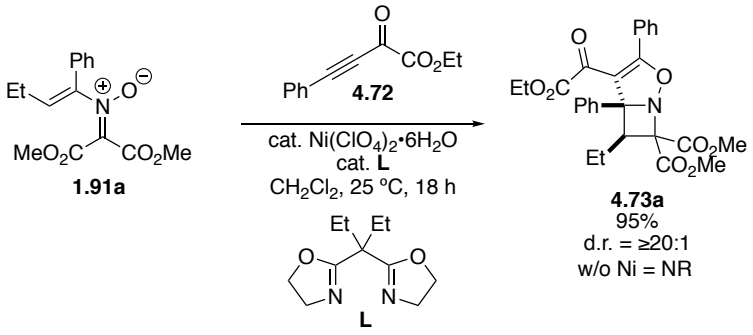
7.46 (m, 1H), 7.44 – 7.40 (m, 1H), 4.54 (d, 1H), 4.05 – 4.01 (m, 1H), 3.91 (s, 6H), 3.74 (s, 3H), 1.86 – 1.76 (m, 1H), 1.61 – 1.53 (m, 1H), 0.84 (t, 3H).



4.66b

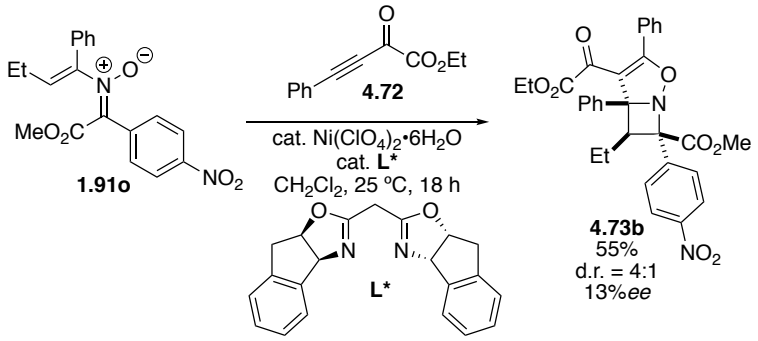
Pyrroline 4.66b: Pyrroline **4.66b** was prepared by general procedure **D** using nitrone **1.93e** (0.0242 g, 0.10 mmol), methyl propiolate (0.0168 g, 0.20 mmol) in 1.0 mL of iPrOAc for 18 h. Chromatography (1:2, EtOAc:hexane) afforded pyrroline **4.66b** as a yellow oil (0.0293 g, 90%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.02 (d, 1H), 3.80 (s, 6H), 3.66 (s, 3H), 3.16 – 3.11 (m, 1H), 2.73 – 2.70 (m, 1H), 2.25 – 2.23 (m, 1H), 2.20 – 2.14 (m, 1H), 1.98 – 1.81 (m, 1H), 1.39 –1.21 (m, 2H), 1.17 – 1.14 (m, 2H).

4.5.6 Lewis Acid Catalyzed Cascade Reaction of *N*-Vinylnitrones



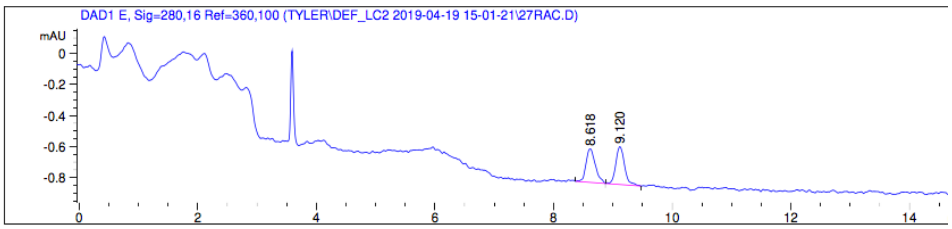
General Procedure E: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91a** (0.0584 g, 0.20 mmol, 1.0 equiv), alkyne **4.72** (0.0484 g, 0.24 mmol, 1.2 equiv), $Ni(ClO_4)_2$•$6H_2O$ (7.32 mg, 0.02 mmol, 10mol%), Ligand (4.63 mg, 0.022 mmol, 11mol%), diluted with 2.0 mL of CH_2Cl_2, and the vial was sealed with a Teflon screw cap. The solution was stirred at 25 ºC for 18 h. The reaction mixture was filtered through SiO_2, concentrated and analyzed by NMR. This crude mixture was then wet-loaded with CH_2Cl_2 and purified on SiO_2 by medium pressure chromatography (1:5 – 1:1, EtOAc: hexane) to afford azetidine **4.73a** as a yellow solid (0.0938 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.82 – 7.81 (d, 2H), 7.54 – 7.48 (m, 3H), 7.41 – 7.37 (m, 4H), 7.33 – 7.30 (m, 1H), 4.04 (t, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.76 – 3.69 (m, 1H),

3.62 – 3.55 (m, 1H), 1.42 – 1.34 (m, 1H), 1.28 – 1.26 (m, 1H), 1.01 (t, 3H), 0.67 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.8, 172.4, 167.0, 166.0, 163.5, 138.3, 132.7, 130.0, 128.5, 128.3, 128.1, 127.3, 126.3, 116.1, 81.5, 78.4, 61.8, 53.7, 52.9, 47.4, 20.8, 13.6, 11.2. **Book 12, Pg. 63.**



General Procedure E: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.91o** (0.0850 g, 0.24 mmol, 1.0 equiv), alkyne **4.72** (0.0582 g, 0.288 mmol, 1.2 equiv), $Ni(ClO_4)_2$•$6H_2O$ (8.78 mg, 0.024 mmol, 10mol%), Ligand (8.72 mg, 0.0264 mmol, 11mol%), diluted with 2.4 mL of CH_2Cl_2, and the vial was sealed with a Teflon screw cap. The solution was stirred at 25 ºC for 18 h. The reaction mixture was filtered through SiO_2, concentrated and analyzed by NMR. This crude mixture was then wet-loaded with CH_2Cl_2 and purified on SiO_2 by medium pressure chromatography (1:5 – 1:1, EtOAc: hexane) to afford azetidine **4.73b** as a yellow solid (0.0938 g, 55%, d.r. = 4:1 13%*ee*). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.30 (d, 2H), 7.86 (d, 2H), 7.77 (d, 2H), 7.43 – 7.38 (m, 3H), 7.36 – 7.33 (m, 1H), 7.22 – 7.19 (m, 2H), 6.79 – 6.77 (m, 2H), 4.10 (t, 1H), 3.77 (s, 3H), 3.62 – 3.55 (m, 1H), 3.32 – 3.26 (m, 1H), 1.59 – 1.47 (m, 2H), 0.79 – 0.73 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.9, 172.5, 170.0, 163.5, 147.8, 140.7, 138.6, 132.8, 130.1, 129.3, 128.4, 128.3, 128.2, 127.5, 125.4, 123.3, 117.0, 80.7, 79.1, 61.8, 52.8, 47.1, 21.5, 13.3, 11.5. **Book 12, Pg. 95.**

Racemic:



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

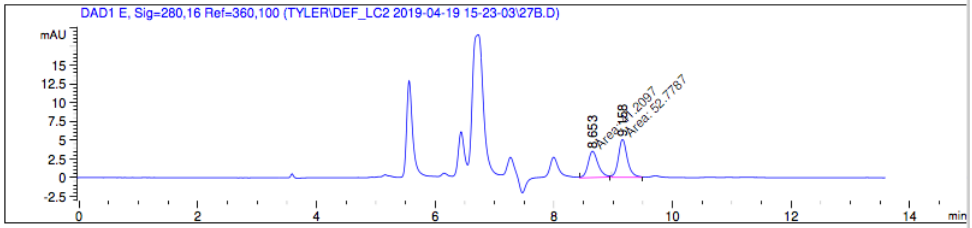
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.618	BB	0.1632	2.34814	2.15434e-1	48.5354
2	9.120	BB	0.1573	2.48985	2.43500e-1	51.4646

Totals : 4.83799 4.58934e-1

*** End of Report ***

Chiral run: 10% $Ni(ClO_4)_2$•$6H_2O$, 11% L*, CH_2Cl_2 0.1M, 18 h: 55%, 13%*ee*

Data File C:\CHEM32\1\DATA\TYLER\DEF_LC2 2019-04-19 15-23-03\27B.D
Sample Name: 27B



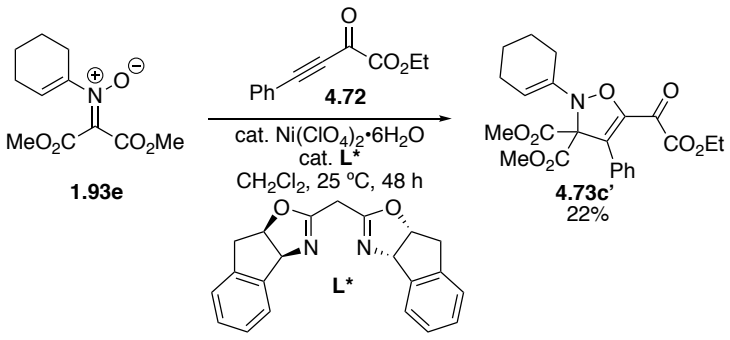
Area Percent Report

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.653	MM	0.1949	41.20967	3.52441	43.8455
2	9.158	MM	0.1738	52.77869	5.06131	56.1545

Totals : 93.98836 8.58572

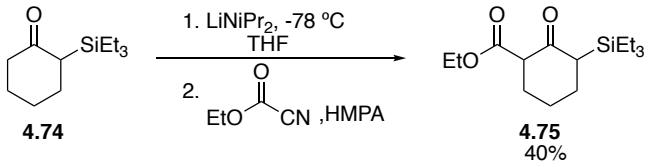
*** End of Report ***



General Procedure E: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **1.93e** (0.120 g, 0.50 mmol, 1.0 equiv), alkyne **4.72** (0.152 g, 0.75

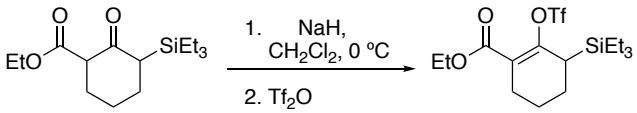
mmol, 1.5 equiv), $Ni(ClO_4)_2$•$6H_2O$ (18.3 mg, 0.05 mmol, 10mol%), Ligand (19.9 mg, 0.055 mmol, 11mol%), diluted with 10.0 mL of CH_2Cl_2, and the vial was sealed with a Teflon screw cap. The solution was stirred at 25 ºC for 18 h. The reaction mixture was filtered through SiO_2, concentrated and analyzed by NMR. This crude mixture was then wet-loaded with CH_2Cl_2 and purified on SiO_2 by medium pressure chromatography (1:5 – 1:1, EtOAc: hexane) to afford N-vinyl isoxazoline **4.73c'** as a bright yellow oil (0.0488 g, 22%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.06 – 8.04 (m, 2H), 7.60 – 7.56 (m, 1H), 7.48 – 7.45 (m, 2H), 5.60 – 5.59 (m, 1H), 4.07 (q, 2H), 3.86 (s, 6H), 1.86 – 1.83 (m, 4H), 1.36 – 1.31 (m, 2H), 1.22 – 1.16 (m, 2H), 1.03 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.5, 165.3, 158.5, 136.5, 136.0, 134.7, 134.0, 130.1, 129.4, 128.6, 126.4, 97.8, 60.9, 53.4, 28.4, 24.7, 22.4, 21.1, 13.8. **Book 13, Pg. 39.**

4.5.7 Synthesis of Cyclic Allenoate and Cascade Reaction with *N*-Vinylnitrone



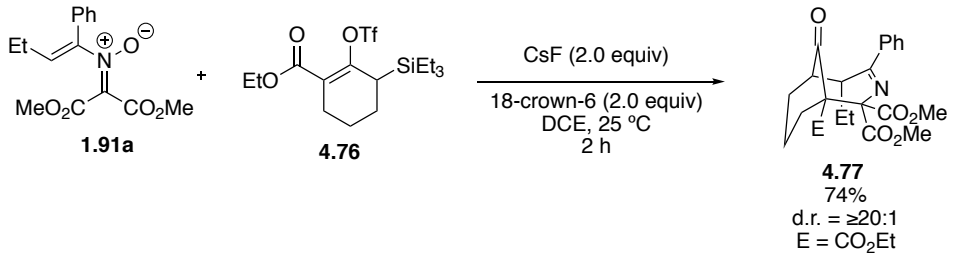
Synthesis of keto-ester 4.75: A flame-dried 25 mL round bottom flask equipped with a stir bar was allowed to cool under $N_{2(g)}$ and charged with iPr_2NH (0.80 mL, 5.64 mmol, 1.2 equiv) in THF (9.4 mL). The flask was cooled in a -78 ºC dry ice bath. A solution of nBuLi (2.26 mL, 2.5 M, 5.64 mmol, 1.2 equiv) was added dropwise over 4 min. The LDA was stirred at -78 ºC for 25 min, then at 25 ºC for 10 min. After cooling to -78 ºC, silyl ketone **4.74** (0.998 g, 4.7 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The reaction was stirred at -78 ºC for 2 h. HMPA (0.82 mL) and Ethyl cyano formate (0.557 mL, 5.64 mmol, 1.2 equiv) were added sequentially at -78 ºC. After stirring for 1 h at this temperature, the reaction was quenched with cold H_2O and warmed to 25 ºC. The crude reaction was extracted with Et_2O (3 x 20 mL), dried with anhydrous Na_2SO_4, and concentrated. NMR analysis indicated a 1:1 mixture of the β-ketoester and the vinyl carbonate. The crude mixture was wet-loaded with 1 mL Et_2O and purified on SiO_2 by medium pressure chromatography (1:99 – 1:39, Et_2O:hexane) to afford β-ketoester **4.75** as a clear colorless oil (0.535 g, 40%) as well as ketone **4.74** (0.500 g, 2.35 mmol, 50%)

due to hydrolysis of the vinyl carbonate. ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.16 – 4.06 (m, 2H), 2.29 – 2.22 (m, 1H), 2.11 – 2.03 (m, 1H), 1.98 – 1.93 (m, 1H), 1.79 – 1.72 (m, 1H), 1.67 – 1.60 (m, 1H), 1.56 – 1.47 (m, 1H), 1.44 – 1.36 (m, 1H), 1.27 – 1.24 (m, 1H), 1.22 (t, 3H), 0.90 (t, 9H), 0.61 (q, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 172.7, 95.5, 59.7, 27.6, 27.5, 24.2, 22.7, 14.2, 7.4, 3.3. **Book 13, Pg. 12.**



4.75 **4.76** 65%

Synthesis of cyclic allenoate precursor 4.76: A flame-dried 25 mL round bottom flask equipped with a stir bar was allowed to cool under $N_{2(g)}$ and charged with NaH (0.148 g, 60%wt/wt, 3.69 mmol, 2.1 equiv) and diluted with anhydrous CH_2Cl_2 (12 mL). The flask was cooled in an ice bath to 0 ºC and **4.75** (0.500 g, 1.76 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (6 mL) was added dropwise over 20 minutes. The reaction was allowed to warm to 25 ºC and stirred for 1 h. The flask was then cooled to -78 ºC in a dry ice bath and neat Tf_2O (0.385 mL, 2.29 mmol, 1.3 equiv) was added over 1 minute. The reaction was stirred at -78 ºC for 15 minutes then warmed to 25 ºC and stirred for 2 h. After cooling to 0 ºC, the mixture was quenched with 50 mL H_2O, extracted with CH_2Cl_2 (3 x 60.0 mL), dried with anhydrous Na_2SO_4, wet-loaded with 1 mL CH_2Cl_2 and purified on SiO_2 by medium pressure chromatography (0:100 – 1:99, Et_2O:hexane) to afford cyclic allenoate precursor **4.76** as a clear colorless oil (0.476 g, 65%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.23 – 4.17 (m, 1H), 4.13 – 4.05 (m, 1H) 2.73 – 2.67 (m, 1H), 2.21 – 2.08 (m, 1H), 2.07 – 2.00 (m, 1H), 1.96 – 1.89 (m, 1H), 1.73 – 1.66 (m, 1H), 1.64 – 1.57 (m, 1H), 1.45 – 1.37 (m, 1H), 1.22 (t, 3H), 0.92 (t, 9H), 0.65 (q, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 156.1, 119.7, 118.7 (q, $J_{19F\text{-}13C}$ = 313 Hz), 60.9, 28.2, 26.7, 25.2, 21.2, 13.6, 6.9, 2.6. **Book 13, Pg. 19.**



Cascade reaction of precursor 4.76 and 1.91a: A scintillation vial equipped with a stir bar was charged with **1.91a** (0.0728 g, 0.25 mmol, 1.0 equiv), CsF (0.0760 g, 0.5 mmol, 2.0 equiv), 18-crown-6 (0.132 g, 0.5 mmol, 2.0 equiv), and diluted with anhydrous DCE (2.5 mL, 0.1 M). With rapid stirring, **4.76** (0.156 g, 0.375 mmol, 1.5 equiv) in anhydrous DCE (1.0 mL) was added in one portion. The reaction was allowed to stir for 2 h, filtered through celite, the celite washed with EtOAc (3 x 5.0 mL) and concentrated. The crude reaction was wet-loaded with 1 mL CH_2Cl_2 and purified on SiO_2 by medium pressure chromatography (0:100 – 1:6, Et_2O:hexane) to afford bicyclic imino ketone **4.77** as a white solid (0.0820 g, 74%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.35 – 7.22)m, 3H), 7.12 – 7.06 (m, 2H), 4.29 – 4.16 (m, 2H), 3.77 (s, 3H), 3.73 (3H), 3.21 – 3.12 (m, 1H), 2.80 – 2.72 (m, 1H), 2.57 – 2.46 (m, 1H), 2.34 – 2.27 (m 1H), 2.18 – 2.08 (m, 1H), 2.05 – 1.95 (m, 2H), 1.86 – 1.77 (m, 1H), 1.60 – 1.50 (m, 1H), 1.26 (t, 3H), 1.20 – 1.15 (m, 1H), 0.91 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.1, 170.3, 168.2, 167.0, 141.0, 136.0, 128.6, 128.4, 127.8, 121.8, 74.5, 62.6, 61.5, 56.2, 53.8, 52.3, 36.3, 33.7, 30.3, 28.8, 28.7, 21.0, 14.2, 13.9, 13.8. **Book 13, Pg. 20.**

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