Electrocyclizations of *N*-Vinylnitrones and [3,3']-Sigmatropic Rearrangement of *N,O*-Divinylhydroxylamines

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THESIS

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LIST OF ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
bipy	2,2'-bipyridyl
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
DABCO	1,4-Diazabicyclo[2.2.2]octyane
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dicholorethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DMAD	Dimethyl acetylenedicarboxylate
DMAP	*N,N*-4-Dimethylaminopyridine
DMEDA	*N,N'*-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DTBP	2,6-Di-tert-butylpyridine
DNA	Deoxyribonucleic acid
dr	Diastereoselective
ee	Enantioselective
EDG	Electron donating group
EWG	Electron withdrawing group
h	Hour
Hz	Hertz
Me	Methyl
M.S	Molecular Sieves
Ms	Mesyl
NMR	Nuclear Magnetic Resonance
Pd	Palldium
PhMe	Toluene
Pr	Propyl
Py	Pyridine
rac	Racemic
rt	Room Temperature
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical
Tf	Trifluoromethansulfonyl
TFA	Trifluoroacetic Acid
TFE	Trifluoroethane
THF	Tetrahydrofuran
TLC	Thin Layer Chromatrography
TMEDA	Tetramethyethylenediamine

TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

SUMMARY

Chapter 1 demonstrates the synthesis of unsaturated morpholine *N*-oxides through C–N bond formations from oximes and vinylboronic acids via spontaneous 6π-electrocyclization. A variety of examples for highly-substituted morpholines were described. After initial discovery of 2*H*-1,4-oxazines by Dr. Dong-Liang Mo, I contributed to this project by screening substrates, optimizing and preparing examples of unsaturated morpholine *N*-oxides as well as extensive functionalizations to access highly-substituted morpholines. An undergraduate student, Ki Hwan Kim, contributed to making several oximes and nitrones, and professor Donald Wink assisted in elucidating some unknown structures by X-ray crystallographic analysis.

Chapter 2 discusses the 4π-electrocyclization of *N*-vinylnitrones, which produces thermally stable azetidine nitrones. Preparation of *N*-vinylnitrones from oximes and vinylboronic acids is shown, and optimization and scope of azetidine nitrones are discussed. Functionalizations such as cycloadditions, reductions, and C–C bond formations are demonstrated to prepare complex azetidines. My labmate, Tyler Reidl, contributed to this project primarily by investigating optimization and expanding the scope of the *N*-vinylnitrones and azetidine nitrones. My contribution involved screening several reaction conditions and preparing novel vinylboronic acids.

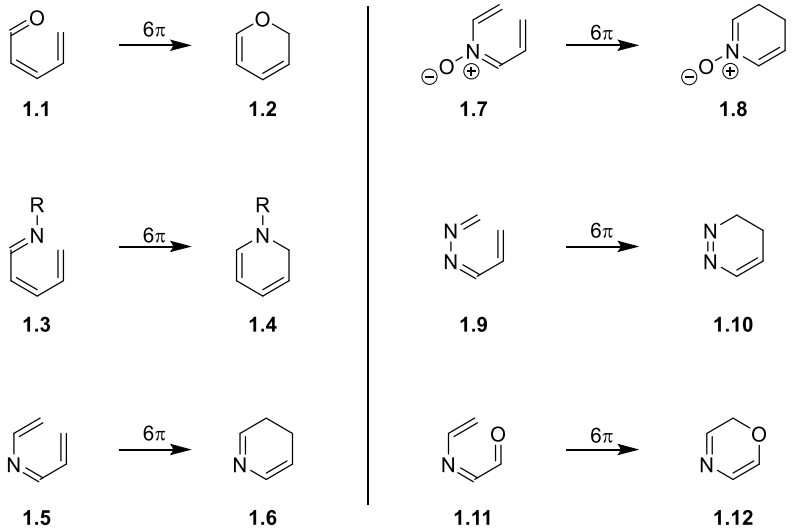
Chapter 3 describes the generation of nucleoside analogues through [3,3']-sigmatropic rearrangement of *N*,*O*-divinylhydroxylamines. The reactive intermediate for the rearrangement is prepared *in situ* from the treatment of *N*-vinylhydroxylamine in the presence of electron deficient allenes, which is revealed to undergo spontaneous [3,3']-rearrangement to 2-aminotetrahydrofurans. The scope of this transformation is described with the use of a variety of *N*-vinylhydroxylamines and allenes. Also, the functionalization study of nucleoside analogues is described. My contribution is to discover the reaction and reactivity of substrates as well as functionalization studies. A coworker, Tyler Reidl explored optimization of the Ullmann reaction to access *N*-vinylhydroxylamines and preparation of vinyliodides

Chapter 1. 6π-Electrocyclization of *N*-Alkenylnitrones For the Preparation of Morpholine *N*-Oxides

1.1. Introduction - 6π-Electrocyclization of Heteroatom-Containing Hexatrienes

6π-Electrocyclizations of acyclic heteroatom-containing 1,3,5-hexatriene motifs have emerged as transformative tools for accessing a variety of heterocycles.[1-8] Six different types of reported 6π-electrocyclizations of heteroatom-containing 1,3,5-hexatrienes are shown in Scheme 1.1. Specific examples of these reactions will be described in this section to emphasize the synthetic advantages of these approaches such as robust mild reaction conditions and high stereoselectivity.[9-20] This discussion will then be used to establish literature context for our contributions in the area of *N*-alkenylnitrone 6π-electrocyclizations.[18]

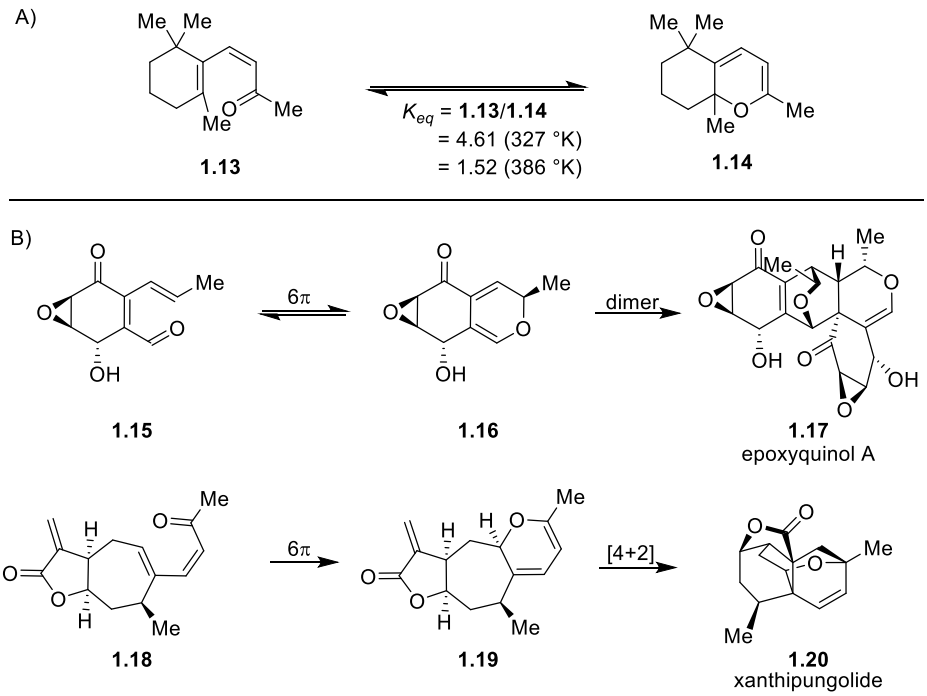
Scheme 1.1. Examples of Heteroatom 6π-Electrocyclization



The 6π-electrocyclization of 1-oxal-3,5-hextrienes is an attractive transformation to synthesize oxygen-containing heterocycles because of readily accessible oxa-hexatriene motifs towards cyclized isomers. Alternative approaches to form these molecules involve functionalization of conjugated ketones and the use of electrocyclization is advantageous because of practically usefulness and predicted stereochemistry. In 1966, the Marvell group first reported the rapid interconversion of *cis*-β-ionone **1.13** and 2*H*-pyran **1.14** through a 6π-electrocyclization (Scheme 1.2A).[9] When 2*H*-pyran **1.14** was heated, a ^{1}H NMR spectrum in blank showed an increased intensity of *cis*-β-ionone **1.13** with a compensating decrease of **1.14**. While the temperature of the sample was returned to room

temperature, cycloreversion was observed as an increase in the intensity of **1.14**. This preference for cyclization at higher temperatures and cycloreversion at lower temperatures is consistent with ^{1}H NMR spectra. Further studies shows that the installation of electron-withdrawing groups at the 2-position of **1.13** also favors cyclization to **1.14**.[10,11] This observation is also consistent with the similarity to their initial observations. Further development of related transformations has broadened their application to natural product synthesis (Scheme 1.2B). For example, **1.15** and **1.18** have been used as precursors to **1.17** and **1.20**.[19-21] This strategy for the synthesis of **1.17** was unique because it showed a hetero-dimerization pf **1.16** with its diastereomer to afford **1.17**. This strategy for the synthesis of **1.20** was unique because of its cascade pericyclic processes for the preparation of **1.20**.

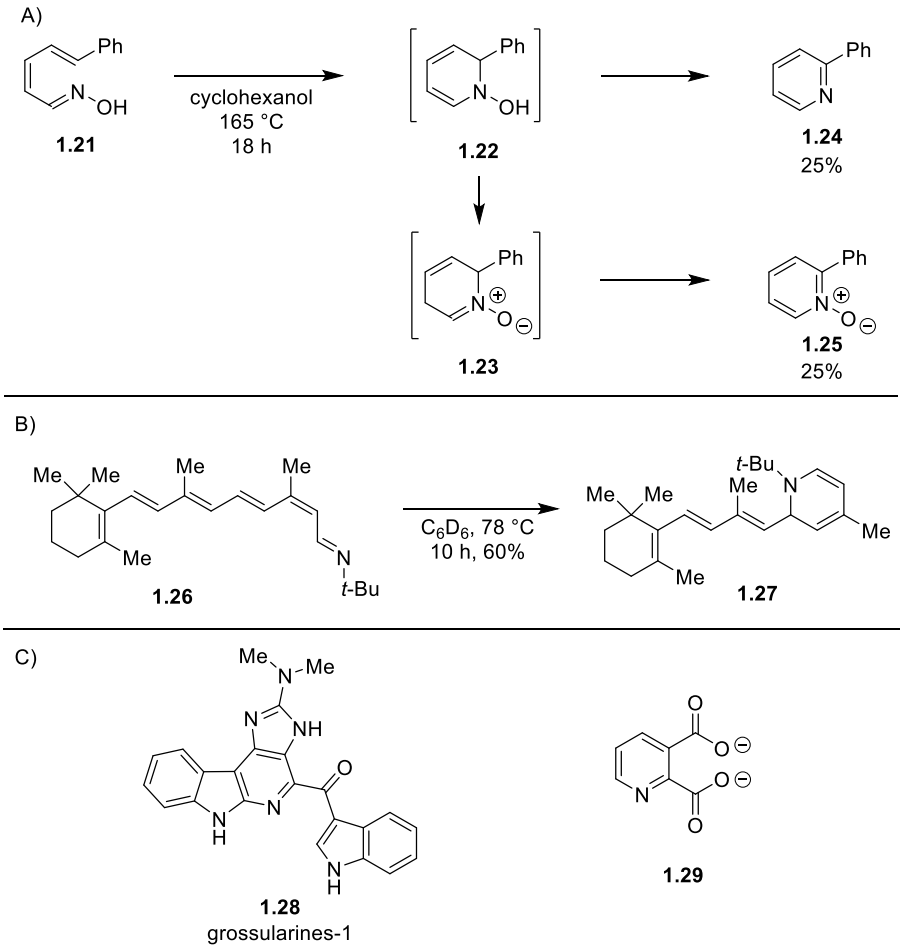
Scheme 1.2 6π-Electrocyclization of 1-Oxatriene Systems[9-11, 19-21]



The 6π-electrocyclization of 1-aza-1,3,5-hexatrienes has also been exploited to prepare valuable nitrogen-containing heterocycles, particularly for alkaloid synthesis. In 1972, the Ringele group reported that 5-phenyl-pentadienaldoxime **1.21** undergoes an aza-6π-electrocyclization, to provide a 1:1 mixture of **1.22** and **1.23** under refluxing conditions in cyclohexanol (Scheme 1.3A).[12] The proposed mechanism for this transformation suggests that initially formed electrocyclization products **1.22** and **1.23**, are subsequently oxidized to **1.24** and **1.25** under harsh reaction conditions. Further studies showed that Schiff base formation with retinal promotes an aza-6π-

electrocyclization to give **1.27** and that steric and conformational issues play a role in affecting the rate of cyclization. Specifically, *tert*-butyl substituent on nitrogen shows faster electrocyclization behavior than *n*-butyl (Scheme 1.3B).[8] The electrocyclization of 1-aza-1,3,5-hexatrienes have also been used in natural product synthesis for the preparation of grossularines-1 [22] and pyridine ring of nicotinamide adenine dinucleotide phosphate (NAD^+).[13] The strategy for the synthesis of **1.28** was unique because of oxidative dimerization-electrocyclization sequence and the strategy for the synthesis of **1.29** was unique because of its non-enzymatic process for pyridine ring of NAD (Scheme 1.3C).

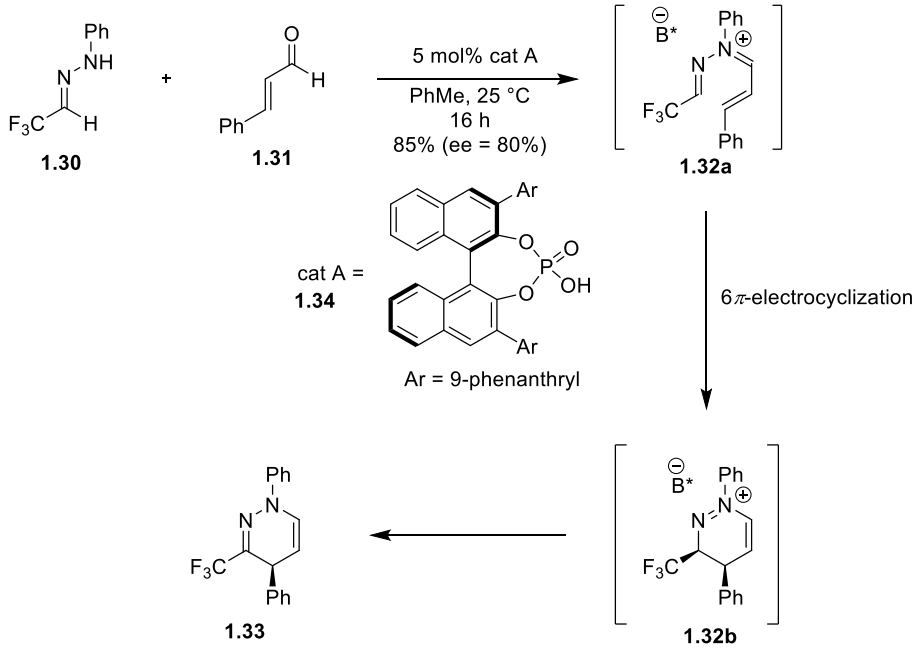
Scheme. 1.3 6π-Electrocyclization of 1-Azatriene Systems[8,12,13]



A similar condensation and electrocyclization strategy was reported by the Rueping group for the generation of 2,3-diazahextrienes and their electrocyclization to 1,4-dihydropyridazines (Scheme 1.4).[16] Condensation of hydrazine **1.30** with (*E*)-cinnamaldehyde **1.31** in the presence of chiral Brønsted acid catalyst **1.34** gives hydrazone **1.32a**, which undergoes spontaneous enantioselective 6π-electrocyclization to form **1.32b** that can isomerize via

deprotonation to **1.33**. The observed stereoselectivity is proposed to arise from a disrotatory electrocyclization. This selectivity is dependent on the structure of phosphoric acid for this type of transformation due to its paired asymmetrical environment. In this transformation, hydrazones with electron-rich aryl groups display faster conversion, which is consistent with Fischer-Indole synthesis. In addition, hydrazones with 1-naphthyl provide increased enantioselectivity due to sterics. This study showed that creative condensation methods could be used to access heteroatom-containing hexatriene systems beyond 1-azahexatrienes.

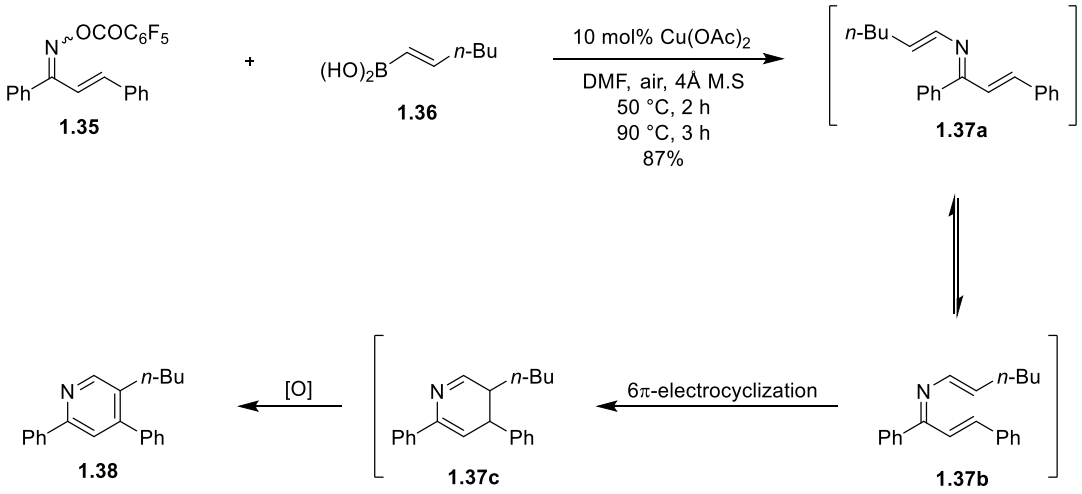
Scheme 1.4 6π-Electrocyclizations of a 2,3-Diazahexatriene System[16]



Beyond the use of condensation methods to access heteroatom-containing substrates for 6p-electrocyclization, cross-coupling methods have also been designed for this purpose. In 2008, the Liebeskind group reported a modular synthesis of substituted pyridines through a copper-catalyzed *N*-vinylation and 6π-electrocyclization cascade process (Scheme 1.5).[14] Unsaturated *O*-pentafluorobenzoate ketoxime **1.35** and alkenylboronic acid **1.36** undergo a C–N bond forming event in the presence of catalytic amount of $Cu(OAc)_2$, leading to the generation of **1.37a**. Under the reaction conditions, *trans*-**1.37a** can equilibrate to *cis*-**1.37b**, which triggers a thermal 6π-electrocyclization to form **1.37c** and oxidation to give **1.38**. The limitations of this method were shown to be side reactions, 1,5-hydrogen shifts in the 3-azatriene intermediate from alkylketoximine substrate. The synthetic advantages of this method are readily available starting materials and broader range of substituents for highly-

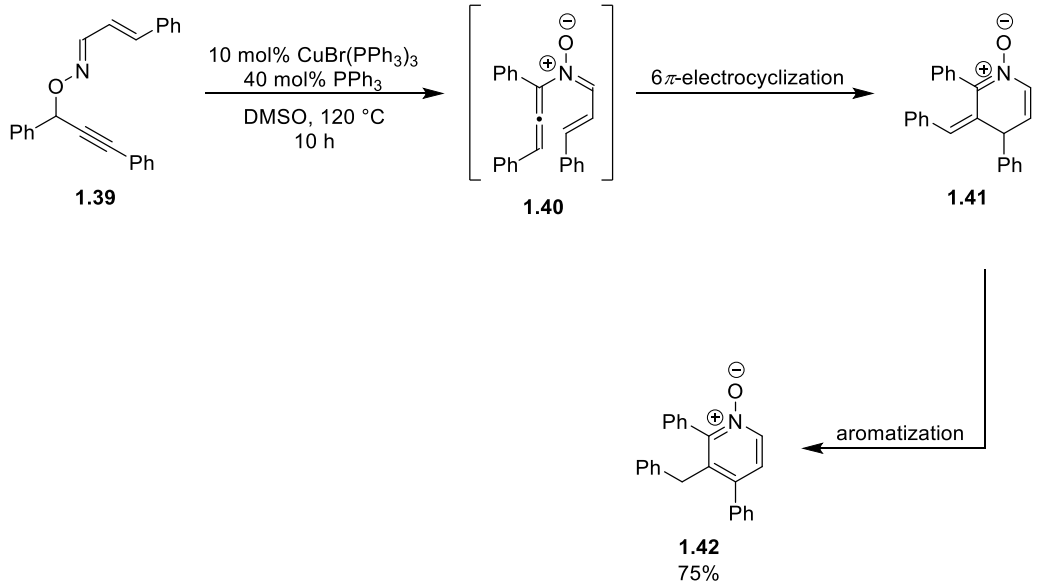
substituted pyridines in comparison to related condensation processes and the reactivity advances are copper-catalyzed *N*-iminovinylation to construct 3-azahexatrienes in comparison to conventional C–N bond formations.

Scheme. 1.5. 6π-Electrocyclization of 3-Azatrienes for the Synthesis of Pyridines[14]



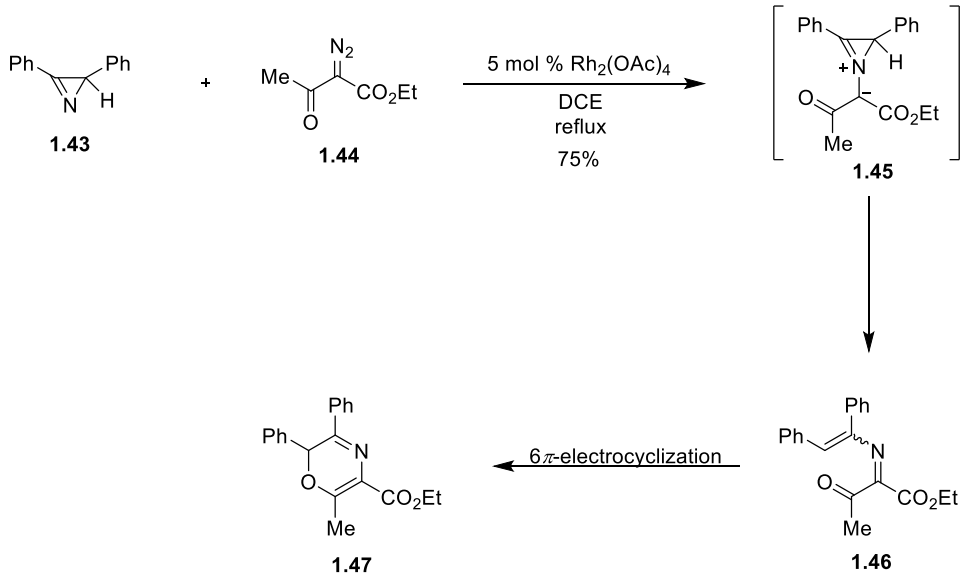
As another alternative approach to the generation of heteroatom-containing hexatriene systems, the Terada group has shown that 3-*N*-oxide hexatrienes can be prepared via the [2,3]-rearrangement of *O*-propargylic oximes (Scheme 1.6).[15] This research group reported that copper-catalysis promotes the [2,3]-rearrangement of (*E*)-*O*-propargylic oxime ether **1.39** to give (*E*)-*N*-allenylnitrone **1.40** that undergoes a 3-aza-6π-electrocyclization to provide a corresponding 3,4-dihydropyridine *N*-oxide **1.41** that aromatizes under the reaction conditions to give, pyridine *N*-oxide **1.42**. Consistent with the proposed electrocyclization reaction pathway, (*E*)-oxime ether **1.39** afforded a major pyridine *N*-oxide product **1.42** but the corresponding (*Z*)-isomer failed to convert to the same product. In contrast, 4p-electrocyclization of the (*Z*)-isomer was favored. These results established the [2,3]-rearrangement of *O*-propargylic oximes such as **1.39** as precursors to 3-azahexatrienes for electrocyclization. The limitations of this method were harsh reaction conditions and oxime ether substrates because of (*E*)/(*Z*)-isomerization which favors by-product azetidine formation. The advances illustrated by this method were shown to be tolerated substrate scopes with aryl, alkyl, and a protected alcohol on oxime ethers and cascade transformation of pyridine *N*-oxide because of synthetic versatility of heterocycle *N*-oxides.

Scheme. 1.6. 6π-Electrocyclization of *N*-Allenylnitrones Generated via the [2,3]-Rearrangement of O-Propargylic Oximes



To further complement the multiple approaches to the synthesis of the azahexatriene systems described above, Novikov and coworkers developed an azirene ring-expansion approach to the preparation of 1-oxa-4-aza-hexatrienes and their subsequent electrocyclization to 2*H*-1,4-oxazines (Scheme 1.7) [17]. When 2*H*-Azirine **1.43** was treated with 2-acyl-2-diazoacetate **1.44** in the presence of a Rh(II) catalyst, ring-opening of **1.45** was proposed to give acyclic 4-aza-1-oxa-1,3,5-hexatriene **1.46** followed by 6π-electrocyclization to provide 2*H*-1,4-oxazine **1.47**. The stability of these products was not good. The limitations of this method were use of expensive transition metal, instability of azirine substrates, limited scope of 2-diazoacetoacetates, and the lack of functionalization study of 2*H*-1,4-oxazines. The advantages of this method were shown to be a preparation of non-fused 2*H*-1,4-oxazines and a modular synthesis of 2*H*-1,4-oxazines through 6π-electrocyclization. Further investigation of this system revealed that **1.46** could undergo reversible cyclization and cycloreversion in C_6D_6, under the influence of heating and UV irradiation. These studies showed an advance from other methods due to unexplored 6π-electrocyclization of 4-oxa-1-aza-hexatrienes and limitations due to accessing azirines with different substituents and functionalization of 2*H*-1,4-oxazines.

Scheme. 1.7. 6π-Electrocyclization of 4-Aza-1-Oxa-1,3,5-Hexatriene System



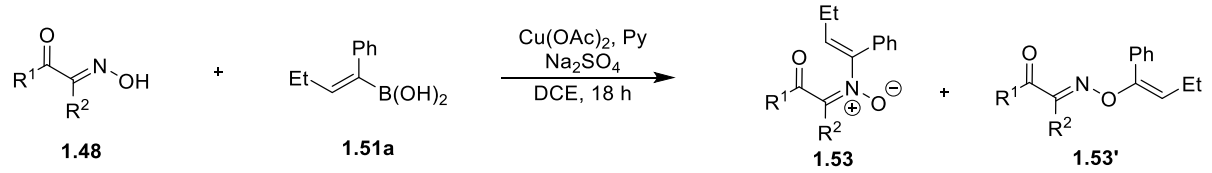
The examples described above illustrate the different approaches to heterocycle synthesis via electrocyclization of heteroatom-containing hexatrienes. Highlights of these developments include blank, blank, and blank. To further advance these ideas, we wondered if we could design a heterocycle synthesis using the electrocyclization of a heteroatom-containing hexatriene system that would form a partially unsaturated heterocycle that could be used for the divergent synthesis of saturated derivatives.

1.2 Discovery of *N*-Vinylnitrone Synthesis and Electrocyclization Cascade

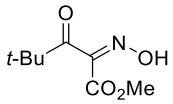
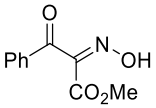
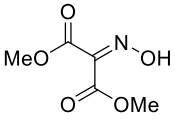
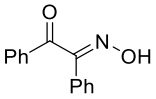
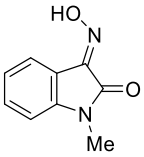
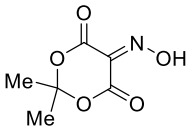
The Anderson group has previously used the Chan-Lam reaction with oxime substrates to generate *O*-vinyloximes and *N*-vinylnitrones.[23,24] While exploring the selectivity of this transformation for these chemoselective C–N or C–O bond forming events, a variety of electron-poor oximes **1.48a**–**1.48f** were tested with vinylboronic acid **1.51a** under standard conditions with $Cu(OAc)_2$ and pyridine (Table 1.1).[24] Ketoester- and malonate-derived oximes **1.48a** and **1.48b** gave *N*-vinylated nitrones **1.53a** and **1.53b** in moderate yield (Table 1.1, entries 1 and 2). *N*-Methyl isatin oxime **1.48c** also gave a 2:1 *E*/*Z*-ratio of **1.53c** (Table 1.1, entry 3). β-Ketoester oxime **1.48d** afforded *N*-vinylnitrone **1.53d** over shorter reaction times but the desired product converted to a byproduct over the course of 18 h (Table 1.1, entry 4). Deoxybenzoin-derived oxime **1.48e** gave a 1:1 mixture of *N*-vinylnitrone **1.53e** and *O*-vinyloxime **1.54e** (Table 1.1, entry 5), and no vinylation was observed for oxime **1.48f** (Table 1.1, entry 6). These results

indicated that substitution patterns play a significant role in determining the chemoselective outcome of the Chan-Lam reaction even when oxime substrates have similar carbonyl functional groups.

Table 1.1. Oximes Tested Under Chan-Lam Conditions for the Synthesis of *N*-Vinylnitrones



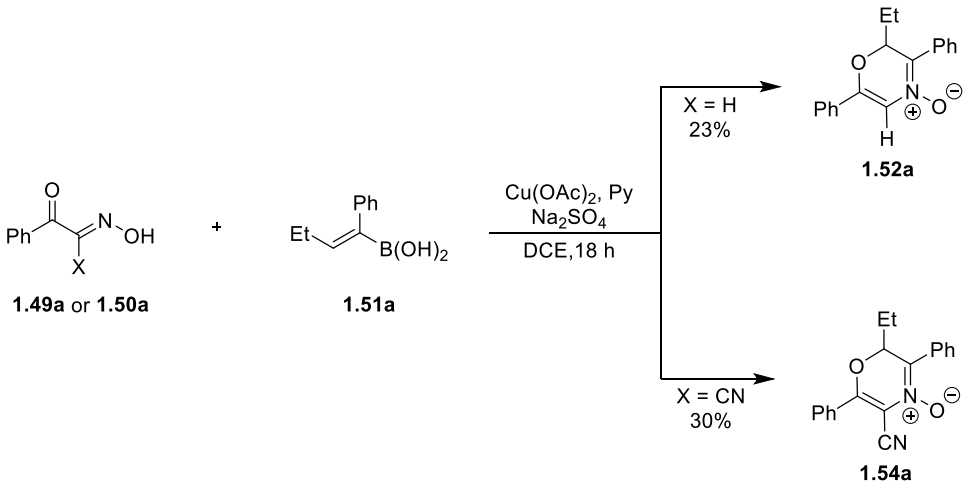
1.48 **1.51a** **1.53** **1.53'**

Entry	**1.48**	Oximes	% Yield[a]	Entry	**1.48**	Oximes	% Yield[a]
1	**1.48a**		59[b]	4	**1.48d**		31[c]
2	**1.48b**		57	5	**1.48e**		21[d]
3	**1.48c**		(*E*)/(*Z*) = 2:1	6	**1.48f**		NR

[a] Yield was determined by ^{1}H NMR using CH_2Br_2 as a reference. Conditions: oxime **1.48** (1 equiv), **1.51a** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 18 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] 2 h reaction. [c] 2 h gave in 31% and 18 h gave in 0% [d] Isolated as a mixture with 25% *O*-vinylation **1.53'**.

While screening different oximes to better understand their reactivity in the Chan-Lam reaction, we also tested two other types of oximes **1.49a** and **1.50a** that surprisingly gave unsaturated morpholine *N*-oxides **1.43a** and **1.45a**, respectively, under the same reaction conditions (Scheme 1.8). We hypothesized that these products could arise from a subsequent 6π-electrocyclization of an *N*-vinylnitrone intermediate but this compound was not observed at shorter reaction times. Our interest in the potential to use these products for the divergent synthesis of highly-substituted morpholines encouraged use to pursue the development of this new method.[18]

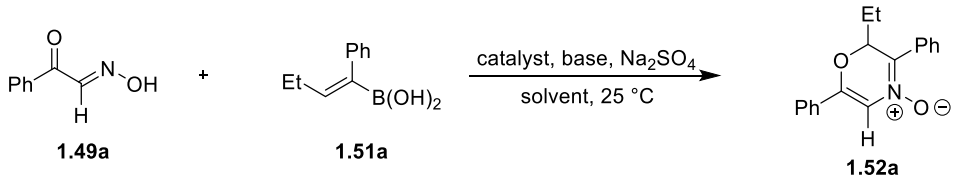
Scheme 1.8 Observation of Direct Conversion of Oximes and Vinylboronic Acids to Unsaturated Morpholine *N*-Oxides



1.3 Optimization and Scope of the Single-Flask Generation of *N*-Vinylnitrones and Spontaneous Electrocyclization to Unsaturated Morpholine *N*-Oxides

Reaction conditions were optimized for the synthesis of morpholine *N*-oxides **1.52a** from aldoxime **1.49a** and vinyl boronic acid **1.51a** by varying the selection of copper salt, base, solvent, and reaction time (Table 1.2). A variety of copper sources were tested and $Cu(OAc)_2$ was identified as the optimal copper reagent for the synthesis of morpholine nitrone **1.52a** (Table 1.2, entries 1-6). Several bases were investigated and pyridine was the best choice among the amine and inorganic bases listed in Table 1.2, entries 9-13. A subsequent solvent screen identified DCE as the optimal solvent for this transformation (Table 1.2, entries 14-17). The optimal reaction conditions for the conversion of **1.49a** to **1.52a** shown in Table 1.2, entry 1 are analogous to conditions determined for *N*-vinylnitrone syntheses previously reported by the Anderson group.[24] Reaction mixtures that were exposed to longer reaction times gave attenuated yields of **1.52a** and competing formation of a byproduct analogous to the byproduct observed when **1.52a** was treated with Chan-Lam reaction conditions for longer reaction times (Table 1.2, entries 7 and 8). Although optimal conditions for the conversion of **1.49a** to **1.52a** required 1 equiv of $Cu(OAc)_2$, 20 mol % $Cu(OAc)_2$ was also an effective catalyst for this transformation and promoted the conversion of nitrone to oxazine **1.52a** in somewhat attenuated yields. (Table 1.2, entry 18). Further exploration of the scope of the conversion of α-ketooximes to unsaturated morpholine *N*-oxides was further investigated using the optimal reaction conditions given in Table 1.2, entry 1.

Table 1.2. Optimization of Reaction Conditions for the Synthesis of Unsaturated Morpholine *N*-Oxides



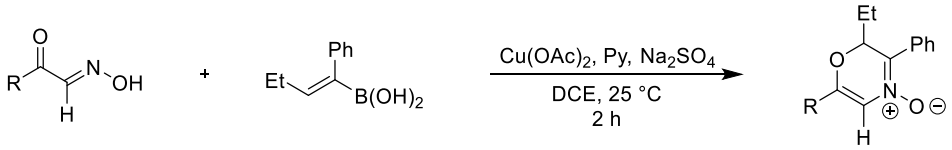
Entry	Catalyst	Base	Solvent	Time (h)	% Yield[a],[b]
1	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	DCE	2	79
2	$CuBr_2$ (1 equiv)	Py (3 equiv)	DCE	2	6
3	$Cu(acac)_2$ (1 equiv)	Py (3 equiv)	DCE	2	11
4	CuO (1 equiv)	Py (3 equiv)	DCE	2	45
5	CuI (1 equiv)	Py (3 equiv)	DCE	2	0
6	CuCN (1 equiv)	Py (3 equiv)	DCE	2	0
7	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	DCE	6	32
8	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	DCE	18	23
9	$Cu(OAc)_2$ (1 equiv)	Et_3N (3 equiv)	DCE	2	26
10	$Cu(OAc)_2$ (1 equiv)	DABCO (3 equiv)	DCE	2	46
11	$Cu(OAc)_2$ (1 equiv)	TMEDA (3 equiv)	DCE	2	7
12	$Cu(OAc)_2$ (1 equiv)	DMAP (3 equiv)	DCE	2	57
13	$Cu(OAc)_2$ (1 equiv)	K_2CO_3 (3 equiv)	DCE	2	48
14	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	PhMe	2	61
15	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	DMF	2	30
16	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	EtOH	2	43
17	$Cu(OAc)_2$ (1 equiv)	Py (3 equiv)	THF	2	51
18	$Cu(OAc)_2$ (10 mol %)	Py (3 equiv)	DCE	2	47

[a] Conditions: oxime **1.49a** (1 equiv), vinylboronic acid **1.51a** (5 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in solvent, 25 ˚C, air. Py = pyridine, DCE = 1,2-dichloroethane. [b] Yield was determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference.

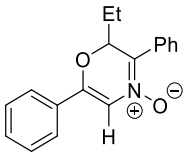
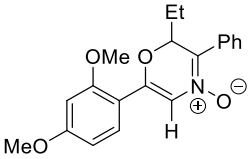
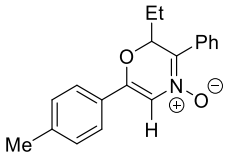
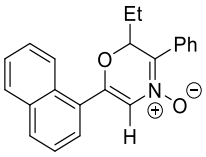
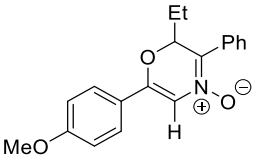
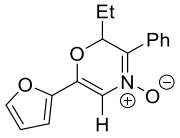
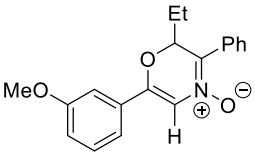
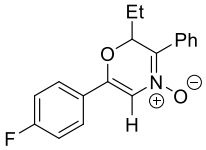
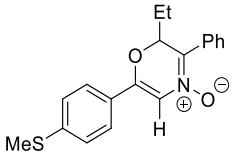
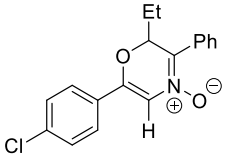
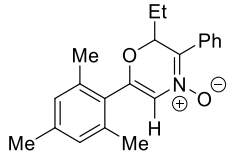
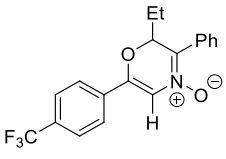
The scope of the synthesis of unsaturated morpholine *N*-oxides from aldoximes was investigated by varying the ketone substituent (Table 1.3). Unsubstituted, p-substituted, and m-substituted aryl ketones, as well as a mesityl and a 2-naphthyl ketones were tolerated as aldoxime substituents and gave the desired unsaturated morpholine N-oxides products in moderate to good yield (Table 1.3, entries 1–12). The structure of nitrone **1.52c** was confirmed by X-ray crystallography study performed by Prof. Donald J. Wink (Figure 1.1). While various steric environments were tolerated at the ketone substituent, the Chan-Lam reaction and electrocyclization cascade was more sensitive to electronically different aryl ketones. While improved reactivity was observed for electron-rich aryl ketone aldoxime **1.49c**, electron-poor aryl ketone aldoxime **1.49l** gave **1.52l**, in attenuated yield. Similarly, electron-rich heterocyclic ketone such as **1.52i** were well-tolerated for this transformation (Table 1.3, entry 12) and aldoximes with halogenated aryl ketone substituents smoothly gave **1.52j**–**1.52k**. Unexpectedly, pivaloyl aldoxime **1.49m**

underwent an oxidation process that gave pivaloyl cyanide **1.52m** instead of the desired unsaturated oxazine (Scheme 1.9). A UIC undergraduate student, Mr. Kihwan Kim, contributed to this study by synthesizing several of the oximes and boronic acids required to understand the scope of the transformation complete Table 1.3. The successful examination of the scope of the conversion of α-keto aldoximes to unsaturated morpholine *N*-oxides motivated our continued exploration of scope of this transformation for other types of oxime substrates.

Table 1.3. Tolerance of Aldoxime Substrates for the Synthesis of Unsaturated Oxazine *N*-Oxides

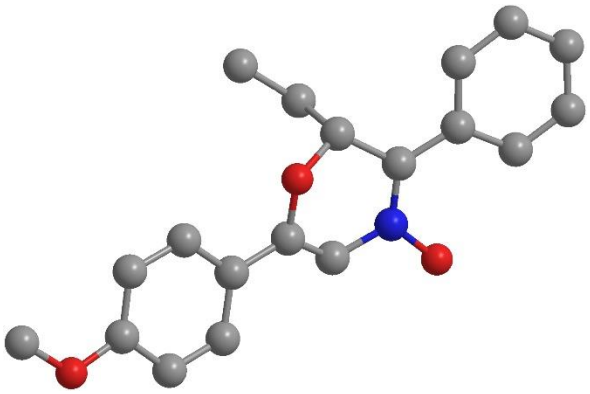


1.49 + **1.51a** → **1.52**

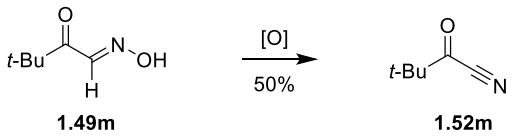
Entry	**1.52**	Product	% Yield[a][b]	Entry	**1.52**	Product	% Yield[a],[b]
1	**1.52a**		73	7	**1.52g**		49
2	**1.52b**		60	8	**1.52h**		57
3	**1.52c**		72[c]	9	**1.52i**		67
4	**1.52d**		58	10	**1.52j**		54[c]
5	**1.52e**		55	11	**1.52k**		56
6	**1.52f**		59[c]	12	**1.52l**		31

[a] Conditions: oxime **1.49** (1 equiv), vinylboronic acid **1.51a** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 2 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Percent isolated yield. [c] Mr. Kihwan Kim contributed to preparation of corresponding oximes and nitrones.

Figure 1.1. X-Ray Crystal Structure of **1.52c** (CCDC 1506785) by Prof. Donald J. Wink



Scheme 1.9. Observation of the Generation of Pivaloyl Cyanide from Pivaloyl Aldoxime **1.49m**

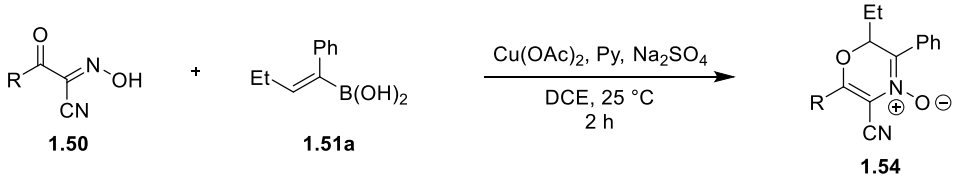


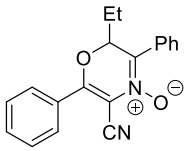
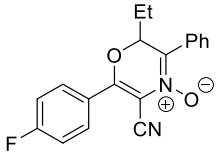
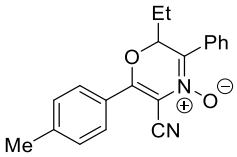
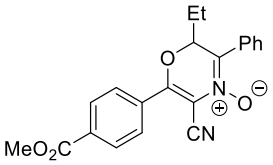
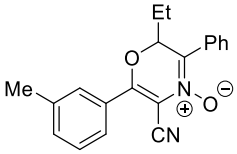
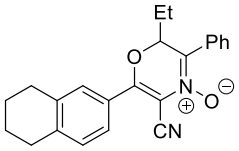
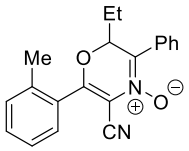
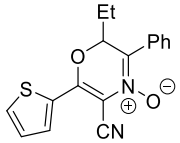
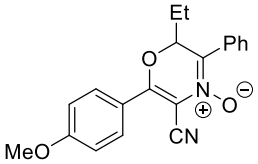
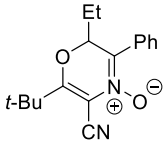
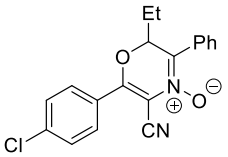
1.49m **1.52m**

The scope of the synthesis of unsaturated morpholine *N*-oxides was further explored using α-aryl ketone cyano-substituted oximes **1.50** (Table 1.4). Similar to our observations with the aldoximes described in Table 1.4, cyano-substituted oximes tolerated a variety of aryl and heteroaromatic ketones. Electron-neutral and electron-rich aryl groups gave excellent yields of the corresponding oxazines (Table 1.4, entries 1–5), while halogen-substituted aryl ketones gave the desired products in good yield (Table 1.4, entries 6–7), and electron-poor aryl ketone gave the corresponding oxazine in attenuated yield (Table 1.4, entry 8). In general, all of the *N*-vinylnitrone generation and electrocyclization yields for these substrates were higher than the corresponding aldoximes illustrated in Table 1.3. The structure of **1.54e** was also characterized by an X-ray crystallography study performed by Prof. Donald J. Wink that verified the similarity of the structure of this compound to **1.43c** (Figure 1.2). In contrast to aldoxime **1.49m**, pivaloyl oxime **1.50k** was smoothly converted to **1.54k** in good yield without the observation of competing oxidation products (Table 1.4., entry 11). These studies defined the scope of our single-flask conversion of **1.50** to

1.54 and provide an array of compounds to investigated for further reactivity and rapid conversion to highly-substituted morpholine compounds.

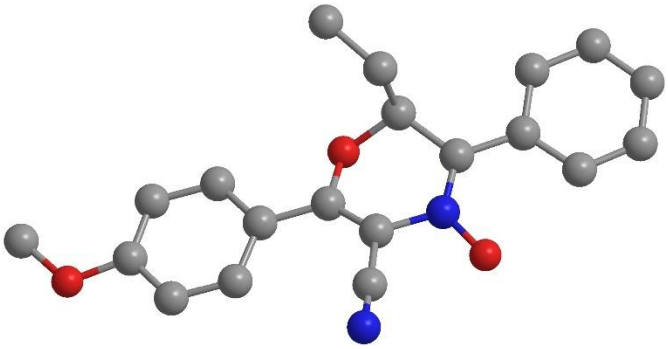
Table 1.4. Tolerance of Cyano-Substituted Oxime Substrates for the Synthesis of Unsaturated Oxazine *N*-Oxides.



Entry	**1.54**	Product	% Yield[a][b]	Entry	**1.54**	Product	% Yield[a][b]
1	**1.54a**		76	7	**1.54g**		72
2	**1.54b**		80	8	**1.54h**		40
3	**1.54c**		47	9	**1.54i**		80
4	**1.54d**		44	10	**1.54j**		80
5	**1.54e**		91	11	**1.54k**		74
6	**1.54f**		73				

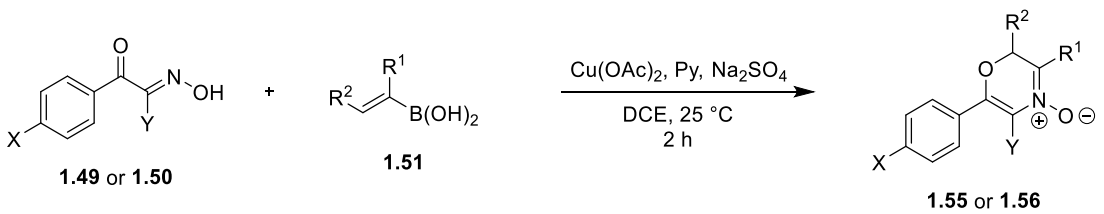
[a] Conditions: oxime **1.50** (1 equiv), vinylboronic acid **1.51a** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 2 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Percent isolated yield.

Figure 1.2. X-Ray Crystal Structure of **1.54e** (CCDC 1506786) by Prof. Donald J. Wink

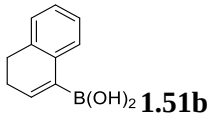
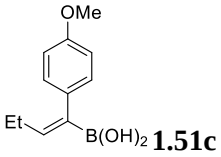
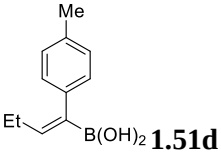
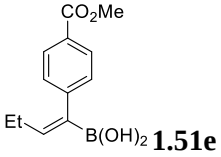
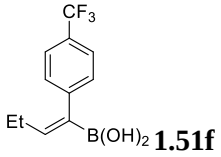
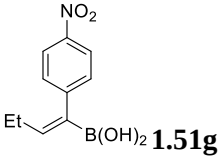
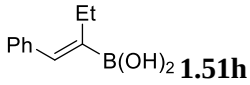
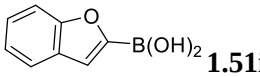
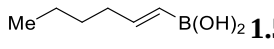
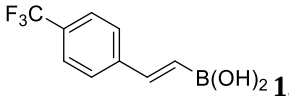
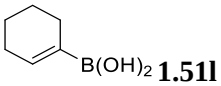


To determine the tolerance of the vinylboronic acid reagent for the synthesis of unsaturated morpholine *N*-oxides **1.55**, the oximes **1.49c** and **1.50e** were tested with several vinylboronic acids **1.51b**–**1.51l**. As shown in Table 1.5, both cyclic and acyclic 1-aryl-2-alkyl-vinylboronic acids **1.51b-g** were tolerated for this transformation. Tetralone-derived cyclic alkenylboronic acid **1.51b** and electron-rich *α*-styrenyl boronic acid **1.51c** were smoothly converted to **1.55b**–**1.55c** and **1.55c**–**1.56c** when treated with **1.51b** or **1.51c** (Table 1.5, entries 1–2). Electron-poor *α*-styrenylboronic acids such as **1.51e**–**1.51g** gave increased yields of **1.55e**–**1.55g** and **1.56e**–**1.56g** in comparison to electron-rich and electron-neutral examples. (Table 1.5, entries 7-12). *p*-Tolyl-substituted alkenylboronic acid **1.51d** gave **1.55d** and **1.56d** in attenuate yield due to difficulties with product separation. Beyond these 1-aryl-2-alkyl-alkenylboronic acids, a wider range of alternatively substituted alkenylboronic acids were tested but did not show any reactivity with **1.49c** or **1.50e** under the optimized reaction conditions (Table 1.5, entries 13-17). A plausible explanation for the selectivity of the *N*-vinylnitrone generation and electrocyclization sequence is expected as a competent oxidation of aldoxime or vinylboronic acid degradation.[27] Even with this minor limitation in substrate scope with respect to the vinylboronic acid component of the reaction, the collection of unsaturated morpholine nitrones that we were able to prepare using this method was quite large and facilitated our further study of the reactivity of these unusual heterocycles.

Table 1.5. Tolerance of Vinyl Boronic Acids for Unsaturated Oxazine *N*-Oxide Synthesis.



Entry	X	**1.55, 1.56**	Y	Boronic Acid	% Yield[a],[b]

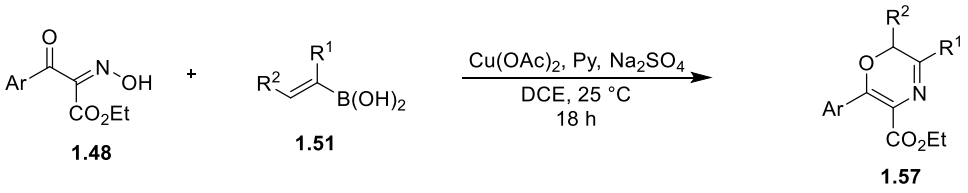
1	MeO	**1.55b**	CN	 **1.51b**	81
2	MeO	**1.56b**	H		78
3	MeO	**1.55c**	CN	 **1.51c**	78
4	MeO	**1.56c**	H		65
5	MeO	**1.55d**	CN	 **1.51d**	40
6	MeO	**1.56d**	H		27
7	MeO	**1.55e**	CN	 **1.51e**	93
8	MeO	**1.56e**	H		66
9	MeO	**1.55f**	CN	 **1.51f**	93
10	MeO	**1.56f**	H		78
11	MeO	**1.55g**	CN	 **1.51g**	94
12	MeO	**1.56g**	H		78
13	H	**1.56h**	H	 **1.51h**	NR
14	H	**1.56i**	H	 **1.51i**	NR
15	H	**1.56j**	H	 **1.51j**	Decomp.
16	H	**1.56k**	H	 **1.51k**	Decomp.
17	H	**1.56l**	H	 **1.51l**	Decomp.

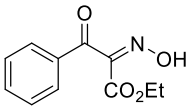
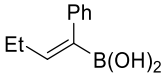
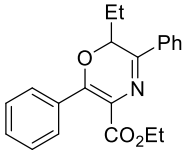
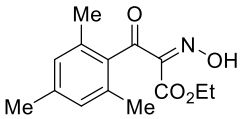
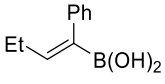
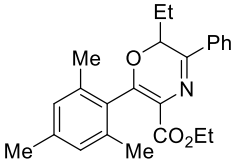
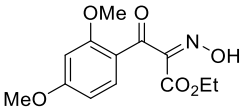
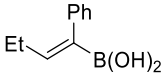
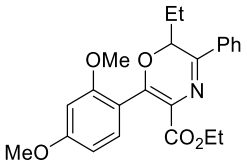
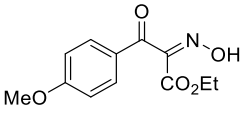
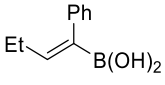
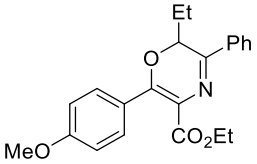
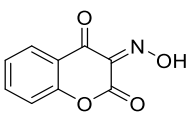
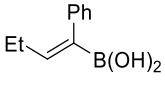
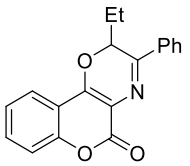
[a] Conditions: oxime **1.49** or **1.50** (1 equiv), **1.51** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 2 h. Py = pyridine, DCE = 1,2-dichloroethane, NR = no reaction, Decomp. = decomposition. [b] Percent yield of isolated yield.

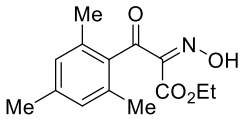
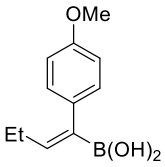
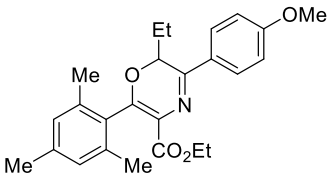
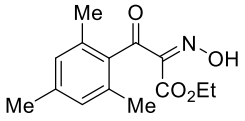
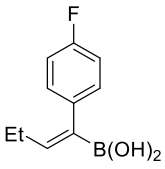
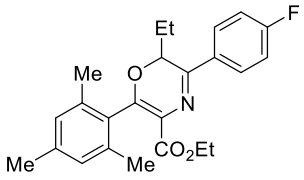
While initially screening oxime reagents for the Chan-Lam synthesis of *N*-vinylnitrones and *O*-vinyloximes (Table 1.6), we observed that when ester-substituted oxime **1.48** was treated with alkenylboronic acid **1.51** *N*-vinylnitrone **1.53** was isolated at short reaction times and a byproduct was isolated at longer reaction times (entry 1). This byproduct was eventually identified as oxazine **1.57a**. The deoxygenation of pyridine *N*-oxides has been observed under similar reaction conditions.[25] We wondered if this trend of electrocyclization followed by deoxygenation

might be consistent for other *β*-ketoester oxime substrates. To test this hypothesis, both acyclic and cyclic *β*-ketoester oximes **1.48h**–**1.48j** were tested under the Chan-Lam reaction conditions with vinylboronic acid **1.51** and extended reaction times. As shown in Table 1.6 oxazines **1.57c**–**1.57e** were isolated in high yields (entries 3-5). Surprisingly, larger aryl substituents favored this transformation. A plausible explanation for the decreased rate and concomitant deoxygenation observed for these substrates is a steric factor.[28] Further investigations were pursued to determine if this was a general trend for other substrates.

Table 1.6. Scope of β-Ketoester Oximes and Vinylboronic Acids for the Synthesis of 1,4-Oxazines.



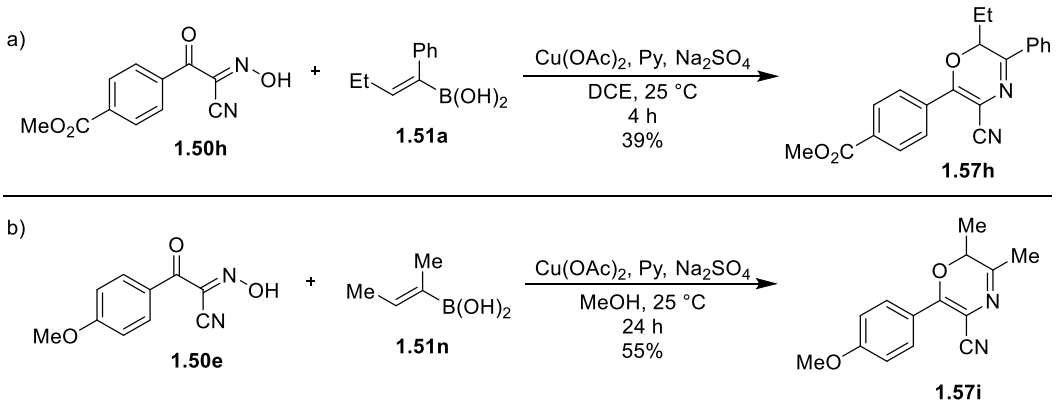
Entry	Oxime	Boronic Acid	Product	% Yield[a][b]
1	 **1.48d**	 **1.51a**	 **1.57a**	40
2	 **1.48g**	 **1.51a**	 **1.57b**	87
3	 **1.48h**	 **1.51a**	 **1.57c**	75
4	 **1.48i**	 **1.51a**	 **1.57d**	63
5	 **1.48j**	 **1.51a**	 **1.57e**	48

6	 **1.48g**	 **1.51c**	 **1.57f**	96
7	 **1.48g**	 **1.51m**	 **1.57g**	79

[a] Conditions: oxime **1.48** (1 equiv), vinylboronic acid **1.51** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 18 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Percent yield of isolated yield.

To determine if the deoxygenation process was consistent for other *N*-vinylnitrone syntheses and electrocyclizations under longer reaction times, cyano-substituted oximes **1.50h** and **1.50e** were tested under identical reaction conditions for 18 h (Scheme 1.10). In contrast to the previously described formation of oxazine nitrone **1.54h** in 2 h, *N*-vinylnitrone formation, electrocyclization, and deoxygenation gave oxazine **1.57h** at 18 h (Scheme 1.10a). Similarly, the scope of the *N*-vinylnitrone generation and electrocyclization process was extended to alkenylboronic acid **1.51n** at longer reaction times in MeOH for the formation of **1.57i** (Scheme 1.10b). These results suggested that the scope of the Chan-Lam reaction and electrocyclization process could be extended to include a much wider range of substrates over longer reaction times with concomitant deoxygenation.

Scheme 1.10. Preparation of Unsaturated Morpholines from Cyano-Substituted Oximes

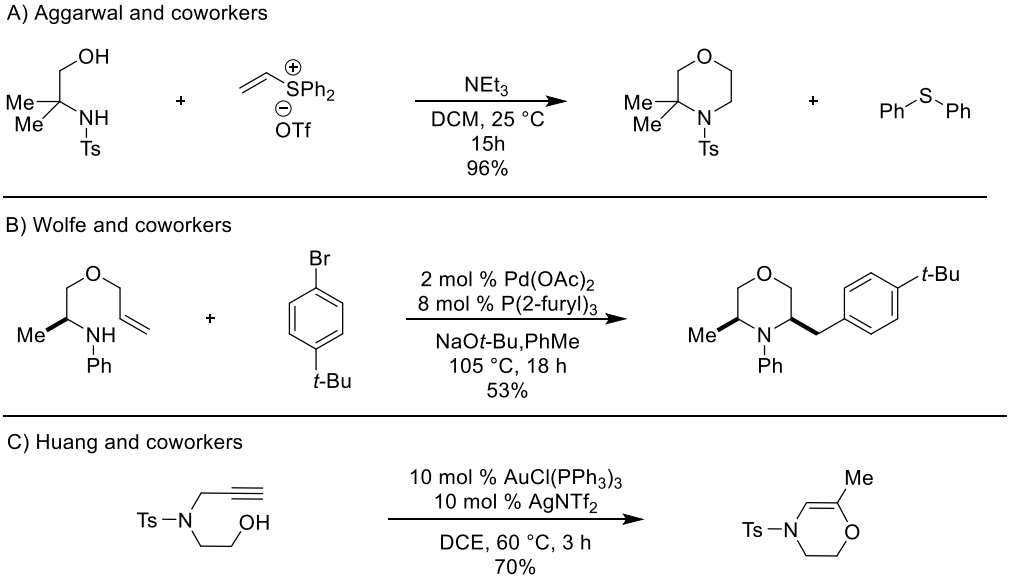


The studies described above established a new method for the synthesis of 1,4-oxazine *N*-oxides **1.52, 1.54-1.56** and 1,4-oxazines **1.57** using a cascade reaction involving a Chan-Lam reaction and a spontaneous 6π-electrocyclization. The examination of several oximes showed that aldoximes and cyano-substituted oximes gave unsaturated morpholine nitrones when subjected to Chan-Lam reactions conditions over short reaction times, while *β*-ketoester oximes and cyano-substituted oximes gave unsaturated morpholines over longer reaction times. These investigations provided a new route to previously unknown heterocyclic compounds.

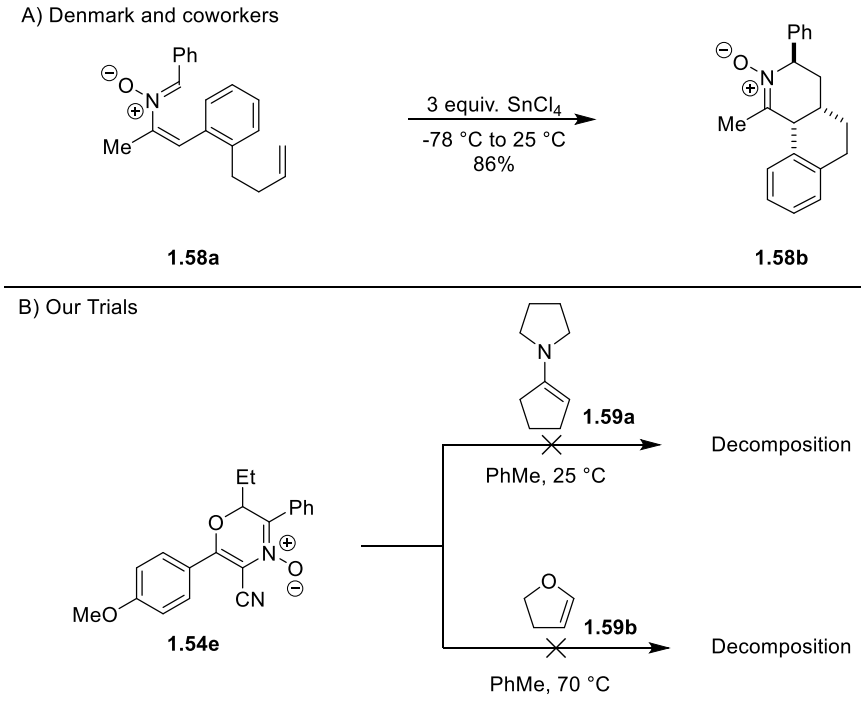
1.4 Functionalization of Unsaturated Morpholine *N*-Oxides

Having established a new method for the synthesis of morpholine nitrones, the reactivity of these compounds was investigated to explore the opportunity to design new divergent routes to highly-substituted morpholines.[18] Owing to the prevalence of these heterocycles in agrochemicals, material applications, and biologically-active molecules, the synthesis of substituted morpholines has significant value.[29,30] Traditional approaches to these molecules include nucleophilic displacement, hydroamination, and hydroalkoxylation, as shown in Scheme 1.11.[31-33] While these approaches have been used in the synthesis of biologically active drugs such as Emand and Manifaxine respectively, there are still limitations with these methods such as preparations for substrates, sensitive reaction conditions, and installation of more substituents on morpholine rings.[31-34] We wondered if facile access to unsaturated morpholine *N*-oxides **1.52** and **1.54** could address these challenges and facilitate the synthesis of sophisticated morpholines.

Scheme 1.11. Inverse Electron-Demand Diels-Alder Cycloaddition

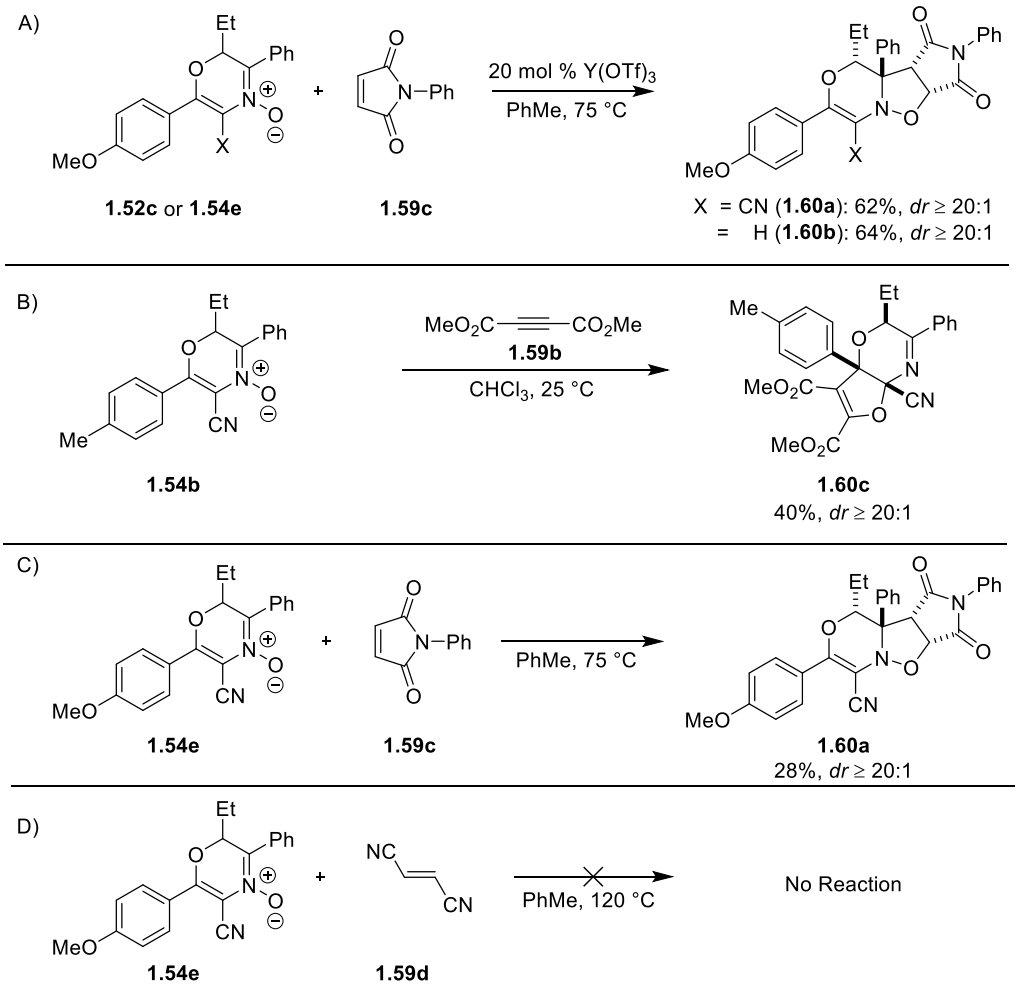


Scheme 1.12. Inverse Electron-Demand Diels-Alder Cycloaddition



Due to the electrophilic nature of morpholine *N*-oxides **1.52** and **1.54**, we initially tested the cycloaddition reactivity of these molecules with several inverse-demand Diels-Alder dienophiles. Denmark and coworkers previously reported that related *N*-vinylnitrone **1.58a** underwent an intramolecular Diels-Alder reaction (Scheme 1.12A).[35] As shown in Scheme 1.12B, when morpholine nitrone **1.54e** was treated with **1.59a** and **1.59b** under several different reaction conditions, only decomposition of the starting materials was observed (Scheme 1.12B). The different in reactivity could be explained by steric and electronic issues of heteroatom-containing diene.[36] As an alternative cycloaddition pathway, we decided to investigate [3+2]-cycloadditions of these morpholine nitrones.

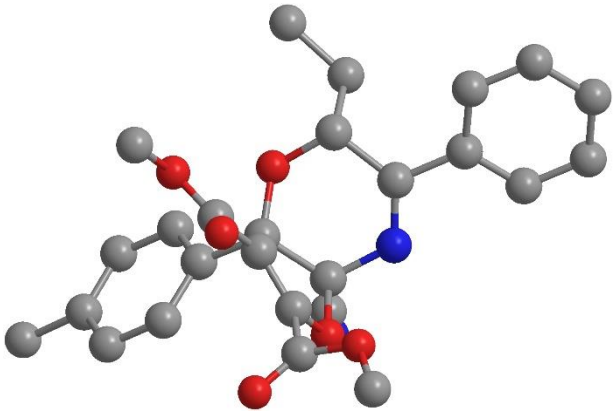
Scheme 1.13. [3+2]-Cycloaddition of Unsaturated Morpholine *N*-Oxides



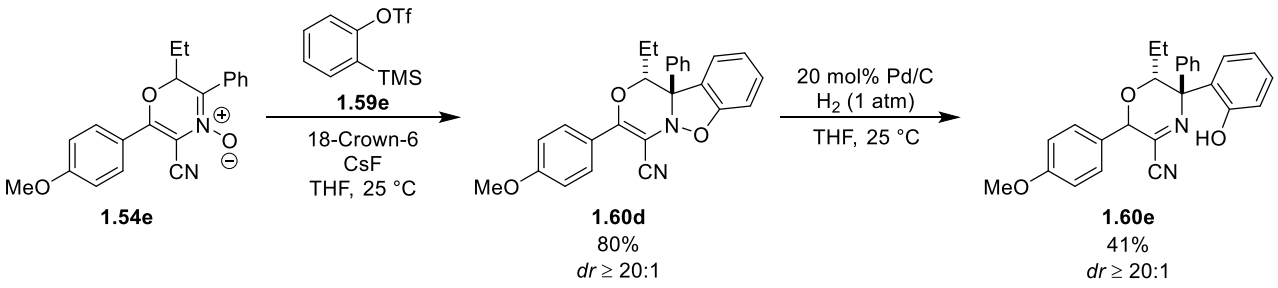
Several dipolarophiles were tested for [3+2]-cycloaddition reactivity with morpholine nitrones (Scheme 1.13). Gratifyingly, we were pleased to find that nitrones with other dipolarophiles were successfully resulted in [3+2]-cycloadditions toward complex morpholines.[18] Initially, we discovered that treatment of **1.54e** with *N*-phenylmaleimide at 75 °C in toluene provided cycloadduct **1.60a** in 28% yield (Scheme 1.13c). Addition of a catalytic amount of $Y(OTf)_3$ to this reaction mixture increased the yield of **1.60a** to 62% with dr = 20:1 and the same conditions were also shown to be effective for **1.60b**.[18] Further screening of the dipolar cycloaddition reactivity of nitrone **1.54b** with dimethylacetylene dicarboxylate resulted in the formation of **1.60c**, which can be explained by an initial [3+2]-cycloaddition to form a transient fused-isoxazolidine followed by rearrangement to form bicyclic morpholine **1.60c** (Scheme 1.11b). The relative stereochemistry of **1.60c** was characterized through an X-ray crystallographic study performed by Prof. Donald J. Wink (Figure 1.3). Unfortunately, a mixture of nitrone **1.54e** and fumaronitrile **1.59d** resulted in the recovery of both starting materials at 120 °C and further heating resulted in toluene (Scheme 1.13d). Although we were unable to determine appropriate catalytic conditions to

promote the dipolar cycloaddition of electron-deficient alkenes, the transformations described in Scheme 1.13 established that morpholine nitrones **1.52c** and **1.54e** could be used to rapidly prepare novel heterocycles such as **1.60a**, **1.60b** and **1.60c** through dipolar cycloaddition reactions with activated dipolarophiles.

Figure 1.3. X-Ray Crystal Structure of **1.60c** (CCDC 1507727) by Prof. Donald J. Wink

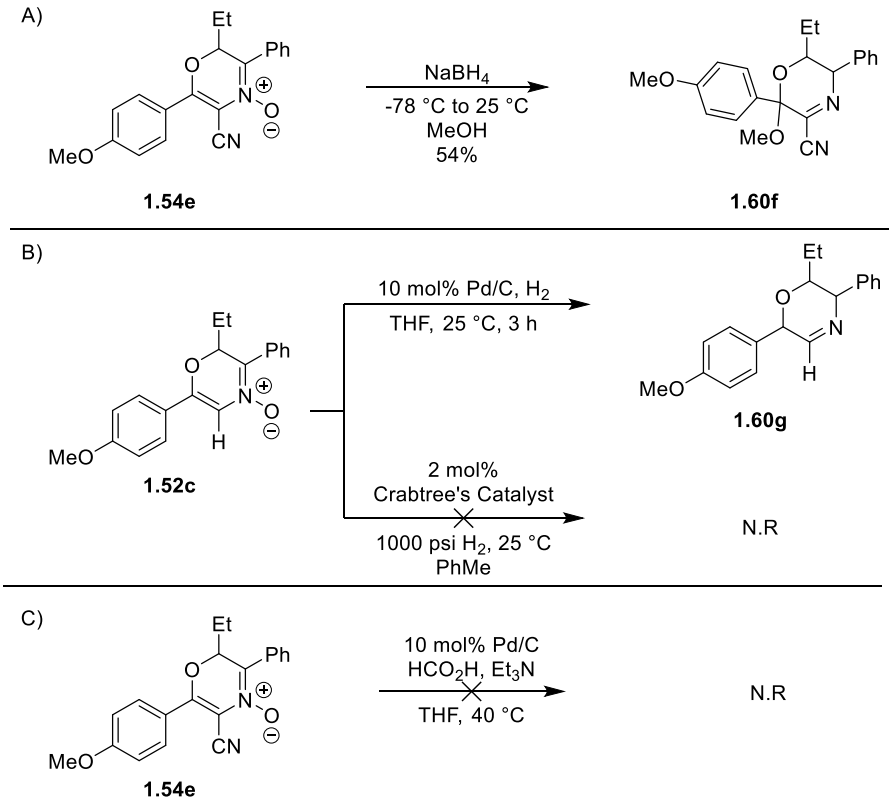


Scheme 1.14. [3+2]-Cycloaddition of an Unsaturated Morpholine *N*-Oxide with Benzyne



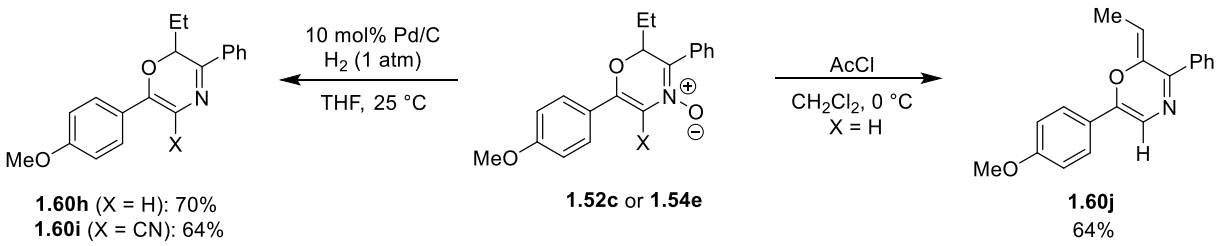
To further expand the use of morpholine nitrones for the preparation of bicyclic oxazole motifs, the [3+2]-cycloaddition of **1.54e** was also tested with benzyne. As shown in Scheme 1.14, when a benzyne intermediate was generated from **1.59e** and treated with **1.54e** benzoxazole-fused-bicyclic morpholine **1.60d** was isolated in high yield with excellent diastereoselectivity.[18] Further investigation of derivatization of the product showed that treatment of **1.60d** with hydrogenation conditions gave reductive *N–O* bond cleavage to form **1.60e** without any erosion of diastereoselectivity.

Scheme 1.15. Reduction Attempts for Unsaturated Morpholine Nitrones.



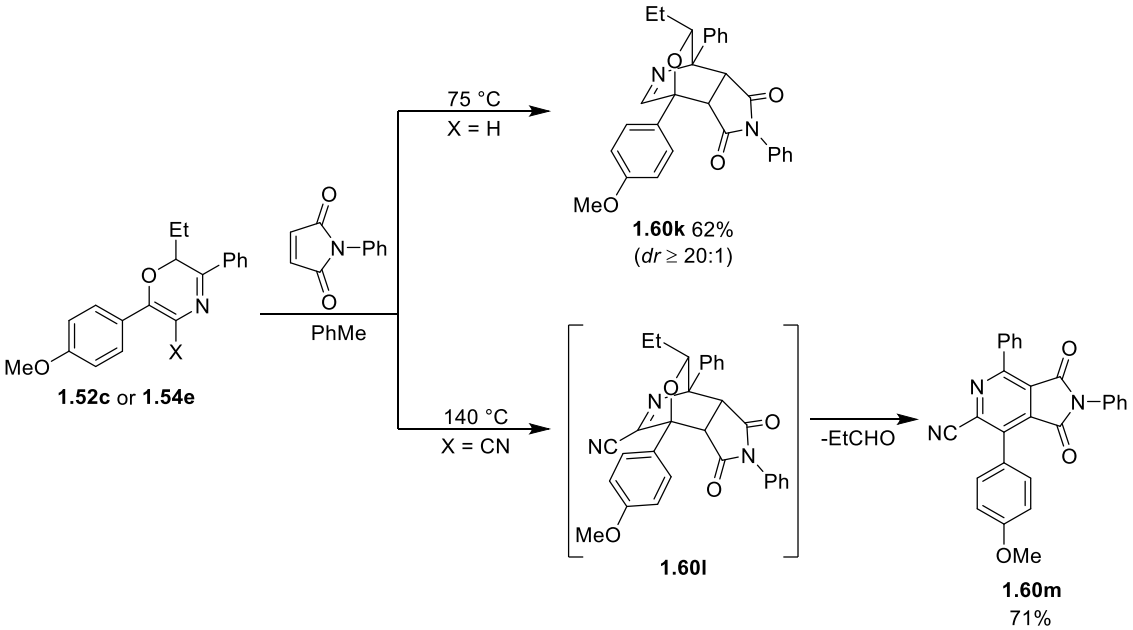
In addition to cycloaddition reactions, reductions were also screened to evaluate the utility of unsaturated morpholine *N*-oxides as precursors to saturated morpholine *N*-oxides.[18] As shown in Scheme 1.15, hydride reduction condition of **1.54e** resulted in reduction and addition product **1.60f** (Scheme 1.15A). Surprisingly, Pd/C catalyzed reduction of **1.52c** occurred over 3 h to give reduction product of morpholine **1.60g** with low yield and diastereoselectivity, however, Crabtree's catalyzed hydrogenation system of **1.52c** did not undergo reduction and nitrone **1.52c** was recovered in 100% yield (Scheme 1.15B).[37] This trial gave an insight for the use of Pd-catalyzed hydrogenation. Similar, Pd-catalyzed transfer hydrogenation condition was also unsuccessful for the reduction of nitrone **1.54e** (Scheme 1.15C). Since we observed the formation of **1.60g**, we speculated that the reduction of morpholine nitrones **1.52c** under same condition with shorter reaction times could give more selective reduced product. Indeed, shorter reaction times resulted in a selective deoxygenation of morpholine *N*-oxides **1.60h** and **1.60i** in high yields (Scheme 1.16). An alternative deoxygenation process was also observed with acetyl chloride, which when used to treat **1.52c** provided unsaturated morpholine **1.60j**.[18] While our initial investigation of reduction conditions for **1.52c** and **1.54e** were not clear, we decided to further pursue the deoxygenation products **1.60h** and **1.60i** to investigate differences in reactivity.

Scheme 1.16. Deoxygenations of Unsaturated Morpholine Nitrones.



Oxazines **1.52c** and **1.54e** contain a 2-aza-1,3-butadiene functionality that we decided to targeted for screening [4+2]-cycloaddition reactivity.[18] As shown in Scheme 1.17, these compounds were shown to undergo [4+2]-cycloadditions with *N*-phenylmaleimide. Specifically, unsaturated morpholine **1.52c** gave bridged morpholine **1.60k** with excellent diastereoselectivity. In contrast, **1.54e** required harsh reaction condition for successful cycloaddition with **1.59c**, which resulted in the formation of pyridine **1.60m**. A plausible explanation for the formation of this heterocycle is that initially formed cycloadduct **1.60l** could eliminate the propioaldehyde and aromatized to **1.60m**. These derivatization reactions showed that morpholines, generated via deoxygenation of **1.52c** or **1.54e**, show unique cycloaddition behavior and can access [4+2]-cycloaddition modes.

Scheme 1.17. [4+2]-Cycloaddition of Unsaturated Morpholines with *N*-Phenylmaleimide



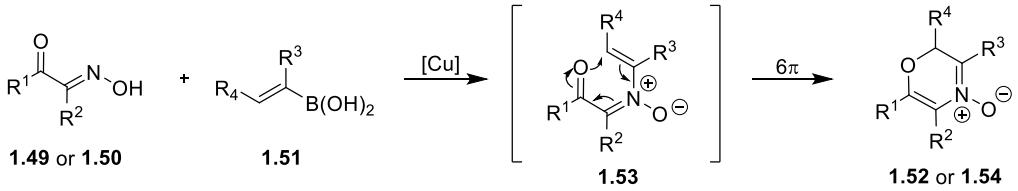
In summary, a survey of the reactivity of **1.52c** and **1.54e** revealed that a variety of sophisticated morpholines can be accessed through dipolar cycloadditions, reductions, and deoxygenations. Similarly, deoxygenation of **1.52c** and

1.54e afforded unsaturated morpholines that exhibited unique cycloaddition behavior to their nitrone analogues and provided access to bicycle compounds such as **1.60k** and pyridines such as **1.60m**. These reactions showed that our new method for the synthesis of unsaturated morpholine N-oxides can be used for the diverse synthesis of substituted morpholines.

1.5 Proposed Mechanism and Mechanistic Experiments

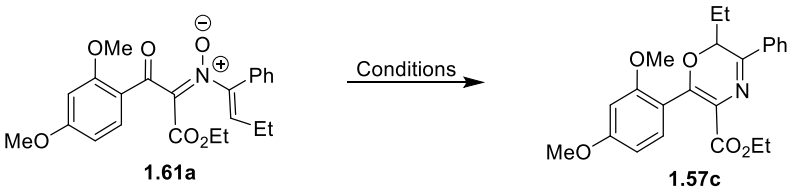
Our proposed mechanism for the two-step, single-flask synthesis of oxazine *N*-oxides **1.52** or **1.54** from oximes **1.49** or **1.50** and vinylboronic acids **1.51** is illustrated in Scheme 1.18 and involves an initial Chan-Lam reaction to form the necessary *N*-vinylnitrone followed by a spontaneous electrocyclization. To better understand this reaction pathway, several experiments were used to probe the intermediacy of the vinylnitrone **1.53**.

Scheme 1.18. Plausible Reaction Mechanism



While *N*-vinylnitrone intermediate **1.53** was not observed in the conversion of **1.48h** and **1.51a** to **1.57c** (Table 1.6), (*E*)-*N*-vinylnitrone **1.61a** was isolated after exposure to the Chan-Lam reaction conditions for 2 h. Isolation of **1.61a**, allowed us to independently explore the conversion of **1.61a** to **1.48c** (Table 1.7). Surprisingly, when intermediate **1. 61a** was treated with $Cu(OAc)_2$ and pyridine, no reaction was observed although extended exposure to the Chan-Lam reaction conditions without isolation of **1.61a** cleanly provided **1.57c**. In addition, when **1.61a** was treated with BF_3-OEt_2, azetidine **1.67** was isolated as the sole product of the transformations and the structure was confirmed by an X-ray crystallography studied performed by Prof. Donald J. Wink (Scheme 1.20 and Figure 1.4). Further screening showed that a mixture of $Cu(OAc)_2$ and Cu(OAc) afforded the conversion of **1.61a** to **1.57c** in 31% yield (Table 1.7, entry 1). We speculated that a specific mixture of copper salts is required to promote the isomerization of *E*-**1.53** to *Z*-**1.53** to promote the desired electrocyclization. Isomerizations of nitrones have been observed previously using Lewis acid and increased temperature.[38,39]

Table 1.7. Conversion of *N*-Vinylnitrone **1.61a** to Unsaturated Morpholine Nitrone **1.57c**

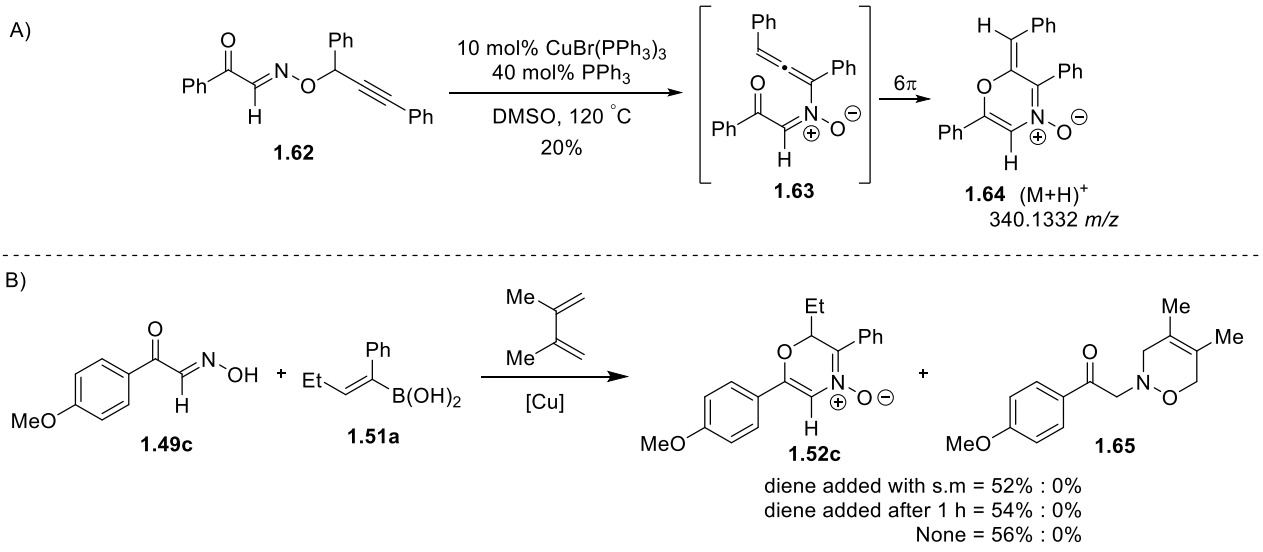


1.61a **1.57c**

Entry	Condition	% Yield
1	$Cu(OAc)_2$, $Cu(OAc)_1$	31
2	$Cu(OAc)_2$	0
3	$Cu(OAc)_2$, Py	0
4	$Cu(OAc)_1$	0
5	Recycled [Cu]	0
6	PPh_3	0
7	BF_3-OEt_2	0

To further investigate the likelihood of *N*-vinylnitrone **1.53** as a plausible intermediate in the conversion of a mixture of $Cu(OAc)_2$ and $Cu(OAc)_1$ to **1.57c**, we decided to independently synthesize **1.62** and generate the corresponding *N*-allenylnitrone under different conditions (Scheme 1.19). *O*-Propargylic oxime **1.62** was prepared following a procedure reported by Nakamura and coworkers for a similar compound. Nakamura and coworkers have developed a method for the conversion of *N*-allenylnitrones such as **1.63** to substituted pyridines via a [2,3]-rearrangement and electrocyclization process.[15]Treatment of **1.62** under the conditions reported by Nakamura and coworkers resulted in the isolation of **1.64**. This result supports our hypothesis that the Chan-Lam coupling and electrocyclization process may also be proceeding through a similar intermediate **1.63**. In addition to the independent generation of **1.63** and electrocyclization to **1.64**, we also tested our two-step, single-flask synthesis of **1.65** for potential nitroso intermediates. Boger and coworkers have shown that nitroso intermediates occur in hetero Diels-Alder reactions and we wondered in the morpholine nitrone synthesis could be proceeding via a [4+2]-cycloaddition pathway.[40] Addition of 2,3-dimethyl-1,3-butadiene to a mixture of **1.49c** and **1.51a** and treatment with Chan-Lam reaction conditions resulted in the sole formation of **1.52c** thus eliminating the potential for nitroso compounds as viable intermediates.

Scheme 1.19. Mechanistic Study for 6π-Electrocyclization of Reactive Acyclic (*Z*)–Nitrone



Scheme 1.20. Azetidine Nitrone from (*E*)-Vinylnitrone

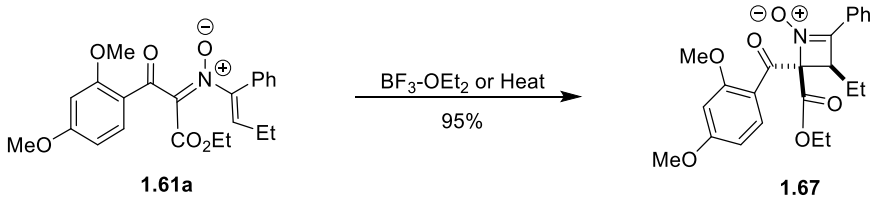
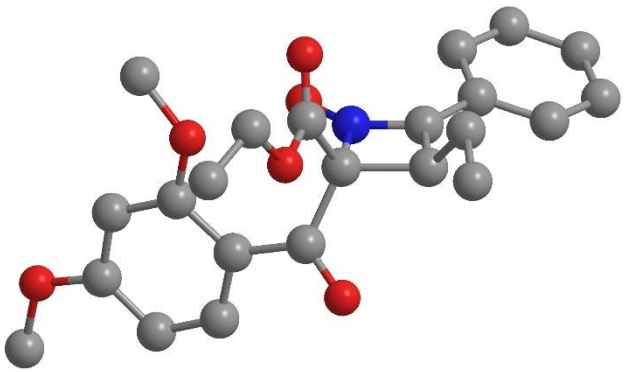


Figure 1.4. X-Ray Crystallography of **1.67** (CCDC 1560573) by Prof. Donald J. Wink



1.6 Conclusion

In summary, we investigated the modular synthesis of novel 2*H*-1,4-oxazine *N*-oxides from oximes and boronic acids through a C–N bond forming and electrocyclization cascade reaction. The scope of the synthesis displayed

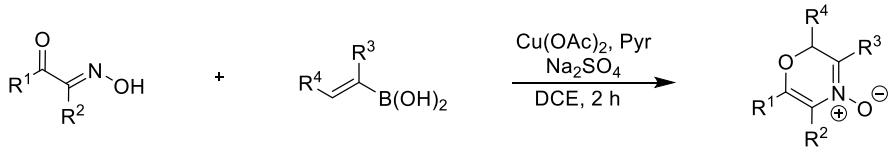
broad tolerance for a variety of α-ketooximes and somewhat more limited tolerance for the type of vinylboronic acid. Extended reaction time were shown to expand the substrate scope and give deoxygenated 2*H*-1,4-oxazines products. With these novel heterocycles in hand, we decided to evaluate their reactivity for the divergent synthesis of substituted morpholines. We determined that [3+2]-cycloaddition and Diels-Alder reactions could be used to rapidly access complex multicyclic products from these interesting intermediates. We postulated that the reaction mechanism undergoes copper-promoted C–N bond formation to produce a transient acyclic *N*-vinylnitrone intermediate followed by spontaneous electrocyclization to give 1,4-oxazine *N*-oxides. Mechanistic studies suggested that a 4π-electrocyclization pathway is also accessible through this reaction manifold and initiated the project described in the following chapter.

1.7 Supporting Information

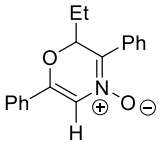
1.7.1 General Experimental Information

^{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..[41]

1.7.2 Experimental Procedures and Characterization Data (Table 1.3, 1.4 and 1.5)

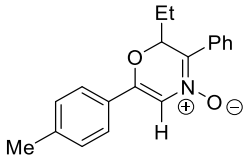


General Procedure A: Preparation of Morpholine *N*-oxides from Oximes and Boronic Acids. A scintillation vial was charged with oxime **1.49** or **1.50** (1 equiv), $Cu(OAc)_2$ (1 equiv), Na_2SO_4 (6.6 equiv), and alkenylboronic acid **1.51** (5 equiv). These solids were dissolved in 1,2-dichloroethane (DCE) to make a 0.1 M solution of oxime 1 and pyridine (3 equiv) was added via syringe. The vial was then capped with rubber septum and punctured with a ventilation needle to expose the reaction mixture to air. The reaction mixture was stirred for 2 h at 25 °C. At this time, the reaction mixture was filtered through silica gel, which was washed with 50 mL of EtOAc. The filtrate was then concentrated under vacuum to give the crude product, which was purified by medium pressure chromatography (1:5 – 1:1; Et_2O:pentane) to give oxazine *N*-oxide **1.52**, **1.54**, **1.55** or **1.56**.



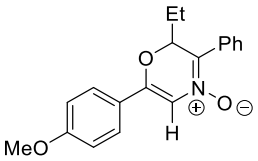
1.52a

Oxazine *N*-Oxide 1.52a: Compound **1.52a** was prepared using general procedure A with the following reagents: oxime **1.49a** (0.0448 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52a** as a yellow solid (0.0611 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.0 Hz, 2H), 7.71-7.69 (m, 2H), 7.49-7.40 (m, 6H), 7.00 (s, 1H), 5.57 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.36-2.30 (m, 1H), 1.74-1.69 (m, 1H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 131.3, 130.7, 130.3, 130.0, 129.6, 128.8, 128.5, 127.7, 125.6, 114.3, 78.5, 22.7, 9.9; IR (thin film) 3124, 3049, 2955, 2917, 1639, 1577, 1537, 1507, 1496, 1448; HRMS(ESI) *m/z* calcd. for $C_{18}H_{18}NO_2$ $(M+H)^+$ 280.1332, observed 280.1336; m.p: 123-126 °C.



1.52b

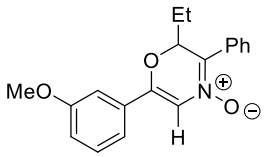
Oxazine *N*-Oxide 1.52b: Compound **1.52b** was prepared using general procedure A with the following reagents: oxime **1.49b** (0.0490 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52b** as a yellow solid (0.0529 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.48-7.39 (m, 3H), 7.25-7.22 (m, 2H), 6.96 (s, 1H), 5.55 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.41 (s, 3H), 2.36-2.28 (m, 1H), 1.74-1.66 (m, 1H), 1.11 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 141.2, 131.0, 129.9, 129.7, 129.5, 128.5, 127.7, 127.5, 125.6, 113.8, 78.4, 22.7, 21.4, 9.9; IR (thin film) 3119, 2961, 2929, 1634, 1569, 1504, 1443, 1432, 1411, 1376; HRMS(ESI) *m/z* calcd. for $C_{19}H_{20}NO_2$ $(M+H)^+$ 294.1489, observed 294.1498; m.p: 106-110 °C.



1.52c

Oxazine *N*-Oxide 1.52c: Compound **1.52c** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.52c** as a yellow solid (0.0668 g, 72%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.48-7.39 (m, 3H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.90 (s, 1H), 5.54 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 3.14 (s, 3H), 2.36-2.29 (m, 1H), 1.73-1.68 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 148.4, 130.8, 129.86, 129.80, 128.5, 127.7, 127.4, 122.6, 114.3, 113.0, 78.4, 55.4, 22.6, 9.9; IR (thin film) 3051, 2968, 2933, 2875, 2837, 1638, 1605, 1573, 1509, 1459; HRMS(ESI) *m/z* calcd. for $C_{19}H_{20}NO_3$ $(M+H)^+$ 310.1438, observed 310.1441; m.p: 115-118 °C.

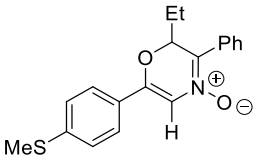
Larger scale preparation of 1.52c: A 250mL round bottom flask was charged with oxime **1.49c** (1.23 g, 6.86 mmol, 1 equiv), $Cu(OAc)_2$ (1.25 g, 6.86 mmol, 1 equiv), Na_2SO_4 (6.43 g, 45.2 mmol, 6.6 equiv), and alkenylboronic acid **1.51a** (3.62 g, 20.6 mmol, 3 equiv). These solids were dissolved in 1,2-dichloroethane (69.0 mL) to make a 0.1 M solution of oxime and pyridine (1.63 g, 20.6 mmol, 3 equiv) was added via syringe. The flask was stirred without rubber septum to expose the reaction mixture to air. The reaction mixture was stirred for 2 h at 25 °C. At this time, the reaction mixture was filtered through silica gel, which was washed with 250 mL of CH_2Cl_2. The filtrate was then concentrated under vacuum to give the crude product, and diethyl ether (50 mL) and hexane (10 mL) were added to the crude product mixture. The resulting solution was stored in a -40 °C refrigerator overnight to precipitate a yellow crystalline solid that was filtered over a glass frit and washed with 1:1 mixture of cold diethyl ether and hexane (30 mL) to give **1.52c** (1.40 g, 66%).



1.52d

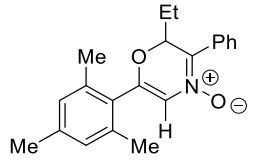
Oxazine *N*-Oxide 1.52d: Compound **1.52d** was prepared using general procedure A with the following reagents: oxime **1.49d** (0.0538 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52d** as a yellow oil (0.0538 g, 58%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.0 Hz, 2H), 7.48-7.45 (m, 2H), 7.43-7.40 (m, 1H), 7.37-7.33 (m, 1H), 7.29-7.28

(m, 1H), 7.22 (s, 1H), 7.00-6.99 (m, 2H), 5.56 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 3.84 (s, 3H), 2.36-2.27 (m, 1H), 1.75-1.68 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 148.2, 131.7, 131.4, 130.0, 129.9, 129.6, 128.6, 127.7, 118.1, 116.6, 114.6, 110.9, 78.5, 55.4, 22.7, 10.0; IR (thin film) 3080, 2968, 2934, 2875, 2835, 1731, 1688, 1642, 1600, 1579; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}NO_3$ $(M+H)^+$ 310.1438, observed 310.1445.



1.52e

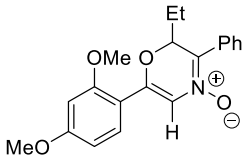
Oxazine *N*-Oxide 1.52e: Compound **1.52e** was prepared using general procedure A with the following reagents: oxime **1.49e** (0.0585 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.52e** as a yellow solid (0.0537 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.48-7.36 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.96 (s, 1H), 5.55 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 2.52 (s, 3H), 2.34-2.28 (m, 1H), 1.73-1.68 (m, 1H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 142.7, 131.1, 129.9, 129.7, 128.6, 127.7, 126.6, 125.9, 125.8, 113.8, 78.4, 22.7, 15.1, 9.9; IR (thin film) 3106, 2958, 2919, 1644, 1594, 1566, 1509, 1493, 1451, 1435; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}NO_2S$ $(M+H)^+$ 326.1209, observed 326.1218; m.p: 123-125 °C.



1.52f

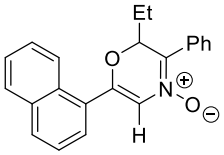
Oxazine *N*-Oxide 1.52f: Compound **1.52f** was prepared from general procedure A with the following reagents: oxime **1.49f** (0.0574 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:5; Et_2O:pentane) afforded **1.52f** as a white solid (0.0553 g, 59%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.43 (d, *J* = 7.5 Hz, 2H), 7.47-7.40 (m, 3H), 6.94 (s, 2H), 6.34 (s, 1H), 5.76 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 2.44-2.38 (m, 1H), 2.34 (s, 6H), 2.28 (s, 3H), 1.87-1.79 (m, 1H), 1.03 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 148.8, 139.3, 137.0, 130.4, 129.3, 128.5, 128.3, 128.2, 128.1, 127.5, 118.1, 77.9, 23.9,

20.2, 18.9, 9.2; IR (thin film) 3048, 2970, 2923, 2876, 1655, 1611, 1570, 1514, 1491, 1454; HRMS(ESI) *m/z* calcd. for $C_{21}H_{24}NO_2$ $(M+H)^+$ 322.1802, observed 322.1797; m.p: 108-111 °C.



1.52g

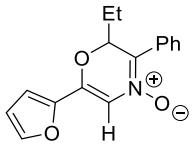
Oxazine *N*-Oxide 1.52g: Compound **1.52g** was prepared from general procedure A with the following reagents: oxime **1.49g** (0.0628 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.52g** as a yellow oil (0.0499 g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.47-7.37(m, 4H), 6.57 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.51 (s, 1H), 5.48 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.37-2.30 (m, 1H), 1.69-1.63 (m, 1H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 159.2, 144.6, 130.6, 130.0, 129.6, 129.2, 128.5, 127.7, 118.1, 112.0, 104.8, 98.7, 77.6, 55.55, 55.51, 22.3, 10.0; IR (thin film) 3173, 3050, 2968, 2935, 2875, 2837, 1626, 1604, 1570, 1505; HRMS(ESI) *m/z* calcd. for $C_{20}H_{22}NO_4$ $(M+H)^+$ 340.1543, observed 340.1543.



1.52h

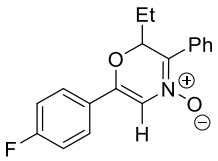
Oxazine *N*-Oxide 1.52h: Compound **1.52h** was prepared from general procedure A with the following reagents: oxime **1.49h** (0.0598 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.51h** as an orange solid (0.0563 g, 57%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.49 (d, *J* = 8.0 Hz, 2H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.65-7.58 (m, 3H), 7.51-7.43 (m, 3H), 6.74 (s, 1H), 5.57 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H), 2.52-2.43 (m, 1H), 1.96-1.87 (m, 1H), 1.08 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 149.1, 133.9, 130.8, 130.6, 130.3, 129.5, 129.3, 128.9, 128.6, 128.3, 127.6, 127.5, 127.1, 126.4, 125.28, 124.9, 118.6, 78.2, 23.3,

9.3; IR (thin film) 3132, 3050, 2969, 2933, 2875, 1644, 1589, 1572, 1508, 1491; HRMS(ESI) *m/z* calcd. for $C_{22}H_{20}NO_2$ $(M+H)^+$ 330.1489, observed 330.1484; m.p: 104-110 ˚C



1.52i

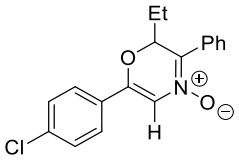
Oxazine *N*-Oxide 1.52i: Compound **1.52i** was prepared using general procedure A with the following reagents: oxime **1.49i** (0.0417 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52i** as a yellow solid (0.0541 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.0 Hz, 2H), 7.52 (s, 1H), 7.47-7.40 (m, 3H), 6.92 (s, 1H), 6.81 (d, *J* = 3.5 Hz, 1H), 6.52 (d, *J* = 1.5 Hz, 1H), 5.49 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.37-2.28 (m, 1H), 1.71-1.66 (m, 1H), 1.08 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 144.8, 140.6, 131.6, 130.0, 129.6, 128.5, 127.7, 113.6, 111.99, 111.97, 78.4, 22.6, 9.6; IR (thin film) 3121, 3060, 2963, 2928, 1657, 1560, 1508, 1480, 1459, 1441; HRMS (ESI) *m/z* calcd. for $C_{16}H_{16}NO_3$ $(M+H)^+$ 270.1125, observed 270.1128; m.p: 116-119 °C.



1.52j

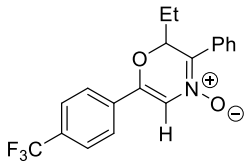
Oxazine *N*-Oxide 1.52j: Compound **1.52j** was prepared using general procedure A with the following reagents: oxime **1.49j** (0.0501 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711 g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52j** as a yellow solid (0.0570 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.68 (dd, *J* = 9.0 Hz, 2.7 Hz, 2H), 7.48-7.40 (m, 3H), 7.13 (t, *J* = 8.5 Hz, 2H), 6.94 (s, 1H), 5.56 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 2.35-2.26 (m, 1H), 1.75-1.69 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2 (d, *J* = 250.2 Hz), 147.5, 131.2, 130.1, 129.5, 128.6, 127.8, 127.7, 126.5 (d, *J* = 2.5 Hz), 116.0 (d, *J* = 21.8 Hz), 114.1, 78.6, 22.8, 9.9; IR (thin film) 3124, 3038, 2965, 2933,

1643, 1597, 1508, 1453, 1443, 1433; HRMS(ESI) *m/z* calcd. for $C_{18}H_{17}FNO_2$ $(M+H)^+$ 298.1238, observed 298.1243; m.p: 118-121 °C.



1.52k

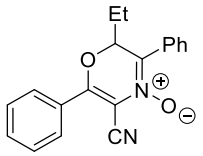
Oxazine *N*-Oxide 1.52k: Compound **1.52k** was prepared from general procedure A with the following reagents: oxime **1.49k** (0.0550 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52k** as a yellow solid (0.0527 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.49 (m, 5H), 6.97 (s, 1H), 5.57 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.35-2.25 (m, 1H), 1.74-1.69 (m, 1H), 1.10 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 136.8, 131.5, 130.1, 129.5, 129.1, 128.8, 128.6, 127.7, 126.8, 114.5, 78.6, 22.8, 9.9; IR (thin film) 3097, 2960, 1650, 1524, 1492, 1462, 1445, 1434, 1404, 1376; HRMS(ESI) *m/z* calcd. for $C_{18}H_{17}ClNO_2$ $(M+H)^+$ 314.0942, observed 314.0952; m.p: 119-124 ˚C.



1.52l

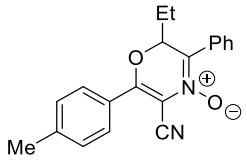
Oxazine *N*-Oxide 1.52l: Compound **1.52l** was prepared using general procedure A with the following reagents: oxime **1.49l** (0.0651 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.52l** as a yellow solid (0.0323 g, 31%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.50-7.47 (m, 2H), 7.45-7.42 (m, 1H), 7.07 (s, 1H), 5.61 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.35-2.26 (m, 1H), 1.78-1.69 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 133.8, 132.3 (q, *J* = 32.6 Hz), 132.0, 130.3, 129.3, 128.6, 127.7, 125.8 (d, *J* = 3.3 Hz), 125.7, 123.7 (q, *J* = 270.2 Hz), 115.7, 78.7, 22.9, 9.9; IR (thin film) 3094, 2971, 2935,

2880, 1646, 1614, 1576, 1507, 1490, 1456; HRMS (ESI) *m/z* calcd. for $C_{19}H_{17}F_3NO_2$ $(M+H)^+$ 348.1206, observed 348.1205; m.p: 149-150 °C.



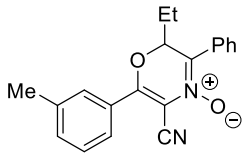
1.54a

Oxazine *N*-Oxide 1.54a: Compound **1.54a** was prepared using general procedure **A** with the following reagents: oxime **1.50a** (0.0522 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54a** as a yellow solid (0.0693 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.25 (m, 2H), 8.01 (d, *J* = 7.5 Hz, 2H), 7.64-7.61 (m, 1H), 7.56-7.53 (m, 2H), 7.51-7.47 (m, 3H), 5.76 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 2.35-2.24 (m, 1H), 1.93-1.85 (m, 1H), 1.19 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 133.5, 131.0, 130.9, 129.12, 129.11, 128.8, 128.5, 128.1, 127.7, 112.3, 105.4, 79.9, 24.0, 10.0; IR (thin film) 2973, 2224, 1607, 1574, 1529, 1496, 1445, 1431, 1395, 1328, 1227, 1193; HRMS (ESI) *m/z* calcd. for $C_{19}H_{17}N_2O_2$ $(M+H)^+$ 305.1285, observed 305.1292; m.p: 120-123 °C.



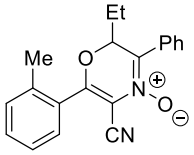
1.54b

Oxazine *N*-Oxide 1.54b: Compound **1.54b** was prepared using general procedure A with the following reagents: oxime **1.50b** (0.0564 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54b** as a yellow solid (0.0764 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.50-7.46 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.74 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 2.45 (s, 3H), 2.35-2.25 (m, 1H), 1.91-1.85 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 144.6, 130.9, 130.8, 129.8, 129.1, 128.8, 128.6, 127.7, 125.2, 112.5, 104.9, 79.7, 23.9, 21.8, 10.0; IR (thin film) 3069, 2982, 2962, 2925, 2869, 2225, 1606, 1568, 1516, 1505; HRMS(ESI) *m/z* calcd. for $C_{20}H_{19}N_2O_2$ $(M+H)^+$ 319.1441, observed 319.1449; m.p: 123-127 °C.



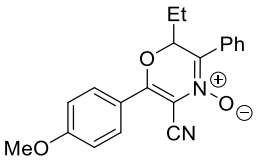
1.54c

Oxazine *N*-Oxide 1.54c: Compound **1.54c** was prepared from general procedure A with the following reagents: oxime **1.50c** (0.0565 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% Et_3N) afforded **1.54c** as a yellow solid (0.0449 g, 47%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.5 Hz, 2H), 7.81-7.79 (m, 2H), 7.50-7.46 (m, 3H), 7.43 (d, *J* = 5.5 Hz, 2H), 5.74 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 2.44 (s, 3H), 2.33-2.26 (m, 1H), 1.93-1.85 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 139.0, 134.3, 130.9, 130.8, 129.4, 129.0, 128.8, 128.5, 128.1, 127.7, 126.3, 112.4, 105.3, 79.8, 24.0, 21.4, 10.1; IR (thin film) 3054, 2972, 2933, 2224, 1598, 1579, 1519, 1493, 1443, 1394; HRMS (ESI) *m/z* calcd. for $C_{20}H_{19}N_2O_2$ $(M+H)^+$ 319.1441, observed 319.1448; m.p: 82-84 ˚C.



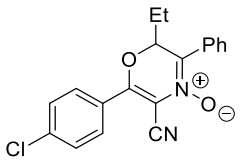
1.54d

Oxazine *N*-Oxide 1.54d: Compound **1.54d** was prepared from general procedure A with the following reagents: oxime **1.50d** (0.0565 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% Et_3N) afforded **1.54d** as a yellow solid (0.0420 g, 44%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.24-8.22 (m, 2H), 7.51-7.45 (m, 5H), 7.34-7.32 (m, 2H), 5.75 (dd, *J* = 9.0 Hz, 4.5 Hz, 1H), 2.52 (s, 3-H), 2.39-2.28 (m, 1H), 2.03-1.96 (m, 1H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 137.7, 132.1, 131.3, 130.9, 130.4, 129.8, 128.8, 128.5, 128.4, 127.8, 126.3, 111.2, 107.8, 80.4, 24.9, 19.8, 9.9; IR (thin film) 2971, 2933, 2228, 1619, 1572, 1520, 1493, 1456, 1443, 1393; HRMS (ESI) *m/z* calcd. for $C_{20}H_{19}N_2O_2$ $(M+H)^+$ 319.1441, observed 319.1447; m.p: 104-109 ˚C.



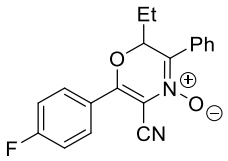
1.54e

Oxazine *N*-Oxide 1.54e: Compound **1.54e** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.54e** as a yellow solid (0.0912 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.49-7.45 (m, 3H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.71 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.89 (s, 3H), 2.32-2.23 (m, 1H), 1.89-1.84 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 160.1, 131.2, 130.8, 130.7, 128.7, 128.6, 127.7, 120.0, 114.5, 113.0, 103.9, 79.6, 55.6, 23.7, 10.0; IR (thin film) 2932, 2219, 1597, 1566, 1510, 1443, 1424, 1407, 1345, 1304; HRMS (ESI) *m/z* calcd. for $C_{20}H_{19}N_2O_3$ $(M+H)^+$ 335.1390, observed 335.1391; m.p: 100-102 °C.



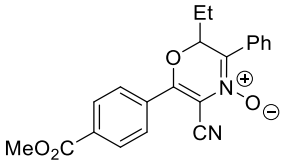
1.54f

Oxazine *N*-Oxide 1.54f: Compound **1.54f** was prepared using general procedure A with the following reagents: oxime **1.50f** (0.0626 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54f** as a yellow solid (0.0742 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25-8.23 (m, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.52-7.48 (m, 5H), 5.76 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H), 2.31-2.25 (m, 1H), 1.92-1.86 (m, 1H), 1.17 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 139.9, 131.1, 131.0, 130.2, 129.5, 128.8, 128.4, 127.7, 126.5, 112.1, 105.6, 80.0, 24.0, 10.0; IR (thin film) 2975, 2934, 2222, 1602, 1591, 1561, 1514, 1488, 1457, 1443; HRMS(ESI) *m/z* calcd. for $C_{19}H_{16}ClN_2O_2$ $(M+H)^+$ 339.0895, observed 339.0906; m.p: 143-145 °C.



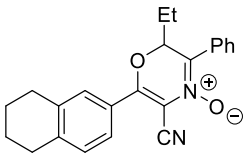
1.54g

Oxazine *N*-Oxide 1.54g: Compound **1.54g** was prepared using general procedure A with the following reagents: oxime **1.50g** (0.0576 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.54g** as a yellow solid (0.0696 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25-8.23 (m, 2H), 8.05-8.02 (m, 2H), 7.51-7.45 (m, 3H), 7.23 (t, *J* = 8.5 Hz, 2H), 5.76 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 2.32-2.24 (m, 1H), 1.92-1.85 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, *J* = 255.2 Hz), 159.1, 131.6 (d, *J* = 8.7 Hz), 131.0, 128.8, 128.4, 127.7, 124.32, 124.30, 116.5 (d, *J* = 21.2 Hz), 112.3, 105.3, 79.9, 24.0, 10.0; IR (thin film) 3057, 2973, 2935, 2877, 2224, 1611, 1600, 1506, 1458, 1443; HRMS (ESI) *m/z* calcd. for $C_{19}H_{16}FN_2O_2$ $(M+H)^+$ 323.1190, observed 323.1189; m.p: 103-107 ˚C.



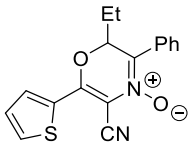
1.54h

Oxazine *N*-Oxide 1.54h: Compound **1.54h** was prepared using general procedure A with the following reagents: oxime **1.50h** (0.0697 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711 g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:5; Et_2O:pentane with 1% NEt_3) afforded **1.54h** as a yellow solid (0.0435 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.25 (m, 2H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.50-7.49 (m, 3H), 5.79 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.97 (s, 3H), 2.34-2.25 (m, 1H), 1.94-1.89 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 158.9, 134.2, 132.0, 131.3, 131.16, 130.12, 128.9, 128.8, 128.3, 127.7, 111.9, 106.5, 80.1, 52.6, 24.2, 10.0; IR (thin film) 2982, 2963, 2926, 2870, 2227, 1717, 1606, 1566, 1517, 1454; HRMS(ESI) *m/z* calcd. for $C_{21}H_{19}N_2O_4$ $(M+H)^+$ 363.1339, observed 363.1340; m.p: 145-148 °C.



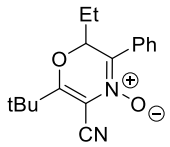
1.54i

Oxazine *N*-Oxide 1.54i: Compound **1.54i** was prepared using general procedure A with the following reagents: oxime **1.50i** (0.0685 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54i** as a yellow solid (0.0860 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.50-7.46 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 1H), 5.72 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 2.90-2.78 (m, 4H), 2.34-2.25 (m, 1H), 1.92-1.87 (m, 1H), 1.86-1.83 (m, 4H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 144.0, 138.2, 130.7, 129.88, 129.84, 129.1, 128.78, 128.70, 127.7, 126.0, 125.1, 112.6, 104.8, 79.7, 29.7, 29.3, 23.9, 22.7, 22.6, 10.1; IR (thin film) 2931, 2858, 2222, 1599, 1565, 1518, 1499, 1443, 1395, 1342; HRMS(ESI) *m/z* calcd. for $C_{23}H_{23}N_2O_2$ $(M+H)^+$ 359.1754, observed 359.1760; m.p: 84-87 °C.



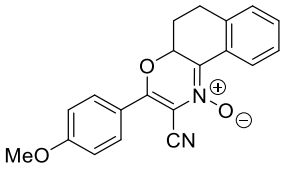
1.54j

Oxazine *N*-Oxide 1.54j: Compound **1.54j** was prepared using general procedure A with the following reagents: oxime **1.50j** (0.0541 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54j** as a yellow solid (0.0745 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24-8.22 (m, 2H), 8.17 (dd, *J* = 4.0 Hz, 1.0 Hz, 1H), 7.75-7.74 (m, 1H), 7.49-7.45 (m, 3H), 7.25-7.24 (m, 1H), 5.69 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 2.32-2.23 (m, 1H), 1.85-1.77 (m, 1H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 133.8, 133.1, 131.3, 130.9, 130.7, 129.2, 128.8, 128.5, 127.6, 112.4, 103.1, 79.9, 23.8, 9.8; IR (thin film) 3099, 3053, 2970, 2934, 2876, 2220, 1593, 1521, 1493, 1455; HRMS (ESI) *m/z* calcd. for $C_{17}H_{15}N_2O_2S$ $(M+H)^+$ 311.0849, observed 311.0851; m.p: 150-151 °C.



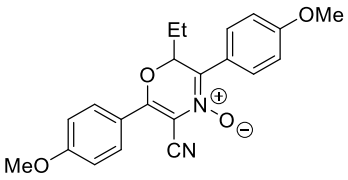
1.54k

Oxazine *N*-Oxide 1.54k: Compound **1.54k** was prepared using general procedure A with the following reagents: oxime **1.50k** (0.0462 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711 g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 1 h at 25 °C. Chromatography (1:4; Et_2O:pentane with 1% NEt_3) afforded **1.54k** as a pale yellow oil (0.0631 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19-8.17 (m, 2H), 7.47-7.41 (m, 3H), 5.57 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H), 2.15-2.06 (m, 1H), 1.80-1.72 (m, 1H), 1.42 (s, 9H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 130.7, 129.2, 128.7, 128.5, 127.6, 111.7, 106.0, 79.3, 36.8, 27.6, 23.7, 10.0; IR (thin film) 2973, 2936, 2876, 2226, 1600, 1524, 1480, 1461, 1444, 1404; HRMS (ESI) *m/z* calcd. for $C_{17}H_{21}N_2O_2$ $(M+H)^+$ 285.1598, observed 285.1594.



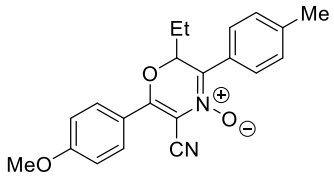
1.55b

Oxazine *N*-Oxide 1.55b: Compound **1.55b** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51b** (0.156 g, 0.900 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.55b** as a yellow solid (0.0807 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44 (m, 1H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.39-7.36 (m, 2H), 7.24-7.22 (m, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.17 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H), 3.90 (s, 3H), 2.99-2.94 (m, 1H), 2.93-2.86 (m, 1H), 2.62-2.58 (m, 1H), 2.39-2.31 (m, 1H); ^{13}C NMR (125 MHz, CDCl3): δ 164.0, 163.4, 138.5, 131.6, 130.8, 129.2, 128.3, 128.0, 127.2, 125.8, 119.4, 114.5, 112.9, 105.4, 77.6, 55.6, 27.5, 27.0; IR (thin film) 3059, 2936, 2842, 2222, 1592, 1566, 1505, 1460, 1439, 1422; HRMS (ESI) *m/z* calcd. for $C_{20}H_{17}N_2O_3$ $(M+H)^+$ 333.1234, observed 333.1237; m.p: 147-150 °C.



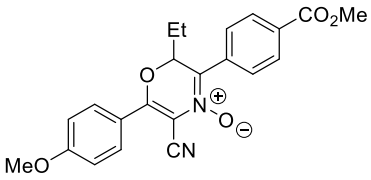
1.55c

Oxazine *N*-Oxide 1.55c: Compound **1.55c** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51c** (0.309 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:2; Et_2O:pentane with 1% NEt_3) afforded **1.55c** as a yellow solid (0.0852 g, 78%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.70 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.28-2.22 (m, 1H), 1.85-1.79 (m, 1H), 1.16 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 161.2, 159.2, 131.0, 130.7, 129.6, 121.1, 120.2, 114.5, 114.1, 113.1, 103.8, 79.3, 55.6, 55.4, 23.7, 10.1; IR (thin film) 2925, 2847, 2225, 1591, 1533, 1507, 1459, 1440, 1417, 1388; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_2O_4$ $(M+H)^+$ 365.1496, observed 365.1492; m.p: 146-148 °C.



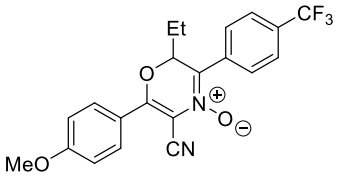
1.55d

Oxazine *N*-Oxide 1.55d: Compound **1.55d** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51d** (0.285 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.55d** as a yellow solid (0.0418 g, 40%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.72 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.90 (s, 3H), 2.41 (s, 3H), 2.32-2.24 (m, 1H), 1.88-1.83 (m, 1H), 1.17 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 159.6, 141.4, 131.1, 130.9, 129.4, 127.6, 125.8, 120.1, 114.5, 113.0, 104.0, 79.5, 55.6, 23.7, 21.6, 10.1; IR (thin film) 3051, 2972, 2935, 2877, 2840, 2222, 1597, 1567, 1511, 1457; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_2O_3$ $(M+H)^+$ 349.1547, observed 349.1549; m.p: 150-153 °C.



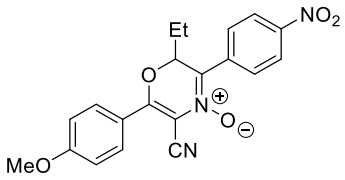
1.55e

Oxazine *N*-Oxide 1.55e: Compound **1.55e** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51e** (0.351g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:2; Et_2O:pentane with 1% NEt_3) afforded **1.55e** as a yellow solid (0.109 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.75 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.34-2.28 (m, 1H), 1.91-1.85 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 164.0, 160.4, 132.6, 131.39, 131.33, 129.8, 129.7, 127.4, 119.8, 114.6, 112.7, 104.2, 79.4, 55.7, 52.3, 23.8, 10.0; IR (thin film) 2952, 2225, 1713, 1597, 1507, 1495, 1460, 1431, 1419, 1397; HRMS (ESI) *m/z* calcd. for $C_{22}H_{21}N_2O_5$ $(M+H)^+$ 393.1445, observed 393.1445; m.p: 132-136 °C.



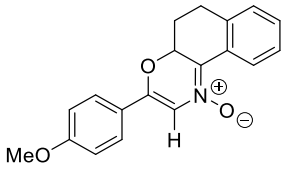
1.55f

Oxazine *N*-Oxide 1.55f: Compound **1.55f** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51f** (0.366 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.55f** as a yellow solid (0.112 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.73 (dd, *J* = 11.0 Hz, 4.0 Hz, 1H), 3.90 (s, 3H), 2.35-2.26 (m, 1H), 1.91-1.83 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 160.6, 132.0, 131.8 (q, *J* = 32.6 Hz), 131.3, 129.2, 127.8, 125.6 (d, *J* = 3.3 Hz), 123.5 (q, *J* = 270.5 Hz), 119.7, 114.6, 112.6, 104.1, 79.4, 55.7, 23.8, 10.0; IR (thin film) 3005, 2976, 2940, 2844, 2224, 1595, 1574, 1561, 1505, 1457; HRMS (ESI) *m/z* calcd. for $C_{21}H_{18}F_3N_2O_3$ $(M+H)^+$ 403.3807, observed 403.1261; m.p: 123-127 °C.



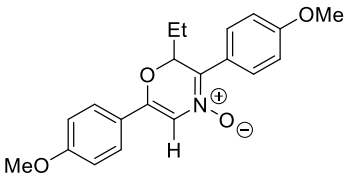
1.55g

Oxazine *N*-Oxide 1.55g: Compound **1.55g** was prepared using general procedure A with the following reagents: oxime **1.50e** (0.0612 g, 0.300 mmol), boronic acid **1.51g** (0.324 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:2; Et_2O:pentane with 1% NEt_3) afforded **1.55g** as a yellow solid (0.107 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, *J* = 9.0 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.76 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.91 (s, 3H), 2.37-2.29 (m, 1H), 1.92-1.86 (m, 1H), 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 160.9, 147.7, 134.5, 131.4, 128.5, 128.2, 123.9, 119.5, 114.7, 112.4, 104.2, 79.3, 55.7, 23.8, 10.0; IR (thin film) 3116, 2981, 2932, 2222, 1596, 1565, 1510, 1500, 1488, 1461; HRMS (ESI) *m/z* calcd. for $C_{20}H_{18}N_3O_5$ $(M+H)^+$ 380.1241, observed 380.1239; m.p: 175-179 °C.



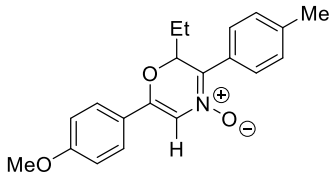
1.56b

Oxazine *N*-Oxide 1.56b: Compound **1.56b** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51b** (0.156 g, 0.900 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711 g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.56b** as a yellow solid (0.0719 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.35-7.30 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 1H), 6.95 (d, *J* = 5.0 Hz, 2H), 6.93 (s, 1H), 5.07 (dd, *J* = 9.5 Hz, 6.0 Hz, 1H), 3.85 (s, 3H), 2.96-2.92 (m, 1H), 2.89-2.83 (m, 1H), 2.58-2.52 (m, 1H), 2.36-2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 152.7, 138.5, 129.9, 129.2, 128.3, 127.8, 127.7, 126.9, 126.8, 122.1, 115.0, 114.2, 76.6, 55.4, 27.9, 27.4; IR (thin film) 3098, 2931, 1640, 1604, 1573, 1505, 1456, 1437, 1420, 1381; HRMS (ESI) *m/z* calcd. for $C_{19}H_{18}NO_3$ $(M+H)^+$ 308.1281, observed 308.1285; m.p: 118-121 °C.



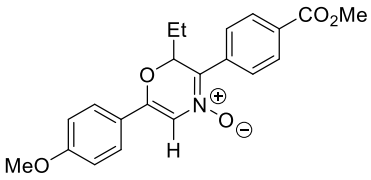
1.56c

Oxazine *N*-Oxide 1.56c: Compound **1.56c** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51c** (0.309 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 2 h at 25 °C. Chromatography (1:2; Et_2O:pentane) afforded **1.56c** as a yellow solid (0.0665 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.87 (s, 1H), 5.53 (dd, *J* = 10.5 Hz, 3.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.34-2.28 (m, 1H), 1.69-1.65 (m, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 160.5, 147.5, 130.7, 129.5, 127.2, 122.8, 122.3, 114.2, 113.9, 113.0, 78.1, 55.4, 55.3, 22.5, 10.0; IR (thin film) 3094, 2970, 2934, 2837, 1644, 1605, 1561, 1512, 1456, 1438; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}NO_4$ $(M+H)^+$ 340.1543, observed 340.1542; m.p: 124-126 °C.



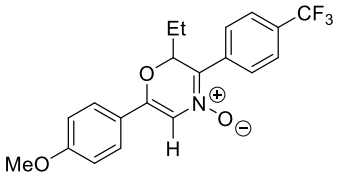
1.56d

Oxazine *N*-Oxide 1.56d: Compound **1.56d** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51d** (0.285 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane with 1% NEt_3) afforded **1.56d** as a yellow solid (0.0262 g, 27%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 5.52 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 2.37-2.24 (m, 1H), 1.70-1.64 (m, 1H), 1.09 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 148.0, 140.2, 130.8, 129.2, 127.6, 127.3, 127.0, 122.8, 114.3, 113.0, 78.3, 55.4, 22.5, 21.5, 10.0; IR (thin film) 3042, 2968, 2933, 2874, 2838, 1638, 1606, 1574, 1511, 1456; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.3995, observed 324.1599; m.p: 151-153 °C.



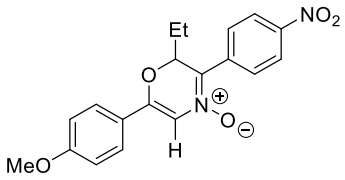
1.56e

Oxazine *N*-Oxide 1.56e: Compound **1.56e** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51e** (0.351 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711 g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.56e** as a yellow solid (0.0727 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.92 (s, 1H), 5.58 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 2.37-2.29 (m, 1H), 1.74-1.68 (m, 1H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 162.0, 149.1, 133.9, 130.5, 129.7, 129.5, 127.5, 127.3, 122.4, 114.4, 113.2, 78.2, 55.4, 52.2, 22.6, 9.9; IR (thin film) 3118, 2926, 2837, 1715, 1634, 1603, 1574, 1560, 1513, 1494; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1492, observed 368.1489; m.p: 146-148 °C.



1.56f

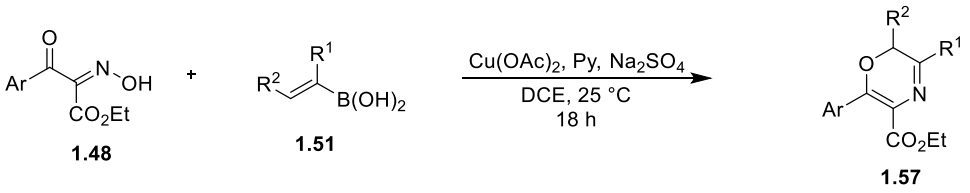
Oxazine *N*-Oxide 1.56f: Compound **1.56f** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51f** (0.366 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:3; Et_2O:pentane) afforded **1.56f** as a yellow solid (0.0883 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.92 (s, 1H), 5.56 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 3.87 (s, 3H), 2.39-2.29 (m, 1H), 1.73-1.68 (m, 1H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 149.2, 133.18, 130.8 (q, *J* = 32.5 Hz), 129.0, 127.8, 127.5, 125.4 (d, *J* = 2.8 Hz), 123.7 (q, *J* = 270.3 Hz), 122.3, 114.4, 113.0, 78.2, 55.4, 22.6, 9.9; IR (thin film) 3112, 2967, 1638, 1605, 1575, 1514, 1491, 1462, 1453, 1441; HRMS(ESI) *m/z* calcd. for $C_{20}H_{19}F_3NO_3$ $(M+H)^+$ 378.1312, observed 378.1308; m.p: 135-137 °C.



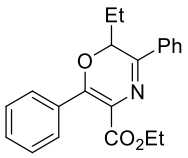
1.56g

Oxazine *N*-Oxide 1.56g: Compound **1.56g** was prepared using general procedure A with the following reagents: oxime **1.49c** (0.0538 g, 0.300 mmol), boronic acid **1.51g** (0.324 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 2 h at 25 °C. Chromatography (1:2; Et_2O:pentane) afforded **1.56g** as a yellow solid (0.0832 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 9.0 Hz, 2H), 8.28 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H), 5.60 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 3.86 (s, 3H), 2.40-2.31 (m, 1H), 1.73-1.68 (m, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 149.8, 147.11, 135.7, 128.3, 128.0, 127.7, 123.7, 122.0, 114.4, 113.3, 78.0, 55.5, 22.7, 9.9; IR (thin film) 3119, 2962, 2930, 1637, 1605, 1590, 1574, 1509, 1499, 1483; HRMS (ESI) *m/z* calcd. for $C_{19}H_{19}N_2O_5$ $(M+H)^+$ 355.1288, observed 355.1284; m.p: 142-146 °C.

1.7.3 Experimental Procedures and Characterization Data (Table 1.6)

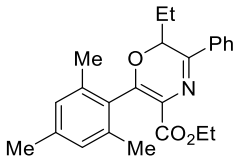


General Procedure B: A scintillation vial was charged with oxime **1.48** (1 equiv), $Cu(OAc)_2$ (1 equiv), Na_2SO_4 (6.6 equiv), and alkenylboronic acid **1.51** (5 equiv). These solids were dissolved in 1,2- dichloroethane (DCE) to make a 0.1 M solution of oxime **1.48** and pyridine (3 equiv) was added via syringe. The vial was then capped with rubber septum and punctured with a ventilation needle to expose the reaction mixture to air. The reaction mixture was stirred for 18 h at 25 °C. At this time, the reaction mixture was filtered through silica gel, which was washed with 50 mL of EtOAc. The filtrate was then concentrated under vacuum to give a crude product, which was purified by medium pressure chromatography (1:5 – 1:1; Et_2O:pentane) to give oxazine **1.57**.



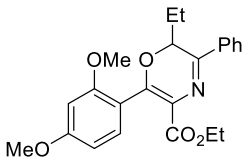
1.57a

Oxazine 1.57a: Compound **1.57a** was prepared using general procedure B with the following reagents: oxime **1.48d** (0.0664 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57a** as a yellow liquid (0.0402 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56 (d, *J* = 7.0 Hz, 2H), 7.45-7.39 (m, 6H), 5.46 (dd, *J* = 10.0 Hz, 4.5 Hz, 1H), 4.18 (q, *J* = 7.5 Hz, 2H), 2.13-2.04 (m, 1H), 1.72-1.67 (m, 1H), 1.20 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 152.0, 151.7, 134.8, 133.0, 130.6, 130.4, 129.8, 128.7, 127.9, 126.9, 120.2, 73.7, 60.6, 21.5, 13.9, 10.2.



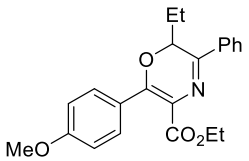
1.57b

Oxazine 1.57b: Compound **1.57b** was prepared using general procedure B with the following reagents: oxime **1.48g** (0.0790 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57b** as a yellow solid (0.103 g, 91%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.98-7.97 (m, 2H), 7.46-7.45 (m, 3H), 6.92 (s, 1H), 6.87 (s, 1H), 5.43 (dd, *J* = 10.0 Hz, 4.5 Hz, 1H), 4.13-4.06 (m, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.19-2.11 (m, 4H), 1.82-1.77 (m, 1H), 1.09 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 153.3, 152.2, 138.6, 137.3, 135.3, 135.1, 130.7, 130.6, 128.7, 128.07, 128.02, 126.8, 120.7, 73.9, 60.2, 22.8, 21.2, 19.4, 19.2, 13.8, 10.1; IR (thin film) 2973, 2934, 2877, 2838, 1708, 1607, 1595, 1573, 1514, 1461; HRMS (ESI) *m/z* calcd. for $C_{24}H_{28}NO_3$ $(M+H)^+$ 378.2064, observed 378.2066; m.p: 162-164 ˚C.



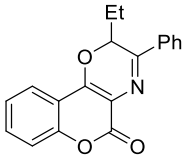
1.57c

Oxazine 1.57c: Compound **1.57c** was prepared using general procedure B with the following reagents: oxime **1.48h** (0.0844 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57c** as a yellow liquid (0.0889 g, 75%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.95-7.94 (m, 2H), 7.43-7.42 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.54 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.41 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 4.17-4.10 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.16-2.08 (m, 1H), 1.70-1.65 (m, 1H), 1.16 (t, *J* = 7.5 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 162.5, 159.0, 151.4, 148.2, 135.1, 132.2, 130.3, 128.6, 126.8, 121.7, 115.7, 104.3, 98.4, 73.9, 60.2, 55.46, 55.41, 21.5, 14.0, 10.2; IR (thin film) 3054, 2971, 2936, 2838, 1709, 1609, 1580, 1503, 1462, 1446; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_5$ $(M+H)^+$ 396.1805, observed 396.1805; m.p: 112-115 °C.



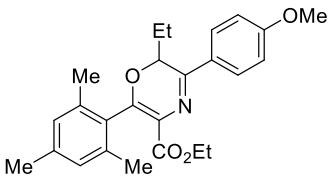
1.57d

Oxazine 1.57d: Compound **1.57d** was prepared using general procedure B with the following reagents: oxime **1.48i** (0.0754 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57d** as a yellow liquid (0.0687 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.44-7.43 (m, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.46 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 4.22 (q, *J* = 7.5 Hz, 2H), 3.85 (s, 3H), 2.12-2.02 (m, 1H), 1.71-1.63 (m, 1H), 1.22-1.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 161.5, 151.6, 151.4, 134.9, 131.6, 130.5, 128.7, 126.8, 125.0, 119.3, 113.4, 73.8, 60.5, 55.3, 21.4, 14.1, 10.2 ; IR (thin film) 3056, 2974, 2935, 2875, 2383, 1704, 1606, 1578, 1552, 1504; HRMS (ESI) *m/z* calcd. for $C_{22}H_{24}NO_4$ $(M+H)^+$ 366.1700, observed 366.1698.



1.57e

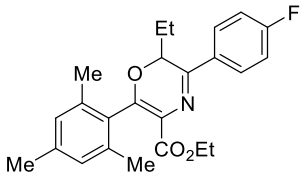
Oxazine 1.57e: Compound **1.57e** was prepared using general procedure B with the following reagents: oxime **1.48j** (0.0573 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57e** as a yellow liquid (0.0443 g, 48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.58-7.55 (m, 1H), 7.50-7.45 (m, 3H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.35-7.32 (m,1H), 5.62 (dd, *J* = 10.0 Hz, 3.0 Hz, 1H), 2.02-1.94 (m, 1H), 1.78-1.73 (m, 1H), 1.09 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 157.6, 152.5, 149.8, 134.3, 132.4, 131.6, 128.8, 127.0, 124.4, 122.8, 117.0, 115.4, 114.9, 74.4, 23.8, 9.4; IR (thin film) 3057, 2970, 2934, 2877, 1726, 1612, 1565, 1556, 1491, 1451; HRMS (ESI) *m/z* calcd. for $C_{19}H_{16}NO_3$ $(M+H)^+$ 306.1125, observed 306.1132; m.p: 165-170 ˚C.



1.57f

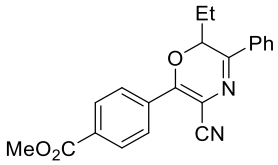
Oxazine 1.57f: Compound **1.57f** was prepared using general procedure B with the following reagents: oxime **1.48g** (0.0790 g, 0.300 mmol), boronic acid **1.51c** (0.309 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4

(0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57f** as a white solid (0.116 g, 95%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.90 (s, 1H), 6.85 (s, 1H), 5.38 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 4.10–4.04 (m, 2H), 3.87 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.19-2.01 (m, 4H), 1.81-1.72 (m, 1H), 1.08 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 161.6, 152.5, 151.9, 138.5, 137.3, 135.4, 130.9, 128.4, 128.0, 127.9, 127.7, 120.6, 114.0, 73.7, 60.2, 55.4, 22.9, 21.1, 19.4, 19.2, 13.8, 10.1; IR (thin film) 3052, 2977, 2936, 2877, 1708, 1613, 1565, 1446, 1370, 1326; HRMS (ESI) *m/z* calcd. for $C_{25}H_{30}NO_4$ $(M+H)^+$ 408.2169, observed 408.2164; m.p: 155-158 °C.



1.57g

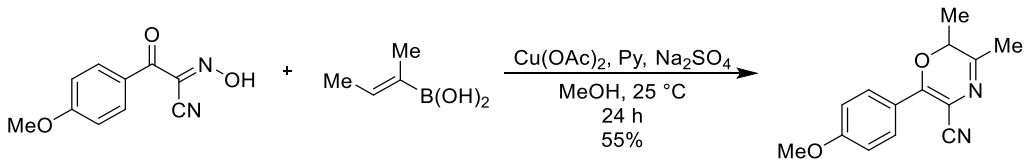
Oxazine 1.57g: Compound **1.57g** was prepared using general procedure B with the following reagents: oxime **1.48g** (0.0790 g, 0.300 mmol), boronic acid **1.51m** (0.291 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 18 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57g** as a yellow solid (0.0938 g, 79%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 2H), 7.13 (t, *J* = 8.5 Hz, 2H), 6.90 (s, 1H), 6.85 (s, 1H), 5.37 (dd, *J* = 9.5 Hz, 4.5 Hz, 1H), 4.10–4.04 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.18-2.10 (m, 1H), 1.79-1.74 (m, 1H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 164.3, (d, *J* = 250.1 Hz), 153.1, 151.1, 138.6, 137.2, 135.3, 131.3, 130.6, 128.9, 128.8, 128.0 (d, *J* = 7.5 Hz), 120.6, 115.7 (d, *J* = 21.6 Hz), 73.8, 60.2, 22.8, 21.1, 19.4, 19.1, 13.8, 10.0; IR (thin film) 3050, 2975, 2922, 2878, 1708, 1613, 1599, 1586, 1567, 1509; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}FNO_3$ $(M+H)^+$ 396.1969, observed 396.1969; m.p: 133-135 °C.



1.57h

Oxazine 1.57h: Compound **1.57h** was prepared from general procedure B, using a shorter reaction times, with the following reagents: oxime **1.50h** (0.0697 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$

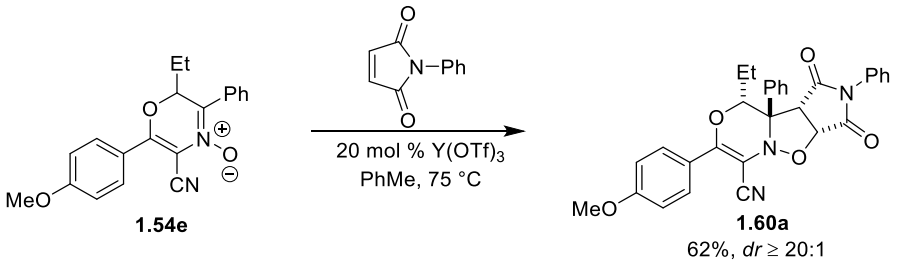
(0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The reaction mixture was stirred for 4 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57h** as a white solid (0.0400 g, 39%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.51-7.46 (m, 3H), 5.54 (dd, *J* = 9.5 Hz, 3.5 Hz, 1H), 3.95 (s, 3H), 2.06-1.99 (m, 1H), 1.75-1.68 (m, 1H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 155.6, 151.8, 134.1, 133.6, 132.5, 131.7, 129.9, 129.0, 128.1, 126.9, 118.0, 104.2, 74.1, 52.4, 22.4, 9.8; IR (thin film) 3058, 2972, 2951, 2877, 2218, 1721, 1592, 1577, 1566, 1504; HRMS (ESI) *m/z* calcd. for $C_{21}H_{19}N_2O_3$ $(M+H)^+$ 347.1390, observed 347.1389; m.p: 83-86 °C.



1.50e **1.51n** **1.57i**

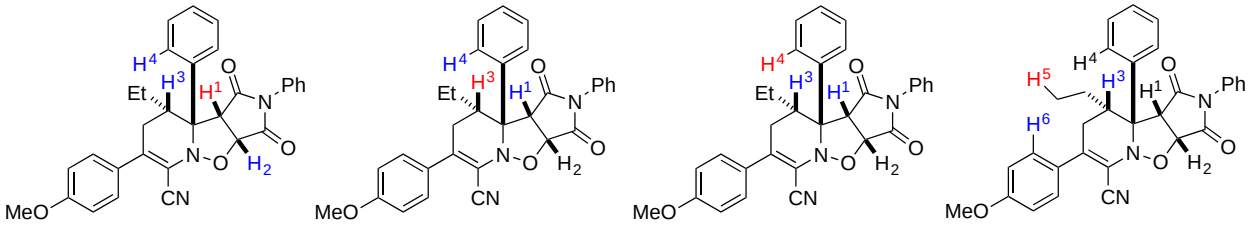
Oxazine 1.57i: Compound **1.57i** was prepared using general procedure B, substituting MeOH (3.0 mL) as the solvent, and using the following reagents: oxime **1.50e** (0.0613 g, 0.300 mmol), boronic acid **1.51n** (0.0899 g, 0.900 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), and pyridine (0.0711g, 0.900 mmol). The reaction mixture was stirred for 24 h at 25 °C. Chromatography (1:4; Et_2O:pentane) afforded **1.57i** as a white solid (0.0426 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.64 (q, *J* = 7.0 Hz, 1H), 3.85 (s, 3H), 2.15 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 158.9, 154.2, 130.2, 128.6, 122.1, 118.6, 114.1, 71.4, 55.4, 22.0, 15.0; IR (thin film) 2979, 2938, 2839, 2211, 1633, 1605, 1582, 1562, 1506, 1454; HRMS (ESI) *m/z* calcd. for $C_{14}H_{15}N_2O_2$ $(M+H)^+$ 243.1128, observed 243.1126; m.p: 166-169 °C.

1.7.4 Experimental Procedures for Cycloadditions and Characterization Data (Scheme 1.13 and 1.14)

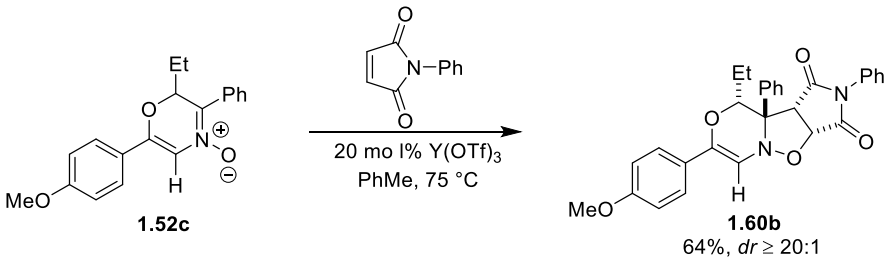


[3+2]-Cycloaddition of 1.54e and *N*-phenylmaleimide: A scintillation vial was charged with oxazine *N*-oxide **1.54e** (0.0669 g, 0.200 mmol), *N*-phenylmaleimide (0.0523 g, 0.3 mmol) and $Y(OTf)_3$ (0.0215 g, 0.0400 mmol). These solids were mixed with 1.0 mL of dry toluene to form a slurry and the reaction mixture was allowed to stir under N_2 for 3.5 h at 75 °C. The reaction mixture was filtered over celite and washed with CH_2Cl_2 (2 x 5.0 mL). The solution of the crude product mixture was concentrated under vacuum and purified by flash chromatography (1:6; EtOAc:hexane) to afford cycloadduct **1.60a** as a pale yellow solid (0.0632 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.50-7.46 (m, 2H), 7.42-7.32 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.18 (d, *J* = 7.5 Hz, 1H), 4.80 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 4.05 (d, *J* = 7.5 Hz, 1H), 3.86 (s, 3H), 1.15-1.08 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 169.1, 161.2, 155.8, 137.7, 130.7, 129.2, 129.1, 128.8, 128.7, 128.48, 128.43, 128.3, 126.6, 125.9, 125.3, 114.1, 112.1, 93.4, 82.1, 71.6, 66.9, 55.3, 54.7, 24.5, 10.4; IR (thin film) 3058, 2972, 2936, 1723, 1612, 1584, 1514, 1498, 1457, 1449; HRMS (ESI) *m/z* calcd. for $C_{30}H_{26}N_3O_5$ $(M+H)^+$ 508.1867, observed 508.1866; m.p: 129-131 °C.

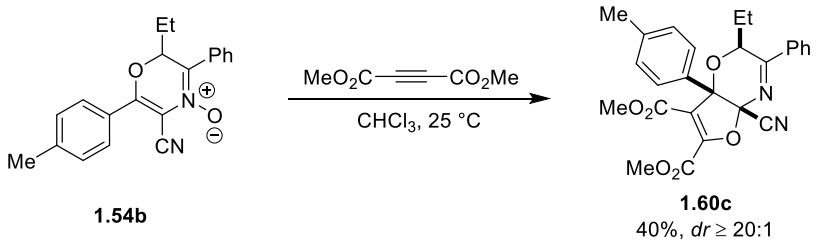
nOe Analysis of 1.60a:



When H^1 was irradiated, H^2- H^4 were inverted. When H^3 was irradiated, H^1 and H^4 were inverted. When H^4 was irradiated, H^1 and H^3 were inverted. These data suggested that the phenyl group is on the same side of the tricyclic structure as H^1 – H^3. When H^5 was irradiated, only H^3 and H^6 were inverted. These data suggested that H^1 and H^2 are on the opposite side of the tricyclic structure as the ethyl group.



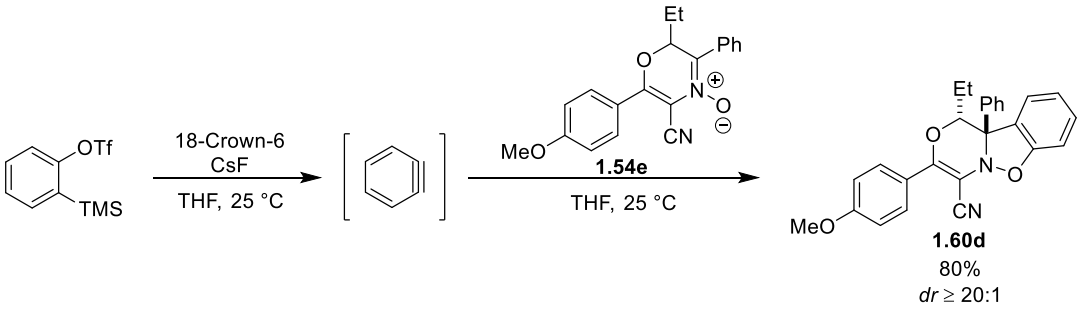
[3+2]-Cycloaddition of 6c and *N*-phenylmaleimide: A scintillation vial was charged with oxazine *N*-oxide **1.52c** (0.0619 g, 0.200 mmol), *N*-phenylmaleimide (0.0523 g, 0.300 mmol) and $Y(OTf)_3$ (0.0215 g, 0.0400 mmol). These solids were mixed with 1.0 mL of dry toluene to form a slurry and the reaction mixture was allowed to stir under N_2 for 3.5 h at 75 °C. The reaction mixture was filtered over celite and washed with CH_2Cl_2 (2 x 10.0 mL). The solution of the crude product mixture was concentrated under vacuum and purified by flash chromatography (1:10; EtOAc:hexane) to afford cycloadduct **1.60b** as a pale yellow liquid (0.0617 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.49-7.44 (m, 2H), 7.40-7.31 (m, 5H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* = 7.5 Hz, 1H), 4.72 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 4.01 (d, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 1.12-1.03 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 170.0, 168.4, 160.3, 139.2, 131.5, 131.1, 129.0, 128.9, 128.5, 128.4, 127.8, 127.7, 126.6, 126.0, 125.9, 113.9, 92.0, 81.9, 71.7, 65.0, 55.5, 55.3, 24.7, 10.6; IR (thin film) 3058, 2966, 1720, 1611, 1597, 1514,



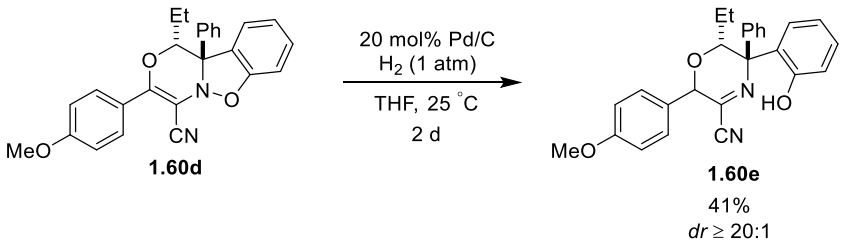
Cycloaddition and rearrangement of 1.54b and DMAD: A 10 mL round bottom flask was charged with oxazine *N*-oxide **1.54b** (0.104 g, 0.326 mmol) and DMAD (0.0928 g, 0.653 mmol). These solids were then dissolved in $CHCl_3$ (3.0 mL) and the reaction mixture was allowed to stirred for 14 h at 25 °C. At this time, the reaction mixture was concentrated under vacuum and the sample was purified by medium pressure chromatography (1:15; EtOAc:hexane) to afford **1.60c** as a pale brown solid (0.0600 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.0 Hz, 2H), 7.54-7.49 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.13-5.11 (m, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 2.40 (s, 3H), 2.15-2.09 (m, 1H), 1.90-1.85 (m, 1H), 0.98 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 161.8, 158.5, 151.2, 139.6, 135.4, 133.0, 131.6, 129.7, 128.6, 127.3, 125.3, 114.9, 113.2 89.8,

85.1, 71.1, 53.2, 52.5, 27.0, 21.2, 8.3; IR (thin film) 3058, 2954, 2878, 1758, 1742, 1725, 1654, 1631, 1577, 1513; HRMS (ESI) *m/z* calcd. for $C_{26}H_{25}N_2O_6$ $(M+H)^+$ 461.1707, observed 461.1708; mp: 116-118 °C.

1497, 1456, 1417, 1382; HRMS (ESI) *m/z* calcd. for $C_{29}H_{27}N_2O_5$ $(M+H)^+$ 483.1920, observed 483.1912.



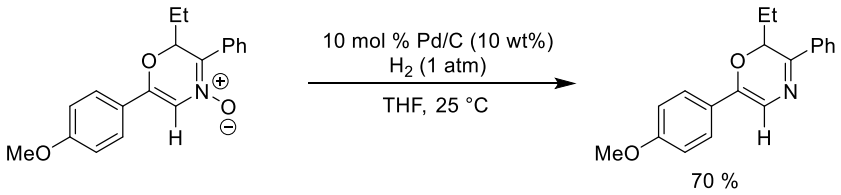
[3+2]-Cycloaddition of 1.54e and benzyne: A 25 mL round bottom flask was charged with 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (0.358 g, 1.20 mmol) and 18-crown-6-ether (0.633 g, 2.40 mmol). These solids were dissolved in THF (6.0 mL) and allowed to stir at 25 °C for 5 min. At this time, CsF (0.364 mg, 2.40 mmol) was added as a solid and the reaction mixture was stirred for another 5 min at 25 °C. After generation of the benzyne reagent, a solution of oxazine *N*-oxide **1.54e** (0.200 g, 0.600 mmol) in 3.0 mL of THF was added dropwise and the reaction mixture was allowed to stir for 40 min. The reaction mixture was then concentrated under vacuum and the sample was purified by crystallization from Et_2O by slow diffusion of hexane at -35 °C to afford **1.60d** as a pale yellow solid (0.196 g, 80%, dr > 20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38-7.31 (m, 3H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.92-4.90 (m, 1H), 3.80 (s, 3H), 2.15-2.07 (m, 1H), 1.93-1.85 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 160.0, 156.5, 135.8, 131.6, 131.3, 131.2, 128.5, 127.3, 127.1, 125.7, 124.8, 123.4, 114.7, 113.8, 112.6, 90.1, 84.4, 70.4, 55.2, 26.9, 8.4; IR (thin film) 3054, 2970, 2935, 1634, 1609, 1599, 1578, 1510, 1463, 1446; HRMS (ESI) *m/z* calcd. for $C_{26}H_{23}N_2O_3$ $(M+H)^+$ 411.1703, observed 411.1700; m.p: 105-107 °C.



N–O Bond Reduction of 1.60d: A 10 mL round bottom flask was charged with 10 wt% Pd/C (0.0353 g, 0.0332 mmol) and THF (2.0 mL) to form a slurry. The slurry was then purged with an H_2 balloon for 5 min using a

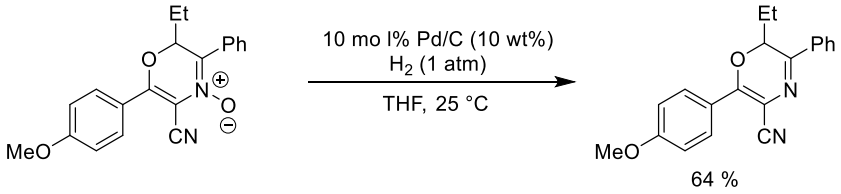
ventilation needle. A solution of **1.60d** (0.0680 g, 0.166 mmol) in 2.0 mL of THF was then added to the activated Pd/C via syringe. The reaction mixture was then placed under an H_2 atmosphere with a balloon and allowed to stir for 2 d at 25 °C. The reaction mixture was then filtered through celite and washed with CH_2Cl_2 (2 x 10.0 mL). The filtrate was concentrated under vacuum to give the crude product and flash chromatography (1:8; EtOAc:hexane) afforded **1.60e** as a white solid (0.0281 g, 41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.42 (m, 1H), 7.37-7.33 (m, 6H), 7.27-7.24 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.87-6.84 (m, 2H), 6.82 (br, 1H), 5.58 (s, 1H), 4.69-4.68 (m, 1H), 3.80 (s, 3H), 2.03-1.96 (m, 1H), 1.95-1.87 (m, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 160.0, 155.5, 136.2, 131.1, 130.89, 130.81, 128.6, 127.7, 127.1, 126.5, 121.8, 120.0, 117.9, 115.8, 114.1, 79.1, 74.6, 55.8, 55.2, 26.4, 9.2; IR (thin film) 3061, 3001, 2968, 2935, 2874, 2839, 2704, 2243, 1625, 1605; HRMS (ESI) *m/z* calcd. for $C_{26}H_{25}N_2O_3$ $(M+H)^+$ 413.1860, observed 413.1859; m.p: 160-163 °C.

1.7.5 Experimental Procedures for Deoxygenations and Characterization Data (Scheme 1.16)

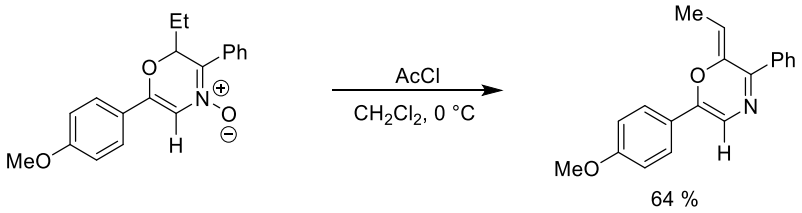


Deoxygenation of 1.52c: A 25 mL round-bottom flask was charged with 10 wt% Pd/C (0.0213 g, 0.0200 mmol) and THF (1.0 mL). The slurry was purged for 5 min with an H_2 balloon and a vent needle. Oxazine *N*-oxide **1.52c** (0.0619 g, 0.200 mmol) was then dissolved in THF in a scintillation vial and added to reaction mixture via syringe. The reaction flask with then fitted with an H_2 balloon and then stirred for ~40 min at 25 °C. The reaction mixture was monitored by TLC (R_f = 0.2; 1:8, EtOAc:hexanes). The reaction mixture was then filtered through celite and washed with CH_2Cl_2 (2 x 10.0 mL). Volatile materials were removed from the filtrate under vacuum to give the crude product mixture, which was purified by flash chromatography (1:12; EtOAc:hexane) to give oxazine **1.60h** as a bright yellow solid (0.0410 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.0 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.43-7.41 (m, 3H), 7.12 (s, 1H), 6.93 (d, *J* = 7.5 Hz, 2H), 5.36 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 3.85 (s, 3H), 2.14-2.07 (m, 1H), 1.58-1.53 (m, 1H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 153.1, 141.3, 135.7, 129.9, 128.7, 126.7, 126.2, 125.4, 114.0, 113.6, 73.1, 55.3, 20.8, 9.8; IR (thin film) 3059, 2964, 2932, 2838,

1681, 1599, 1573, 1507, 1444, 1419; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}NO_2$ $(M+H)^+$ 294.1489, observed 294.1454; m.p: 117-119 °C.



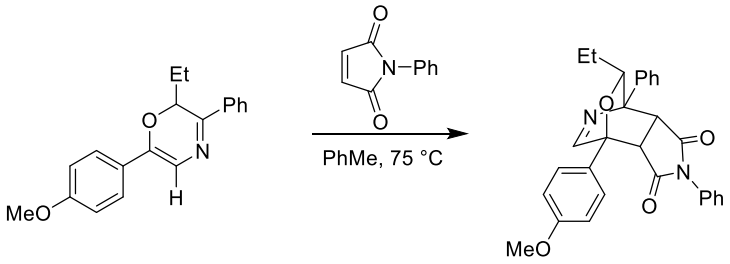
Deoxygenation of 1.54e: A 10 mL round-bottom flask was charged with 10 wt% Pd/C (0.0213 g, 0.0200 mmol,) and THF (1.0 mL). The slurry was purged for 5 min with an H_2 balloon and a vent needle. Oxazine *N*-oxide **1.54e** (0.0669 g, 0.2 mmol) was then dissolved in THF in a scintillation vial and added to reaction mixture via syringe. The reaction flask with then fitted with an H_2 balloon and then stirred for ~40 min at 25 °C. The reaction mixture was monitored by TLC (R_f = 0.2; 1:8, EtOAc:hexanes). The reaction mixture was then filtered through celite and washed with CH_2Cl_2 (2 x 10.0 mL). Volatile materials were removed from the filtrate under vacuum to give the crude product mixture, which was purified by flash chromatography (1:12; EtOAc:hexane) to give oxazine **1.60i** as a bright yellow solid (0.0275 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 6.5 Hz, 2H), 7.47-7.45 (m, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 5.49 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 3.87 (s, 3H), 2.07-1.98 (m, 1H), 1.71-1.66 (m, 1H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 154.1, 153.2, 134.0, 131.2, 130.2, 128.9, 126.7, 122.2, 118.9, 114.2, 101.7, 74.1, 55.5, 22.2, 9.9; IR (thin film) 3056, 2970, 2935, 2876, 2839, 2213, 1605, 1578, 1550, 1506; HRMS (ESI) *m/z* calcd. for $C_{20}H_{19}N_2O_2$ $(M+H)^+$ 319.1441, observed 319.1439; m.p: 111-113 °C.



Boekelheide rearrangement of 1.52c: A 10 mL round bottom flask was charged with oxazine *N*-oxide **1.52c** (0.0928 g, 0.300 mmol) and CH_2Cl_2 (3.0 mL). The solution of **1.52c** was then cooled to 0 °C and stirred for 5 min. Acetyl chloride (0.0259 g, 0.330 mmol) was dropwise at 0 °C and the reaction mixture was allowed to stir for 20 min. The reaction mixture was then warmed to 25 °C, diluted with H_2O (5.0 mL), and extracted with CH_2Cl_2 (3 x 5.0 mL). The organic layer was dried over $MgSO_4$ and then volatile materials were removed under vacuum. The crude mixture was purified by flash chromatography (1:20; EtOAc: hexane) to afford **1.60j** as an orange solid

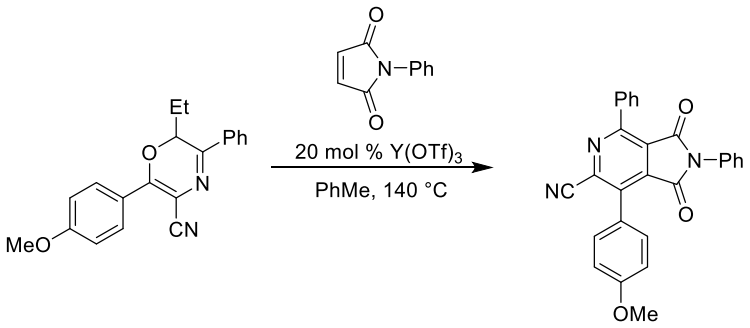
(0.0710 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.68 (m, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.41-7.39 (m, 3H), 6.97 (s, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.26 (q, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 1.83 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 156.6, 145.6, 144.7, 137.3, 129.7, 128.3, 128.2, 126.1, 124.1, 114.1, 113.5, 106.9, 55.3, 10.0; IR (thin film) 3055, 3000, 2932, 2912, 2836, 1728, 1682, 1605, 1573, 1508; HRMS (ESI) *m/z* calcd. for $C_{19}H_{18}NO_2$ $(M+H)^+$ 292.1332, observed 292.1340; m.p: 91-93 °C.

1.7.6 Experimental Procedures for [4+2]-Cycloaddition and Characterization Data (Scheme 1.17)



1.52c → **1.60**k, 62% (*dr* ≥ 20:1)

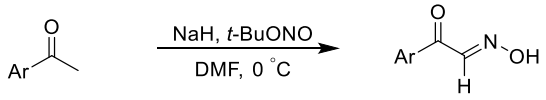
[4+2]-Cycloaddition of 1.52c and *N*-phenylmaleimide: A 10 mL round bottom flask was charged with **1.52c** (0.0587 g, 0.200 mmol), *N*-phenylmaleimide (0.0693 g, 0.200 mmol), and toluene (2.0 mL). The reaction mixture was then heated at 75 °C for 18 h. The reaction mixture was then concentrated under vacuum and the crude product was purified by column chromatography (1:8; EtOAc:Hex) to afford **1.60k** as a pale brown solid (0.0579 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 7.52-7.49 (m, 3H), 7.39-7.34 (m, 3H), 7.31-7.28 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.37 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 3.86 (s, 3H), 3.84-3.81 (m, 2H), 1.12-1.05 (m, 1H), 1.01-0.92 (m, 1H), 0.75 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 170.2, 160.0, 138.0, 131.3, 128.9, 128.8, 128.63, 128.60, 128.4, 128.0, 127.6, 126.2, 125.0, 113.8, 82.0, 71.8, 66.4, 55.3, 49.7, 46.8, 23.7, 10.3; IR (thin film) 3059, 2964, 2933, 2875, 2838, 1779, 1712, 1614, 1582, 1517; HRMS (ESI) *m/z* calcd. for $C_{29}H_{27}N_2O_4$ $(M+H)^+$ 467.1965, observed 467.1965; m.p: 188-190 °C.



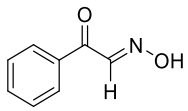
1.54e **1.60m** 71%

[4+2]-Cycloaddition and Rearrangement of 1.54e and *N*-phenylmaleimide: A 5 mL round bottom flask was charged with **1.54e** (0.0637 g, 0.200 mmol), $Y(OTf)_3$ (0.0215 g, 0.04 mmol), *N*-phenylmaleimide (0.173 g, 1.00 mmol), and toluene (0.8 mL). The reaction mixture was then heated at 140 °C for 3 d. Volatile materials were then removed from the reaction mixture under vacuum and the crude product was purified by column chromatography (1:6; EtOAc:Hex) to afford **1.60m** as a yellow solid (0.0613 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 6.5 Hz, 2H), 7.58-7.53 (m, 5H), 7.49-7.46 (m, 2H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 163.8, 161.4, 156.6, 138.9, 137.7, 136.7, 134.1, 131.5, 131.1, 130.7, 130.3, 129.1, 128.8, 128.2, 126.5, 123.9, 121.2, 115.7, 114.1, 55.4. IR (thin film) 3054, 1727, 1608, 1579, 1553, 1515, 1500, 1449, 1420, 1403; HRMS (ESI) *m/z* calcd. for $C_{27}H_{18}N_3O_3$ $(M+H)^+$ 432.1343, observed 432.1342; m.p: 197-200 °C

1.7.7 Preparation of Aldoximes 1.49a-1.49l

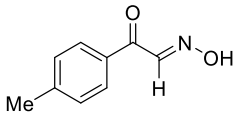


General procedure C.[42,43] A flame-dried, 50 mL round bottom flask was charged with NaH (2 equiv) and DMF (25 mL) to form a 0.3 M solution slurry. The NaH slurry was then cooled to 0 °C and a solution of an acetophenone in DMF (1 equiv, 5 mL of DMF) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C. At this time, *t*-butyl nitrite (1.1 equiv) was added dropwise and the reaction mixture was stirred for an additional 1 h at 0 ˚C. EtOAc (25 mL) was then added to dilute the reaction mixture and H_2O (15 mL) was added slowly to quench any remaining NaH. Saturated NH_4Cl solution (15 mL) was added and stirred for 5 min. The aqueous layer was then extracted with EtOAc (2 x 20.0 mL) and the organic layer was washed with brine (2 x 50.0 mL) and concentrated under vacuum. The crude product was then purified by flash chromatography (1:16 – 1:4; EtOAc:hexane).



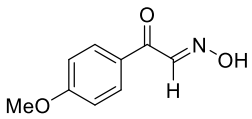
1.49a (only *E*-isomer)

Oxime 1.49a:[44-47] Oxime **1.49a** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), acetophenone (1.20 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:8; EtOAc:hexane) afforded **1.49a** as a white solid (0.648 g, 43%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.98 (s, 1H), 7.62-7.60 (m, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 188.8, 148.4, 136.3, 133.1, 129.9, 128.3. IR (thin film) 3247, 3068, 3008, 1674, 1592, 1576, 1495, 1459, 1447, 1333; HRMS (ESI) *m/z* calcd. for $C_8H_6NO_2$ $(M-H)^-$ 148.0399, observed 148.0398; m.p: 126-128 °C.



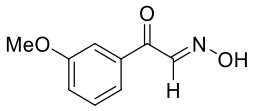
1.49b (*E*:*Z* = 3:1)

Oxime 1.49b: [44-47] Oxime **1.49b** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 4'-methylacetophenone (1.34 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:8; EtOAc:hexane) afforded **1.49b** as an white solid (0.250 g, 15%). ^{1}H NMR spectroscopy indicated an *E*:Z ratio of 3:1. ^{1}H NMR (500 MHz, acetone-d_6): δ_{major} 7.97 (d, *J* = 8.0 Hz, 2H), 7.96 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), (the O–*H* resonance was not observed); ^{1}H NMR (500 MHz, acetone-d_6): δ_{minor} 7.86 (d, *J* = 8.0 Hz, 2H), 7.61 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ_{major} 188.1, 148.4, 145.1, 133.7, 130.0, 128.9, 20.7; ^{13}C NMR (125 MHz, acetone-d_6): δ_{minor} 190.8, 145.3, 144.0, 132.7, 129.5, 129.2, 20.9; IR (thin film) 3238, 3059, 3015, 1668, 1606, 1572, 1463, 1408, 1332, 1313, 1298; HRMS (ESI) *m/z* calcd. for $C_9H_8NO_2$ $(M-H)^-$ 162.0561, observed 162.0555; m.p: 82-86 °C.



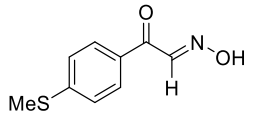
1.49c (*E*:*Z* = 3:1)

Oxime 1.49c:[42-44, 46-47] Compound **1.49c** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 4'-methoxyacetophenone (1.62 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:4; EtOAc:hexane) afforded **1.49c** as an pale yellow solid (0.784 g, 44%). ^{1}H NMR spectroscopy indicated an *E*:Z ratio of 3:1. ^{1}H NMR (500 MHz, acetone-d_6): δ_{major} 7.95-7.93 (m, 2H), 7.62 (s, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 3H), (the O–*H* resonance was too broad to be observed); ^{1}H NMR (500 MHz, acetone-d_6): δ_{minor} 8.09 (d, *J* = 8.5 Hz, 2H), 7.93 (s, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ_{major} 189.4, 164.6, 144.9, 131.5, 128.1, 114.2, 55.2; ^{13}C NMR (125 MHz, acetone-d_6): δ_{minor} 186.7, 164.6, 148.4, 132.2, 128.9, 113.5, 55.1; IR (thin film) 3168, 3041, 2844, 1658, 1595, 1569, 1511, 1471, 1421, 1322; HRMS (ESI) *m/z* calcd. for $C_9H_{10}NO_3$ $(M+H)^+$ 180.0655, observed 180.0659; m.p: 116-120 °C.



1.49d (only *E*-isomer)

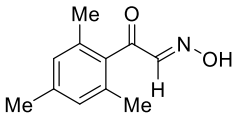
Oxime 1.49d: Compound **1.49d** was prepared by general procedure C using following reagents; NaH (0.800 g, 20.0 mmol), DMF (30.0 mL, 0.3 M), 3'-methoxyacetophenone (1.50 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography afforded **1.49d** as a pale yellow solid (0.806 g, 45%) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.57 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.19 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1, 150.7, 148.1, 147.7, 121.9, 112.6. IR (thin film) 3248, 3065, 3011, 2889, 1675, 1591, 1578, 1462, 1434, 1338; HRMS (ESI) *m/z* calcd. for $C_9H_{10}NO_3$ $(M+H)^+$ 180.0655, observed 180.0660; m.p: 110-114˚C



1.49e (*E*:*Z* = 1:1)

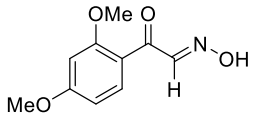
Oxime 1.49e:[48] Compound **1.49e** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL, 0.3 M), 4'-thiomethoxyacetophenone (1.66 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:8; EtOAc:hexane) afforded **1.49e** as an pale yellow solid (1.23 g, 63%, *E*:*Z* = 1:1). ^{1}H NMR (500 MHz, acetone-d_6): δ_{major} 8.01 (d, *J* = 8.5 Hz, 2H), 7.94 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 2.56 (s, 3H), δ_{minor} 7.86 (d, *J* = 8.5 Hz, 2H), 7.60 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz,

acetone-d_6): δ 190.1, 147.8, 145.0, 132.3, 129.4, 124.5, 13.65; 187.3, 148.4, 146.4, 131.4, 130.3, 124.8, 13.6; IR (thin film) 3166, 3037, 2986, 2867, 1655, 1606, 1583, 1545, 1505, 1488; HRMS (ESI) *m/z* calcd. for $C_9H_9NO_2S$ $(M-H)^-$ 194.0280, observed 194.0279; m.p: 133-136 °C.



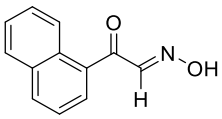
1.49f (*E*-only)

Oxime 1.49f: Compound **1.49f** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 4'-trifluoromethylacetophenone (1.88 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:16; EtOAc:hexane) afforded **1.49f** as a pale yellow solid (0.560 g, 26%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.21 (d, *J* = 8.0 Hz, 2H), 7.96 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 188.3, 148.4, 139.5, 133.3 (q, *J* = 32.1 Hz), 130.5, 125.1 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 269.6 Hz); IR (thin film) 3286, 3066, 3018, 2914, 1675, 1595, 1580, 1513, 1462, 1410; HRMS (ESI) *m/z* calcd. for $C_9H_5F_3NO_2$ $(M-H)^-$ 216.0278, observed 216.0273; m.p: 104-106 °C.



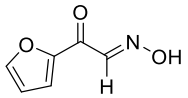
1.49g (only *E*-isomer)

Oxime 1.49g: Compound **1.49g** was prepared by general procedure C using following reagents; NaH (0.800 g, 20.0 mmol), DMF (30.0 mL, 0.3 M), 2',4'-dimethoxyacetophenone (1.62 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography afforded **1.49g** as an pale yellow solid (0.314 g, 15%) ^{1}H NMR (500 MHz, acetone-d_6): δ = 11.19 (br, 1H), 8.07 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 187.6, 164.6, 160.7, 149.2, 132.1, 120.7, 105.6, 98.3, 55.3, 55.1. IR (thin film) 3177, 2982, 1657, 1604, 1586, 1468, 1432, 1332, 1316, 1279; HRMS (ESI) *m/z* calcd. for $C_{10}H_{12}NO_4$ $(M+H)^+$ 210.0761, observed 210.0762; m.p: 127-132 ˚C



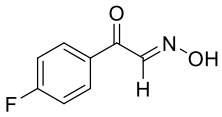
1.49h (only *E*-isomer)

Oxime 1.49h: Compound **1.49h** was prepared by general procedure C using following reagents; NaH (0.800 g, 20.0 mmol), DMF (30.0 mL, 0.3 M), 1-acetonaphthone (1.70 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography afforded **1.49h** as an pale yellow solid (0.930 g, 47%) NMR spectra indicates 1:1 ratio of (*E*)- and (*Z*)- oximes which are unknown. ^{1}H NMR (500 MHz, acetone-d_6): δ_{major} = 8.07 (d, *J* = 9.0 Hz, 2H), 7.93 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), δ_{minor} = 7.95 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 193.5, 192.8, 150.1, 146.6, 134.8, 134.6, 134.1, 133.8, 133.1, 132.0, 131.4, 130.6, 130.2, 129.5, 128.8, 128.7, 128.5, 127.5, 126.8, 126.4, 125.5, 125.3, 124.9, 124.4. IR (thin film) 3282, 3042, 3002, 1668, 1592, 1579, 1507, 1452, 1301, 1276; HRMS (ESI) *m/z* calcd. for $C_{12}H_8NO_2$ $(M-H)^-$ 198.0561, observed 198.0552; m.p: 114-120 ˚C



1.49i (*E*-only)

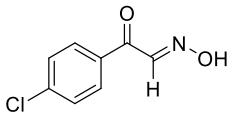
Oxime 1.49i:[49] Compound **1.49i** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 2-furyl methyl ketone (1.10 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:4; EtOAc:hexane) afforded **1.49i** as an pale yellow solid (0.221 g, 16%) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.71 (s, 1H), 7.53 (d, *J* = 3.5 Hz, 1H), 6.58 (dd, *J* = 3.5 Hz, 1.5 Hz, 1H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 150.7, 148.1, 147.7, 121.9, 112.6. IR (thin film) 3171, 3131, 3112, 3051, 2996, 2915, 2883, 2740, 1627, 1593; HRMS (ESI) *m/z* calcd. for $C_6H_6NO_3$ $(M+H)^+$ 140.0342, observed 140.0341; m.p: 115-119 °C.



1.49j (*E*-only)

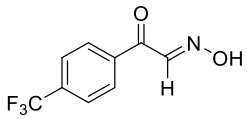
Oxime 1.49j:[44] Compound **1.49j** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 4'-fluoroacetophenone (1.38 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:10; EtOAc:hexane) afforded **1.49j** as an pale yellow solid (0.428 g, 26%) ^{1}H NMR (500 MHz, acetone-d_6): δ 8.15 (dd, *J* = 9.0 Hz, 5.8 Hz, 2H), 7.93 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 187.1, 165.6 (d, *J* = 251.0 Hz), 148.4, 132.8 (d, *J* = 37.0

Hz), 132.6, 115.2 (d, *J* = 87.5 Hz); IR (thin film) 3228, 3082, 1673, 1595, 1508, 1422, 1314, 1283, 1248, 1230; HRMS (ESI) *m/z* calcd. for $C_8H_5FNO_2$ $(M+H)^+$ 166.0310, observed 166.0307; m.p: 125-130 °C.



1.49k (only *E*-isomer)

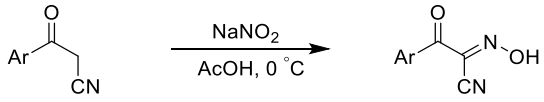
Oxime 1.49k: Compound **1.49k** was prepared by general procedure C using the following reagents; NaH (0.800 g, 20.0 mmol), DMF (30.0 mL, 0.3 M), 4'-chloroacetophenone (1.54 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography afforded **1.49k** as an pale yellow solid (0.4448 g, 24%) NMR spectra indicates 13:1 ratio of (*E*)- and (*Z*)- oximes which are unknown. ^{1}H NMR (500 MHz, acetone-d_6): δ_{major} = 8.07 (d, *J* = 9.0 Hz, 2H), 7.93 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), δ_{minor} = 7.95 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6): δ_{major} = 187.6, 148.3, 138.8, 134.8, 131.6, 128.4, δ_{minor} = 190.3, 145.0, 139.8, 133.8, 130.7, 129.1,. IR (thin film) 3235, 1668, 1584, 1568, 1450, 1399, 1322, 1290, 1248, 1181; HRMS (ESI) *m/z* calcd. for $C_8H_5ClNO_2$ $(M-H)^-$ 182.0014, observed 182.0007; m.p: 147-151 ˚C



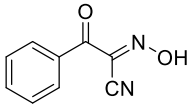
1.49l (*E*-only)

Oxime 1.49l: Compound **1.49l** was prepared by general procedure C using the following reagents: NaH (0.800 g, 20.0 mmol), DMF (30.0 mL), 4'-trifluoromethylacetophenone (1.88 g, 10.0 mmol), and *t*-butyl nitrite (1.45 mL, 11.0 mmol). Chromatography (1:16; EtOAc:hexane) afforded **1.49l** as a pale yellow solid (0.560 g, 26%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.21 (d, *J* = 8.0 Hz, 2H), 7.96 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 188.3, 148.4, 139.5, 133.3 (q, *J* = 32.1 Hz), 130.5, 125.1 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 269.6 Hz); IR (thin film) 3286, 3066, 3018, 2914, 1675, 1595, 1580, 1513, 1462, 1410; HRMS (ESI) *m/z* calcd. for $C_9H_5F_3NO_2$ $(M-H)^-$ 216.0278, observed 216.0273; m.p: 104-106 °C.

1.7.8 Preparation of Cyanooximes 1.50a-1.50k

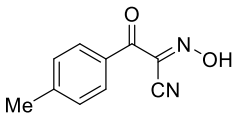


General procedure D.[50,51] A round bottom flask was charged with ketone (1 equiv) and enough AcOH to form a 2.0 M solution. The solution of ketone in AcOH was cooled to 0 °C and a solution of $NaNO_2$ (2 equiv) in 2.0 mL of H_2O was dropwise. The reaction mixture was then allowed to stir for 1 h at 0 °C. At this time, the reaction mixture was diluted with H_2O (25.0 mL) and saturated $NaHCO_{3(aq)}$ (4.0 mL), and extracted with EtOAc (3 x 25.0 mL). The organic layer was then washed with 2% $NaHCO_{3(aq)}$ (2 x 50.0 mL) and brine (2 x 50.0 mL) and concentrated under vacuum. The crude product was purified by medium pressure chromatography (1:3 – 1:1; EtOAc:hexane).



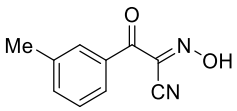
1.50a (*E*-only)

Oxime 1.50a:[50] Compound **1.50a** was prepared by general procedure D with the following reagents: benzoylacetonitrile (1.00 g, 6.89 mmol), AcOH (3.5 mL), $NaNO_2$ (0.950 g, 15.2 mmol), and H_2O (2.0 mL). Chromatography (1:4, EtOAc:hexane) afforded **1.50a** as a yellow solid (0.680 g, 56%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.90-7.88 (m, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.53-7.50 (m, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.0, 135.2, 134.0, 133.6, 130.7, 128.7, 109.5; IR (thin film) 3269, 1642, 1594, 1572, 1447, 1424, 1325, 1307, 1150; HRMS (ESI) *m/z* calcd. for $C_9H_5N_2O_2$ $(M-H)^-$ 173.0349, observed 173.0357; m.p: 122-125 °C.



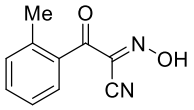
1.50b (*E*-only)

Oxime 1.50b: Compound **1.50b** was prepared prepared by general procedure D with the following reagents; 4-toluoylacetonitrile (1.59 g, 10.0 mmol), AcOH (5.0 mL), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (2.0 mL). Chromatography (1:5, EtOAc:hexane) afforded **1.50b** as an white solid (1.63 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (br, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.4, 145.8, 134.0, 131.3, 130.7, 129.3, 107.6, 21.8; IR (thin film) 3263, 3144, 2957, 1694, 1642, 1603, 1566, 1505, 1408, 1385, 1325; HRMS (ESI) *m/z* calcd. for $C_{10}H_7N_2O_2$ $(M-H)^-$ 187.0513, observed 187.0506; m.p: 136-140 °C.



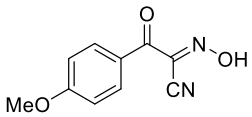
1.50c (*E*-only)

Oxime 1.50c: Compound **1.50c** was prepared nitrosation of 3-oxo-3-*m*-tolylpropanenitrile with the following reagents; 3-oxo-3-*m*-tolylpropanenitrile (0.800 g, 5.00 mmol), AcOH (2.5 mL, 2 M), $NaNO_2$ (0.690 g, 10.0 mmol) in 1.0 mL of H_2O. Chromatography afforded **1.50c** as a yellow solid (0.874 g, 93%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 9.79 (br, 1H), 7.79 (m, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 184.6, 138.6, 135.4, 133.9, 133.6, 130.9, 128.5, 127.9, 107.6, 21.2. IR (thin film) 3294, 1646, 1639, 1594, 1577, 1409, 1393, 1378, 1317, 1306; HRMS (ESI) *m/z* calcd. for $C_{10}H_7N_2O_2$ $(M-H)^-$ 187.0513 observed 187.0505; m.p: 86-94 ˚C



1.50d (*E*-only)

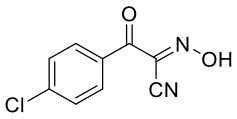
Oxime 1.50d: Compound **1.50d** was prepared nitrosation of 3-oxo-3-*o*-tolylpropanenitrile with the following reagents; 3-oxo-3-*o*-tolylpropanenitrile (0.800 g, 5.00 mmol), AcOH (2.5 mL, 2 M), $NaNO_2$ (0.690 g, 10.0 mmol) in 1.0 mL of H_2O. Chromatography afforded **1.50d** as a yellow solid (0.848 g, 90%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 9.45 (br, 1H), 7.50-7.44 (m, 2H), 7.31-7.27 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 187.5, 138.7, 134.6, 134.0, 132.5, 131.6, 130.3, 125.3, 107.3, 20.3. IR (thin film) 3194, 3137, 2982, 2931, 2839, 2257, 1666, 1601, 1569, 1539; HRMS (ESI) *m/z* calcd. for $C_{10}H_7N_2O_2$ $(M-H)^-$ 187.0513 observed 187.0508; m.p: 89-91 ˚C



1.50e (*E*-only)

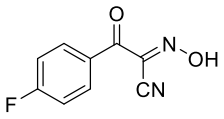
Oxime 1.50e:[50] Compound **1.50e** was prepared by general procedure D with the following reagents: 4-methoxybenzoylacetonitrile (1.75 g, 10.0 mmol), AcOH (5.0 mL), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (2.0 mL). Chromatography (1:3, EtOAc:hexane) afforded **1.50e** as a bright yellow solid (1.79 g, 87%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.04 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H), (the O–*H* resonance was too broad to

be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 182.7, 164.5, 133.6, 132.9, 127.2, 113.7, 108.4, 55.2; IR (thin film) 3250, 1630, 1572, 1508, 1457, 1440, 1424, 1379, 1328, 1309; HRMS (ESI) *m/z* calcd. for $C_{10}H_7N_2O_3$ $(M-H)^-$ 203.0462, observed 203.0456; m.p: 135-138 °C.



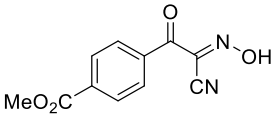
1.50f (*E*-only)

Oxime 1.50f:[50] Compound **1.50f** was prepared by general procedure D with the following reagents: 4-chlorobenzoylacetonitrile (1.59 g, 10.0 mmol), AcOH (5.0 mL), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (2.0 mL). Chromatography (1:4, EtOAc:hexane) afforded **1.50f** as an white solid (1.63 g, 87%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 183.8, 164.5, 133.6, 133.0, 127.2, 113.8, 108.4, 55.2; IR (thin film) 3220, 3148, 3105, 2989, 2848, 2251, 1675, 1652, 1583, 1563, 1506; HRMS (ESI) *m/z* calcd. for $C_9H_4ClN_2O_2$ $(M-H)^-$ 209.9967 observed 206.9959; m.p: 130-132 °C.



1.50g

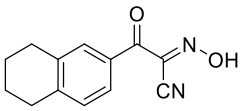
Oxime 1.50g: Compound **1.50g** was prepared nitrosation of 4-fluorobenzoylacetonitrile with the following reagents; 4-fluorobenzoylacetonitrile (1.00 g, 6.13 mmol), AcOH (3.0 mL, 2 M), $NaNO_2$ (0.842 g, 12.2 mmol) in 1.0 mL of H_2O. Chromatography afforded **1.50g** as a pale yellow solid (0.986 g, 84%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.11 (m, 2H), 7.30 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6): δ 183.4, 165.9 (d, *J* = 252.3 Hz), 133.6, 133.4 (d, *J* = 9.3 Hz), 131.3, 115.4 (d, *J* = 22.1 Hz), 108.1. IR (thin film) 3151, 2996, 2837, 2256, 1656, 1591, 1503, 1431, 1315, 1300; HRMS (ESI) *m/z* calcd. for $C_9H_4FN_2O_2$ $(M-H)^-$ 191.0262, observed 191.0252; m.p: 113-118 ˚C



1.50h (*E*-only)

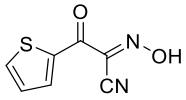
Oxime 1.50h: Compound **1.50h** was prepared prepared by general procedure D with the following reagents: methyl 4-(cyanoacetyl)benzoate (1.00 g, 4.92 mmol), AcOH (2.5 mL), $NaNO_2$ (0.678 g, 9.83 mmol), and H_2O (1.0 mL).

Chromatography (1:2, EtOAc:hexane) afforded **1.50h** as a white solid (0.828 g, 73%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.11(d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 3.92 (s, 3H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 184.8, 165.5, 138.4, 134.1, 133.8, 130.4, 129.0, 108.0, 51.9; IR (thin film) 3198, 3149, 2984, 2960, 2823, 1698, 1655, 1605, 1588, 1567; HRMS (ESI) *m/z* calcd. for $C_9H_4ClN_2O_2$ (M-H)$^-$ 209.9967 observed 206.9959; m.p: 149-152 °C.



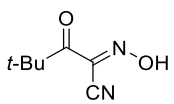
1.50i (*E*-only)

Oxime 1.50i: Compound **1.50i** was prepared by general procedure D with the following reagents: (5,6,7,8,-tetrahydro-2-naphthoyl)acetonitrile (1.00 g, 4.92 mmol), AcOH (2.5 mL), $NaNO_2$ (0.678 g, 9.83 mmol), H_2O (1.0 mL). Chromatography (1:4, EtOAc:hexane) afforded **1.50i** as a white solid (0.828 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.20 (br, 1H), 7.70 (s, 2H), 7.15 (d, J = 8.5 Hz, 1H), 2.82-2.80 (m, 4H), 1.83-1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.8, 145.3, 137.8, 133.9, 131.4, 131.3, 129.4, 127.6, 107.6, 29.8, 29.3, 22.7, 22.6; IR (thin film) 3261, 3162, 2944, 2924, 1641, 1589, 1559, 1457, 1433, 1418; HRMS (ESI) *m/z* calcd. for $C_{13}H_{11}N_2O_2$ (M-H)$^-$ 227.0826 observed 227.0819; m.p: 115-116 °C.



1.50j (*E*-only)

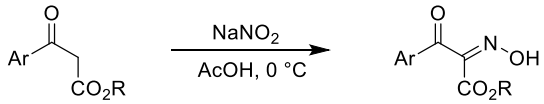
Oxime 1.50j: Compound **1.50j** was prepared by general procedure D with the following reagents: 3-oxo-3-(2-thienyl)propionitrile (1.51 g, 10.0 mmol), AcOH (5.0 mL), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (2.0 mL). Chromatography (1:4, EtOAc:hexane) afforded **1.50j** as a white solid (1.40 g, 78%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.13 (d, J = 3.5 Hz, 1H), 8.02 (d, J = 5.0 Hz, 1H), 7.25-7.24 (m, 1H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 175.6, 138.5, 137.0, 136.4, 133.4, 128.4, 107.8; IR (thin film) 3217, 3108, 3093, 3016, 1627, 1616, 1600, 1508, 1496, 1431; HRMS (ESI) *m/z* calcd. for $C_7H_3N_2O_2S$ (M-H)$^-$ 178.9921 observed 178.9912; m.p: 157-159 °C.



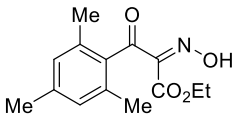
1.50k (*E*-only)

Oxime 1.50k:[52-54] Compound **1.50k** was prepared by general procedure D with the following reagents: 4,4-dimethylpentanenitrile (1.25 g, 10.0 mmol), AcOH (5.0 mL, 2 M), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (2.0 mL). Chromatography (1:8, EtOAc:hexane) afforded **1.50k** as a white solid (1.07 g, 69%). ^{1}H NMR (500 MHz, acetone-d_6): δ 1.30 (s, 9H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz, acetone-d_6): δ 197.4, 132.4, 108.0, 44.1, 26.2; IR (thin film) 3270, 2983, 1673, 1482, 1462, 1394, 1304, 1265, 1217, 1053; HRMS (ESI) *m/z* calcd. for $C_7H_9N_2O_2$ $(M-H)^-$ 153.0670 observed 153.0658; m.p: 162-177 °C.

1.7.9. Preparation of Oximes 1.48g-1.48j

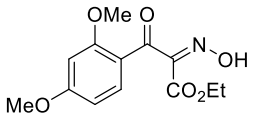


General procedure E. A round bottom flask was charged with β-ketoester (1 equiv), AcOH (10.0 mL), and NaOH (0.6 equiv). This solution was then cooled to 0 ˚C and $NaNO_2$ (2 equiv) was added dropwise as a solution in H_2O (4.0 M). The reaction mixture was then stirred for 1 h at 0 °C. At this time, the reaction mixture was diluted with H_2O (25.0 mL) and filtered over a glass frit. The precipitate was washed with H_2O (2 x 10.0 mL), 2% $NaHCO_{3(aq)}$ (2 x 10.0 mL), and brine (2 x 10.0 mL), and then dissolved in CH_2Cl_2 (X mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford oxime without further purification.



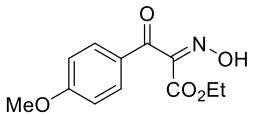
1.48g (*Z*-only)

Oxime 1.48g: Compound **1.48g** was prepared using general procedure E with the following reagents: ethyl 3-mesityl-3-oxopropanoate (1.00 g, 4.26 mmol), AcOH (2.1 mL), NaOH (0.128 g, 3.20 mmol), $NaNO_2$ (0.587 g, 8.52 mmol), and H_2O (2.0 mL). Filtration and extraction afforded **1.48g** as a white solid (0.716 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (br, 1H), 6.86 (s, 2H), 4.43 (q, *J* = 7.5 Hz, 2H), 2.29 (s, 3H), 2.28 (s, 6H), 1.39 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$): δ 194.4, 161.0, 152.0, 139.7, 134.74, 134.71, 128.4, 62.5, 21.2, 19.2, 14.1; IR (thin film) 3187, 3029, 2986, 2859, 1698, 1673, 1623, 1609, 1574, 1557; HRMS (ESI) *m/z* calcd. for $C_{14}H_{17}NNaO_4$ $(M+Na)^+$ 286.1055 observed 286.1054; m.p: 112-114 °C.



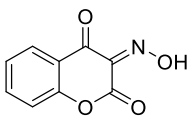
1.48h (*Z*-only)

Oxime 1.48h: Compound **1.48h** was prepared using general procedure E with the following reagents: ethyl 3-(2,4-dimethoxyphenyl)-3-oxopropanoate (1.76 g, 7.00 mmol), AcOH (4.0 mL), NaOH (0.210 g, 5.25 mmol), $NaNO_2$ (0.966 g, 14.0 mmol), and H_2O (4.0 mL). Filtration and extraction afforded **1.48h** as a white solid (1.46 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96 (br, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 6.60 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$): δ 185.6, 166.5, 162.3, 160.9, 152.2, 132.7, 118.1, 106.7, 98.2, 61.9, 55.79, 55.74, 14.0; IR (thin film) 3207, 2982, 1742, 1721, 1651, 1632, 1588, 1502, 1463, 1422; HRMS (ESI) *m/z* calcd. for $C_{13}H_{16}NO_6$ $(M+H)^+$ 282.0972 observed 282.0977; m.p: 123-125 °C.



1.48i (*Z*-only)

Oxime 1.48i:[55] Compound **1.48i** was prepared by general procedure E with the following reagents: ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (8.88 g, 40.0 mmol), AcOH (10.0 mL), NaOH (1.12 g, 28.0 mmol), $NaNO_2$ (5.52 g, 80.0 mmol), and H_2O (12.0 mL). Filtration and extraction afforded **1.48i** as a white solid (5.40 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.29 (q, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), (the O–*H* resonance was too broad to be observed); ^{13}C NMR (125 MHz $CDCl_3$): δ 188.1, 164.9, 160.8, 149.9, 131.7, 127.4, 114.4, 62.5, 55.6, 13.9; IR (thin film) 3396, 1690, 1662, 1589, 1509, 1420, 1410, 1385, 1362, 1330; HRMS (ESI) *m/z* calcd. for $C_{12}H_{13}NNaO_5$ $(M+Na)^+$ 274.0691 observed 274.0690; m.p: 98-100 °C.



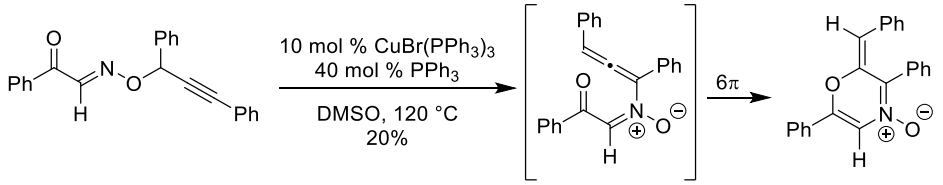
1.48j (*E*:*Z* = 5.5:1)

Oxime 1.48j: Compound **1.48j** was prepared using general procedure E with the following reagents: 4-hydroxycoumarin (1.62 g, 10.0 mmol), AcOH (5.0 mL), $NaNO_2$ (1.38 g, 20.0 mmol), and H_2O (7.0 mL). Filtration and extraction afforded **1.48j** as a dark brown solid (0.731 g, 38%). ^{1}H NMR spectroscopy indicated an *E*:Z ratio

of 6:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ_{major} 8.14 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), (the O–*H* resonance was too broad to be observed); ^{1}H NMR (500 MHz, $CDCl_3$): δ_{minor} (diagnostic peaks) 8.21 (d, *J* = 7.5 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$): δ_{major} 179.7, 155.4, 155.1, 153.5 141.2, 139.8, 128.3, 125.8, 118.4; ^{13}C NMR (125 MHz $CDCl_3$): δ_{minor} (diagnostic peaks) 137.8, 126.5, 118.0; IR (thin film) 3187, 3029, 2986, 2859, 1698, 1673, 1623, 1609, 1574, 1557; HRMS (ESI) *m/z* calcd. for $C_9H_6NO_4$ $(M\text{-}H)^-$ 190.0146 observed 190.0140; m.p: 142-145 °C.

1.7.10. Independent Generation of an α-Keto-*N*-Allenylnitrone with a *cis*-Relationship Between the Allenyl Group and the Ketone Substituent and Subsequent 6π-Electrocyclization of this Intermediate (Scheme 1.19a)

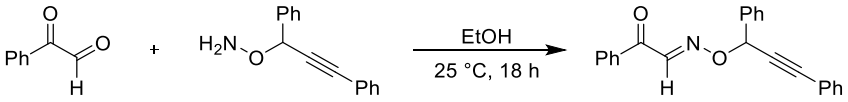
Nakamura and coworkers previously prepared *O*-propargylic oxime ethers via condensation and reported that these compounds undergo a copper-catalyzed [2,3]-rearrangement to form *N*-allenylnitrones followed by subsequent 6π-electrocyclization when the allenyl group and an α,β-unsaturated functionality are oriented on the same side of the intermediate nitrone.[16] To support our hypothesis that α-keto-*N*-alkenylnitrones (generated via a Chan-Lam reaction) with a ketone substituent and an *N*-alkenyl group in a *cis*-relationship undergo 6π-electrocyclization to form oxazines, the Nakamura method was used to independently synthesize analogous *N*-allenylnitrone intermediates.



1.62 **1.63** **1.64**

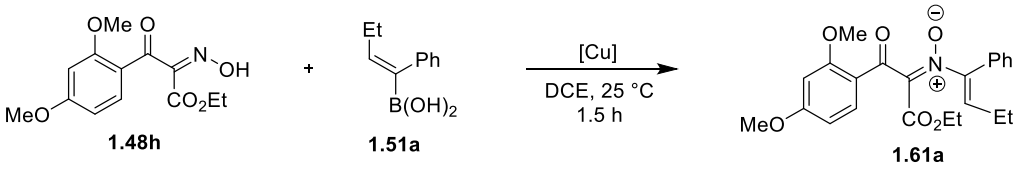
Compound 1.64:[15] A conical vial was charged with **1.62** (0.200 g, 1 equiv, 0.589 mmol), $CuBr(PPh_3)_3$ (0.0548 g, 0.1 equiv, 0.0589 mmol), and PPh_3 (0.0154 g, 0.1 equiv, 0.0589 mmol). The reaction mixture was then dissolved in 1.0 mL of DMSO, the vial was capped, and the mixture was stirred for 2 h at 120 °C. At this time, the reaction mixture was cooled to 25 °C, diluted with H_2O (3 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash column chromatography (1:3 – 1:1; EtOAc:hexane) to give a **1.64** as a deep red solid (0.0400 g, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77-7.76 (d, *J* = 6.5 Hz, 2H), 7.61-7.58 (m, 3H), 7.55-7.51 (m, 5H), 7.36-7.33 (m, 3H), 7.24-7.22 (m, 2H), 7.03 (s, 1H), 5.54 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 145.3, 137.8, 134.3, 131.2, 130.1, 129.8, 129.7, 129.3, 129.1, 128.9, 128.8, 128.5, 127.2, 125.2, 114.7, 109.5; IR (thin film) 3055,

1652, 1596, 1506, 1495, 1473, 1445, 1392, 1295, 1277; HRMS(ESI) *m/z* calcd. for $C_{23}H_{18}NO_2$ $(M+H)^+$ 340.1332, observed 130.1323; m.p: 140-142 °C.

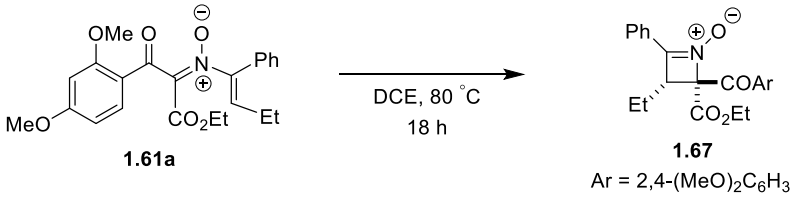


Oxime 1.62:[15] To a solution of *O*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine[15] (1.88 g, 1 equiv, 8.42 mmol) in EtOH (16.8 mL), phenylglyoxal hydrate (1.24 g, 1.1 equiv, 9.26 mmol) was added dropwise at 25 °C, and the reaction mixture was allowed to stir for 18 h. The reaction mixture was concentrated under vacuum and extracted with EtOAc (30 mL x 3 times). The EtOAc solution was washed with brine (100 mL), concentrated under vacuum, and purified by flash column chromatography (1:10 – 1:5: EtOAc:hexane) to afford **1.62** as a pale yellow liquid (1.18 g, 41%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.08 (d, *J* = 7.5 Hz, 2H), 8.01 (s, 1H), 7.73-7.72 (d, *J* = 7.0 Hz, 2H), 7.64-7.61 (m, 1H), 7.56-7.54 (m, 1H), 7.48-7.44 (m, 5H), 7.41-7.37 (m, 4H), 6.36 (s, 1H); ^{13}C NMR (126 MHz, acetone-d_6) δ 187.7, 148.0, 137.1, 135.7, 133.4, 131.7, 130.1, 129.2, 129.1, 128.6, 128.5, 128.4, 128.3, 122.1, 88.3, 86.2, 77.0; IR (thin film) 3061, 3033, 2227, 1654, 1596, 1576, 1489, 1446, 1325, 1313; HRMS(ESI) *m/z* calcd. for $C_{23}H_{17}NNaO_2$ $(M+Na)^+$ 362.1157, observed 362.1168.

1.7.11. Formation and Characterization of *N*-Alkenylnitrone and Azetidine Nitrone (Scheme 1.20)



***N*-Alkenyl nitrone 1.61a:** Compound **1.61a** was prepared from general procedure A with the following reagents: oxime **1.48h** (0.0844 g, 0.300 mmol), boronic acid **1.51a** (0.264 g, 1.50 mmol), $Cu(OAc)_2$ (0.0545 g, 0.300 mmol), Na_2SO_4 (0.300 g, 2.00 mmol), pyridine (0.0711g, 0.900 mmol), and DCE (3.0 mL). The mixture was stirred for 1.5 h at 25 °C. Chromatography (1:3; Et_2O:hexane) afforded **1.61a** as an yellow oil (0.0617 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 1H), 7.63-7.62 (m, 2H), 6.59 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 5.94 (t, *J* = 8.0 Hz, 1H), 4.15 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 3.41 (s, 3H), 2.26 (q, *J* = 7.5 Hz, 2H), 1.12-1.08 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.6, 166.0, 161.7, 158.8, 145.0, 138.9, 133.3, 129.9, 129.4, 128.7, 128.0, 118.1, 106.3, 97.9, 61.4, 55.6, 55.3, 21.3, 14.0, 13.3; IR (thin film) 3055, 2967, 2935, 2873, 2840, 1726, 1651, 1594, 1574, 1525; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_6$ $(M+H)^+$ 412.1755, observed: 412.1747



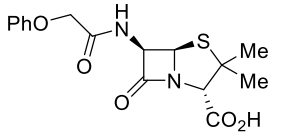
Azetidine Nitrone 1.67: Compound **1.67** was prepared with the following reagents; nitrone **1.61a** (0.0823 g, 0.2 mmol) and 1,2-dichloroethane (2.0 mL). The reaction mixture was stirred for 18 h at 80 °C. Chromatography afforded **1.67** as an white solid (0.0774 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95-7.94 (m, 2H), 7.77 (d, 1H, *J* = 9.0 Hz), 7.38-7.36 (m, 3H), 6.52 (dd, 1H, *J* = 9.0 Hz, 2.0 Hz), 6.47 (d, 1H, *J* = 2.0 Hz), 4.34-4.29 (m, 2H), 3.97 (dd, 1H, *J* = 10.0 Hz, 4.5 Hz), 9.90 (s, 3H), 3.84 (s, 3H), 2.10-2.01 (m, 1H), 1.82-1.72 (m, 1H), 1.28 (t, 3H, *J* = 7.5 Hz), 1.15 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.6, 165.7, 164.3, 162.1, 152.4, 133.5, 130.3, 128.5, 127.3, 126.6, 118.8, 106.1, 98.1, 93.6, 62.0, 55.5, 55.2, 44.1, 20.2, 14.1, 12.4. IR (thin film) 3057, 2974, 2938, 2879, 2840, 1743, 1658, 1596, 1500, 1463; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_6$ $(M+H)^+$ 412.1755, observed 412.1757; m.p: 42-50 ˚C

Chapter 2. Synthesis and Functionalization of Azetidine Nitrones

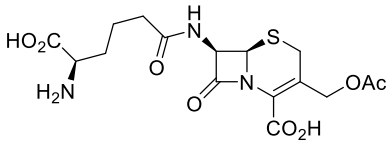
2.1 Introduction

N-Heterocyclic scaffolds are commonly found in natural products and marketed pharmaceuticals. Within this class of privileged molecules β-lactams have been extensively targeted for their antibiotic properties.[56-58] One example is penicillin V (2.1), known as phenoxymethylpenicillin (Scheme 2.1). It was first prepared in 1959 after Fleming's historical discovery in 1929, and is the first antibiotic to show activity against to a variety of pathogenic species.[59-61] In clinical uses, it is prescribed for the treatment of diseases such as dental abscesses, anthrax, and streptococcal skin infections. Similarly, cephalosporin C (2.2) is another β-lactam that was isolated and characterized by Newton and Abraham and exhibits significant antibacterial activity.[62-65] Azetidines that are not β-lactams have been studied less extensively.[66-71] Mugineic acid **2.3** was isolated from water-cultured oats and exhibits iron-chelating abilities for the transport of iron in plants.[66] Gelsemoxonine **2.4** was isolated from the leaves of *Gelsemium elegans* and its structure was initially proposed without the presence of the azetidine backbone.[67] Later, the structure of gelsemoxonine was fully revised with the help of X-ray crystallographic analysis.[68] The *Gelsemium* alkaloids show intriguing potent cytotoxicity.[69] Penaredisin A, an azetidine alkaloid, was extracted from Okinawan marine sponge *Penares sp.*.[70,71] This four-membered ring alkaloid shows actomyosin ATPase-activating activity.[72] As described above, azetidines are an important scaffold in molecules with a variety of biological properties. Due to a limited number of methods to access these compounds, know synthetic examples tend to lack structural complexity.

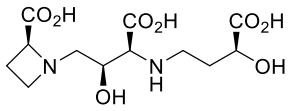
Scheme. 2.1. Azetidine-Containing Natural Products and Biologically Active Molecules



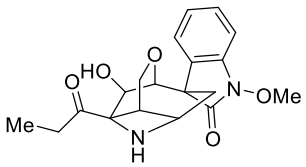
2.1
Penicillin V



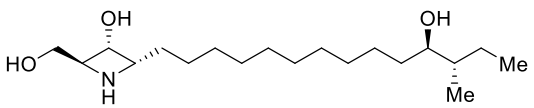
2.2
Cephalosporin C



2.3
Mugineic Acid

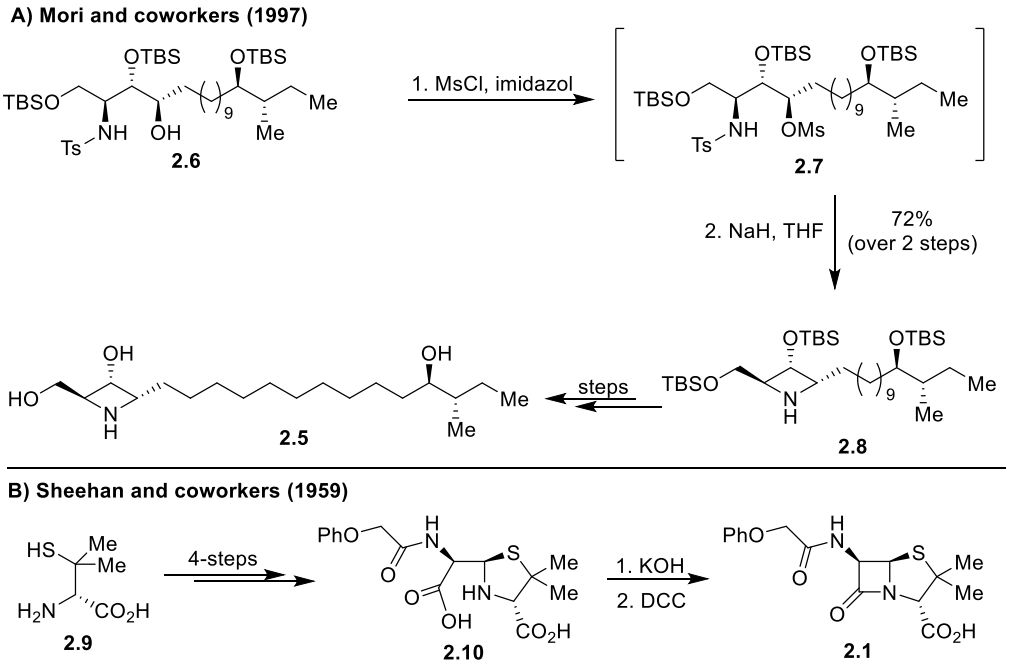


2.4
Gelsemoxonine



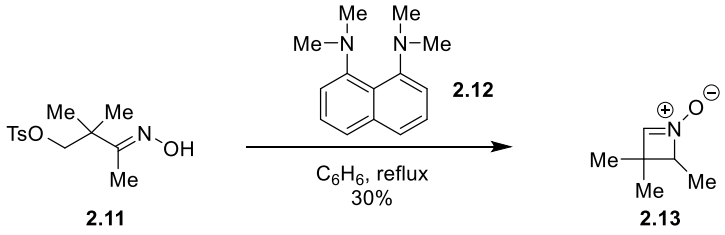
2.5
Penaresidin A

Scheme. 2.2. Preparation of Azetidines Using Base-Promoted Displacement Reactions[72-73]



One of the most widely applied methods for the synthesis of azetidines is intramolecular nucleophilic displacement. As shown in Scheme 2.2A, Mori and coworkers utilized this transformation for synthesis of Penaresidin A **2.2**.[72] 1,3-Aminoalcohol **2.6** was mesylated to install a good leaving group and then treatment of **2.7** with NaH promoted an intramolecular nucleophilic substitution to afford **2.8**. Using a similar strategy, Sheehan and Henery-Logan reported the preparation of penicillin V **2.1** (Scheme 2.2B) using the DCC promoted amide formation illustrated in Scheme 2.2.[73] While effective, these displacement processes are often hindered by sterics, require multiple step reaction sequences and require pre-installation of defined stereocenters.

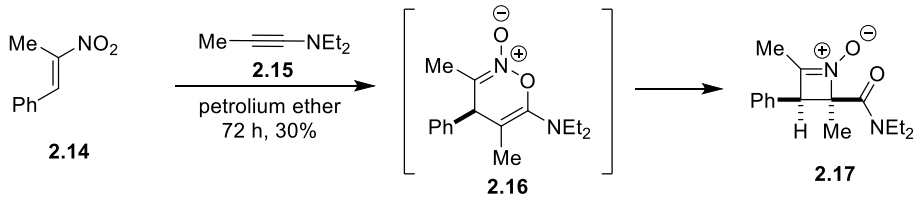
Scheme 2.3. Base-Mediated Synthesis of Azetidine Nitrone [74]



Azetidine nitrones are rare examples of azetidines but interesting to consider as synthetic intermediates due to their potential for functionalization. The first azetidine nitrone synthesis was reported by the Brown group in 1974.[74] When screening reaction parameters, they prepared an azetidine nitrone **2.13** by cyclization of an oxime **2.11** in the

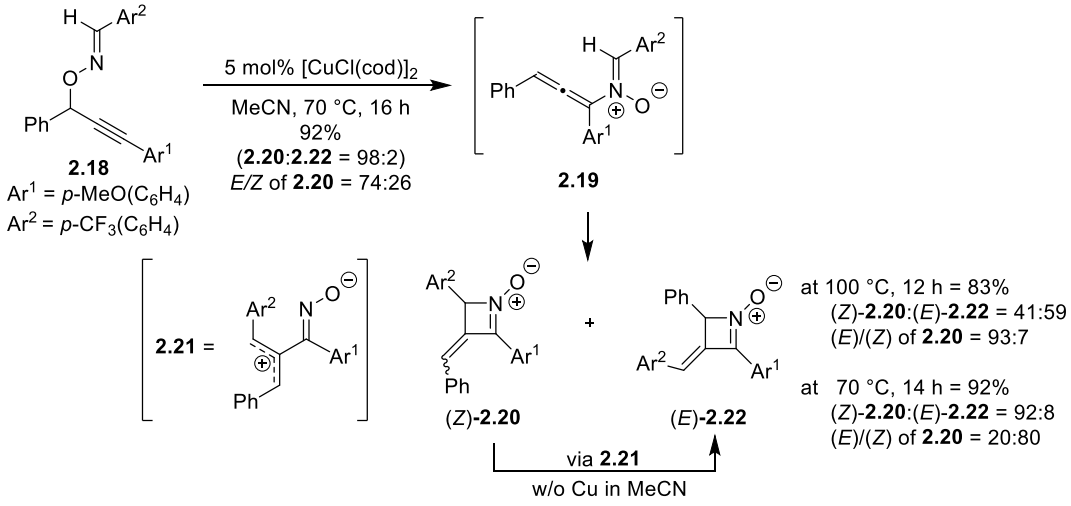
presence of **2.12** in benzene as an optimal condition. While examples of base and substrate, this study is indispensable starting point to explore azetidine nitrones via nucleophilic displacement process even if the transformation requires less sterically hindered substrates.

Scheme 2.4. Azetidine Nitrone through a Cycloaddition and Rearrangement Process [75]



Beyond displacement reactions, the synthesis of azetidine nitrones was approached via a cycloaddition and ring-contraction in the Reinhoudt group.[75] Nitroalkene **2.14** was added to alkynyl amine **2.15** to generate [4+2]-cycloaddition products **2.16** that spontaneously undergoes *N–O* bond cleavage rearrangement to give azetidine nitrone **2.17**. These researchers proposed a possible concerted mechanism for the formation of azetidine nitrone **2.17** where the *N–O* cleavage occurs via a [1,3]-rearrangement. This study enables to prepare examples of azetidine nitrones with multiple substituents bearing stereocenters from two achiral motifs **2.14** and **2.15** by avoiding traditional nucleophilic displacement method that requires less sterics.

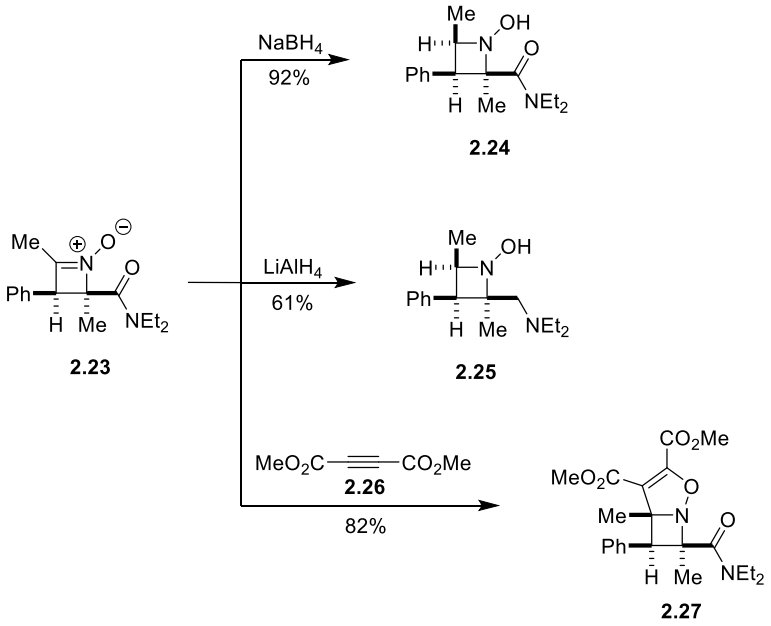
Scheme. 2.5. Azetidine Nitrone Synthesis from *O*-Propargylic Oximes [76]



Terada and coworkers also reported that azetidine nitrones can be prepared from *O*-propargylic oximes via a [2,3]-rearrangement and electrocyclization sequence.[76] They optimized a copper-catalyzed system for the synthesis of

2.19 from **2.18** and a subsequent 4π-electrocyclization of **2.19** to give (*Z*)-**2.20** and (*E*)-**2.22**, respectively. This reaction system gives low regioisomers of azetidine nitrones. Further investigations for isomerization, they observed the conversion of (*Z*)-**2.20** to (*E*)-**2.22** at 70 °C for 14 h. Interestingly, when the substrate was exposed to higher temperature (100 °C), increased formation of (*E*)-**2.22** was found. Changing This study shows that azetidine nitrones can be prepared by 4π-electrocyclization of *N*-vinylnitrones and that azetidine nitrones are not thermally stable due to thermal isomerization. In short, [2,3]-rearrangement / electrocyclization cascade of alkyne-containing oxime ethers provides a promising insight for azetidine nitrone synthesis.

Scheme 2.6. Conversion of Nitrones to Azetidines[77,78]



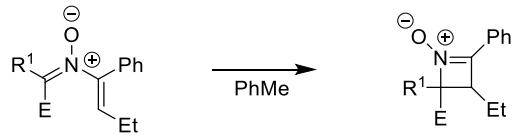
Although several syntheses of azetidine nitrones have been reported, little is known about the reactivity of these compounds. Reinhoult and coworkers initially established that **2.23** underwent several different transformations to form saturated azetidines.[77,78] Firstly, mild hydride reduction of azetidine nitrone **2.23** with $NaBH_4$ gave *N*-hydroxyazetidine **2.24**. This reactivity is similar from unstrained nitrones which suggests selective hydride addition to nitronium center. Moreover, $LiAlH_4$, was shown to reduce both the nitrone and the amide to give azetidine product **2.25**. Lastly, azetidine nitrone **2.23** underwent a cycloaddition with dimethylacetylene dicarboxylate (DMAD) to give fused bicyclic azetidine **2.27**. These preliminary explorations of azetidine nitrones towards azetidines motivated us to investigate further reductions and cycloadditions of azetidine nitrones.

2.2 Synthesis of Azetidine *N*-oxides Though the 4π-Electrocyclization of *N*-Vinylnitrones

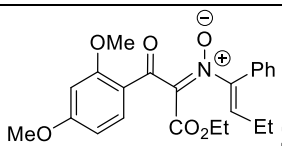
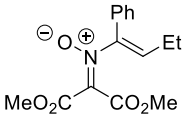
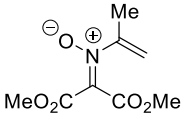
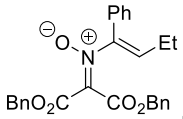
While exploring the 6π-electrocyclization of α-keto-*N*-vinylnitrones, we observed the formation of a new heterocycle when isolated *N*-vinylnitrone **2.28a** was heated in the absence of a copper salt. This observation led us to propose that *N*-vinylnitrones can undergo both 6π- and 4π-electrocyclization processes (Scheme 1.20). The development of a general method for the synthesis of azetidine nitrones from **2.32** and **2.35** was led by my labmate Tyler Reidl. I contributed to the project by initially identifying the 4π-electrocyclization product and by assisting Tyler in expanding the scope of the reaction.

To begin looking at the tolerance of the 4π-electrocyclization of *N*-vinylnitrone for the synthesis of azetidine nitrones, several *N*-vinylnitrones were tested to determine which type of substitution pattern functioned best for the desired product formation (Table 2.1). Preliminarily, *N*-vinylnitrone **2.28a** prepared from ketoester oxime afforded azetidine *N*-oxide **2.32a** formation in excellent yield (entry 1). An analogous transformation was observed for *N*-vinylnitrone **2.29a** (entry 2). *N*-Vinylnitrone **2.30a** prepared from methyl malonate and 1-methylvinylboronic acid, unfortunately, did not participate in the desired transformation. Also, no reaction was observed from benzyl malonate-derived *N*-vinylnitrone **2.31a** (entry 4). These initial screening of *N*-vinylnitrones indicated that 4π-electrocyclization process requires 1-phenyl and 2-alkyl groups on *N*-vinyl motif as well as esters with less sterically hindered alkyl groups.

Table 2.1. Azetidine Nitrones from *N*-Vinylnitrones Under Thermal Condition



2.28a - 2.31a **2.32a - 2.35a**

Entry	*N*-Vinylnitrone	Azetidine *N*-Oxide	T (°C)	Time (h)	% Yield[a]
1	 **2.28a**	**2.32a**	80	18	94
2	 **2.29a**	**2.33a**	80	18	92
3	 **2.30a**	**2.34a**	80	18	N.R
4	 **2.31a**	**2.35a**	80	18	N.R

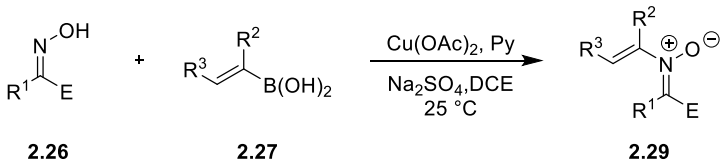
[a] Percent isolated yield

2.3 Preparation of *N*-Vinylnitrones through Copper Mediated C–N Bond Formation

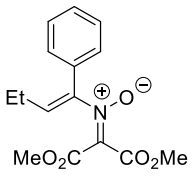
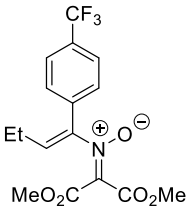
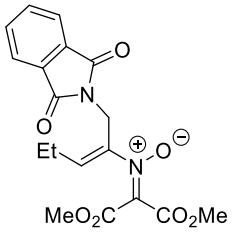
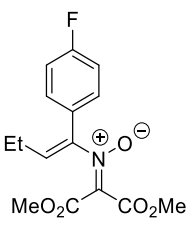
As we observed that *N*-vinylnitrones **2.32a** and **2.33a**, prepared from oximes and a boronic acid, showed 4π-electrocyclization reactivity to azetidines (Table 2.1), we anticipated the preparation of *N*-vinylnitrones **2.29** could be performed initially using Chan-Lam coupling condition before screening for 4π-electrocyclization reactivity of **2.29** (Table 2.2).[24] Treatment of methyl malonate-derived oxime with 1-phenyl-2-ethylvinylboronic acid **2.27a** gave an excellent reactivity for *N*-vinylnitrone **2.29a** formation (entry 1). In addition to **2.27a**, 1,2-dialkylvinylboronic acids **2.27b** and **2.27c** were treated to provide corresponding *N*-vinylnitrones **2.29b** and **2.29c** in moderate yield (entry 2 and 3). These results from 1,2-dialkylvinylboronic acids **2.27b** and **2.27c** indicated broader scope of **2.27** beyond 1-aryl-2-alkylvinylboronic acid. Changing alkyl group on 2-positoin of vinylboronic acid **2.27d** with a larger secondary alkyl group bearing a secondary carbon stereocenter at the 2-position also demonstrated C–N bond formation, implying that sterically hindered alkyl group showed slightly diminished reactivity (entry 4).

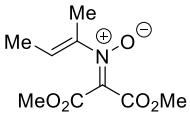
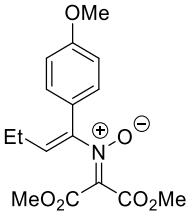
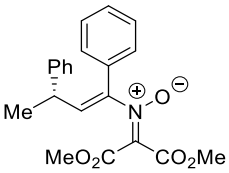
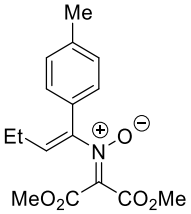
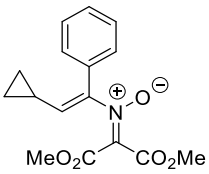
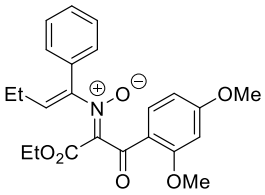
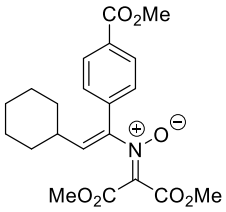
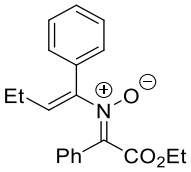
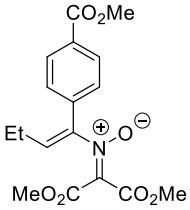
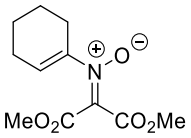
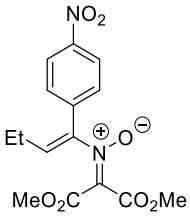
Unfortunately, 2-cyclopropyl-substituted vinylboronic acid did not exhibit *N*-vinylnitrone **2.29e** formation (entry 5). On the other hand, vinyl boronic acid **2.27f** with a cyclohexyl substituent and an electron-deficient aryl group showed the expected *N*-vinylnitrone **2.29f** formation (entry 6). Further screenings using 1-aryl-2-ethylvinylboronic acids revealed that both electron-rich and electron-poor substituents on aryl group were tolerated in this reaction, providing *N*-alkenylnitrones **2.29g**–**2.29l** in high yields (entry 7-12). Interestingly, analogous *N*-vinylnitrones **2.29m** and **2.29n** were observed using other oxime scopes which are prepared from *β*-ketoester and *α*-phenyl ethyl ester (entry 13 and 14). Cyclic 1,2-dialkylvinylboronic acid **2.27m** also afforded desired *N*-vinylnitrone **2.29o** in good yield (entry 15). From these investigations, oximes with 1-aryl-2-alkylvinylboronic acids as well as 1,2-dialkylvinylboronic acids showed an excellent C–N bond coupling reactivity, affording examples of *N*-vinylnitrones except for a vinylboronic acid with cyclopropyl substituent on 2-position. Both electron-rich and electron-deficient 1-aryl-2-alkylvinylboronic acids successfully produced *N*-vinylnitrones in high yield, however, the sterically encumbered secondary substituent on 2-position gave relatively lower yield. These *N*-vinylnitrones, prepared from C–N bond formation, were envisioned on screening for reactivity of electrocyclization (Table 2.4). We first investigated the optimization study to seek the best reaction condition for a desired azetidine nitrone (Table 2.3).

Table 2.2. Scope of Oximes and Boronic Acids for Oxime *N*-Vinylation



2.26 **2.27** **2.29**

Entry[a]	Nitrone	Yield (%)[b]	Entry[a]	Nitrone	Yield (%)[b]
1	 **2.29a**	95[d]	9	 **2.29i**	86
2		40[d]	10		85

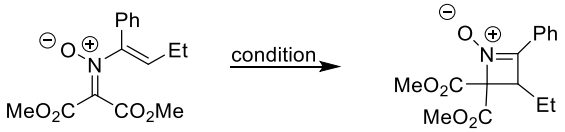
	2.29b			**2.29j**	
3	 **2.29c**	56[d]	11	 **2.29k**	75
4[d]	 **2.29d**	57	12	 **2.29l**	77
5	 **2.29e**	-[c] [d]	13	 **2.29m**	50[d]
6	 **2.29f**	83[d]	14	 **2.29n**	63
7	 **2.29g**	75			
			15	 **2.29o**	73[d]
8	 **2.29h**	76			

[a] Conditions: oxime **2.26** (1 equiv), vinylboronic acid **2.27** (5 equiv), Py (3 equiv), Na_2SO_4 (8.5 equiv), 0.1 M in DCE, 25 ˚C, air, 18 h. Py = pyridine, DCE = 1,2-dichloroethane. [b] Percent yield of isolated yield. [c] Azetidine nitrone **2.33o** from **2.29e** was observed in 82% yield. [d] I contributed to screening and isolation of these compounds. A coworker, Tyler Reidl, was primarily contributed to all compounds in this table.

2.4 Optimization and Preparation of Azetidine Nitrones

The 4π-electrocyclization of *N*-vinylnitrone **2.29a** was optimized for the synthesis of **2.33a** by differentiating the choice of solvent, temperature and reaction time (Table 2.3). A solvent screen of PhMe, THF, DCE, *i*-PrOAc, *p*-$CF_3(C_6H_4)$, DMSO and MeOH indicated that the transformation was highly solvent tolerant but optimal reactivity was observed in DMSO and MeOH (entry 1-7). Further optimization was pursued in MeOH. Further temperature screenings were investigated, which study exhibited that temperature attenuation into 40 ºC might be a better selection, introducing less harsh condition than 60 ºC (entry 8-10). On top of that, it was shown that the reactions treated with shorter reaction time yielded a product in lower yield, implying 18 h was the best reaction time (entry 11-12). Accordingly, an optimization study for a synthesis of azetidine *N*-oxide from *N*-vinylnitrone was successfully accomplished by varying reaction parameters. Additional optimization was also tested with *N*-vinylnitrone **2.29c**. Surprisingly, this substrate was more sensitive to changes in reaction conditions (Table 2.4).

Table 2.3. Optimization of the 4π-Electrocyclization of *N*-Vinylnitrones

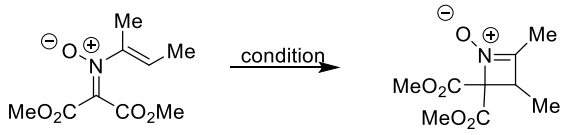


2.29a **2.33a**

Entry	Solvent	T (°C)	Time (h)	% Yield[a]
1	PhMe	80	18	92
2	THF	80	18	94
3	DCE	80	18	98
4	*i*-PrOAc	80	18	97
5	*p*-$CF_3(C_6H_4)$	80	18	97
6	DMSO	80	18	100
7	MeOH	80	18	100
8	MeOH	60	18	100
9	MeOH	40	18	95
10	MeOH	25	18	60
11	MeOH	40	8	72
12	MeOH	40	4	65

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

Table 2.4. Optimization of the 4π-Electrocyclization of *N*-1,2-Dialkylinylnitrones



2.29c **2.33c**

Entry	Solvent	T (°C)	Time (h)	% Yield[a]
1	MeOH	40	18	97
2	MeOH	40	8	31
3	MeOH	25	18	39
4	MeOH	60	18	0
5	PhMe	40	18	18
6	DMSO	40	18	46
7	*i*-PrOAc	40	18	11
8	DCE	40	18	49
9	MeCN	40	18	49

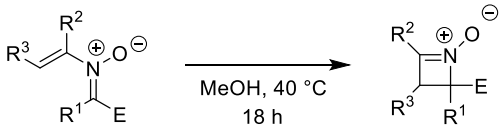
[a] Yield was determined by ^{1}H NMR using CH_2Br_2 as a reference

2.5 Scope of Azetidine *N*-Oxide Synthesis via 4p-Electrocyclization of *N*-Vinylnitrones

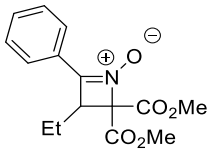
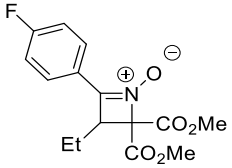
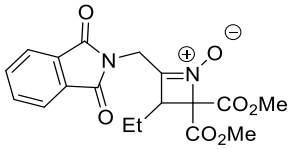
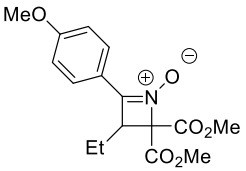
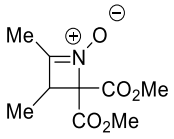
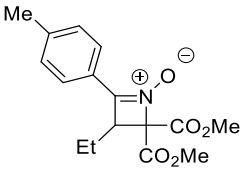
The scope of the synthesis of azetidine *N*-oxides **2.33** through the 4π-electrocyclization of *N*-vinylnitrones **2.29** was explored using the substrates described in Table 2.5. Electrocyclization of nitrone **2.29a** with a 1-phenyl-2-ethyl *N*-substituent afforded an azetidine nitrone **2.33a** in an excellent yield (entry 1). It was surprising that 1,2-dialkyl substituted *N*-vinylnitrones such as **2.29b** and **2.29c** also gave azetidine nitrones **2.33b** and **2.33b** in high yields (entry 2). Also, methyl ester substituent on aromatic system appeared a reactive substrate for a desired azetidine nitrone **2.33d** (entry 4). However, diminished reactivity was resulted, which reason might be bulkier cyclohexyl group on 2-position (entry 5). Further examples bearing electron withdrawing substituents such as nitrobenzene and benzonitrile on 1-position showed readily available reactivity towards azetidine *N*-oxides **2.33f** and **2.33g** (entry 6 and 7). Also, changing substituents with fluorine, methoxy, and methyl substituents were excellent choices for this transformation (entry 8-10). Interestingly, *N*-alkenylnitrones from β-ketoester and α-phenyl ethyl acetate yielded desired azetidine *N*-oxides **2.33k** and **2.33l** in 95% yield respectively (entry 11 and 12). These results indicate extended oxime scopes beyond malonate-derived oxime. It was excited to observe that *N*-vinylnitrone bearing an inherent stereocenter on 2-position displayed an identical transformation quantitatively (entry 13). Beyond two acyclic 1,2-dialkyl substituents on *N*-vinyl motifs, we tested and observed that *N*-cyclohexenyl nitrone **2.29o** didn't provide any of azetidine nitrone product **2.33n** (entry 14). Instead, 31% of isoxazolidine **2.36a** was observed as a

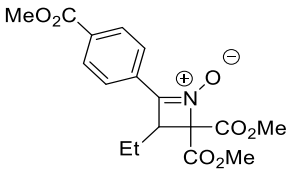
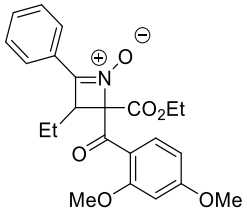
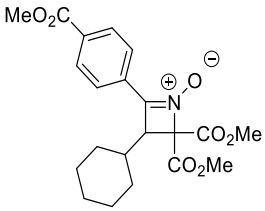
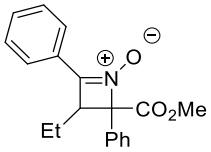
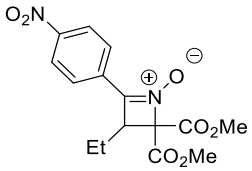
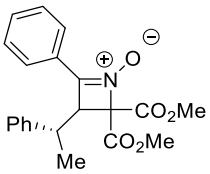
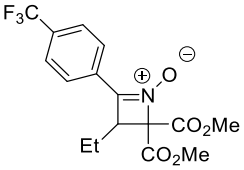
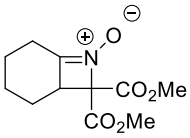
major product (Scheme 2.7). We speculated that methanol solvent might be added to nitronium carbon center during this unknown transformation. By this hypothesis, further experiments produced complex isoxazolidine **2.36b** were observed using ethanol as a solvent under similar thermal condition (Scheme 2.7). Even if an exact mechanism of this transformation is not clear, the formation of isoxazolidines can be explained by a plausible pathway that involves 4π-electrocyclization of *N*-vinylnitrone, ring-expansion due to a ring-strain and addition of an alcohol. The relative stereochemistry of **2.36b** was confirmed by X-ray crystallographic analysis by prof. Donald Wink (Figure 2.1). These results showed that the 4π-electrocyclization tolerated acyclic types of groups at the *N*-vinyl position of the nitrone. This trend suggested electron-rich substituents on aryl group favor electrocyclization about the reaction. A coworker, Tyler Reidl, contributed to investigations and isolations for azetidine nitrones in Table 2.5, and my contribution was to screen for electrocyclization reactivity of *N*-vinylnitrones **2.29b**, **2.29c**, **2.33e**, and **2.33n** and to isolate them.

Table 2.5. Scope of Oximes and Boronic Acids for the Synthesis of Azetidine Nitrones from *N*-Vinylnitrones



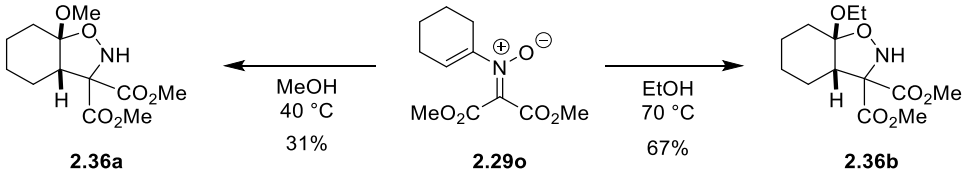
2.29 **2.33**

Entry	*N*-Vinylnitrone	% Yield[a]	Entry	*N*-Vinylnitrone	% Yield[a]
1	 **2.33a**	98	8	 **2.33h**	93
2	 **2.33b**	98	9	 **2.33i**	95
3	 **2.33c**	90	10	 **2.33j**	95

4	 **2.33d**	93	11	 **2.33k**	95
5	 **2.33e**	45	12	 **2.33l**	94
6	 **2.33f**	83	13	 **2.33m**	97
7	 **2.33g**	94	14	 **2.33n**	[b]

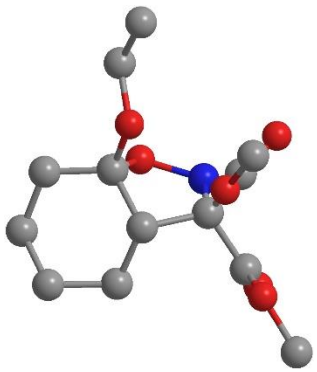
[a] Percent yield of isolated yield. [b] 31% of Isoxazolidine was observed.

Scheme 2.7. Isoxazolidine Formation From *N*-Vinylnitrones



2.36a **2.29o** **2.36b**

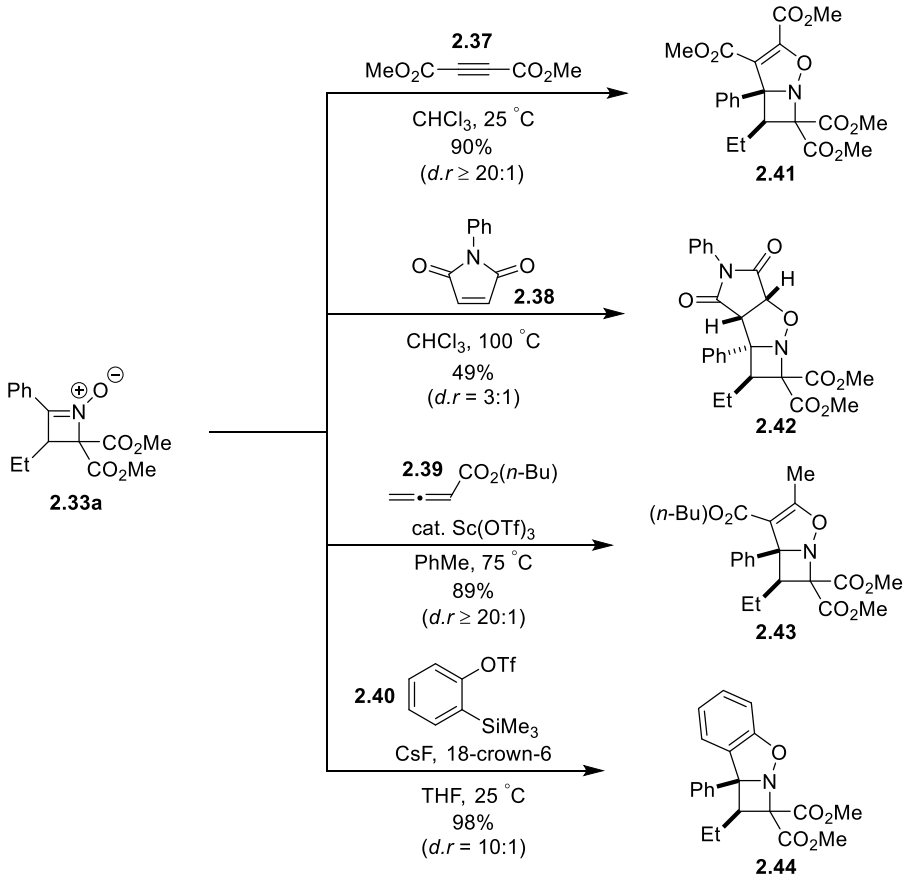
Figure 2.1. X-Ray Crystallography of **2.36b** by Prof. Donald J. Wink



2.6 Functionalization of Azetidine Nitrones

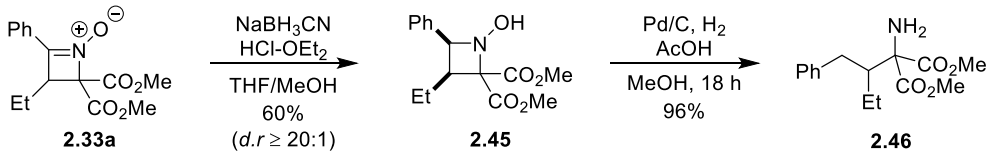
Development of a new modular method for the synthesis of azetidine nitrones, provided the opportunity to investigate the reactivity of these molecules for the divergent synthesis of highly-substituted azetidines as a solution to the challenges with traditional approaches using nucleophilic displacement. We wondered if azetidine nitrones could be transformed into highly-substituted azetidines through cycloaddition, reduction, and alkylation. The robust method for the synthesis of azetidine nitrones described above made this study possible. While this study was primarily done by my labmate Tyler Reidl, it has been included in this chapter to emphasize the broader impact of this work.

Scheme 2.8. [3+2]-Cycloaddition of Azetidine Nitrone



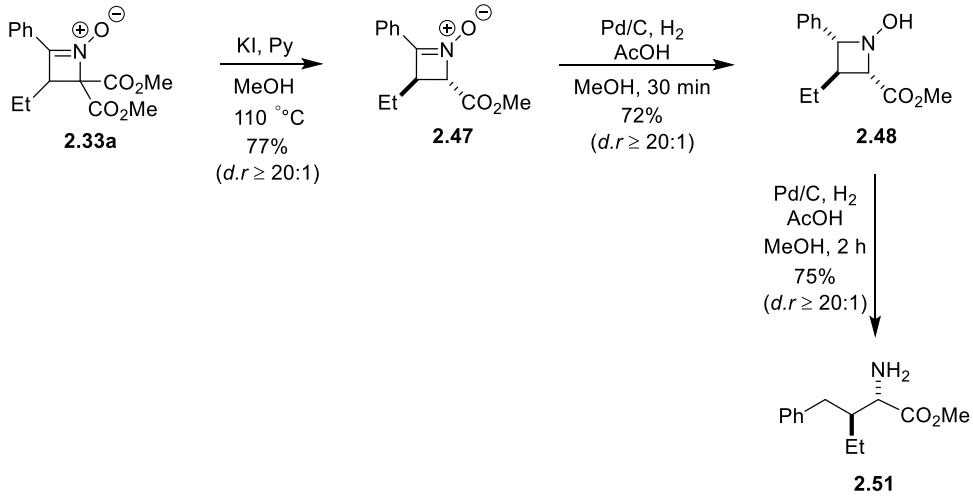
1,3-Dipolar cycloadditions of azetidine nitrone **2.33a** were screened with different dipolarophiles to access complex fused-azetidine systems (Scheme 2.5). Treatment of **2.33a** with DMAD resulted in **2.41** in good diastereoselectivity. In contrast, treatment of **2.33a** with *N*-phenylmaleimide required harsh reaction condition for the formation of **2.42** in moderate yield with low diastereoselectivity. Allenoate **2.39** was also shown to successfully undergo cycloaddition with **2.33a** in the presence of a $Sc(OTf)_3$ catalyst to afford **2.43** with an excellent diastereoselectivity. Lastly, the [3+2]-cycloaddition of **2.33a** with an in situ generated benzyne intermediate also showed smooth formation of **2.44** with good diastereoselectivity. All of these stereochemical relationships were identified by nOe experiments. These results indicated that cycloadditions of azetidine nitrones **2.33a** can be leveraged to rapidly produce a variety of sophisticated fused-azetidines.

Scheme 2.9. Reduction of Azetidine Nitrones and Reductive Ring-Opening

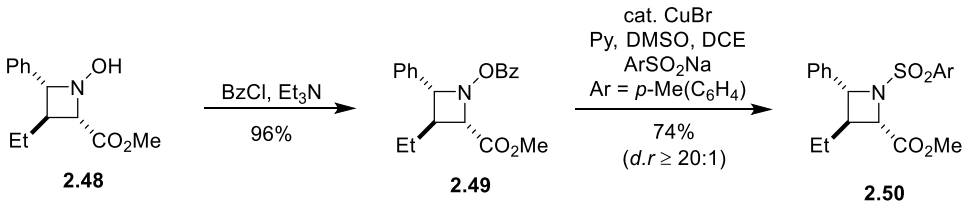


Different types of reductions of azetidine nitrone **2.33a** were tested for selectivity with respect to azetidine formation, ring-opening and deoxygenation (Scheme 2.6). The mild-reducing agent $NaBH_3CN$ selectivity reduced the nitrone functionality of **2.33a** to give azetidine **2.45**. It was also confirmed by ^1H NMR spectroscopy nOe studies that hydride was added to less sterically encumbered side of **2.33a** in high diastereoselectivity. Catalytic hydrogenation conditions did not exhibit deoxygenation as observed for 1,4-morpholine *N*-oxides X.X and X.X but instead showed reductive ring-opening process **2.45** to give aminoester **2.46**. Further exploration of the reactivity of **2.33a** showed that stereoselective carbodealkoxylation could be achieved to form **2.47** (Scheme 2.7). Interestingly, hydrogenation of **2.47** gave *N*-hydroxyazetidine **2.48** in good yield without erosion of the diastereoselectivity achieved in the decarboalkoxylation reaction. Hydrogenation of **2.48** also gave amine **2.51**.

Scheme 2.10. Reduction of Azetidine *N*-Oxide and Reductive Ring-Opening

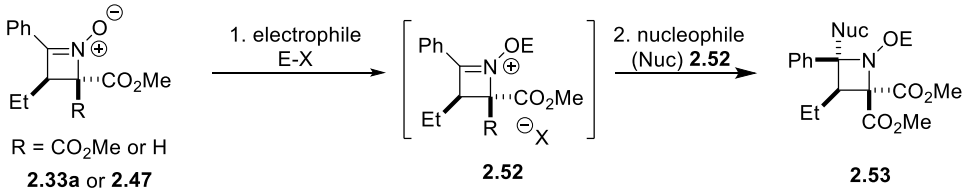


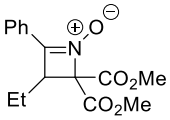
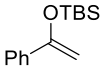
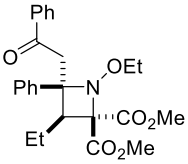
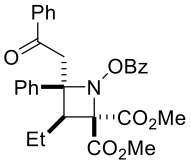
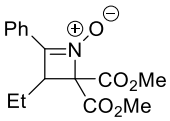
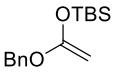
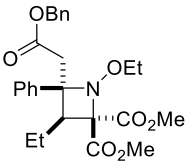
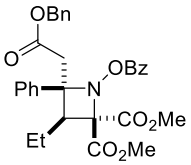
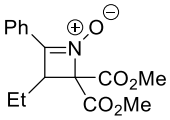
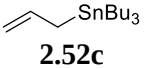
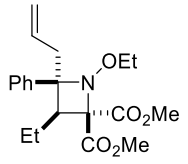
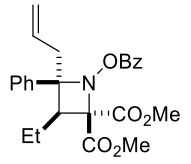
Scheme 2.11. *N*-Sulfination of Azetidine **2.49**

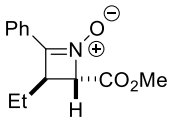
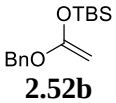
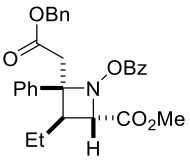
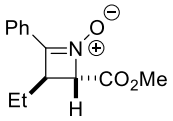
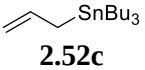
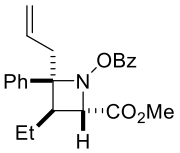


Beyond the potential of **2.33a** to undergo selective reductions, **2.48**, was also tested for potential methods to exchange the *N*-substituent. As shown in Scheme 2.8 when dealkoxycarbonylated compound **2.48** was treated with benzoyl chloride followed by sodium sulfite, exchange of the benzoyl group was observed to give *N*-tosylazetidine **2.50**. This straightforward *N*-functionalization further diversifies the options able for prepared various substituent azetidines from **2.33**.

Table 2.6. Alkylation of Azetidine Nitrones **2.33** and **2.47**



Entry	Nitrone	Nucleophile	Product (*O*-ethylation or *O*-Benzoylation)	
1		 **2.52a**	 **2.53a**[b] 69%, *d.r* ≥ 20:1	 **2.53b**[c] 70%, *d.r* ≥ 2:1
2		 **2.52b**	 **2.53c**[b] 97%, *d.r* ≥ 20:1	 **2.53d**[c] 73%, *d.r* ≥ 4:1
3		 **2.52c**	 **2.53e**[b] 72%, *d.r* ≥ 20:1	 **2.53f**[c] 95%, *d.r* ≥ 1:1

4		 **2.52b**		**2.53g**[c]: 73%, *d.r* ≥ 20:1
5		 **2.52c**		**2.53h**[c]: 85%, *d.r* ≥ 20:1

[a] Conditions: **2.33a** or **2.47** (1 equiv) in 0.1 M CH_2Cl_2. [b] Electrophile, $[Et_3O][BF_4]$ (1.1 equiv), was added at 25 °C and stirred for 30 min [c] Electrophile, BzCl (2 equiv), was added with AgOTf (4 equiv) at 0 °C and stirred for 30 min.

Further derivatization of **2.33a** and **2.47** was explored using alkylation reactions. Addition of carbon nucleophiles to **2.33a** was unproductive without an activating agent; however, pretreatment of **2.33a** with either Meerwein's salt or benzoyl chloride promoted the addition of enol silyl ether **2.52a**, silyl ketene acetal **2.52b**, and allylstannane to produce *N*-ethoxy- and *N*-benzoyloxy azetidines **2.53a-2.53f** in good yields (Table 2.6, Entries 1-3). The use of Meerwein's salt resulted in excellent diastereoselectivity for the addition of all nucleophiles. In contrast, the use of in situ generated BzOTf as an activator exhibited an erosion of diastereoselectivity (Table 2.6, Entries 1-3). A plausible explanation for this is the presence of bulky gem-diesters and benzoyl group. We were pleased to find that less crowded azetidine **2.47** gave corresponding highly-substituted azetidines **2.53g** and **2.53h**, accompanying high diastereoselectivity in these transformations (Table 2.5, Entries 7 and 8). These transformations showed that azetidine nitrones **2.33a** or **2.47** can be easily functionalized to form azetidines with defined relative stereochemistry.

In conclusion, we were successfully able to prepare a wealth of complex azetidines throughout diastereoselective functionalizations of azetidine nitrones. Reaction screenings of azetidine nitrone **2.33a** with DMAD, *N*-phenylmaleimide, allenoate, or benzyne resulted in fused-azetidines in high yields through 1,3-dipolar cycloadditions. Also, selective reductions of azetidine nitrones and sequential hydrogenation conditions gave *N*-hydroxy azetidines and corresponding ring-opened aminoesters with excellent diastereoselectivity. Surprisingly, in the presence of azetidine nitrones, treatment of electrophiles and nucleophiles led to new C–C bond formations, affording azetidines with molecular complexity. Since four-membered ring heterocycle units are found within pharmaceuticals and natural products, diastereoselective transformations of azetidine nitrones are practically useful tool to access sophisticated azetidines in synthetic areas.

2.7. Plausible Mechanism

As described above, our working hypothesis for the pathway for the conversion of N-vinylnitrone **2.29m** to azetidine nitrone **2.33k** was a 4π-electrocyclization (Scheme 2.9). Relative stereochemistry of azetidine nitrone **2.33k** was identified by X-ray crystallographic analysis (Figure 2.3) and can be explained by conrotatory ring-closure. The electronic trends of the 4π-electrocyclization were shown that substrates with electron donating substituents gave higher yields. The electronic trends of the 6π-electrocyclization described in Chapter 1 were similar.

Scheme 2.12. Possible Mechanism for Azetidine Nitrone Formation

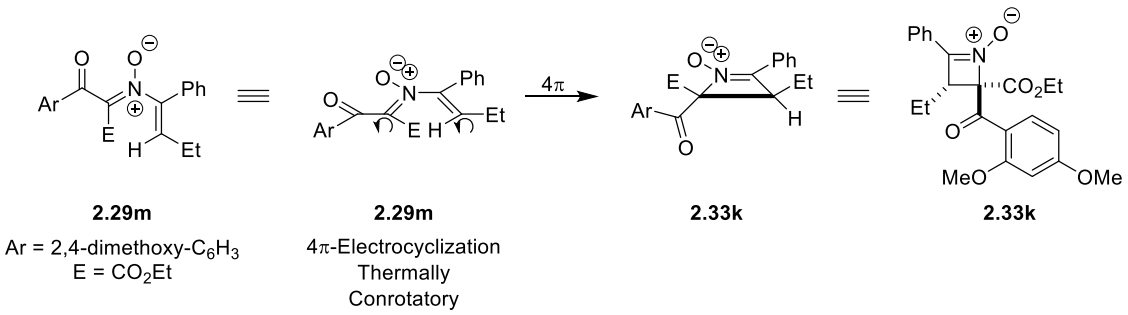
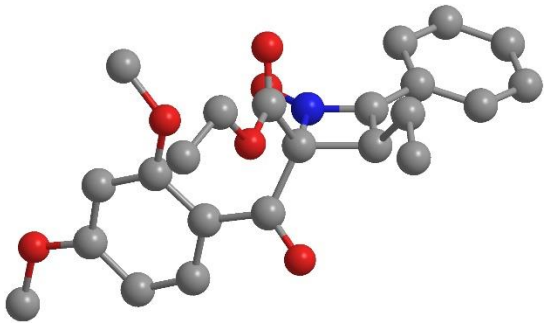


Figure 2.2. X-Ray Crystallography of **2.33k** (CCDC 1560573**)** by Prof. Donald J. Wink



2.8. Conclusion

In summary, we have discovered a modular synthesis of azetidine nitrones from *N*-vinylnitrones through 4π-electrocyclization. A variety of *N*-vinylnitrone substrates were easily accessible via treatment of oximes with a mixture of $Cu(OAc)_2$ and vinyl boronic acids. Optimization of the electrocyclization revealed that the optimal conditions involve mild heating in MeOH for 18 h but that the reaction conditions are somewhat substrate sensitive. After finding optimal conditions for the synthesis of azetidine nitrones, a variety of examples were prepared and

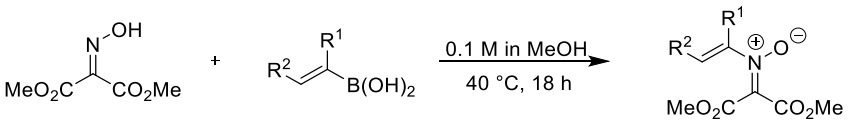
modified to develop divergent synthetic approaches to the preparation of complex azetidines with high diastereoselectivity.

2.9 Supporting Information

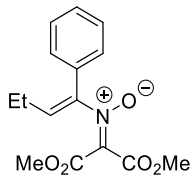
2.9.1 General Experimental Information

^{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.[41]

2.9.2 Experimental Procedures and Characterization Data (Table 2.2)

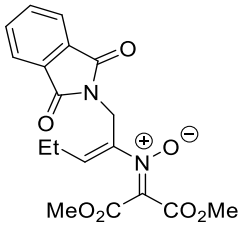


General Procedure A:[18,24,79] A scintillation vial was charged with dimethyl 2-(hydroxyimino)malonate **2.26** (0.30 mmol, 1.0 equiv), alkenylboronic acid **2.27** (3 – 5 equiv), $Cu(OAc)_2$ (1.0 equiv), and anhydrous Na_2SO_4 (8.5 equiv). These solids were diluted with 1,2-dichloroethane (DCE) to form a 0.1 M solution of oxime **2.26**. 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 – 6 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 **2.29** as a white solid or light-yellow oil.



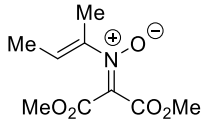
2.29a

Nitrone 2.29a: Nitrone **2.29a** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **2.27a** (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 **2.29a** 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.



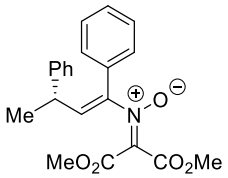
2.29b

Nitrone 2.29b: Nitrone 2.23b was prepared by general procedure A. Oxime **2.26a** (0.0483 g, 0.300 mmol) was treated with (Z)-(1-(1,3-dioxoisoindolin-2-yl)pent-2-en-2-yl)boronic acid **2.27b** (0.233 g, 0.900 mmol), Cu(OAc)2 (0.0545 g, 0.300 mmol), Na2SO4 (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 **2.29b** as a white solid (0.0451 g, 40%). 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): δ 167.5 (2C), 160.6, 159.4, 140.8, 134.3, 134.0 (2C), 132.6, 132.1 (2C), 123.5 (2C), 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 C18H19N2O7 (M+H)+ 375.1187, found 375.1192; m.p.: 119 – 120 °C.



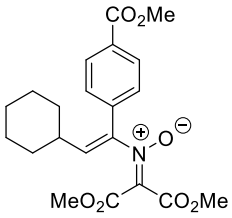
2.29c

Nitrone 2.29c: Nitrone **2.29c** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with 2-butenylboronic acid **2.27c** (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 **2.29c** 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.



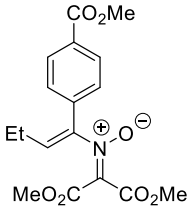
2.29d

Nitrone 2.29d: Nitrone **2.29d** was prepared by general procedure **A**. Oxime **2.26a** (0.0483 g, 0.300 mmol) was treated with (*S*)-(*Z*)-(1,3-diphenylbut-1-en-1-yl)boronic acid **2.27d** (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 **2.29d** 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.



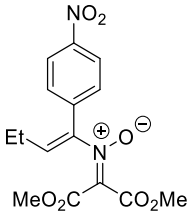
2.29f

Nitrone 2.29f: Nitrone **2.29f** was prepared by general procedure **A**. Oxime **2.26a** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(2-cyclohexyl-1-(4-(methoxycarbonyl)phenyl)vinyl)boronic acid **2.27f** (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 **2.29f** 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.



2.29g

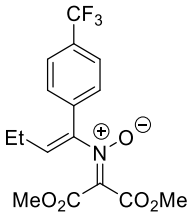
Nitrone 2.29g: Nitrone **2.29g** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(4-(methoxycarbonyl)phenyl)but-1-en-1-yl)boronic acid **2.27g** (0.351 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29g** 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.



2.29h

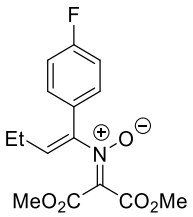
Nitrone 2.29h: Nitrone **2.29h** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(4-nitrophenyl)but-1-en-1-yl)boronic acid **2.27h** (0.332 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol),

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 **2.29h** 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.



2.29i

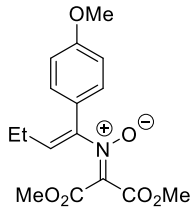
Nitrone 2.29i: Nitrone **2.29i** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)boronic acid **2.27i** (0.366 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 2 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29i** 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.



2.29j

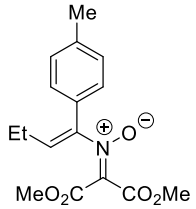
Nitrone 2.29j: Nitrone **2.29j** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(4-fluorophenyl)but-1-en-1-yl)boronic acid **2.27j** (0.291 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE. Chromatography (1:3, EtOAc: hexanes) afforded **2.29j** 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.



2.29k

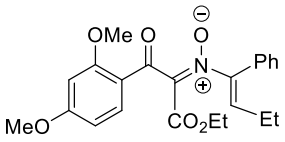
Nitrone 2.29k: Nitrone **2.29k** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(4-methoxyphenyl)but-1-en-1-yl)boronic acid **2.27k** (0.309 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred 5 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29k** 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.



2.29l

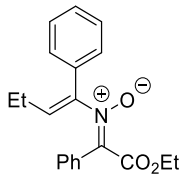
Nitrone 2.29l: Nitrone **2.29l** was prepared by general procedure **A**. Oxime **2.26a** (0.048 g, 0.30 mmol) was treated with (1-(*p*-tolyl)but-1-en-1-yl)boronic acid **2.27l** (0.285 g, 1.50 mmol), $Cu(OAc)_2$ (0.054 g, 0.30 mmol), Na_2SO_4 (0.362 g, 2.55 mmol), and pyridine (0.066 g, 0.90 mmol) in 3.0 mL DCE and stirred for 3 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29l** 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.



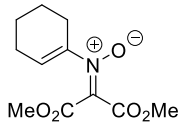
2.29m

Nitrone 2.29m: Nitrone **2.29m** was prepared from general procedure A (See the procedure for compound **1.61a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 1H), 7.63-7.62 (m, 2H), 6.59 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 5.94 (t, *J* = 8.0 Hz, 1H), 4.15 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 3.41 (s, 3H), 2.26 (q, *J* = 7.5 Hz, 2H), 1.12-1.08 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.6, 166.0, 161.7, 158.8, 145.0, 138.9, 133.3, 129.9, 129.4, 128.7, 128.0, 118.1, 106.3, 97.9, 61.4, 55.6, 55.3, 21.3, 14.0, 13.3; IR (thin film) 3055, 2967, 2935, 2873, 2840, 1726, 1651, 1594, 1574, 1525; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}NO_6$ $(M+H)^+$ 412.1755, observed: 412.1747



2.29n (*E*-only)

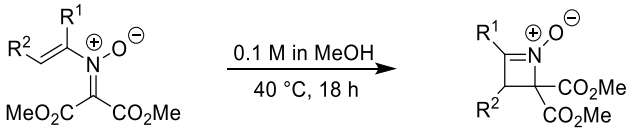
Nitrone 2.29n: Nitrone **2.29n** was prepared by general procedure **A**. Oxime **2.26a** (0.0580 g, 0.300 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **2.27a** (0.264 g, 1.50 mmol), Cu(OAc)2 (0.0545 g, 0.300 mmol), Na2SO4 (0.341 g, 2.50 mmol), and pyridine (0.0712 g, 0.900 mmol) in 5.0 mL DCE and stirred for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29n** as a yellow oil (0.0610 g, 63%). 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): 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 C20H22NO3 (M+H)+ 324.1600, found 324.1599.



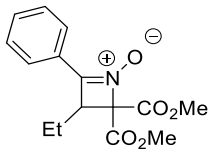
2.29o

Nitrone 2.29o: Nitrone **2.29o** was prepared by general procedure **A**. Oxime **2.26a** (0.0483 g, 0.300 mmol) was treated with (1-phenyl-1-butenyl)boronic acid **2.27m** (0.113 g, 0.9 mmol), Cu(OAc)2 (0.0545 g, 0.300 mmol), Na2SO4 (0.341 g, 2.50 mmol), and pyridine (0.0712 g, 0.900 mmol) in 3.0 mL DCE and stirred for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.29o** as a yellow oil (0.0586 g, 81%). 1 H NMR (500 MHz; CDCl3): δ 5.86-5.85 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.45-2.35 (m, 2H), 2.15-2.12(m, 2H), 1.80-1.76(m, 2H), 1.65-1.61(m, 2H); 13C NMR (125 MHz, CDCl3): δ 160.7, 159.5, 146.6, 131.7, 124.1, 53.1, 52.9, 25.8, 24.0, 21.9, 20.8; IR (thin film) 2994, 2964, 2873, 1726, 1720, 1613, 1574, 1438, 1423, 1387 cm-1 ; HRMS (ESI) m/z calcd. for $C_{11}H_{16}NO_5$ $(M+H)^+$ 242.1023, found 242.1022.

2.9.3. Synthesis of Azetidine-*N*-Oxides 2.33a – 2.33m (Table 2.5)



General Procedure B: A 5 mL conical vial equipped with a magnetic stir bar was charged with nitrone **2.29**, 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 **2.33**.



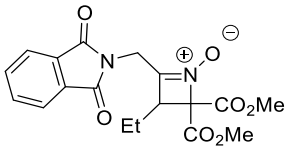
2.33a

Azetidine Nitrone 2.33a: Azetidine nitrone **2.33a** was prepared by general procedure **B** using nitrone **2.29a** (0.0870 g, 0.298 mmol) in MeOH (2.9 mL) and heating for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **2.33a** 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 **2.33a** 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.

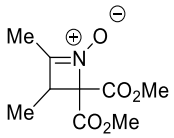
Gram Scale/One-Pot Synthesis of 2.33a: Azetidine nitrone **2.33a** was prepared using a general procedure **A** and a modified general procedure **B** in sequence on a 1 g scale. Oxime **2.26a** (1.00 g, 6.21 mmol, 1.0 equiv) was treated with (1-phenyl-1-butenyl)boronic acid **2.27a** (3.28 g, 18.6 mmol, 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 **2.33a** as a light yellow solid (1.54 g, 85%).

Gram Scale/One-Pot Synthesis of 2.33a with 20 mol% $Cu(OAc)_2$: Azetidine nitrone **2.33a** 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 **2.26a** (1.00 g, 6.21 mmol, 1.0 equiv) was treated with (1-phenyl-1-butenyl)boronic acid **2.27a** (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 **2.33a** as a light yellow solid (1.50 g, 83%).



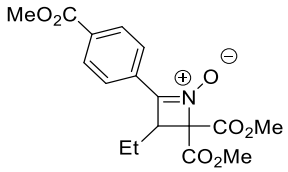
2.33b

Azetidine Nitrone 2.33b: Azetidine nitrone **2.33b** was prepared by general procedure **B** using nitrone **2.29b** (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 **2.33b** 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.



2.33c

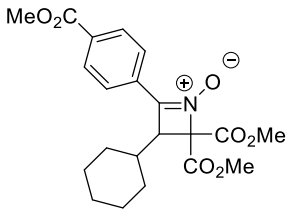
Azetidine Nitrone 2.33c: Azetidine nitrone **2.33c** was prepared by general procedure **B**. Nitrone **2.29c** (0.0183 g, 0.0850 mmol) was heated at 40 °C in MeOH (0.8 mL) for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded azetidine nitrone 2.27c as a pale-yellow oil (0.0177 g, 97%). ^{1}H NMR (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.



2.33d

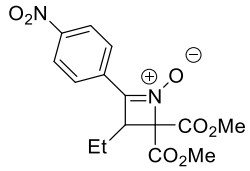
Azetidine Nitrone 2.33d: Azetidine nitrone **2.33d** was prepared by general procedure **B.** Nitrone **2.29g** (0.0370 g, 0.106 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **2.33d** as a white solid (0.0344 g, 93%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.07 – 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.



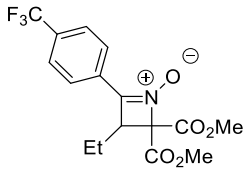
2.33e

Azetidine Nitrone 2.33e: Azetidine nitrone **2.33e** was prepared by general procedure **B**. Nitrone **2.29f** (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 **2.33e** 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.



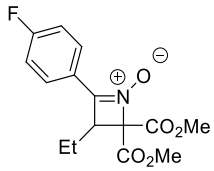
2.33f

Azetidine Nitrone 2.33f: Azetidine nitrone **2.33f** was prepared by general procedure **B** using nitrone **2.29h** (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 **2.33f** 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.



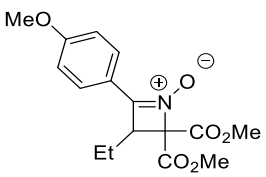
2.33g

Azetidine Nitrone 2.33g: Azetidine nitrone **2.33g** was prepared by general procedure **B** using nitrone **2.29i** (0.0471 g, 0.131 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **2.33g** 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.



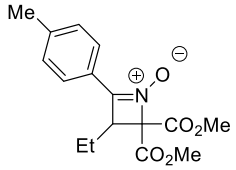
2.33h

Azetidine Nitrone 2.33h: Azetidine nitrone **2.33h** was prepared by general procedure **B** using nitrone **2.29j** (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 **2.33h** 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.



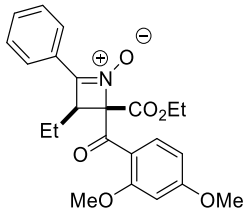
2.33i

Azetidine Nitrone 2.33i: Azetidine nitrone **2.33i** was prepared by general procedure **B.** Nitrone **2.29k** (0.0258 g, 0.0803 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, EtOAc: hexanes) afforded **2.33i** 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 $C_{16}H_{20}NO_6$ $(M+H)^+$ 322.1291, found 322.1287; m.p.: 94 – 96 °C.



2.33j

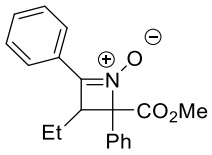
Azetidine Nitrone 2.33j: Azetidine nitrone **2.33j** was prepared by general procedure **B**. Nitrone **2.29l** (0.0339 g, 0.111 mmol) was heated at 40 °C in MeOH for 18 h. Chromatography (1:2, Et_2O: hexanes) afforded **2.33j** as a white solid (0.0322 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.86 – 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.



2.33k

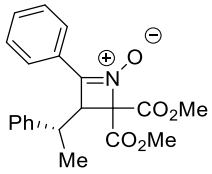
Azetidine Nitrone 2.33k: Azetidine nitrone **2.33k** was prepared by general procedure B. Nitrone **2.29m** (0.100 g, 0.243 mmol) was heated at 40 °C in MeOH (2.0 mL) for 18 h. Chromatography (1:3, EtOAc: hexanes) afforded **2.33m** as a white solid (0.0950 g, 95%). 1 H NMR (500 MHz; CDCl3): δ 7.95 – 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); 13C NMR (125 MHz, CDCl3): 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 C23H26NO6 (M+H)+ 412.1760, found 412.1763; m.p.: 99 – 102 °C. Purified 4m 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.



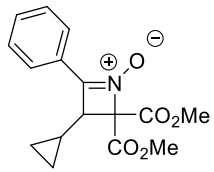
2.33l

Azetidine Nitrone 2.33l: Azetidine nitrone **2.33l** was prepared by general procedure **B**. Nitrone **2.29n** (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 **2.33l** as a yellow amorphous solid (0.0610 g, 94%). 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): 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 C20H22NO3 (M+H)+ 324.1600, found 324.1607.



Azetidine Nitrone 2.33m: Azetidine nitrone **2.33m** was prepared by general procedure **B**. Nitrone **2.29d** (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 ***rac*-4l** 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.

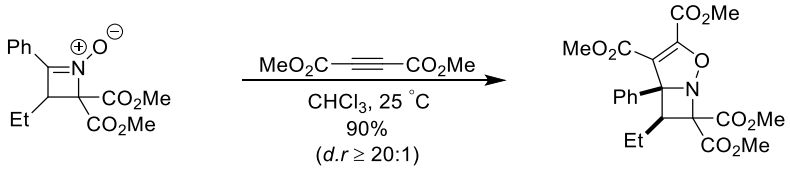


2.33o

Azetidine Nitrone 2.33o: Azetidine nitrone **2.33o** was prepared by general procedure **A:** Oxime **2.29e** (0.0483 g, 0.300 mmol) was treated with (*Z*)-(2-cyclopropyl-1-phenylvinyl)boronic acid **2.27e** (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 **2.33o** 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.

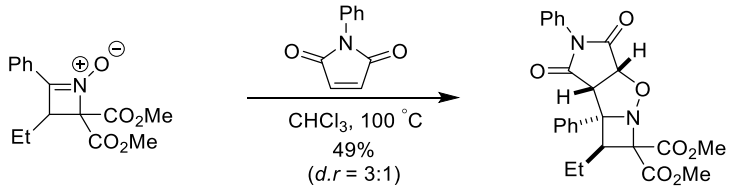
2.9.4. Functionalizations of Azetidine Nitrones

2.9.4.1. Cycloadditions of 2.27a (Scheme 2.8)

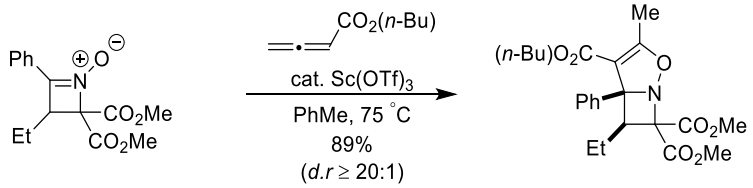


Cycloaddition of 2.33a with DMAD:[80] A flame-dried 25-mL round bottom flask was charged with azetidine **2.33a** (0.150 g, 0.515 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate (DMAD) (0.146 g, 1.03 mmol, 2.0 equiv), and $CHCl_3$ (5.0 mL). The reaction mixture was stirred for 18 h and then concentrated 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 **2.41** (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),

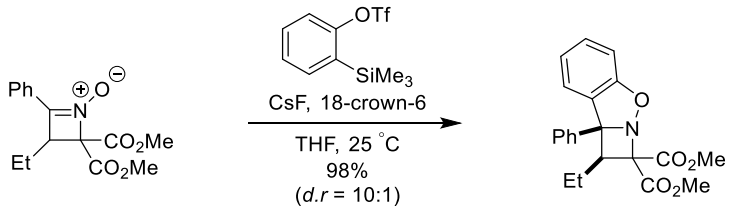
3.82 (s, 3H), 3.81 (s, 3H), 1.39 – 1.30 (m, 1H), 1.27 – 1.18 (m, 1H), 0.64 (dd, *J* = 8.0, 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 166.1, 162.4, 159.0, 154.0, 137.4, 128.3, 128.1, 126.7, 113.7, 80.1, 79.0, 53.8, 53.2, 52.7, 52.2, 48.9, 20.5, 11.2; IR (thin film) 2608, 2339, 1741, 1736, 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 **2.41** 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.



Cycloaddition of 2.33a with *N*-phenyl maleimide: A flame-dried 25-mL round bottom flask was charged with azetidine **2.33a** (0.050 g, 0.172 mmol, 1.0 equiv), N-phenylmaleimide (0.0446 g, 0.257 mmol, 1.5 equiv), and anhydrous CHCl3 (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 Et2O and purified by medium pressure chromatography (1:9 – 1:4; Et2O: hexanes) to afford isoxazoline **2.42** (0.0391 g, 49%, dr = 3:1) as a white solid. 1 H NMR (500 MHz; CDCl3) (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); 13C NMR (125 MHz, CDCl3) (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; CDCl3) (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); 13C NMR (125 MHz, CDCl3) (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 C25H25N2O7 (M+H)+ 465.1662, found 465.1677; m.p.: 106 – 110 °C.



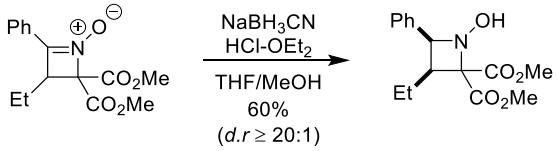
Cycloaddition of 2.33a with *n*-butylallenoate:[81] A flame-dried 25-mL round bottom flask was charged with azetidine **2.33a** (0.150 g, 0.515 mmol, 1.0 equiv), *n*-butyl buta-2,3-dienoate (0.144 g, 1.03 mmol, 2.0 equiv),10 Sc(OTf)3 (0.0131 g, 0.0258 mmol, 0.05 equiv), and toluene (5.0 mL). The reaction 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 **2.43** (0.198 g, 89%, dr >20:1) as a clear oil. 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): 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 C23H30NO7 (M+H)+ 432.2022, found 432.2022.



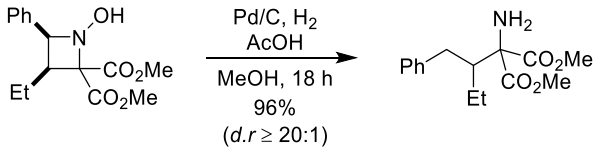
Cycloaddition of 2.33a with benzyne:[18] A flame-dried 25-mL round bottom flask was charged with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.400 g, 1.34 mmol, 2.0 equiv), 18-crown-6 (0.707 g, 2.68 mmol, 4.0 equiv), azetidine **2.33a** (0.195 g, 0.670 mmol, 1.0 equiv), 4 Å MS (0.050 g), and 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 **2.44** (0.241 g, 98%, dr = 10:1) as a colorless solid. Diastereoselectivity determined in analogy to **6**. Major Diasteromer: ^{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.

2.9.4.2. Reduction of 2.33a and Ring-Opening (Scheme 2.9)

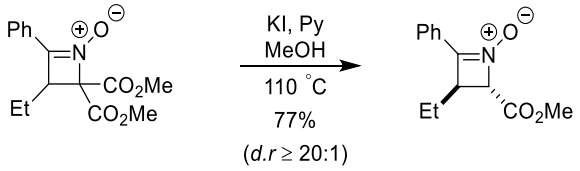


Reduction of 2.33a:[82] A flame-dried 10-mL round bottom flask was flushed with N_2, charged with azetidine **2.33a** (0.075 g, 0.26 mmol, 1.0 equiv), and sealed with a rubber septum. Anhydrous THF (3.0 mL) was then added to the reaction flask via syringe, followed by the addition of a solution of $NaBH_3CN$ (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 **2.45** (0.045 g, 60%, dr = >20:1) as a white solid. ^{1}H 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.



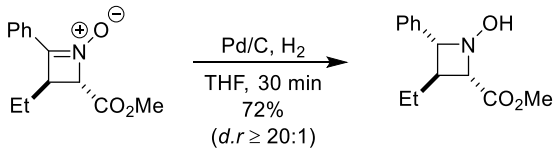
N–O Reduction and Ring-Opening of 2.45: A flame-dried 10-mL round bottom flask was charged with 10 wt% Pd on activated carbon (0.0553 g, 0.0522 mmol, 0.100 equiv), diluted with MeOH (2.5 mL), sealed with a rubber septum, and flushed with N2. A balloon of H2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine hydroxylamine **2.45** (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 H2 atmosphere, then filtered through a plug of celite, rinsed with Et2O (3 x 10 mL), and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et2O and purified by medium pressure chromatography (1:5 – 1:4; Et2O:hexanes) to afford amino ester **2.46** (0.140 g, 96%) as a clear oil. 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): 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 C15H22NO4 (M+H)+ 280.1549, found 280.1545.

2.9.4.3. Dealkoxylcarboxylation and Reduction of Azetidine Nitrone (Scheme 2.10)

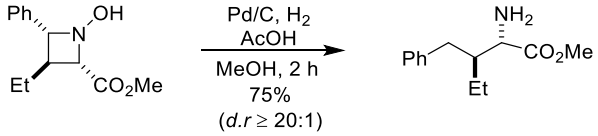


Dealkoxycarbonylation of 2.33a: A 25-mL round bottom flask was flame-dried under N_2, allowed to cool to 25 °C and charged with azetidine **2.33a** (0.150 g, 0.515 mmol, 1.00 equiv) and KI (0.128 g, 0.772 mmol, 1.50 equiv). The reaction mixture was then diluted with pyridine and MeOH (1:1 mixture, 5.2 mL) to form a 0.1 M solution of **2.33a** 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 **2.47** (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 **2.41** 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.

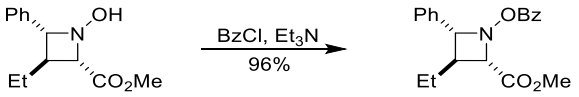


Hydrogenation of 2.47: A flame-dried 10-mL round bottom flask equipped with a magnetic stirring bar was charged with 10 wt% Pd on activated carbon (0.029 g, 0.027 mmol, 0.1 equiv), diluted with anhydrous THF (10.0 mL), sealed with a rubber septum, and flushed with N_2. A balloon of H_2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine nitrone **2.47** (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 **2.48** (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.



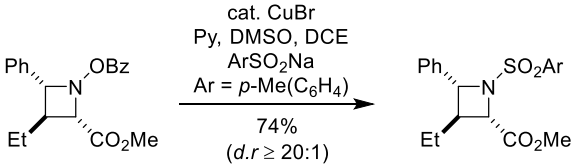
N–O Reduction and Ring-Opening of 2.48: A flame-dried 10-mL round bottom flask was charged with 10 wt% Pd on activated carbon (0.114 g, 0.107 mmol, 0.100 equiv), diluted with MeOH (5.0 mL), sealed with a rubber septum, and flushed with N2. A balloon of H2 gas was then bubbled through the solution with vigorous stirring and a vent needle for 10 min. At this time, a solution of azetidine hydroxylamine **2.48** (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 H2 atmosphere, then filtered through a plug of celite, rinsed with Et2O (3 x 10 mL), and concentrated under vacuum. The crude product mixture was dry-loaded onto celite using Et2O and purified by medium pressure chromatography (1:5 – 1:4; Et2O:hexanes) to afford α-amino ester **2.51** (0.177 g, 75%, dr = >20:1) as a clear oil. 1 H NMR (500 MHz; CDCl3): 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); 13C NMR (125 MHz, CDCl3): 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 C13H20NO2 (M+H)+ 222.1494, found 222.1498.

2.9.4.4. Benzoylation and Sulfination or Ring-Opening of Azetidine (Scheme 2.11)



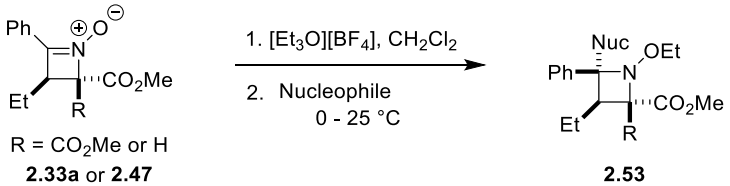
Benzoylation of 2.48: A flame-dried 10-mL round bottom flask was charged azetidine hydroxylamine **2.48** (0.235 g, 1.00 mmol, 1.0 equiv), and diluted with CH_2Cl_2 (10.0 mL, 0.1M). The reaction flask was placed in an ice-bath and NEt_3 (0.202 g, 2.00 mmol, 2.0 equiv) was added with vigorous stirring 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 **2.49** (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.[77,84]



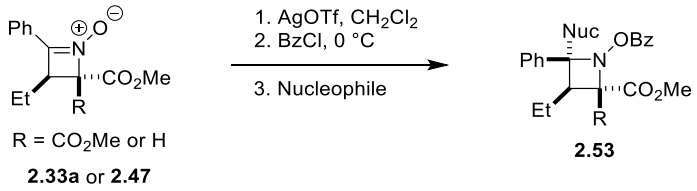
***N*-Tosylazetidine 2.50:**[83] A flame dried 25-mL round bottom flask was charged with azetidine **2.49** (0.126 g, 0.370 mmol, 1.00 equiv), $CuBr_2$ (0.017 g, 0.074 mmol, 0.20 equiv), and sodium 4-methylbenzenesulfinate (0.132 g, 0.740 mmol, 2.0 equiv). These reagents were diluted with DCE to form a 0.1 M solution of **2.43**. 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 then 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 **2.50** (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.[77,84]

2.9.4.5. Electrophilic Activation and Nucleophilic Addition (Table 2.6)

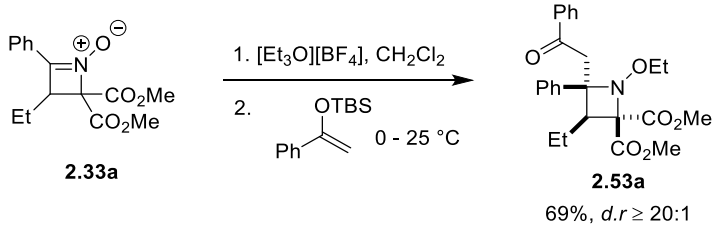


General Procedure C: A flame-dried 10-mL round bottom flask was charged with azetidine **2.33a** or **2.47** (1.00 equiv) and CH_2Cl_2 (5.0 mL) and sealed with a rubber septum. The resulting solution was then treated with a solution of $[Et_3O][BF_4]$ (1.1 equiv) in anhydrous CH_2Cl_2 (1.0 mL) via syringe. 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 **2.53**.

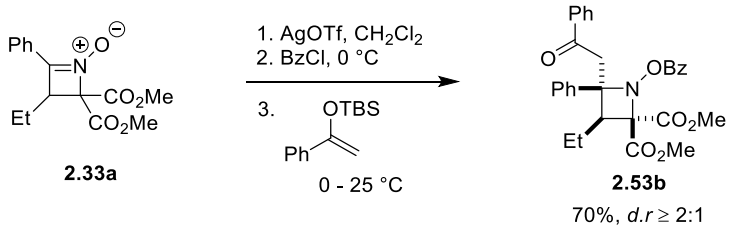


General procedure D: A flame-dried 10-mL round bottom flask was charged with azetidine **2.33a** or **2.47** (1.00 equiv), AgOTf (4.00 equiv), and CH_2Cl_2 (5.0 mL) and sealed with a rubber septum. The reaction mixture was then cooled to 0 °C and benzoyl chloride (0.048 g, 0.34 mmol, 2.0 equiv) was added 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 **2.53**.

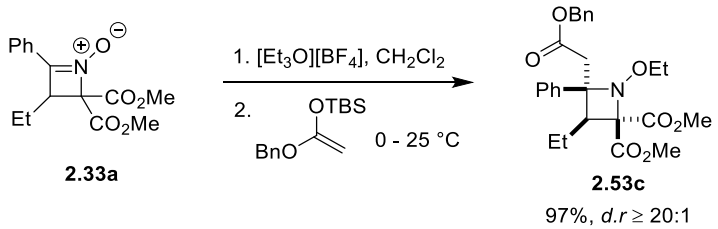


***N*-Ethoxyazetidine 2.53a**: Azetidine **2.53a** was prepared using general procedure C with azetidine nitrone **2.33a** (0.150 g, 0.515 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.108 g, 0.566 mmol, 1.1 equiv) and tertbutyldimethyl((1-phenylvinyl)oxy)silane (0.241 g, 1.03 mmol, 2.0 equiv). After the addition 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 **2.53a** (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

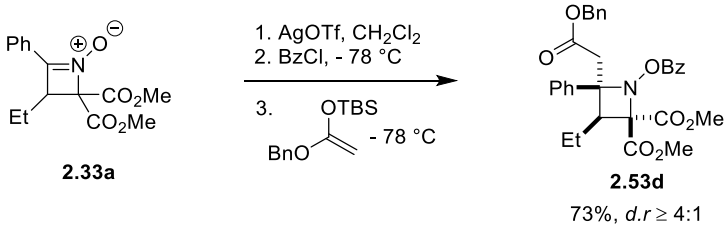
(125 MHz, C_6D_6): δ 195.6, 169.2, 168.7, 142.6, 138.1, 132.3, 128.4, 128.0, 127.8, 127.6, 126.8, 78.7, 74.0, 70.3, 52.2, 51.4, 46.6, 42.0, 20.5, 14.0, 12.1; IR (thin film) 2978, 2950, 2892, 1752, 1732, 1695, 1596, 1494, 1434, 1263 cm^{-1} ; HRMS (ESI) m/z calcd. for $C_{25}H_{30}NO_6$ $(M+H)^+$ 440.2073, found 440.2068; m.p.: 112 – 115 °C. Purified **2.53a** 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*-Benzoyloxyazetidine 2.53b** Azetidine **2.53b** was prepared using general procedure D with azetidine nitrone **2.33a** (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 **2.53b** (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); ^{13}C NMR (125 MHz, C_6D_6): 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 **2.53b** was determined in analogy to **2.53a**

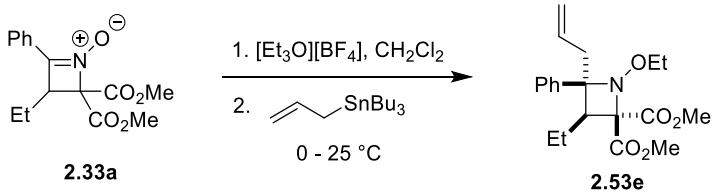


***N*-Ethoxyazetidine 2.53c**: Azetidine **2.53c** was prepared using general procedure C with azetidine nitrone **2.33a** (0.200 g, 0.687 mmol, 1.00 equiv), $[Et_3O][BF_4]$ (0.143 g, 0.755 mmol, 1.10 equiv), and ((1-(benzyloxy)vinyl)oxy)(tert-butyl)dimethylsilane (0.545 g, 2.06 mmol, 3.00 equiv). After 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 **2.53c** (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 **2.53c** was determined in analogy to **2.53a**.



***N*-Benzoyloxyazetidine 2.53d**: Azetidine **2.53d** was prepared using general procedure D with azetidine nitrone **2.33a** (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 **2.53d** (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 **2.53d** was determined in analogy to **2.53a**

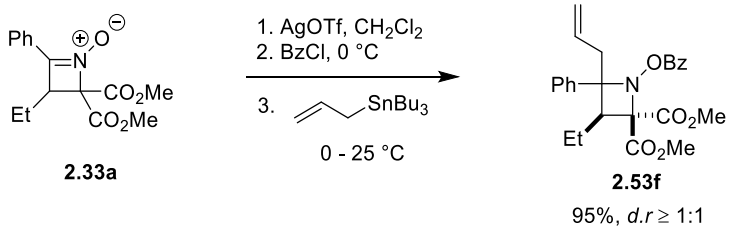


2.33a **2.53e**

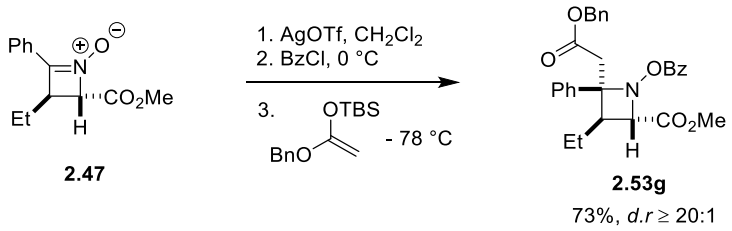
72%, *d.r* ≥ 20:1

***N*-Ethoxyazetidine 2.53e**: Azetidine **2.53e** was prepared using general procedure C with azetidine nitrone **2.33a** (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 **2.53e** (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,

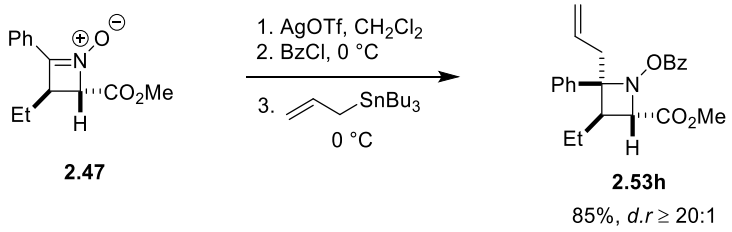
1433, 1382, 1256 cm^{-1} ; HRMS (ESI) m/z calcd. for $C_{20}H_{28}NO_5$ $(M+H)^+$ 362.1967, found 362.1953; m.p.: 86 – 88 °C. The diastereoselectivity of **2.53e** was determined in analogy to **2.53a**.



***N*-Benzoyloxyazetidine 2.53f**: Azetidine **2.53f** was prepared using general procedure D with azetidine nitrone **2.33a** (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 NEt_3 (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 **2.53f** (0.071 g, 95%, dr = 1:1) as a colorless oil. Diastereomer A: ^1H 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: ^1H 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.



***N*-Benzoyloxyazetidine 2.53g**: A flame dried 25 mL round bottom flask was charged with decarboxylated azetidine nitrone **2.47** (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 **2.53g** (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 **2.53a**.



***N*-Benzoyloxyazetidine 2.53h**: Azetidine **2.53h** was prepared using general procedure D with decarboxylated azetidine nitrone **2.47** (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 **2.53h** (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.

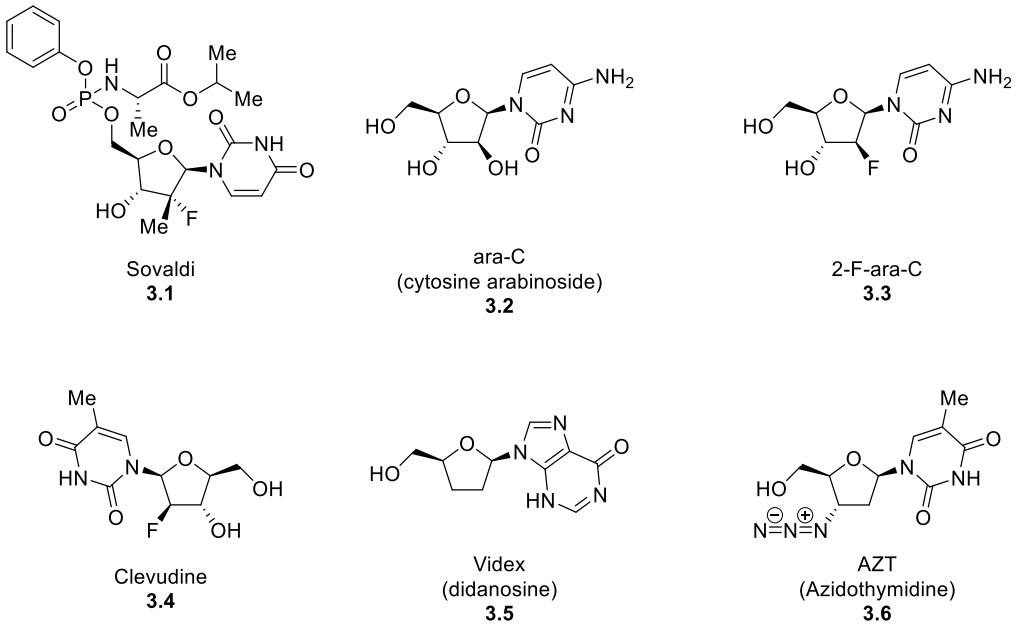
Chapter 3. Synthesis of 2-Aminotetrahydrofurans Through [3,3']-Sigmatropic Rearrangements of *N, O*-Divinylhydroxylamines.

3.1 Introduction

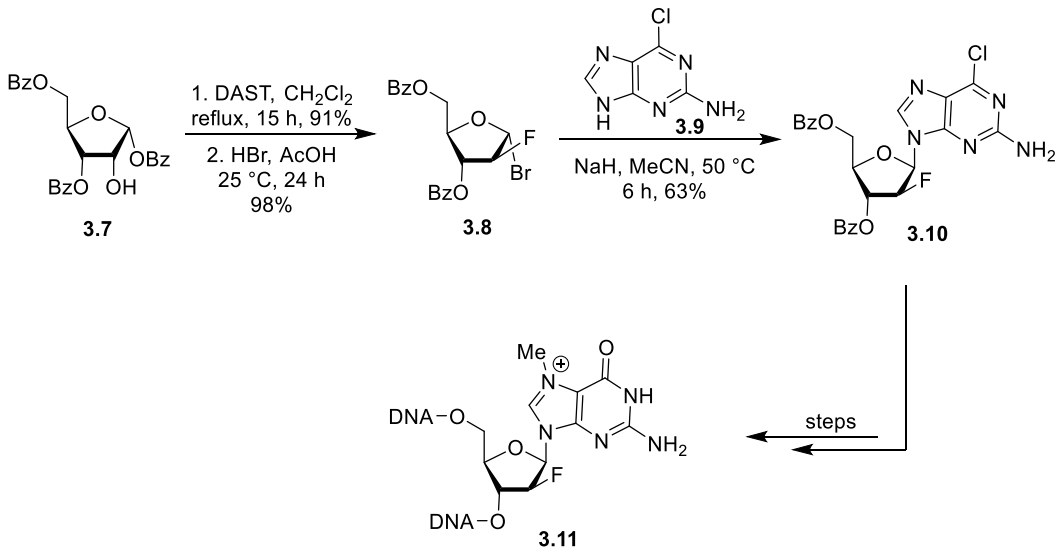
3.1.1 Biological Activity of 2-Aminotetrahydrofuran

Nucleoside analogues are valuable heterocycle motifs with potent biological activity against hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and acquired immune deficiency syndrome (AIDS). This activity has made these compounds particularly important targets for medicinal chemistry and drug discovery. As shown in Scheme 3.1, Sofosbuvir **3.1** is a tetrahydrofuran bearing an uracil base on 2-position and was approved by FDA in 2013 for the treatment for hepatitis C virus (HCV) infection.[85-87] Moreover, cytosine-containing tetrahydrofuran ara-C **3.2** is used as a chemotherapy medication for chronic myelogenous leukemia, acute lymphocytic leukemia, and acute myeloid leukemia.[88] Its fluorinated analogue, 2-F-ara-C X.X, is reported to have potentially strong antiherpetic activity .[88,89] Clevudine **3.4** is another nucleoside analogue with 2-thyminyl base and is an antiviral drug approved in South Korea and Philippines being used for a treatment of chronic hepatitis B virus infection.[90-92] Another example is didanosine **3.5**, a marketed drug approved in 1991 in United States. and prescribed to cure human immunodeficiency virus (HIV).[93-95] Lastly, azidothymidine **3.6** (AZT) is an antiviral drug, shown to inhibit the replication of HIV.[96-98] and is used to treat acquired immune deficiency syndrome (AIDS). As described above, 2-aminotetrahydrofurans undoubtedly are important motifs to study in medicinal chemistry and drug discovery due to their remarkable antiviral properties; however, the strategies for forming these compounds is limited and the impact of these compounds could be improved with an expansion of chemical space around their structures.[99-104]

Scheme 3.1. Marketed Nucleoside Analogue Anti-Virals



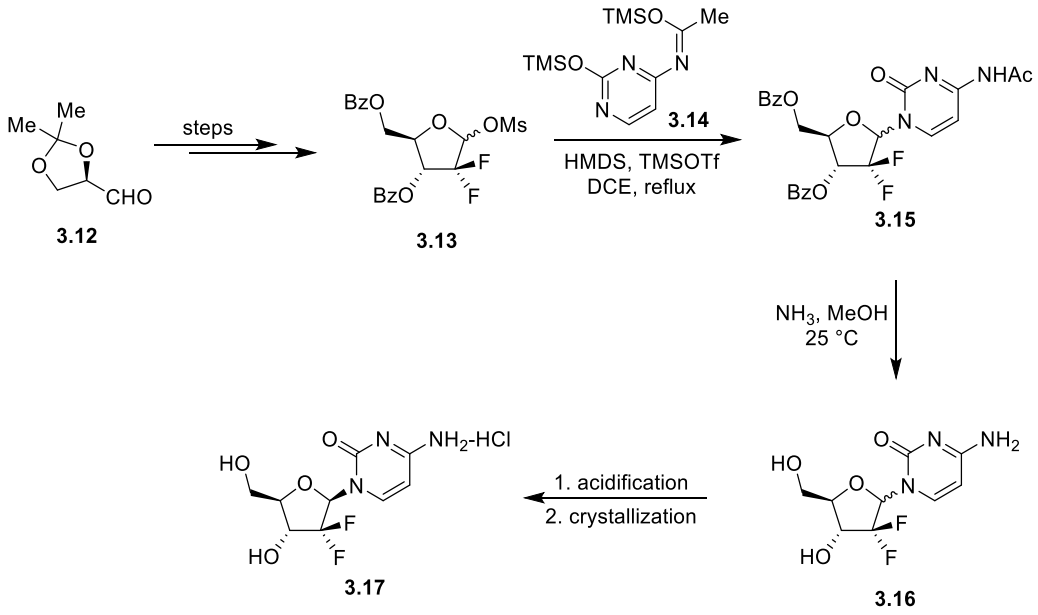
Scheme 3.2. Preparation of Nucleotide **3.11**



The most common method for the preparation of 2-aminotetrahydrofurans is nucleophilic displacement at the glycosidic position of a furanose.[99-103] As an example, Verdine and coworkers developed a synthesis of resin-bound Fm[7]dG-containing oligonucleotide **3.11** from furanose **3.7**. (Scheme 3.2).[99] Initially, furanose **3.7** was fluorinated with DAST and brominated to afford glycosyl bromide **3.8**. Subsequent *N*-glycosidation of activated tetrahydrofuran precursor **3.8** with the purine nucleophile **3.9** provided primarily the *β*-anomer **3.10**. This simple *N*-glycosidation introduces the stereodefined nucleoside backbone from **3.8** and **3.9**. Further manipulation led to

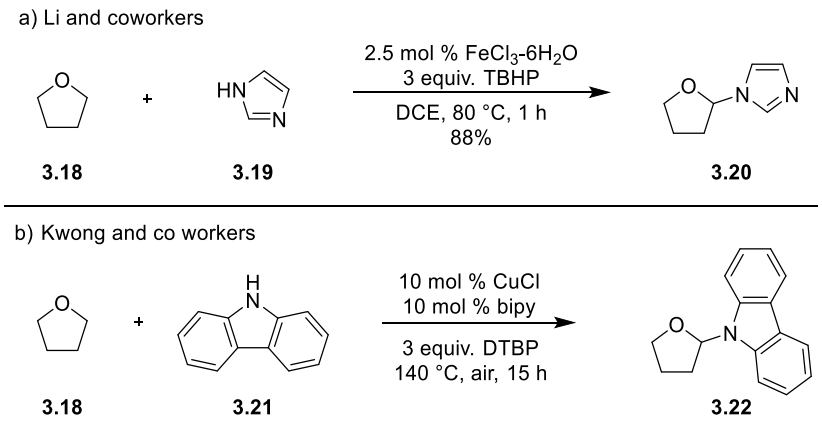
formation of the DNA-bound 2-aminotetrahydrofuran **3.11** that was studied for a structural information of Fm[7]dG-containing DNA.

Scheme 3.3. Preparation of Gemcitabine (Gemzar)



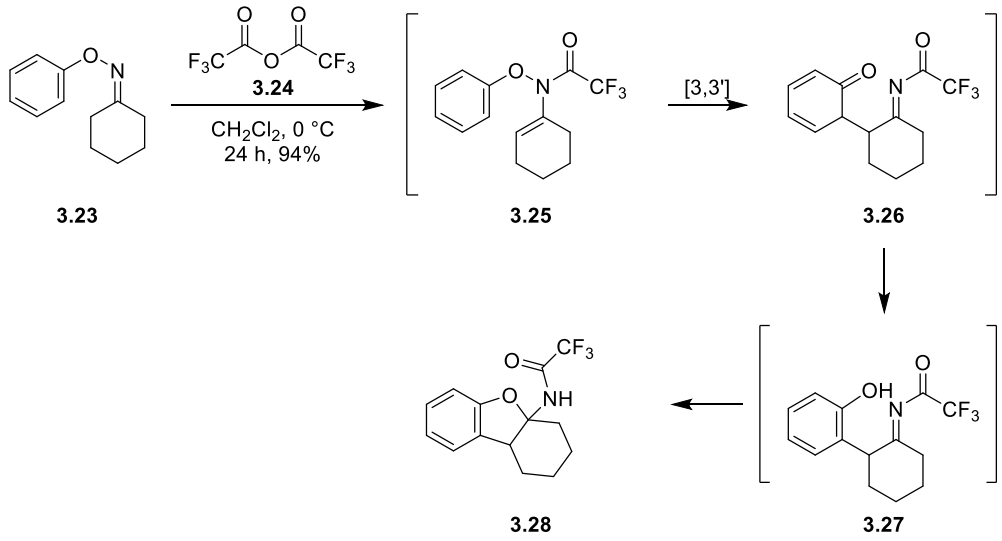
In a related example, Chou and coworkers reported the synthesis of the commercial anticancer nucleoside analogue **3.15** through nucleophilic displacement at the glycosidic position of **3.13**.[100] A mixture of anomers **3.13** was treated with the pyrimidine nucleophile **3.14** to give a 1:1 ratio of **3.15** anomers regardless of their anomeric composition of **3.13**. The authors gave a plausible mechanistic explanation involving an oxocarbenium ion intermediate formed from **3.13**. Further deprotection and acidification of **3.15** to give **3.16** gave a single anomer after crystallization. This example illustrates some of the difficulties involved in dealing with the stereoselectivity of these transformations and potential room for improvement via the development of new synthetic methods.

Scheme 3.4. Cu-Catalyzed C–H Amination of Tetrahydrofuran



As an alternative to glycosylation reactions, a few examples of C–H amination reactions of unactivated tetrahydrofuran **3.18** have been reported with simple amine partners (Scheme 3.4).[101,102] Li and coworkers reported an interesting iron-catalyzed method for the α-amination of tetrahydrofuran **3.18** (Scheme 3.4a).[101] They found that a catalytic amount of iron trichloride hexahydrate and excess *tert*-butyl hydroperoxide converted mixtures of substrates **3.18** and **3.19** to 2-aminated tetrahydrofuran **3.20**. In this study, it is noteworthy that addition of TEMPO results in a TEMPO-adduct, implying a radical process in the initial step. Another similar study was investigated using *N*-heterocycles such as indole and carbazole derivatives (Scheme 3.4b).[102] Tetrahydrofuran **3.18** and amine partner **3.21** successfully undergo an α-amination process in the presence of catalytic amount of copper chloride and 2,2'-bipyridine. It is interesting that this transformation also shows good robustness of halogen substituted amine derivatives at higher temperature. Moreover, the addition of TEMPO also gives a suggestive clue for a radical process, and kinetic isotope experiment distinctively implies C–H cleavage (k_H/k_D=4.0) is the rate-determining step. As described above, copper or iron catalysis shows promising alternative tool for α-amination of unactivated tetrahydrofuran even if there are still challenges for substituted tetrahydrofurans.

Scheme 3.5. [3,3']-Rearrangement of *N*-Alkenyl, *O*-Phenylhydroxylamine

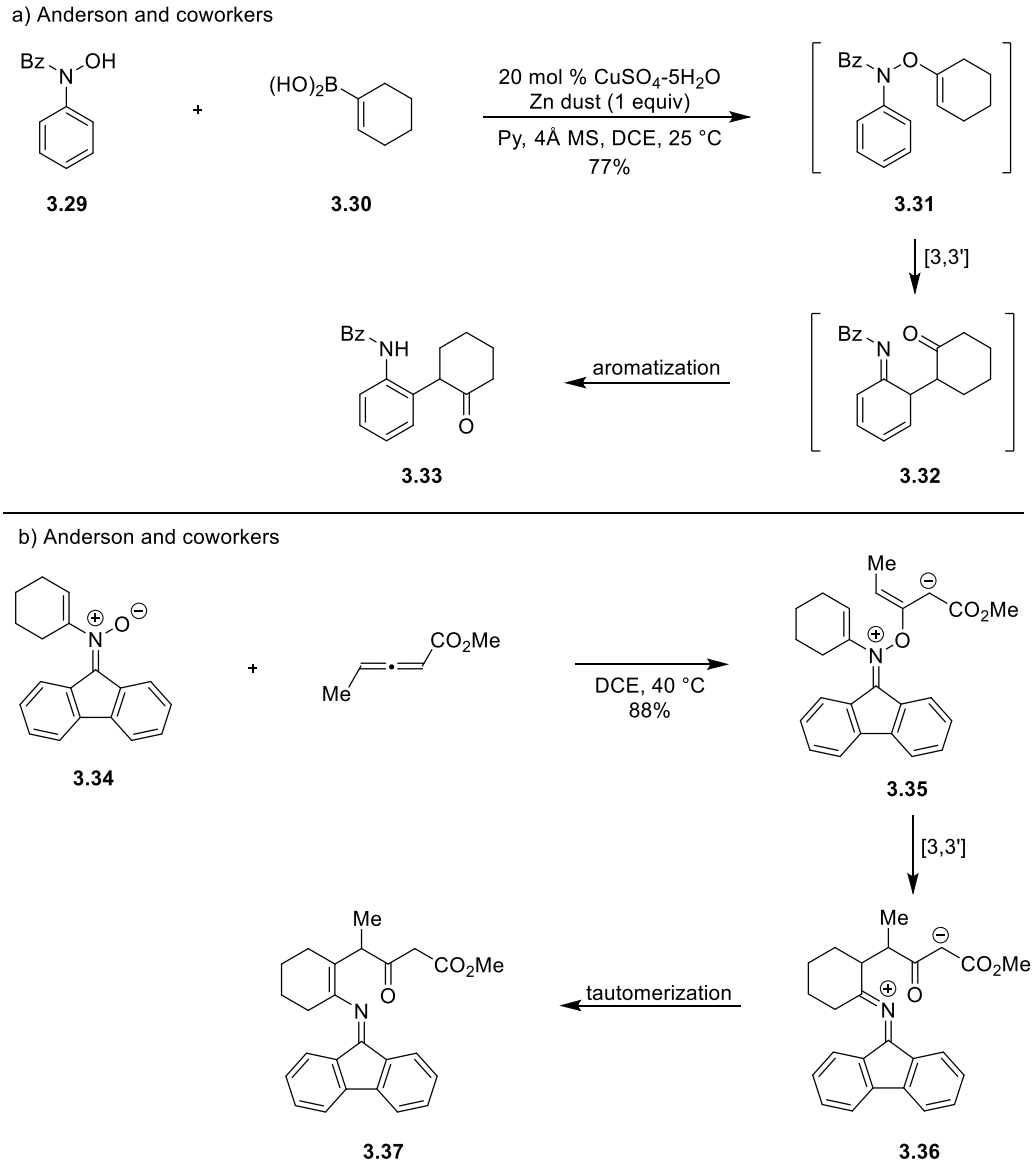


To further expand the synthetic toolbox for the synthesis of nucleoside analogues, we wondered if we might be able to use a [3,3]-sigmatropic rearrangement of *N*,*O*-divinylhydroxylamines (Scheme 3.5). While these transformations had not previously been reported, several other examples of related transformations for the synthesis of benzofurans suggested that this transformation might be possible. Naito and coworkers reported the synthesis of dihydrobenzofuran **3.28** bearing amino group on 2-position through a [3,3']-rearrangement of **3.25** (Scheme 3.5).[103] Activation of **3.23** with trifluoroacetic anhydride **3.24** introduces *N*-trifluoroacetyl hydroxylamine intermediate **3.25**, which undergoes a [3,3']-rearrangement to produce the transitory 1,4-iminoketone intermediate **3.26**. Aromatization of **3.26** towards **3.27** and spontaneous intramolecular ring-closure provides *α*-aminated dihydrobenzofuran **3.28**. Despite of the limited scope of this benzofuran synthesis, the key [3,3']-rearrangement is a novel approach to these types of compounds and the isolation of **3.28** without further aromatization under these reaction conditions is noteworthy. We decided to pursue the generation of *N*,*O*-divinylhydroxylamines to further investigate this transformation for the synthesis of 2-aminotetrahydrofurans.

Previously, our research group disclosed that *N*-aryl-*O*-vinyl hydroxylamines can be generated via the treatment of *N*-arylhydroxamic acids under Chan-Lam reaction conditions (Scheme 3.6a).[104] These compounds undergo a spontaneous interrupted Fischer-Indole reaction to give *α*-(*o*-anilido)ketones **3.33** without concomitant indolization . This attractive modular transformation addresses improved synthetic solutions for *α*-(*o*-anilido)ketones which are challenging to synthesize via palladium-arylation chemistry. In related study, the preparation of 1,4-enamino

ketones was investigated through the [3,3]-rearrangement of *N*,*O*-dialkenylhydroxylamines generated via the addition of an *N*-alkenylnitrone to an electron-deficient allene (Scheme 3.6b).[79] It is noteworthy that installation of *N*-fluorenyl protection group features the isolation of interrupted Trofimov pyrrole intermediate without further spontaneous cyclizations to yield pyrrole. We envisioned that the reactivity trends that we can learned in both of these prior studies could be used to access of *N*,*O*-divinyl intermediates and could result in a new route to 2-aminotetrahydrofurans.

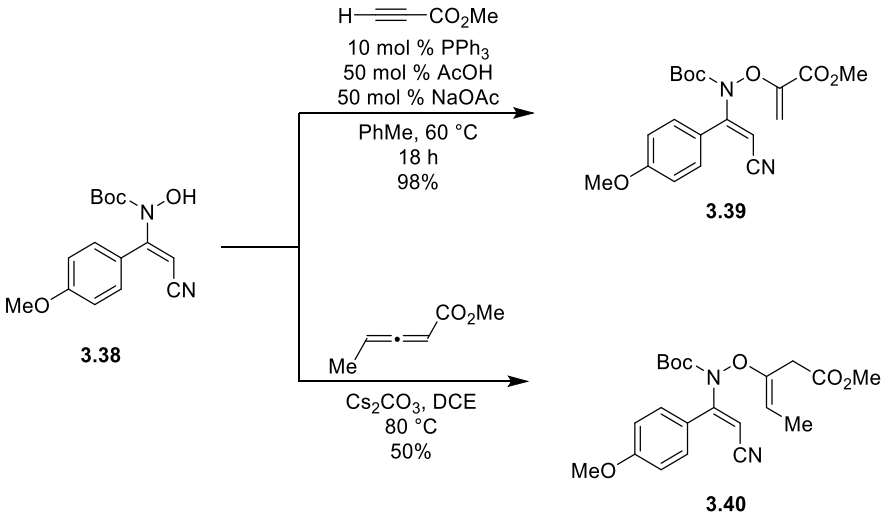
Scheme. 3.6. [3,3']-Rearrangements of *N*,*O*-Divinylhydroxylamines Generated from *N*-Vinyl Hydroxylamines and Allenes



3.2. Discovery of Synthesis of 2-Aminotetrahydrofurans from *N*-Vinylhydroxylamines

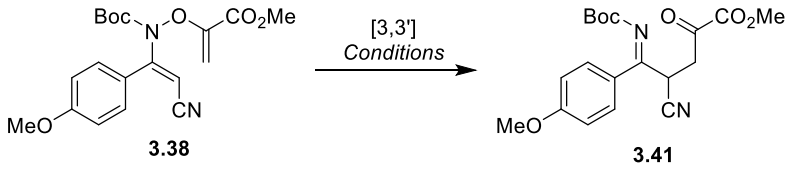
While exploring the opportunity for developing a [3,3']-rearrangement of *N*,*O*-divinylhydroxylamines for the synthesis of 2-aminotetrahydrofurans, we tested a variety of hydroxylamines and Michael acceptors such as electron-poor alkynes and allenes (Scheme 3.7). Phosphine-catalyzed α-hydroalkoxylation of methyl propiolate with *N*-vinylhydroxylamine **3.38**, afforded *N*,*O*-divinylated hydroxylamine **3.39** in high yield.[105] In this case, no further [3,3]-rearrangement of **3.39** was observed. Additionally, we anticipated that hydroxylamine **3.39** could undergo oxa-Michael addition to an electron-poor allene. Formation of *N*,*O*-divinylated product **3.40** was also observed through a oxa-Michael process, however, spontaneous [3,3']-rearrangement of **3.40** was not observed. Based on these initial investigations, we wondered if a catalyst would be required for promoting the our desired reactivity.

Scheme 3.7. Initial Attempts at *O*-Vinylation with Michael Acceptors



As shown in Table 3.1, we selected *N*,*O*-divinylhydroxylamine **3.38** to test under several reaction conditions to promote the desired [3,3']-rearrangement. Exposure to elevated temperatures gave a recovery of starting material, implying that **3.33** is thermally stable substrate (entry 1). Treatment of **3.38** with Lewis acids such as $Cu(OAc)_2$ and $MgBr_2$ also did not show any desired reactivity (entry 2 and 3). Moreover, π-acids did not activate **3.38** toward rearrangement (entry 4-6). On the other hand, stronger Lewis acids and electrophiles initiated unwanted deprotections (entry 7-9). We concluded the substrate **3.38** was an intrinsically inactive species towards [3,3]-rearrangement process, and continued to explore other *N*,*O*-divinylhydroxylamine substrates to observe the desired reactivity.

Table 3.1. Catalyst Screen for the [3,3']-Rearrangement of **3.38**

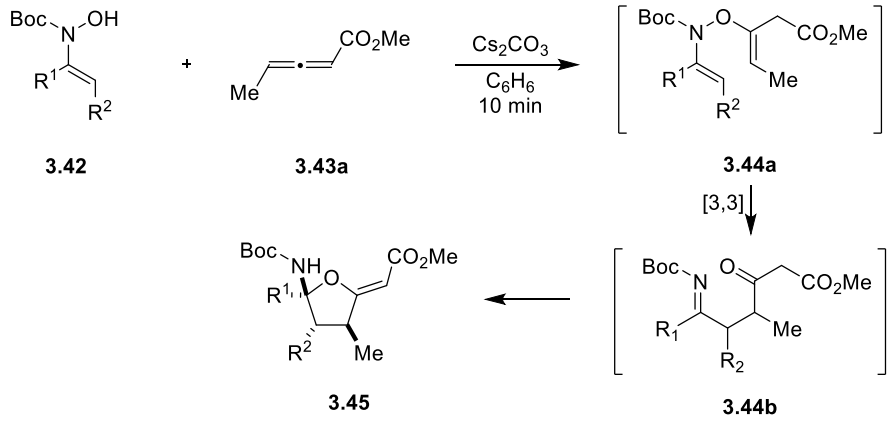


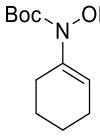
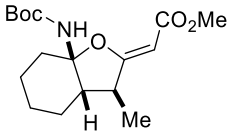
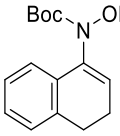
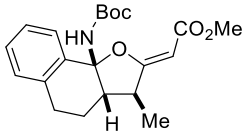
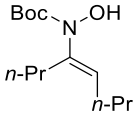
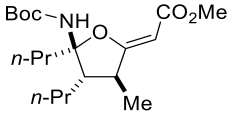
3.38 **3.41**

Entry	Conditons	Result
1	Heat (150 ˚C)	NR
2	$Cu(OAc)_2$, DCE, 100 ˚C	NR
3	$MgBr_2$, DCE, 100 ˚C	NR
4	*t*-BuXphos Palladacycle, DCM	NR
5	*t*-BrettPhos G3 Pd, DCM	NR
6	$AuCl_3$	NR
7	BF_3-OEt_2, 25 ˚C	*N*-, *O*- deprotection
8	$Zn(OTf)_2$, DCE	*N*-, *O*- deprotection
9	TFA	*N*-deprotection

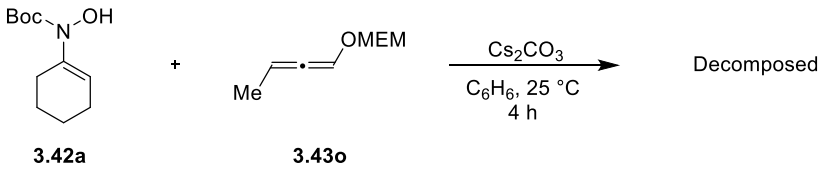
We decided to survey *N*-vinylhydroxylamines **3.42a**-**3.42c** to explore the potential for the desired [3,3]-rearrangement reactivity beyond the inactive substrate **3.38** (Table 3.2). These substrates were treated with allenoate **3.43a** to generate a *N*,*O*-divinylhydroxylamine as previously observed for **3.44a**. Firstly, *N*-cyclohexenyl hydroxylamine **3.42a** was tested with **3.43a** and we were delighted to observe the formation of fused 2-aminotetrahydrofuran **3.45a**. Isolation of this product suggested that transient formation of reactive *N*,*O*-divinyl hydroxylamine intermediate **3.44a** triggered a [3,3]-rearrangement and subsequent cyclization to 2-aminotetrahydrofuran **3.45** in one step. Next, we tested **3.42b** and **3.42c** to determine if the observed reactivity was consistent for other substrates. Both **3.42b** and **3.42c** were smoothly converted to **3.45b** and **3.45c**, respectively, when treated with **3.43a** under basic conditions. In sharp contrast, treatment of *N*-vinylhydroxylamine **3.42a** with electron-rich allene **3.43o** did not exhibit tetrahydrofuran formation but instead only led to decomposition products (Scheme 3.8). With these initial results in hand, we were encouraged to pursue an optimization study.

Table 3.2. Initial Observation of the Addition of *N*-Vinylhydroxylamines to Allenoates and Subsequent Rearrangement to 2-Aminotetrahydrofurans.



Entry	*N*-Vinylhydroxylamine	Temp (ºC)	Product	% Yield
1	 **3.42a**	25	 **3.45a**	53
2	 **3.42b**	25	 **3.45b**	20
3	 **3.42c**	0	 **3.45c**	25

Scheme 3.8. Addition of an *N*-Vinylnitrone to an Electron-Rich Allene

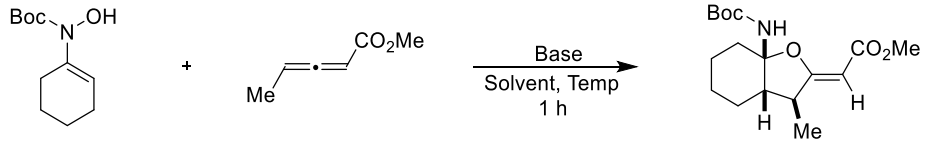


3.3 Optimization of the N-Vinylhydroxylamine Allenoate Addition and Rearrangement

To optimize the synthesis of 2-aminohydrofuran **3.45a**, a variety of reaction parameters were screened (Table 3.3). Our initial result with Cs_2CO_3 at room temperature in toluene is given in entry 1 providing **3.45a** in low yield. Decreasing temperature of the reaction mixture to 0 °C significantly increased the yield for the formation of 2-

aminohydrofuran **2.45a** (entry 2). A screen of several solvents of varying polarities indicated that CH_2Cl_2 was the optimal reaction medium (entries 3-6). Investigation of several inorganic bases such as Na_2CO_3, Li_2CO_3, LiOAc, and K_2CO_3 showed that K_2CO_3 was the optimal reagent (entries 7-10) and further testing of homogeneous amine bases such as Et_3N, DMAP and DABCO showed that these reagents gave the desired product in attenuated yield (entry 11-13). Moreover, we observed recovery of the starting material when reaction was performed in the absence of a base. This observation supported the fact that the base species plays a key role in a desired transformation (entry 14). Also, it was interesting to observe that a catalytic amount of K_2CO_3 exhibited attenuated but reasonable reactivity for the synthesis of 2-aminotetrahydrofuran **3.45a** (entry 15). Reaction time also played a significant role and the best result was observed with shorter reaction time and TLC reaction monitoring (entry 16). Longer reaction times resulted in decreased reactivity for 2-aminotetrahydrofuran **3.45a** with concomitant forming pyrrolidine by-product **3.45a'** (Scheme 3.9). These results showed that the optimal conditions for 2-aminotetrahydrofuran synthesis from **3.42a** and **3.43a** involve the use of K_2CO_3 in CH_2Cl_2 at 0 °C for less than 1 h.

Table 3.3. Optimization of *N*-Vinylhydroxylamine Allenoate Addition and Rearrangement

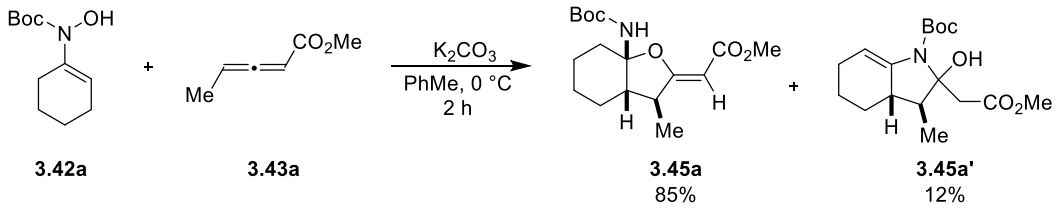


3.42a **3.43a** **3.45a**

Entry	Base	Solvent	Temp. (°C)	% Yield[a]
1	Cs_2CO_3 (1 equiv)	PhMe	25	24
2	Cs_2CO_3 (1 equiv)	PhMe	0	55
3	Cs_2CO_3 (1 equiv)	CH_2Cl_2	0	57
4	Cs_2CO_3 (1 equiv)	DMF	0	46
5	Cs_2CO_3 (1 equiv)	MeCN	0	38
6	Cs_2CO_3 (1 equiv)	Acetone	0	43
7	K_2CO_3 (1 equiv)	CH_2Cl_2	0	83
8	Na_2CO_3 (1 equiv)	CH_2Cl_2	0	58
9	Li_2CO_3 (1 equiv)	CH_2Cl_2	0	54
10	LiOAc (1 equiv)	CH_2Cl_2	0	N.R
11	Et_3N (1 equiv)	CH_2Cl_2	0	N.R
12	DMAP (1 equiv)	CH_2Cl_2	0	15
13	DABCO (1 equiv)	CH_2Cl_2	0	22
14	None	CH_2Cl_2	0	N.R
15	K_2CO_3 (0.2 equiv)	CH_2Cl_2	0	69
16	K_2CO_3 (1 equiv)	CH_2Cl_2	0	93[b]

[a] Condition: **3.42a** (1 equiv), allenoate **3.43a** (2 equiv) in solvent (0.1M).
[b] Reaction time was 30 min.

Scheme 3.9. By-Product Formation with Longer Reaction Time.



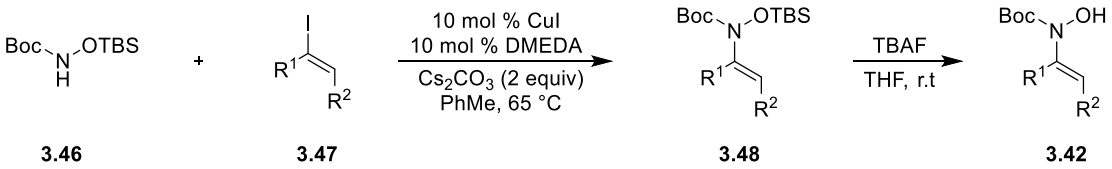
3.42a **3.43a** **3.45a** 85% **3.45a'** 12%

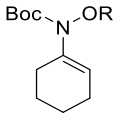
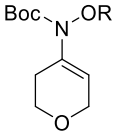
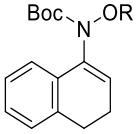
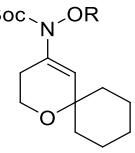
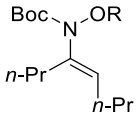
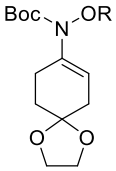
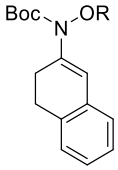
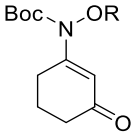
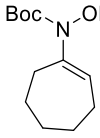
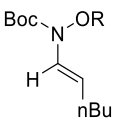
3.4 Ullmann cross-coupling and Deprotection for Preparation of *N*-Alkenylhydroxylamines

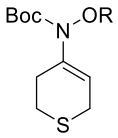
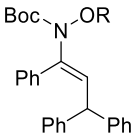
While the *N*-vinylation of hydrazoates have been reported, the corresponding *N*-vinylation of hydroxamates was unknown at the beginning of our study. To prepare a variety of starting materials to test our 2-aminotetrahydrofuran synthesis, we needed to optimize and Ullman coupling process for the synthesis of **3.45** (Table 3.4). I initially discovered our synthetic route to *N*-vinylhydroxylamines **3.42** and my labmate Tyler Reidl helped to optimize the reaction for a variety of substrates. As shown in Table 3.4, an Ullmann C–N coupling of **3.46** and **3.47** generates *N*-alkenyl silyl ethers **3.48**, which are easily demasked by TBAF to introduce *N*-alkenylhydroxylamines **3.42**. For example, *N*-cyclohexenyl silyl ether **3.42a** was successfully prepared in high yield (entry 1). However, reaction with *α*-tetralone-derived vinyliodide **3.47b** gave a decreased yield for **3.48b** (entry 2). Also, it was confirmed that linear alkenyliodide **3.47c** showed promising reactivity for the formation of **3.48c** (entry 3). This symmetrical substitution on *N*-vinyl silyl ether **3.48c** gave an insight for the use of acyclic motif as a starting material. Unlike the *α*-tetralone substrate, *β*-tetralone-derived alkenyliodide afforded **3.48d** in high yield (entry 4). This trend was similarly observed with **3.48a**, Ullmann coupling with 1-iodocycloheptene **3.47e** showed an excellent reactivity for **3.48e** (entry 5). Interestingly, the C–N coupling of **3.46** with heteroatom-containing vinyliodides were shown to be operative to produce **3.48f**-**3.48g**. (entry 6-7). In this case, the vinyliodide bearing an oxygen **3.47g** gave **3.48g** in higher yield than sulfur-containing vinyliodide (entry 7). Also, an installation of spirocyclic substituent on the oxygen-containing ring showed diminished reactivity in lower yield (entry 8). From these resulted screenings (entry 6-8), we presumed that the vinyliodide substrates with less sterics would give better reactivity in C–N bond formations to afford *N*-vinyl silyl ether. In similar, this trend was shown from the coupling with acetal-substituted vinyliodide **3.47I** (entry 9). Installation of ketone on a ring was revealed to provide *N*-alkenyl silyl ether **3.48j** in

lower yield (entry 10). In addition to acyclic vinyliodide **3.47c**, other non-symmetric acyclic vinyliodides such as mono- and disubstituted alkenyliodides were also greatly tolerated in this transformation, providing C–N coupled products **3.48k** and **3.48l** respectively (entry 11 and 12). These results show the *N*-vinyl silyl ethers with acyclic vinyl motifs can be also prepared in good yield with less steric issue. Next deprotection of **3.48a-l** was also tolerated to result in **3.42a-l**. In summary, numerous examples of *N*-vinylhydroxylamines **3.42a-l** were obtained through a copper catalyzed C–N bond formation and silyl deprotection to be investigated for the synthesis of 2-aminotetrahydrofurans.

Table 3.4. Scope of the Synthesis and Deprotection of *N*-Vinylhydroxylamines



Entry	Product	R, % Yield[a][b]	Entry	Product	R, % Yield[a][b]
1	 **3.48a, 3.42a**	TBS = 95 H = 70	7	 **3.48g, 3.42g**	TBS = 94 H = 62
2	 **3.48b, 3.42b**	TBS = 30 H = 77	8	 **3.48h, 3.42h**	TBS = 46 H = 83
3	 **3.48c, 3.42c**	TBS = 76 H = 79	9	 **3.48i, 3.42i**	TBS = 80 H = 60
4	 **3.48d, 3.42d**	TBS = 99 H = 88	10	 **3.48j, 3.42j**	TBS = 51 H = 46
5	 **3.48e, 3.42e**	TBS = 96 H = 54	11	 **3.48k, 3.42k**	TBS = 86 H = 71

6		TBS = 52 H =54	12		TBS = 92 H = 95
	3.48f, 3.42f			**3.48l, 3.42l**	

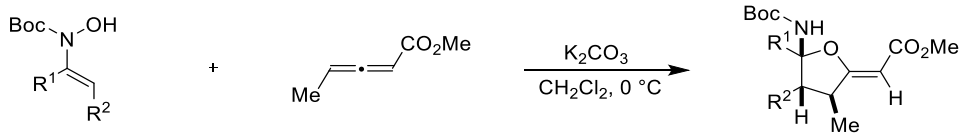
[a]: Isolated yield. Conditions for Ullmann: *O*-Protected hydroxylamine **3.46** (1 equiv), alkenyliodide **3.47** (2 equiv), CuI (0.1 equiv), DMEDA (0.1 equiv), Cs_2CO_3 (2 equiv), 0.1 M in PhMe, 65 ˚C, 18 h. Optimization of Ullmann coupling is listed in supporting information. [b]: Conditions for deprotection: TBAF (1.1 equiv) in 0.1 M THF, 25 ˚C, 30 min.

3.5 Scope of Synthesis of 2-Aminotetrahydrofurans Through the [3,3']-Rearrangement of *N*,*O*-Divinylhydroxylamines

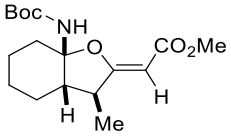
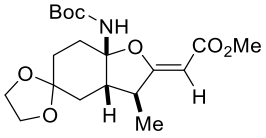
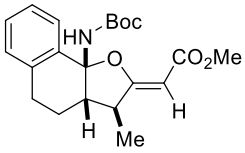
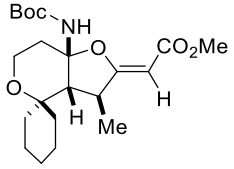
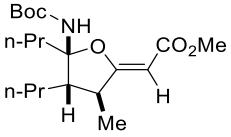
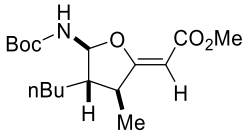
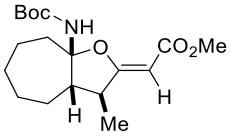
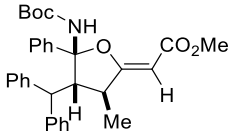
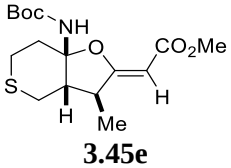
With a variety of *N*-alkenylhydroxylamines **3.42** in hand, we decided to test the reactivity of these compounds for the synthesis of 2-aminotetrahydrofuran **3.45** with allenoate **3.43a**. As shown in Table 3.5, a variety of fused- and non-fused-2-aminotetrahydrofurans **3.45** were successfully obtained in one-pot reaction. Hydroxylamines bearing an *N*-cyclohexenyl group **3.42a** or a *α*-tetralone-derived *N*-vinyl substituent **3.42b** underwent the oxa-Michael addition and spontaneous [3,3']-rearrangement to afford **3.45a** and **3.45b** in high yield with excellent diastereoselectivity (entry 1 and 2). The structure of 2-aminotetrahydrofuran **3.45a** was verified by an X-ray crystallography study performed by Prof. Donald J. Wink. Switching to a symmetrical acyclic alkenyl moiety on nitrogen, showed good reactivity but decreased the diastereoselectivity to 2:1 ratio (entry 3). ^{1}H NMR spectroscopy nOe analysis showed that the minor isomer exhibited inversion at the hemiaminal ether stereocenter. Also, a substrate with a cycloheptenyl substituent **3.42e** smoothly converted to **3.45d** with high diastereoselectivity (entry 4). Cyclic systems bearing heteroatoms were tolerated in this transformation and proved the corresponding products **3.45e-g** with an excellent diastereoselectivity in higher yields (entry 5-7). Cyclic and heterocyclic substrates with ketal **3.42i** and spirocyclohexyl **3.42h** functionalities were also operative with an excellent stereoselectivity (entry 8 and 9). We were surprised that monosubstituted acyclic *N*-alkenyl substrate **3.42k** gave a formation of 2-aminotetrahydrofuran **3.45j** with enhanced diastereoselectivity in comparison to **3.45c** (entry 10). Also, a non-symmetrical disubstitution system with a sterically encumbered substituent on *β*-position provided the desired product **3.45k** with an increased diastereoselectivity (entry 11). These results from acyclic motifs **3.45c**, **3.45j** and **3.45k** imply that manipulating in shape and size of alkenyl groups results in changes in diastereoselectivity. We believe this trend is caused by sterics of vinyl group on nitrogen. Another decrease in dr was observed for cyclic

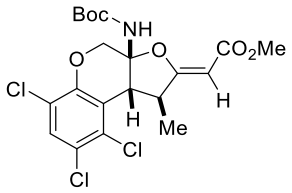
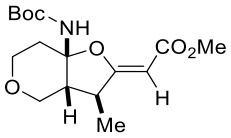
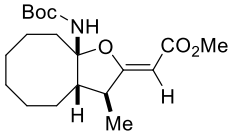
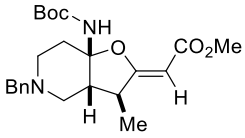
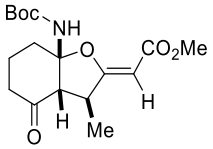
substrates bearing aryl group at the *β*-position (entry 12). In contrast to six- and seven-membered rings **3.45a** and **3.45d**, a product **3.45m** from medium-sized larger ring, however, was not observed (entry 13). Instead, a formation of pyrrolidine **3.45m'** was shown in 45% yield (Scheme 3.9). This suggests that ring-strain favors *N*-cyclization after [3,3']-rearrangement. Moreover, installation of ketone on *β*-position also did not show a desired product **3.39n** (entry 14), but instead gave 2,3-dihydro-pyrrole **3.39n'** (Scheme 3.9). These results showed that cyclic, fused-cyclic, and heterocyclic substrates were tolerated but acyclic substrates' trend seemed to control the diastereoselectivity of these rearrangements and cyclizations.

Table 3.5. Scope of *N*-Vinylhydroxylamines for the Synthesis of 2-Aminotetrahydrofurans



3.42 **3.43a** **3.45**

Entry	Product	% Yield[a]	Entry	Product	% Yield[a]
1	 **3.45a**	91 dr = 20:1	8	 **3.45h**	71 dr = 20:1
2	 **3.45b**	83 dr = 20:1	9	 **3.45i**	89 dr = 20:1
3	 **3.45c**	73 dr = 2:1	10	 **3.45j**	46 dr = 8:1
4	 **3.45d**	73 dr = 20:1	11	 **3.45k**	68 dr = 7:1
5	 **3.45e**	78 dr = 20:1	12		82 dr = 2:1

				 **3.45l**	
6	 **3.45f**	94 dr = 20:1	13	 **3.45m**	0[b]
7	 **3.45g**	85 dr = 20:1	14	 **3.45n**	0[c]

[a]: Isolated yield. Conditions: *N*-alkenylhydroxylamine **3.42** (1 equiv), allene **3.43a** (2 equiv), K_2CO_3 (1 equiv), 0.1 M in CH_2Cl_2, 0 ˚C. Reaction was monitored by TLC.

Scheme 3.10. Formation of Pyrrolidines as By-Product.

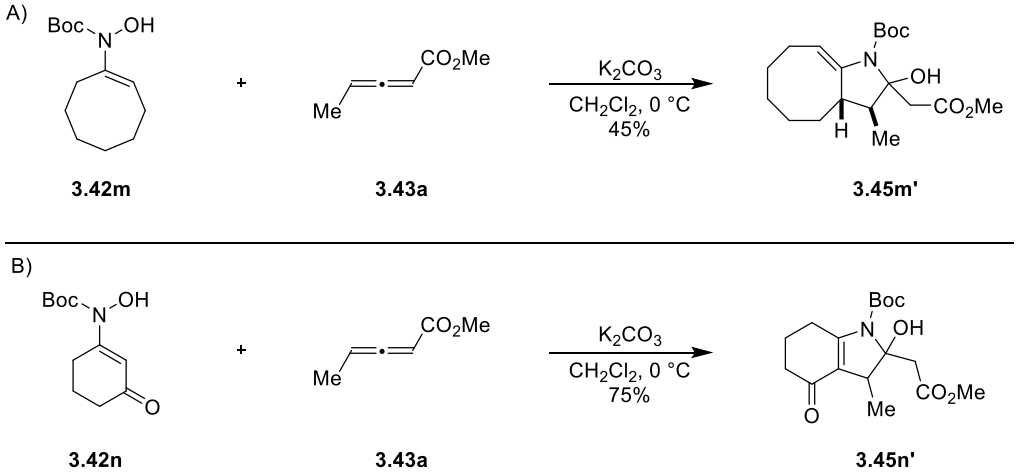
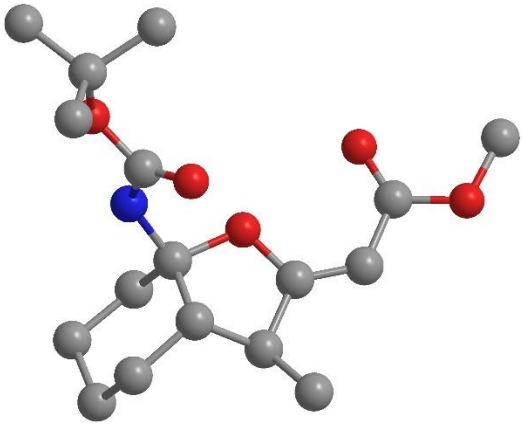
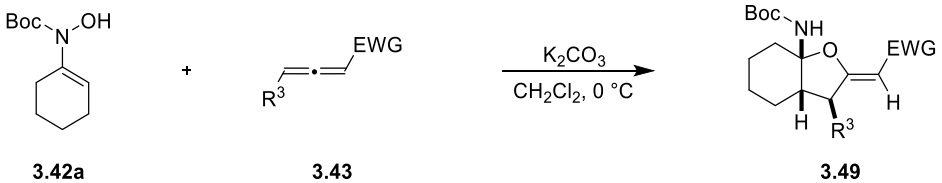


Figure 3.1. X-Ray Crystallography of **3.45a** (CCDC 1814362) by Prof. Donald J. Wink

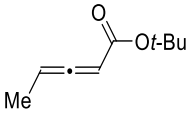
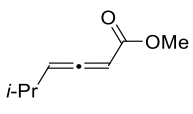


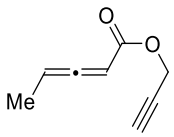
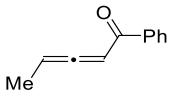
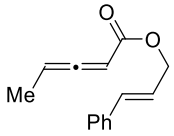
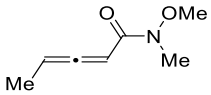
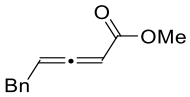
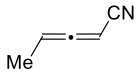
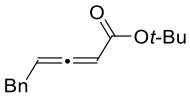
We further investigated the scope of the 2-aminotetrahydrofuran synthesis with several different allenes **3.43** and *N*-cyclohexenylhydroxylamine **3.42a** (Table 3.6). Firstly, *t*-butyl allenoate **3.43b**, propargylic allenoate **3.43c**, and *trans*-phenyl allyl allenoate **3.43d** afforded the desired products **3.49a**, **3.49b** and **3.49c** in high yields with excellent diastereoselectivity (entry 1-3). Variation of the substituent at the γ-position of the allene the blank trend in yield with consistently high diastereoselectivity. Further examination of allenes with other electron-withdrawing groups showed that ketone **3.43h**, Weinreb amide **3.43i**, and nitrile **3.43j** were tolerated for the formation of **3.49g**, **3.49h**, and **3.49i** respectively (entry 7-9). These results indicated the scope of the 2-aminotetrahydrofuran synthesis and provided a variety of compounds to examine the reactivity of these novel compounds.

Table 3.6. Scope of Electron-deficient Allenes



3.42a **3.43** **3.49**

Entry	Allene	% Yield[a] **3.49**	Entry	Allene	% Yield[a] **3.49**
1	 **3.43b**	86 **3.49a**	6	 **3.43g**	34 **3.49f**

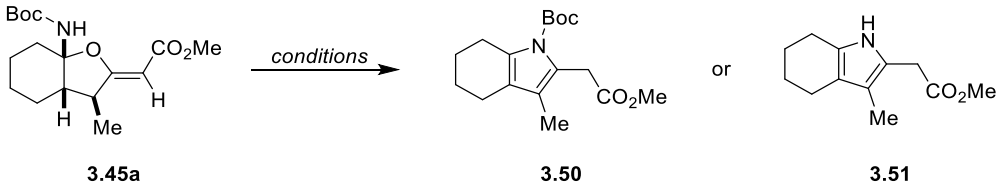
2	 **3.43c**	90 **3.49b**	7	 **3.43h**	72 **3.49g**
3	 **3.43d**	91 **3.49c**	8	 **3.43i**	73 **3.49h**
4	 **3.43e**	81 **3.49d**	9	 **3.43j**	48 **3.49i**
5	 **3.43f**	65 **3.49e**			

[a]: Isolated yield. Conditions: *N*-alkenylhydroxylamine **3.42a** (1 equiv), allene **3.43** (2 equiv), K_2CO_3 (1 equiv), 0.1 M in CH_2Cl_2, 0 ˚C. Reaction was monitored by TLC.

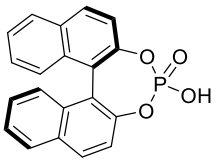
3.6 Functionalization of 2-Aminotetrahydrofurans

While the conditions described for the synthesis of 2-aminotetrahydrofurans **3.45a** from *N*-vinylhydroxylamine **3.42a** and allenoate **3.43a** give the desired product in good yield, treatment of **3.45a** under thermal conditions give the corresponding thermodynamically favored pyrrole. Having determined conditions that allowed us to access these elusive Paal-Knorr intermediates, we decided to determine if these compounds could be used to access other structures from these 1,4-iminoketone derivatives. Unsurprisingly, treatment of **3.45a** with Lewis acid or Brønsted acid led to expected pyrrole formation. Catalytic amount of $TiCl_4$ showed a quantitative transformation towards *N*-protected pyrrole **3.50** (entry 1). Similarly, catalytic 10 wt % Pd/C with H_2 afforded same product **3.50** in high yield (entry 2). Also, phosphoric acid catalyst provided a rapid formation of protected pyrrole **3.50** (entry 3). Longer reaction time in the presence of acid anhydride resulted in a pyrrole **3.51** in 71% yield (entry 4). As an alternative approach we wondered if basic conditions could lead to a C-C bond forming rearrangement instead of pyrrole formation.

Table 3.7. Pyrrole Formations under Acidic Condition



3.45a **3.50** **3.51**

Entry	Condition	% Yield **3.50** or **3.51**[a]
1	10 mol % $TiCl_4$	100 (**3.50**)
2	10 mol % of 10 wt % Pd/C with H_2 (1 atm)	99 (**3.50**)
3	10 mol % of 	94 (**3.50**)
4[b]	TFA (2 equiv)	71 (**3.51**)

[a]: Isolated yield. Conditions: 2-Aminotetrahydrofuran **3.45a** (1 equiv), 0.1 M in CH_2Cl_2, 25 ˚C, 2 h.

As shown in Scheme 3.11, we were excited to observe that 2-aminotetrahydrofurans **3.42a** and **3.42h** convert to fused-cyclopentenone **3.53a** and **3.53b** in excellent diastereoselectivity when treated with base. It is noteworthy that this base-mediated intramolecular aza-Petasis-Ferrier rearrangement is unprecedented. Also, we were delighted to observe that the 2:1 ratio diastereomers of acyclic 2-aminotetrahydrofuran **3.53c** provided cyclopentenone product **3.53c** with diastereomeric ratio increase. Based on this intramolecular [1,3]-rearrangement, we further speculated that the use of an alkyl electrophiles could trap the reactive *β*-ketoester fragment before resulting ring-closure to cyclopentenones **3.53**. In this series, we were gratified to see two consecutive C–C bond formations, yielding methylated cyclopentanone **3.54a** from **3.45a** without cyclopentenone formation. The stereochemistry was confirmed by X-ray crystallographic analysis by prof. Donald Wink (Figure 3.2). It was revealed that alkylation with a propargyl group was also available to introduce **3.54b**. These transformations were general for other substrate such as spirocyclic heterocyclic system **3.45i.** Same conditions provided unexpected cyclopentanones **3.54d** and **3.54e** without any alkylation process. These substrates were shown to be different from the observed transformation, however it is still interesting since the formation of cyclopentanones were resulted in with high diastereoselectivity. All of alkylated cyclopentanones **3.54** were shown without an erosion of diastereoselectivity. In short, we were

successfully able to prepare highly substituted cyclopentenones **3.53** and alkylated cyclopentanones **3.54** through base-mediated aza-Petasis-Ferrier rearrangement of 2-aminotetrahydrofurans.

Scheme 3.11. Functionalizations through Aza-Petasis-Ferrier Rearrangement

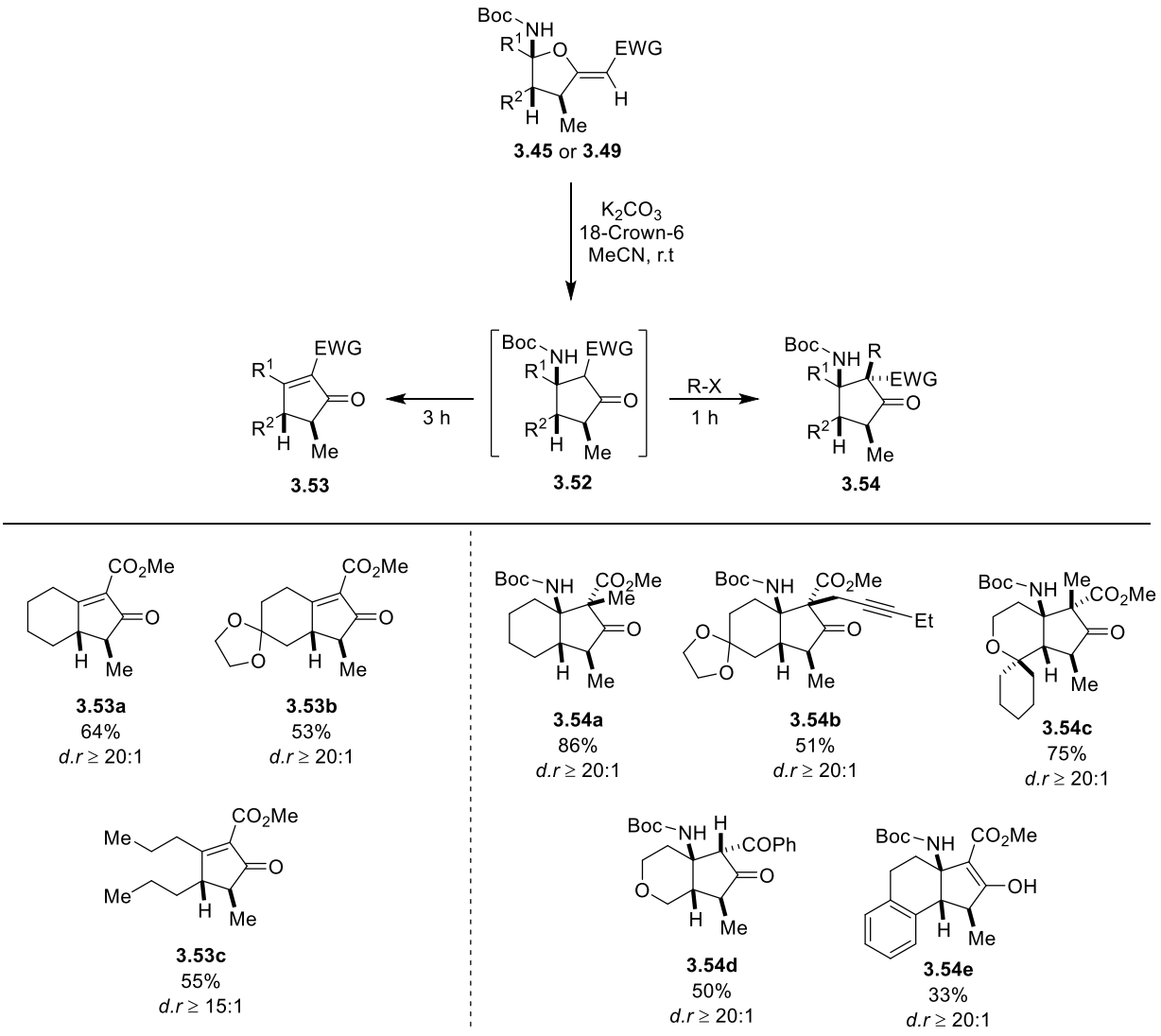
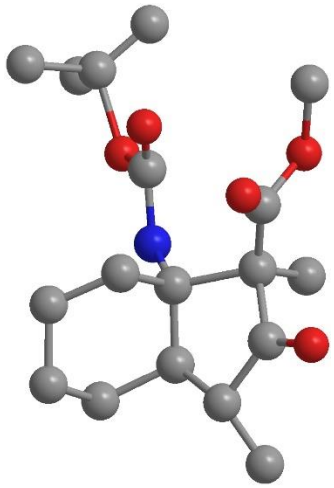


Figure 3.2. X-Ray Crystallography of **3.54a** (CCDC 1814364) by Prof. Donald J. Wink



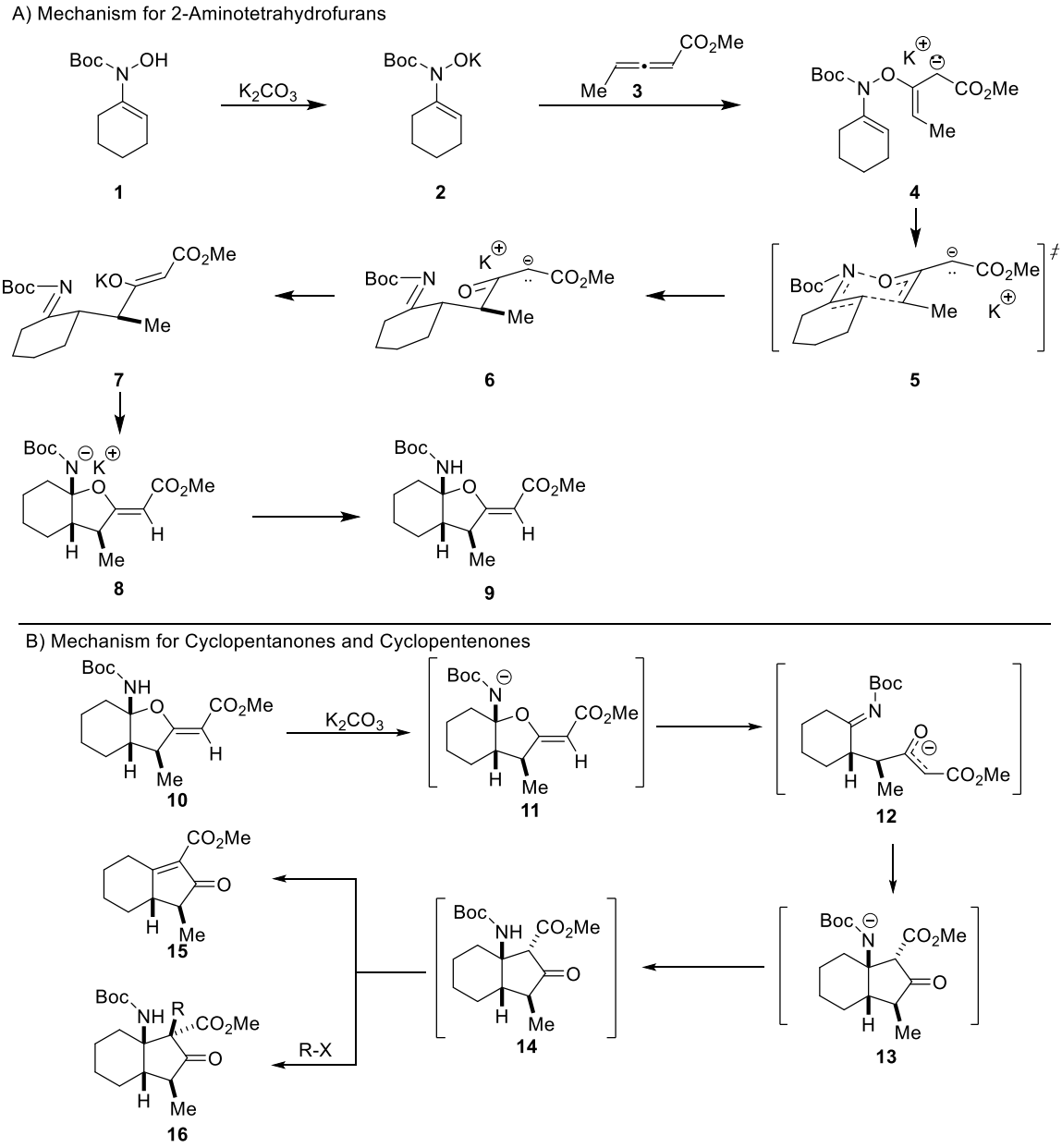
In summary, functionalizations of 2-aminotetrahydrofurans introduce novel accesses to key cyclic motifs through ring-opening process of **3.45**. Pyrroles can be uniformly generated from 2-aminotetrahydrofurans **3.45a** by a series of acids. In contrast to these conditions, the addition of base facilitates the conversion of 2-aminotetrahydrofurans **3.45** via a Aza-Petasis-Ferrier rearrangement to afford cyclopentenones **3.53**. Also, incorporation of alkyl group was observed in the presence of alkyl electrophiles, which provides various sophisticated cyclopentanones **3.54** without an erosion of diastereoselectivity. These discovered valuable transformations shed light on an efficient access to not only highly-substituted pyrroles, but also sophisticated cyclopentanones and cyclopentenones, which scaffolds are abundant in synthetically and naturally occurring compounds expected to have potent biological activities.

3.7 Proposed Mechanism

A plausible reaction mechanism for the formation of 2-aminotetrahydrofuran from *N*-alkenylhydroxylamine **3.42a** and electron-deficient allene **3.43a** is shown in Scheme 3.11A. Potassium carbonate initiates the reaction by deprotonating a proton from hydroxyl group of **1** to form **2**, which undergoes oxa-Michael addition to electron-poor allene **3**. This adduct, *N*,*O*-dialkenylhydroxylamine intermediate **4**, undergoes a [3,3']-rearrangement to form 1,4-iminoketone enolate intermediate **6** via six-membered ring transition state **5**. Then, a potassium enolate **7** cyclizes to **8** through C–O bond formation, affording a desired product **9**. Also, the mechanism for aza-Petasis-Ferrier is described in Scheme 3.12B. It is presumably expected that 2-aminotetrahydrofuran **10** undergoes ring-opening and

ring-closure processes via C–C bond formation to afford cyclopentanone **14** under basic condition. This pre-formed cyclopentanone **14** is converted to cyclopentenones **15** or alkylated cyclopentanones **16**.

Scheme 3.12. Plausible Mechanism



3.8 Conclusion

To summarize, we have successfully explored for a synthesis of 2-aminotetrahydrofurans through a [3,3']-rearrangement by aiming on generation of *N*,*O*-divinylhydroxylamines from *N*-alkenylhydroxylamines and allenoates. Catalytic copper catalyzed Ullmann reaction leverages simply *N*-Boc-hydroxylamine silyl ether and

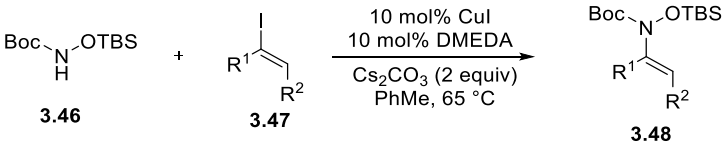
iodoalkene substrates to introduce a variety of *N*-alkenylhydroxylamines with great functional group tolerance. While screening several reaction parameters for preparation of 2-aminotetrahydrofurans, we selected K_2CO_3 (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C as an optimal condition. The scope of the preparation of 2-aminotetrahydrofurans was investigated and displayed to be successfully tolerated for both cyclic and acyclic *N*-alkenylhydroxylamine substrates. Also, a variety of electron-poor allenes were consistent in this transformation, affording 2-aminotetahydrofurans with excellent diastereoselectivity. Interestingly, late-stage diversification of 2-aminotetrahydrofurans uncovered their propensity for ring-openings to yield highly substituted pyrroles, sophisticated cyclopentanones and cyclopentenones. These synthetically versatile functionalizations of nucleoside analogues leverage to afford a plethora of biologically active complicated molecules consisted of pyrroles and cyclopentanones.

3.9. Supporting Information

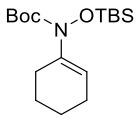
3.9.1 General Experimental Information

^{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.[41]. *N*-(Boc)hydroxylamine silyl ether **3.48**[106] and alkenyl iodides **3.47a**,[107] **3.47c**,[108] **3.47e**,[109] **3.47h**,[110] **3.47l**,[111] and **3.41m**,[112] were prepared by known methods. Alkenyl iodide **3.47k** was purchased from Sigma-Aldrich. A basic workup described for analogous vinyl iodide syntheses was used to maximize yield.[113] Allenes **3.43a**,[114] **3.43b**,[115] **3.43c** and **3.43e**,[79] **3.43g**,[116] and **3.43i**[117] were also prepared by known methods.

3.9.2 Experimental Procedure for 3.42 Through Ullmann C–N Cross-Coupling (Table 3.4)

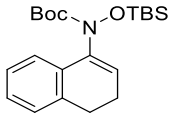


General Procedure A: A conical vial was charged with *N*-Boc-*O*-siloxy hydroxylamine **3.46** (1.0 equiv), CuI (10 mol %), *N*,*N*'-dimethylethylenediamine (DMEDA) (10 mol %), Cs_2CO_3 (2.0 equiv), an alkenyliodide **3.47** (2.0 equiv), and toluene to form a 0.3–1.0 M solution of **3.46**. The reaction 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 **3.48**.



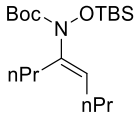
3.48a

***N*-Siloxyenamine 3.48a:** Compound **3.48a** was prepared by general procedure A. *N*-Boc-*N'*-silyl hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 1-iodocyclohexene **3.47a** (0.208 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs2CO3 (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 **3.48a** as a clear oil (0.156 g, 95%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C17H33NO3SiNa (M+Na)+ 350.2127, found 350.2119.



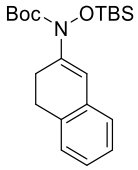
3.48b

***N*-Siloxyenamine 3.48b:** Compound **3.48b** was prepared using general procedure A with the following reagents: *N*-Boc-*N'*-silyl hydroxylamine **3.46** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.010 g, 0.050 mmol, 0.1 equiv), *N*,*N*'-dimethylethylenediamine (0.005 g, 0.050 mmol, 0.1 equiv), Cs_2CO_3 (0.326 g, 1.00 mmol, 2.0 equiv), and 4-iodo-1,2-dihydronaphthalene (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% EtOAc in hexane) to afford *N*-siloxyenamine **3.48b** 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.



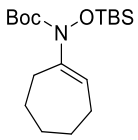
3.48c

***N*-Siloxyenamine 3.48c:** Compound **3.48c** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.231 g, 1.00 mmol) and *(E)*-4-iodooct-4-ene **3.47c** (0.476 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0082 g, 0.10 mmol), Cs2CO3 (0.652 g, 2.00 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 **3.48c** as a colorless oil (0.272 g, 76%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C19H39NO3SiNa (M+Na)+ 380.2597, found 380.2590.



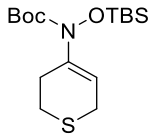
3.48d

***N*-Siloxyenamine 3.48d:** Compound **3.48d** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 3-iodo-1,2-dihydronaphthalene **3.47d** (0.256 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.0050 g, 0.050 mmol), and Cs2CO3 (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 (4% Et2O in hexanes) to afford *N*-siloxyenamine **3.48d** as a yellow oil (0.372 g, 99%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C21H33NO3SiNa (M+Na)+ 398.2127, found 398.2114.



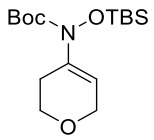
3.48e

***N*-Siloxyenamine 3.48e:** Compound **3.48e** was prepared by general procedure A. *N*-Boc-*N'*- siloxyhydroxylamine **3.46** (0.247 g, 1.00 mmol) and 1-iodocycloheptene **3.47e** (0.222 g, 1.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0090 g, 0.10 mmol), and Cs2CO3 (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 **3.48e** as a white solid (0.328 g, 96%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C18H35NO3SiNa (M+Na)+ 364.2284, found 364.2274; m.p: 25 – 28 °C.



3.48f

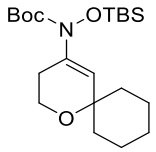
***N*-Siloxyenamine 3.48f:** Compound **3.48f** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 4-iodo-3,6-dihydro-2*H*-thiopyran **3.47f** (0.226 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs2CO3 (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% Et2O in hexanes) to afford *N*-siloxyenamine **3.48f** as a light yellow oil (0.0898 g, 52%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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.



3.48g

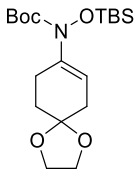
***N*-Siloxyenamine 3.48g:** Compound **3.48g** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 4-iodo-3,6-dihydro-2*H*-pyran **3.47g** (0.210 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs2CO3 (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 **3.48g** as a clear oil (0.153 g, 93%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C16H31NO4SiNa (M+Na)+ 352.1920, found 352. 1911.



3.48h

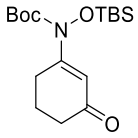
***N*-Siloxyenamine 3.48h:** Compound **3.48h** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 4-iodo-1-oxaspiro[5.5]undec-4-ene **3.47h** (0.278 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs2CO3 (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 **3.48h** as a clear oil (0.0915 g, 46%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C21H39NO4SiNa (M+Na)+ 420.2546, found 420.2540.



3.48i

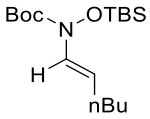
***N*-Siloxyenamine 3.48i:** Compound **3.48i** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and 8-iodo-1,4-dioxaspiro[4.5]dec-7-ene **3.47i** (0.266 g, 1.00 mmol) were treated with CuI (0.0095 g, 0.050 mmol), DMEDA (0.0044 g, 0.050 mmol), and Cs2CO3 (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 **3.48i** as a white solid (0.160 g, 83%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C19H35NO5SiNa (M+Na)+ 408.2182, found 408.2179; m.p.: 61 – 63 °C.



3.48j

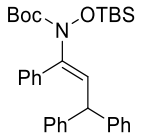
***N*-Siloxyenamine 3.48j:** Compound **3.48j** was prepared using general procedure A with the following reagents: *N*-Boc-*N*'-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.0190 g, 0.100 mmol, 0.2 equiv), *N*,*N*'-dimethylethylenediamine (0.0176 g, 0.200 mmol, 0.4 equiv), Cs_2CO_3 (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.



3.48k

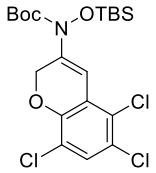
***N*-Siloxyenamine 3.48k:** Compound **3.48k** was prepared by general procedure A. *N*-Boc-*O*-siloxy hydroxylamine **3.46** (0.231 g, 1.00 mmol) and *trans*-1-iodo-1-hexene **3.47k** (0.420 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.0082 g, 0.10 mmol) and Cs2CO3 (0.652 g, 2.00 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 **3.48k** as a colorless oil (0.285 g, 86%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C17H35NO3SiNa (M+Na)+ 352.2284, found 352.2274.



3.48l

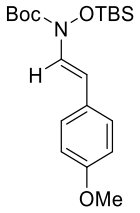
***N*-Siloxyenamine 3.48l:** Compound **3.48l** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol) and (*E*)-(3-iodoprop-2-ene-1,1,3-triyl)tribenzene **3.47l** (0.396 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.005 g, 0.05 mmol), and Cs2CO3 (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 **3.48l** as a yellow oil (0.475 g, 92%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 C32H41NO3SiNa (M+Na)+ 538.2753, found 538.2755; m.p: 75 –78 °C.



S3-1

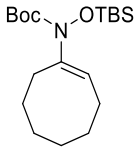
***N*-Siloxyenamine S3-1:** Compound **S3-1** was prepared by general procedure A. *N*-Boc-*N'*-siloxy hydroxylamine **3.40** (0.124 g, 0.500 mmol) and 5,6,8-trichloro-3-iodo-2*H*-chromene **3.41m** (0.361 g, 1.00 mmol) were treated with CuI (0.010 g, 0.050 mmol), DMEDA (0.005 g, 0.05 mmol), and Cs2CO3 (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 **S3-1** as a clear oil (0.418 g, 87%). 1H NMR (500 MHz, CDCl3): 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); 13C{1H} NMR (125 MHz, CDCl3): 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 (EI) *m/z* calcd. for C20H28NO4Cl3Si (M)+ 479.0853, found 479.0853.



S3-2

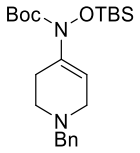
***N*-Siloxyenamine S3-2**: Compound **S3-2** was prepared by general procedure A. *N*-Boc-*O*-siloxy hydroxylamine **3.46** (0.231 g, 1.00 mmol) and (*E*)-1-(2-iodovinyl)-4-methoxybenzene **3.47n** (0.390 g, 2.00 mmol) were treated with CuI (0.0190 g, 0.100 mmol), DMEDA (0.00882 g, 0.100 mmol), and Cs2CO3 (0.651 g, 2.00 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 **S3-2** as a clear oil (0.762 g, 100%). 1H NMR (500 MHz, CDCl3): δ 7.41 (d, *J* = 14.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.08 (d, *J* = 14.0 Hz, 1H), 3.79 (s, 3H), 1.55 (s, 9H), 1.06 (s, 9H), 0.21 (s, 6H); 13C{1H} NMR (125 MHz, CDCl3): δ 158.1, 153.1, 129.3, 126.6, 126.0, 114.1, 108.9, 82.7, 55.3, 28.2, 25.9, 18.1, - 4.7; IR (thin film) 2960, 2931, 2872, 1743, 1709, 1619, 1496, 1455, 1434, 1354 cm-1; HRMS (ESI) m/z calcd. for C20H33NO4SiNa (M+Na)+ 402.2077, found 402.2073.



S3-3

***N*-Siloxyenamine S3-3:** Compound **S3-3** was prepared using general procedure with the following reagents: *N*-Boc-*O*-siloxy hydroxylamine **3.40** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.0190 g, 0.100 mmol, 0.2 equiv), *N*,*N*'-dimethylethylenediamine (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 (2% EtOAc in hexane) to afford *N*-siloxyenamine **S3-3** 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)

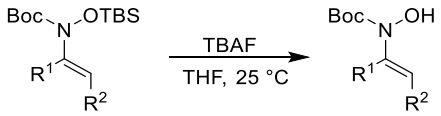
2977, 2915, 2856, 1721, 1705, 1689, 1496, 1479, 1468, 1375 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{37}NNaO_3Si(M+Na)^+$ 378.2440, found 378.2433.



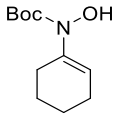
S3-7

***N*-Siloxyenamine S3-7**: Compound **S3-7** was prepared using general procedure A with the following reagents: *N*-Boc-O-siloxy hydroxylamine **3.46** (0.124 g, 0.500 mmol, 1.0 equiv), CuI (0.010 g, 0.050 mmol, 0.1 equiv), *N*,*N*'-dimethylethylenediamine (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 (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 (2% EtOAc in hexane) to afford *N*-siloxyenamine **S3-7** 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.

3.9.3 Experimental Procedure for 3.42 Through Deprotection using TBAF

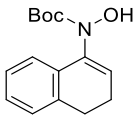


General Procedure B: A round bottom flask was charged with *N*-siloxyenamine **3.48** (1.0 equiv) and diluted with THF to form a 0.1 M solution. TBAF (1.0 M in THF, 1.1 equiv) was then added to the solution of **3.48** via syringe and the reaction mixture was allowed to stir for 20 min at 25 °C. The 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 **3.42**.



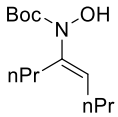
3.42a

***N*-Hydroxyenamine 3.42a:** Compound **3.42a** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48a** (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 **3.42a** 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.



3.42b

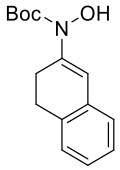
***N*-Hydroxyenamine 3.42b:** Compound **3.42b** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48b** (0.341 g, 0.908 mmol), THF (9.0 mL), and TBAF (1.0 M in THF, 0.9 mL, 0.900 mmol). The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:50 EtOAc:hexanes) to afford *N*-hydroxyenamine **3.42b** 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.



3.42c

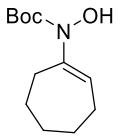
***N*-Hydroxyenamine 3.42c:** Compound **3.42c** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48c** (0.165 g, 0.461 mmol), THF (4.6 mL), and TBAF (1.0 M in THF, 0.461 mL, 0.461 mmol).

The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:50 EtOAc:hexanes) to afford **3.42c** 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 $C_{13}H_{25}NO_3Na$ $(M+Na)^+$ 266.1732, found 266.1731.



3.42d

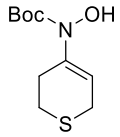
***N*-Hydroxyenamine 3.42d:** Compound **3.42d** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48d** (0.469 g, 1.25 mmol), THF (13.0 mL), and TBAF (1.0 M in THF, 1.25 mL, 1.25 mmol). The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:50 EtOAc:hexanes) to afford **3.42d** 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.



3.42e

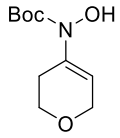
***N*-Hydroxyenamine 3.42e:** Compound **3.42e** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48e** (0.867 g, 2.54 mmol), THF (25.0 mL), and TBAF (1.0 M in THF, 2.54 mL, 2.54 mmol). The crude mixture was purified by medium pressure column chromatography (100% hexanes – 1:25 EtOAc:hexanes) to afford **3.42e** 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, 17H), 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 $C_{12}H_{22}NO_3$ $(M+H)^+$ 228.1594, found 228.1569; m.p: 28 – 33 °C.



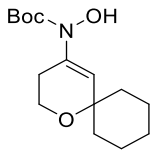
3.42f

***N*-Hydroxyenamine 3.42f:** Compound **3.42f** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48f** (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 (100% hexane – 1:5 EtOAc:hexanes) to afford **3.42f** 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.



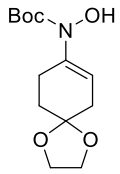
3.42g

***N*-Hydroxyenamine 3.42g:** Compound **3.42g** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48g** (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 (100% hexanes – 1:6 EtOAc:hexanes) to afford **3.42g** as a white solid (0.0607 g, 62%). ^{1}H 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{^{1}H} 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.



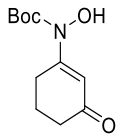
3.42h

***N*-Hydroxyenamine 3.42h:** Compound **3.42h** was prepared using general procedure A with the following reagents: *N*-siloxyenamine **3.48h** (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 (100% hexane – 1:9 EtOAc:hexanes) to afford **3.42h** 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-Boc+ 2H)$^+$ 184.1332, found 184.1337; m.p: 68 – 72 °C.



3.42i

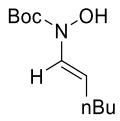
***N*-Hydroxyenamine 3.42i:** Compound **3.42i** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48i** (0.460 g, 1.19 mmol), THF (12.0 mL), and TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol). The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:2 EtOAc:hexanes) to afford **3.42i** 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 294.1316; m.p: 54 – 57 °C.



3.42j

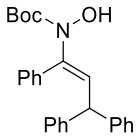
***N*-Hydroxyenamine 3.42j:** Compound **3.42j** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48j** (0.524 g, 1.53 mmol), THF (15.0 mL), and TBAF (1.0 M in THF, 1.53 mL, 1.53 mmol). The crude mixture was purified by medium pressure chromatography (100% hexanes – 1:2 EtOAc:hexanes) to afford **3.42j** as a white solid (0.159 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (br, 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 °C.



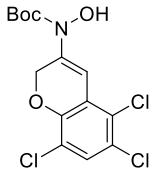
3.42k

***N*-Hydroxyenamine 3.42k:** Compound **3.42k** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48k** (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 (100% hexane – 1:20 EtOAc:hexanes) to afford **3.42k** as a colorless oil (0.0234 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (br, 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.



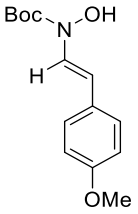
3.42l

***N*-Hydroxyenamine 3.42l:** Compound **3.42l** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **3.48l** (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 (100% hexane – 1:25 EtOAc:hexanes) to afford **3.42l** 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, CDCl3): 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.



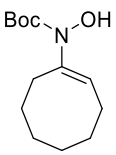
S3-4

***N*-Hydroxyenamine S3-4:** Compound **S3-4** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **S3-1** (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 (100% hexanes – 1:4 EtOAc:hexanes) to afford **S3-4** 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{^{1}H} 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.



S3-5

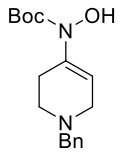
***N*-Hydroxyenamine S3-5:** Compound **S3-5** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **S3-2** (0.748 g, 1.97 mmol), THF (20.0 mL), and TBAF (1.0 M in THF, 1.97 mL, 1.97 mmol). The crude mixture was purified by medium pressure column chromatography (100% hexanes – 1:25 EtOAc:hexanes) to afford **S3-5** as a colorless oil (0.373 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (br, 1H), 7.26 – 7.23 (m, 3H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.23 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 1.54 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.2, 152.1, 129.2, 126.6, 122.7, 114.1, 108.4, 83.7, 55.3, 28.2; IR (thin film) 3184, 3096, 2958, 2932, 1708, 1649, 1607, 1576, 1512, 1456 cm-1; HRMS (ESI) *m/z* calcd. for $C_{14}H_{19}NO_4Na$ $(M+Na)^+$ 288.1212, found 288.1205.



S3-6

***N*-Hydroxyenamine S3-6:** Compound **S3-6** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **S3-3** (0.265 g, 0.745 mmol), THF (7.4 mL), and TBAF (1.0 M in THF, 0.745 mL, 0.745 mmol,

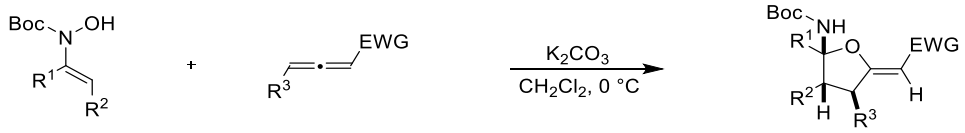
1.0 equiv). The crude mixture was purified by column chromatography (flush with 200 mL of hexane then start to increase polarity to 1:50; EtOAc:hexane) to afford **S3-6** as a white solid (0.113 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (brs, 1H), 5.64 (t, *J* = 8.5 Hz, 1H), 2.41 – 2.28 (m, 2H), 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}.



S3-8

***N*-Hydroxyenamine S3-8:** Compound **S3-8** was prepared using general procedure B with the following reagents: *N*-siloxyenamine **S3-7** (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 (flush with 200 mL of hexane then start to increase polarity to 1:50; EtOAc:hexane) to afford **S3-8** 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.

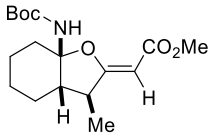
3.9.4 Experimental Procedure for 2-Aminotetrahydrofurans 3.45 and 3.49 (Table 3.5-3.6)



3.42a + **3.43** → **3.45** or **3.49**

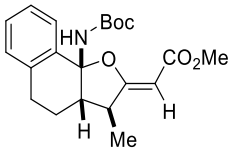
General Procedure C: A scintillation vial was charged with *N*-hydroxyenamine **3.42** (1.0 equiv) and K_2CO_3 (1.0 equiv). These solids were suspended in CH_2Cl_2 to form a 0.1 M solution, which was cooled to 0 °C in an ice bath for 5 min. At this time, allene **3.43** (2.0 equiv) was added dropwise via syringe and the reaction mixture was allowed to continue to stir at 0 °C. After the complete addition of **3.43**, reaction progress was monitored by TLC for disappearance of **3.42** and appearance of **3.45** or **3.49**. Upon consumption of **3.36**, 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:hexanes) to afford the substituted tetrahydrofuran **3.45** or **3.49**.



3.45a

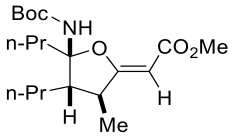
Tetrahydrofuran 3.45a: Compound **3.45a** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43a** (0.0224 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **3.42a** = 0.40 and R_f of **3.45a** = 0.30; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45a** 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.



3.45b

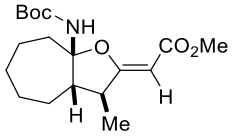
Tetrahydrofuran 3.45b: Compound **3.45b** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42b** (0.0584 g, 0.223 mmol), K_2CO_3 (0.0308 g, 0.223 mmol), CH_2Cl_2 (2.2 mL), and allenoate **3.43a** (0.0500 g, 0.446 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **3.42b** = 0.20 and R_f of **3.45b** = 0.25; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45b** 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 (Br, 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 °C.



3.45c

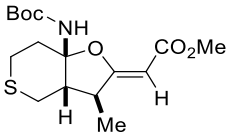
Tetrahydrofuran 3.45c: Compound **3.45c** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42c** (0.0798 g, 0.328 mmol), K_2CO_3 (0.0453 g, 0.328 mmol), CH_2Cl_2 (3.2 mL), and allenoate **3.43a** (0.0736 g, 0.328 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42c** = 0.40 and R_f of **3.45c** = 0.25; PAA stain). Chromatography (1:10; EtOAc:hexanes) afforded **3.45c** as a white solid (0.0851 g, 73%, dr = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 5.00 (br, 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 (br, 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.



3.45d

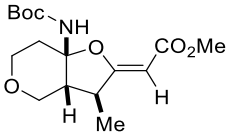
Tetrahydrofuran 3.45d: Compound **3.45d** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42e** (0.0455 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **3.43a** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42e** = 0.35 and R_f of **3.45d** = 0.17; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45d** as a white solid (0.0498 g, 73%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (br, 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; HRMS(ESI) m/z calcd. for $C_{18}H_{29}NO_5Na$ $(M+Na)^+$ 362.1943, observed 362.1938; m.p: 101 – 105 °C.



3.45e

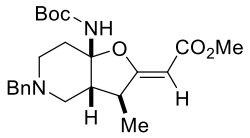
Tetrahydrofuran 3.45e: Compound **3.45e** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42f** (0.0694 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **3.43a** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42f** = 0.20 and R_f of **3.45e** = 0.23; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45e** as a white solid (0.0804 g, 78%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (br, 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.



3.45f

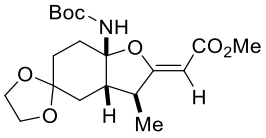
Tetrahydrofuran 3.45f: Compound **3.45f** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42g** (0.0327 g, 0.152 mmol), K_2CO_3 (0.0210 g, 0.152 mmol), CH_2Cl_2 (1.5 mL), and allenoate **3.43a** (0.0280 g, 0.152 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42g** = 0.50 and R_f of **3.45f** = 0.40; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **3.45f** as a white solid (0.0468 g, 94%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (br, 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.



3.45g

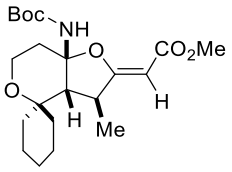
Tetrahydrofuran 3.45g: Compound **3.45g** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42g** (0.0212 g, 0.0696 mmol), K_2CO_3 (0.00962 g, 0.0696 mmol), CH_2Cl_2 (0.7 mL), and allenoate **3.43a** (0.0156 g, 0.139 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.342g** = 0.50 and R_f of **3.45g** = 0.40; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **3.45g** 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 (br, 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 °C.



3.45h

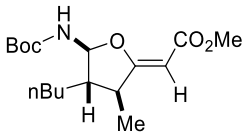
Tetrahydrofuran 3.45h: Compound **3.45h** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42i** (0.0542 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **3.43a** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **3.42i** = 0.15 and R_f of **3.45h** = 0.13; PAA stain). Chromatography (1:2; EtOAc:hexanes) afforded **3.45h** as a white solid (0.0544 g, 71%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.44 (br, 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.



3.45i

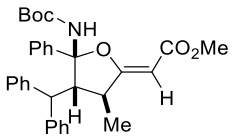
Tetrahydrofuran 3.45i: Compound **3.45i** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42h** (0.0567 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **3.43a** (0.0448 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **3.42h** = 0.50 and R_f of **3.45i** = 0.40; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45i** as a white solid (0.0704 g, 89%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (br, 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.



3.45j

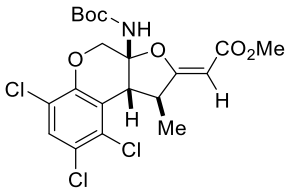
Tetrahydrofuran 3.45j: Compound **3.45j** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42k** (0.0431 g, 0.200 mmol), K_2CO_3 (0.0276 g, 0.200 mmol), CH_2Cl_2 (2.0 mL), and allenoate **3.43a** (0.0449 g, 0.400 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42k** = 0.20 and R_f of **3.45j** = 0.12; PAA stain). The crude product mixture was dissolved in a minimum amount of Et_2O (~ 0.5 mL), layered with hexanes and placed in a -40 °C freezer for 48 h. During this time, white crystals collected on the sides of the vial. The solvent mixture was removed via pipet and the residual

solvent mixture was removed under vacuum to give **3.45j** as a white solid (0.0301 g, 46%, dr = 8:1). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 5.73 – 5.60 (m, 1H), 5.16 (br, 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 (br, 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.



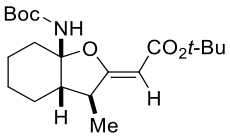
3.45k

Tetrahydrofuran 3.45k: Compound **3.45k** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42l** (0.121 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **3.43a** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42l** = 0.20 and R_f of **3.45k** = 0.25; PAA stain). Chromatography (1:10; EtOAc:hexanes) afforded **3.45k** 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 (br, 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 °C.



3.45l

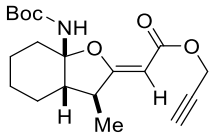
Tetrahydrofuran 3.45l: Compound **3.45l** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42** (0.100 g, 0.273 mmol), K_2CO_3 (0.0377 g, 0.273 mmol), CH_2Cl_2 (2.7 mL), and allenoate **3.43a** (0.0612 g, 0.545 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:6, EtOAc:hexanes; R_f of **3.42** = 0.40 and R_f of **3.45l** = 0.25; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.45l** 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{^{1}H} 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{^{1}H} 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.



3.49a

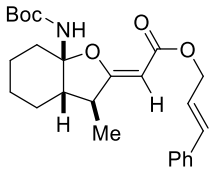
Tetrahydrofuran 3.49a: Compound **3.49a** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43b** (0.0308 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42a** and **3.49a** = 0.20 and 0.15; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **6m** 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 $C_{20}H_{33}NNaO_5$ $(M+Na)^+$ 390.2256, observed 390.2248; m.p: 142 – 144 °C.



3.49b

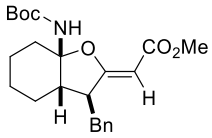
Tetrahydrofuran 3.49b: Compound **3.49b** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43c** (0.0272 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42a** and **3.49b** = 0.20 and 0.15; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **3.49b** as a white solid (0.0314 g, 90%, dr = >20:1). ^{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 $C_{19}H_{27}NNaO_5$ $(M+Na)^+$ 372.1787, observed 372.1780; m.p: 115 – 118 °C.



3.49c

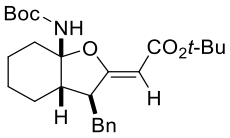
Tetrahydrofuran 3.49c: Compound **3.49c** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43d** (0.0429 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42a** and **3.49c** = 0.20 and 0.15; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **3.49c** 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.



3.49d

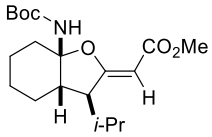
Tetrahydrofuran 3.49d: Compound **3.49d** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43e** (0.0376 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42a** and **3.49d** = 0.25 and 0.15; PAA stain). Chromatography (1:5; EtOAc:hexanes) afforded **3.49d** 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 (br, 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 $C_{23}H_{31}NNaO_5$ $(M+Na)^+$ 424.2100, observed 424.2095; m.p: 163 – 166 °C.



3.49e

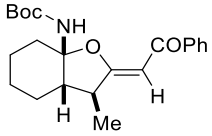
Tetrahydrofuran 3.49e: Compound **3.49e** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allenoate **3.43f** (0.0461 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:2, EtOAc:hexanes; R_f of **3.42a** and **3.49e** = 0.50 and 0.60; PAA stain). Chromatography (1:5; EtOAc:hexanes) afforded **3.49e** 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 (br, 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.



3.49f

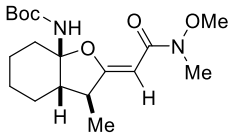
Tetrahydrofuran 3.49f: Compound **3.49f** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allene **3.43g** (0.0280 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:8, EtOAc:hexanes; R_f of **3.42a** and **3.49f** = 0.20 and 0.10; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.49f** 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 $C_{19}H_{31}NNaO_5$ $(M+Na)^+$ 376.2100, observed 376.2094; m.p: 130 – 133 °C.



3.49g

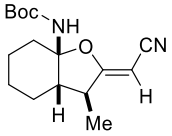
Tetrahydrofuran 3.49g: Compound **3.49g** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0213 g, 0.100 mmol), K_2CO_3 (0.0138 g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and allene **3.43h** (0.0316 g, 0.200 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42a** and **3.49g** = 0.25 and 0.13; PAA stain). Chromatography (1:8; EtOAc:hexanes) afforded **3.49g** 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 $C_{22}H_{29}NNaO_4$ $(M+Na)^+$ 394.1994, observed 394.1984; m.p: 88 – 93 °C.



3.49h

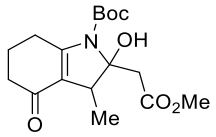
Tetrahydrofuran 3.49h: Compound **3.49h** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0640 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allene **3.49i** (0.0847 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:1, EtOAc:hexanes; R_f of **3.42a** and **3.49h** = 0.75 and 0.10; PAA stain). Chromatography (1:2; EtOAc:hexanes) afforded **3.49h** 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 $C_{18}H_{30}N_2NaO_5$ $(M+Na)^+$ 377.2052, observed 377.2045; m.p: 123 – 125 °C.



3.49i

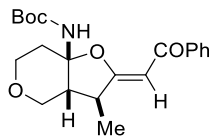
Tetrahydrofuran 3.49i: Compound **3.49i** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42a** (0.0640 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **3.43j** (0.0474 g, 0.600 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42a** and **3.49i** = 0.25 and 0.15; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.49i** 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 $C_{16}H_{24}N_2NaO_3$ $(M+Na)^+$ 315.1685, observed 315.1681; m.p: 140 – 143 °C.



3.45n'

Hydropyrrole 3.45n': Compound **3.45n'** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42j** (0.682 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH_2Cl_2 (3.0 mL), and allenoate **3.43a** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C, and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; R_f of **3.42j** = 0.05 and R_f of **3.45n'** = 0.15; PAA stain). Chromatography (1:4; EtOAc:hexanes) afforded **3.45n'** as a white solid (0.0763 g, 75%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (br, 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.



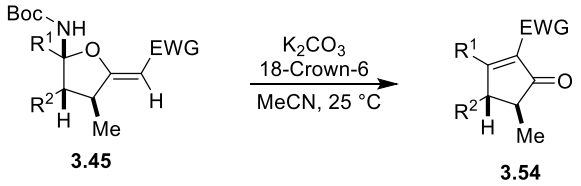
S3-9

Tetrahydrofuran S3-9: Compound **S3-9** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **3.42f** (0.371 g, 1.72 mmol), K_2CO_3 (0.238 g, 1.72 mmol), CH_2Cl_2 (17.0 mL), and allene **3.43h** (0.544 g, 3.44 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:1, EtOAc:hexanes; R_f of **3.43f** = 0.50 and R_f of **S3-9** = 0.30; PAA stain). Chromatography (1:2; EtOAc:hexanes) afforded **S3-9** as a white solid (0.434g, 68%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.71 (br, 1H), 7.49 – 7.46 (m, 1H), 7.43 – 7.40 (m, 2H), 5.99 (s, 1H), 3.98 – 3.82 (m, 4H), 3.26 – 3.18 (m, 2H), 2.59 – 2.56 (m, 1H), 1.97 – 1.91 (m, 1H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.31 (s, 9H) ; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.8, 174.8, 154.4, 140.2, 131.4, 128.2, 127.7, 95.6, 93.3, 79.4, 65.5, 64.0, 42.5, 39.6, 34.9, 28.3, 15.4; IR (thin

film) 3314, 2109, 2957, 2812, 1708, 1701, 1693, 1530, 1482, 1457; HRMS(ESI) m/z calcd. for $C_{21}H_{27}NNaO_5$ $(M+Na)^+$ 396.1787, observed 396.1779; m.p: 102– 104 °C.

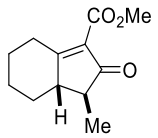
3.9.5 Functionalization of 2-Aminotetrahydrofurans (Table 3.7 and Scheme 3.11)

3.9.5.1 Preparation of Cyclopentenones 3.54



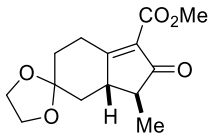
3.45 **3.54**

General Procedure D: A scintillation vial was charged with tetrahydrofuran **3.45** (1.0 equiv) and K_2CO_3 (3.0 equiv). These reagents were diluted with MeCN to form a 0.1 M solution of **3.45** and DMF (0.2 mL) was added via pipet to improve solubility. The vial was then sealed with a Teflon cap and stirred at 25 °C. Reaction progress was monitored by TLC for the disappearance of **3.45**. Once **3.45** 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 **3.54**.



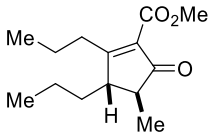
3.53a

Cyclopentenone 3.53a: Compound **3.53a** was synthesized using general procedure D with the following reagents: tetrahydrofuran **3.45a** (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:hexanes, *Rf* of **3.43a** = 0.10 and *Rf* of **3.53a** = 0.20; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.53a** as a colorless oil (0.0401 g, 64%, dr = >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{^{1}H} 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.



3.53b

Cyclopentenone 3.53b: Compound **3.53b** was synthesized using general procedure D with the following reagents: tetrahydrofuran **3.45h** (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, *Rf* of **3.45h** = 0.25 and *Rf* of **3.53b** = 0.50; PAA stain). Chromatography (1:8; EtOAc:hexane) afforded **3.53b** as a colorless oil (0.0423 g, 53%, dr = >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.

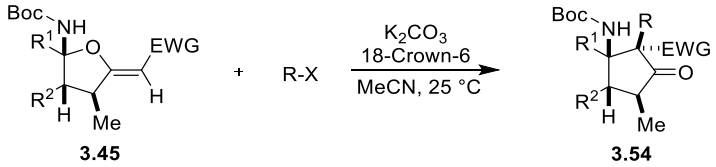


3.53c

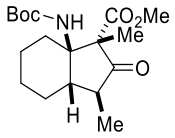
Cyclopentenone derivative 3.53c: Compound **3.53c** was synthesized using general procedure D with the following reagents: tetrahydrofuran **3.45c** (0.0735 g, 0.207 mmol), 18-crown-6 (0.164 g, 0.621 mmol), K_2CO_3 (0.0858 g, 0.621 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored on TLC (TLC eluent = 1:4 (twice); EtOAc:hexanes, *Rf* of **3.45c** = 0.50 and *Rf* of **3.53c** = 0.60; PAA stain). Chromatography (1:10; EtOAc:hexanes) afforded **3.53c** as a yellow oil (0.0272 g, 55%, dr = 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}H NMR (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.

3.9.5.2 Preparationi of Cyclopentanones 3.54

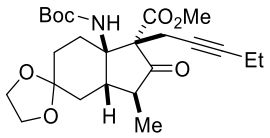


General Procedure E: A scintillation vial was charged with tetrahydrofuran **3.45** (1.0 equiv), an alkyl halide (6.0 equiv), 18-crown-6 (3.0 equiv), and K_2CO_3 (3.0 equiv). These reagents were diluted with MeCN to form a 0.1 M solution of **3.45** and DMF (0.2 mL) was added via pipet to improve solubility. The vial was then sealed with a Teflon cap and stirred at 25 °C. Reaction progress was monitored by TLC for the disappearance of **3.45**. Once **3.45** 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 **3.54**.



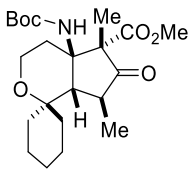
3.54a

β-Amino acid derivative 3.54a: Compound **3.54a** was synthesized using general procedure E with the following reagents: tetrahydrofuran **3.45a** (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 **3.45a** = 0.15 and *Rf* of **3.54a** = 0.25; PAA stain). Chromatography (1:10; EtOAc:hexane) afforded **3.54a** as a white solid (0.0584 g, 86%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.45 (br, 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{^{1}H} 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.



3.54b

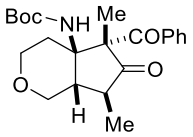
β-Amino acid derivative 3.54b: Compound **3.54b** was synthesized using general procedure E with the following reagents: tetrahydrofuran **3.45h** (0.115 g, 0.300 mmol), 18-crown-6 (0.238 g, 0.900 mmol), K_2CO_3 (0.124 g, 0.900 mmol), 1-bromo-2-pentyne (0.184 mL, 1.80 mmol), MeCN (3.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C, and monitored on TLC (TLC eluent = 1:2; EtOAc:hexane, *Rf* of **3.45h** = 0.25 and *Rf* of **3.54b** = 0.50; stained by PAA). Chromatography (1:8; EtOAc:hexane) afforded **3.54b** as a colorless oil (0.0701 g, 51%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.71 (br, 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.



3.54c

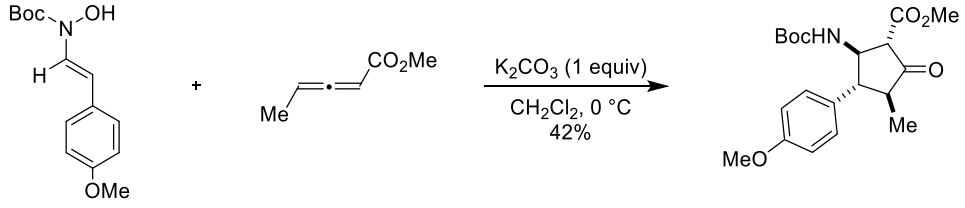
β-Amino acid derivative 3.54c: Compound **3.54c** was synthesized using general procedure E with the following reagents: tetrahydrofuran **3.45i** (0.0791 g, 0.200 mmol), MeI (0.170 g, 1.20 mmol), 18-crown-6 (0.159 g, 0.600 mmol), K_2CO_3 (0.0828 g, 0.600 mmol), MeCN (2.0 mL), and DMF (0.2 mL). The reaction mixture was stirred at 25 °C and monitored by TLC (TLC eluent = 1:2; EtOAc:hexanes, *Rf* of **3.45i** = 0.25 and *Rf* of **3.54c** = 0.6; stained by PAA). Chromatography (1:8; EtOAc:hexanes) afforded **3.54c** as a colorless oil (0.0609 g, 75%, dr = >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{^{1}H} 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.



3.54d

β-Amino acid derivative 3.54d: Compound **3.54d** was synthesized using general procedure E with the following reagents: tetrahydrofuran **S3-9** (0.0747 g, 0.200 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 = 1:2; EtOAc:hexane, *Rf* of **S3-9** = 0.25 and *Rf* of **3.54d** = 0.50; stained by PAA). Chromatography (1:5; EtOAc:hexane) afforded **3.54d** as a colorless oil (0.0381 g, 51%, dr = >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.56 – 7.53 (m, 1H), 7.46 – 7.43 (m, 2H), 4.91 (br, 1H), 4.86 (s, 1H), 3.87 – 3.80 (m, 3H), 3.74 – 3.69 (m, 1H), 2.81 – 2.77 (m, 1H), 2.57 – 2.54 (m, 1H), 2.36 – 2.34 (m, 1H), 1.62 – 1.56 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.14 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 212.9, 195.1, 154.9, 136.7, 133.4, 129.3, 128.4, 79.9, 67.0, 64.1, 62.9, 56.9, 48.6, 44.1, 30.7, 27.9, 13.7; IR (thin film) 3215, 3075, 2963, 1721, 1713, 1657, 1609, 1546, 1432, 1398; HRMS(ESI) m/z calcd. for $C_{21}H_{27}NO_5Na$ $(M+Na)^+$ 396.1787, observed 396.1779.

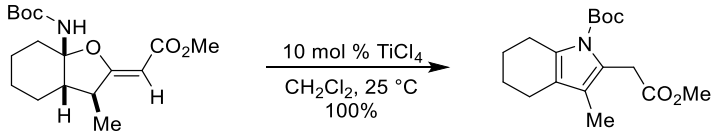


S3-5 **3.43a** **3.54e**

β-Amino acid derivative 3.54e: Compound **3.54e** was prepared using general procedure C with the following reagents: *N*-hydroxyenamine **S3-5** (0.0796 g, 0.300 mmol), K_2CO_3 (0.0415 g, 0.300 mmol), CH2Cl2 (3.0 mL), and allenoate **3.43a** (0.0673 g, 0.600 mmol). The reaction mixture was stirred at 0 °C and monitored by TLC (TLC eluent = 1:4, EtOAc:hexanes; **S3-5** = 0.25 and *Rf* of **3.54e** = 0.20; PAA stain). Chromatography (1:6; EtOAc:hexanes) afforded **3.54e** as a white solid (0.0476 g, 42%, dr = 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 (brd, *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), 3.75 (s, 3H), 3.68 (s 3H), 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.

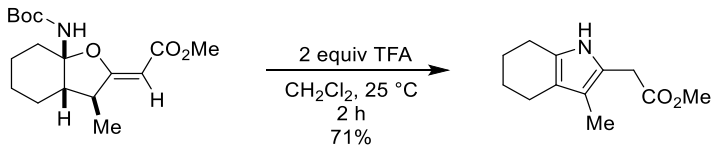
3.9.5.3. Preparation of Pyrroles



3.45a **3.50**

General Procedure F: A scintillation vial was charged with tetrahydrofuran **3.45a** (1.0 equiv) was diluted with CH_2Cl_2 to form a 0.1 M solution of **3.45a**. To a reaction mixture was added $TiCl_4$ (0.1 equiv) slowly and stirred for 1 h at 25 °C. The reaction mixture was concentrated under vacuum. The resulting residue was purified by flash chromatography (1:15 – 1:3; EtOAc:hexane) to afford pyrrole **3.50**.

Pyrrole 3.50: Compound **3.50** was prepared using general procedure **F** with the following reagents: tetrahydrofuran **3.45a** (0.0325g, 0.100 mmol), CH_2Cl_2 (1.0 mL), and $TiCl_4$ (10.0 µL of 1.0 M solution in CH_2Cl_2, 0.0100 mmol). The reaction was stirred for 1 h at 25 ˚C. Chromatography (1:20–1:15; EtOAc:hexane) afforded a pyrrole **3.50** as a white solid (0.0307g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 2H), 3.68 (s, 3H), 2.81-2.70 (m, 2H), 2.37-2.28 (m, 2H), 1.86 (s, 3H), 1.75-1.70 (m, 4H), 1.53 (s, 9H).

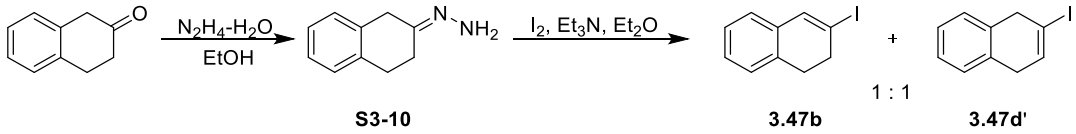


3.45a **3.51**

General Procedure G: A scintillation vial was charged with tetrahydrofuran **3.45a** (1.0 equiv) was diluted with CH_2Cl_2 to form a 0.1 M solution of **3.45a**. To a reaction mixture was added TFA (2.0 equiv) slowly and stirred for 2 h at 25 °C. The reaction mixture was concentrated under vacuum. The resulting residue was purified by flash chromatography (1:15 – 1:1; EtOAc:hexane) to afford pyrrole **3.51**.

Pyrrole 3.51: A scintillation vial was charged with tetrahydrofuran **3.45a** (0.0651g, 0.200 mmol). These reagents were diluted with dichloromethane (2.0 mL), and trifluoroacetic acid (0.0456g, 0.400 mmol) was added via syringe. The vial was then sealed with a Teflon cap and stirred at 25 °C for 2 h. After the reaction was complete, saturated $NaHCO_3$ (aq) (2.0 mL) was added, and the organic layer was extracted with dichloromethane (3 x 3.0 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (1:40–1:20; EtOAc:hexane) to afford a pale yellow liquid **3.51** (0.0294g, 71%). ^{1}H NMR (500 MHz; C_6D_6): δ 7.33 (br, 1H), 3.34 (s, 2H), 3.25 (s, 3H), 2.40 – 2.38 (m, 2H), 2.25 – 2.22 (m, 2H), 1.97 (s, 3H), 1.64 – 1.63 (m, 4H). This spectrum matches literature values.[79]

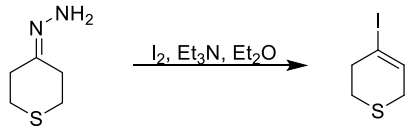
3.9.6. Preparation of Vinyl Iodides



S3-10 3.47b 3.47d'

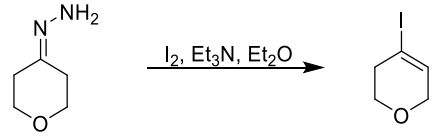
Alkenyl iodide 3.47b: A flame dried 250-mL round bottom flask was charged with β-tetralone (10.0 g, 68.4 mmol, 1.0 equiv) and diluted with methanol (140 mL). Hydrazine hydrate (20.0 mL, 410.4 mmol, 6.0 equiv) was added dropwise over 10 min and then the reaction mixture was refluxed at 65 °C for 2 h. The reaction mixture was then cooled to room temperature and concentrated under vacuum. The concentrated reaction mixture was diluted with CH_2Cl_2 (100.0 mL) and the MeOH layer was extracted with CH_2Cl_2 (3 x 50.0 mL). The combined organic extracts were dried over Na2SO4 and concentrated under vacuum to give **S3-10** as a clear oil (10.9 g, >95%), which was used without further purification.

Hydrazine **S3-10** (10.9 g, 68.0 mmol) was dissolved in Et_2O (200.0 mL) and treated with NEt_3 (95.4 mL, 684.0 mmol, 10.0 equiv). While stirring, a solution of I_2 (31.2 g, 123.1 mmol, 1.8 equiv) in Et_2O (200.0 mL) was added dropwise to the hydrazine solution over 30 min and stirred for 1 h at room temperature. The reaction mixture 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 give a crude product residue, which was purified by medium pressure chromatography (hexane) to yield a 1:1 mixture of **3.47b:3.47b'** as a yellow oil (15.7 g, 90%). This mixture was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) (**3.47b**): 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, $CDCl_3$) (**3.47b**): 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, $CDCl_3$) (**3.47b'**): 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, $CDCl_3$) (**3.47b'**): 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 (EI) m/z calcd. for $C_{10}H_9I$ (M)+ 255.9749, observed 255.9760.



S3-11

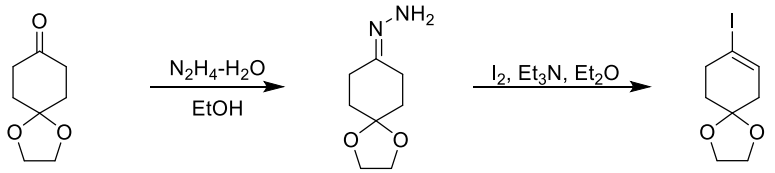
Alkenyl iodide 3.47f: Hydrazone **S3-11**[118] (6.5 g, 50.0 mmol, 1.0 equiv) was dissolved in Et_2O (150.0 mL) and treated with Et_3N (69.7 mL, 500.0 mmol, 10.0 equiv). While stirring, a solution of I_2 (22.9 g, 90.0 mmol, 1.8 equiv) in Et_2O (100.0 mL) was added dropwise to the solution of **S3-11** over 30 min and stirred 1 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$(aq) (75.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with sat. NH_4Cl(aq) (5 x 100 mL), dried over Na_2SO_4, and concentrated under vacuum to give a crude product residue. This residue was dissolved in Et_2O (200.0 mL) and mixed with 1,1,3,3-tetramethylguanidine (10.0 mL, 79.7 mmol, 1.6 equiv). The mixture was refluxed at 80 °C for 2 h, cooled to room temperature, and quenched with sat. NH_4Cl(aq) (50.0 mL). The mixture was then 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) (3 x 50 mL), water (3 x 50 mL), brine (3 x 50 mL), and dried over $MgSO_4$. Purification by medium pressure chromatography (hexane) afforded **3.47f** 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(EI) m/z calcd. for C_5H_7SI $(M)^+$ 225.9313, observed 225.9321.



S3-12 **3.47g**

Alkenyl iodide 3.47g: Hydrazone **S3-12**[119] (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. A solution of I_2 (45.7 g, 180.0 mmol, 1.8 equiv) in Et_2O (200.0 mL) was then added dropwise to the solution of **S3-12** over 30 min at room temperature. The complete reaction mixture was then stirred for 1 h at room temperature. The reaction mixture was quenched by the addition of sat. $Na_2S_2O_3$(aq) (100.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with sat. NH_4Cl(aq) (5 x 100 mL), dried over Na_2SO_4, and concentrated under vacuum to give a crude product residue that was dissolved in Et_2O (200.0 mL) and placed in an ice bath. While vigorously stirring, solid KO*t*-Bu (22.4 g, 200.0 mmol, 2.0 equiv) was added in one portion. The dark brown mixture was then allowed to warm to 25 °C for 1 h. At this time, the mixture was diluted with H_2O (100 mL), extracted with Et_2O (3 x 100 mL), and the combined organic layers were dried over Na_2SO_4. Concentration under vacuum gave the pure vinyl iodide

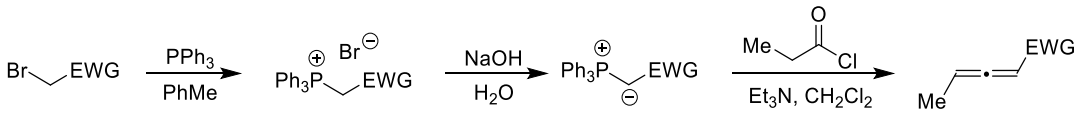
as a light brown oil (18.1g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 – 6.32 (m, 1H), 4.12 – 4.11 (m, 2H), 3.78 – 3.76 (m, 2H), 2.57 – 2.56 (m, 2H). These data matched literature values.[120]



S3-13 **3.47g**

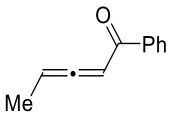
Alkenyl iodide 3.47g: A flame dried 250-mL round bottom flask was charged with 1,4-cyclohexanedione monoethylene acetal (15.6 g, 100.0 mmol, 1.0 equiv) and diluted with methanol (100 mL). Hydrazine hydrate (7.60 mL, 156.0 mmol, 10.0 equiv) was added dropwise over 10 min and then the reaction mixture was stirred at 25 °C for 18 h. The reaction mixture was then concentrated under vacuum and diluted with CH_2Cl_2 (150.0 mL). The MeOH layer was extracted with CH_2Cl_2 (3 x 50.0 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to afford (1,4-dioxaspiro[4.5]decan-8-ylidene)hydrazine **S3-13** as a clear oil (16.5 g, >95%), which was taken on to the next step of the synthesis without further purification. Hydrazone **S3-13** (16.5 g, 96.9 mmol, 1.0 equiv) was dissolved in Et_2O (200.0 mL) and treated with Et_3N (135.1 mL, 969.0 mmol, 10.0 equiv). This mixture was then stirred at 25 °C 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. The complete reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched by the addition of sat. $Na_2S_2O_3$(aq) (100.0 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with sat. NH_4Cl(aq) (5 x 100 mL), dried over Na_2SO_4, and concentrated to afford a crude product residue, which was dissolved in Et_2O (200.0 mL) and placed in an ice bath. While vigorously stirring, solid KO*t*-Bu (21.7 g, 193.8 mmol, 2.0 equiv) was added in one portion. The dark brown mixture was then allowed to warm to 25 °C for 1 h. The reaction mixture was then quenched with H_2O (100 mL), extracted with Et_2O (3 x 100 mL), and dried over Na_2SO_4. Concentration of the Et_2O solution under vacuum afforded alkenyl iodide **2c** as a clear oil (17.0 g, 66%). ^{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). These data matched literature values.[120]

3.9.7 Preparation of Allenes



S3-14 **S3-15** **S3-16** **3.43**

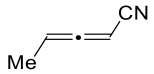
General Procedure H: Bromide **S3-14** (1 equiv) was added dropwise to a solution of PPh_3 (1 equiv) in toluene (0.3 M) to form a slurry. The slurry was stirred overnight and then filtered and washed with toluene (2 x 100 mL) and hexane (2 x 100 mL) to give the corresponding phosphonium bromide salt **S3-15** as a white solid. The white solid was dissolved in water (100 mL) and NaOH (2.0 M) was added to keep the aqueous solution at a pH > 7, while a white precipitate formed. The reaction mixture was then stirred for 30 min and then CH_2Cl_2 (100 mL) was added to dissolve the precipitate. The organic layer was separated, washed with brine (100 mL), dried over $MgSO_4$, and filtered. The filtrate was then concentrated to give phosphorene **S3-16** as a white solid, which was used in the next step of the allene synthesis without further purification. Phosphorane **S3-16** was dissolved in CH_2Cl_2 (100 mL) under N_2. NEt_3 (1 equiv) was then added to the solution and stirred for 15 min. Propionyl chloride (1 equiv) was then added dropwise slowly over 30 min at room temperature and the reaction mixture was stirred overnight. At this time, water (80 mL) was added to the reaction mixture and allowed to stir for 5 min. The aqueous phase was then extracted with CH_2Cl_2 (2 x 50 mL), the organic layers were combined, washed with brine (50 mL), and dried with $MgSO_4$. The filtrate was concentrated and flash column chromatography (1:100 – 1:50; EtOAc:hexane) provided allene **3.43** as an oil.



3.43h

Allene 3.43h: Compound **3.43h** was prepared using general procedure F. Phosphorene **S3-16h** was prepared using 2-bromoacetophenone (9.95 g, 50.0 mmol), PPh_3 (13.1 g, 50.0 mmol), and toluene (100 mL). Phosphorene **S3-16h** (19.0 g, 50 mmol) was then diluted with CH_2Cl_2 (100 mL) and NEt_3 (6.97 mL, 50.0 mmol), and treated with propionyl chloride (4.37 mL, 50.0 mmol) to afford **3.43h** as a clear yellow oil (2.53 g, 32%) after chromatography (1:50; EtOAc:hexanes). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.50 – 7.46 (m, 1H), 7.41 – 7.36 (m, 4H), 6.32 – 6.27 (m, 1H), 5.55 – 5.49 (m, 1H), 1.74 – 1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.4, 191.8, 137.7, 132.5, 128.6, 128.2, 93.3, 89.8, 12.8; IR (thin film) 3058, 2980, 2919, 1944, 1815, 1760, 1690, 1650, 1596, 1578 cm-1; HRMS

(ESI) m/z calcd. for $C_{11}H_{11}O$ $(M+H)^+$ 159.0810, observed 159.0808. Compound **3.43h** was isolated as a mixture but was used without further purification.



3.43j

Allene 3.43j. Compound **3.43j** was prepared from phosphorene **S3-16j**[121] (21.8 g, 72.3 mmol) using general procedure H with the following reagents: propionyl chloride (6.32 mL, 72.3 mmol), CH_2Cl_2 (100 mL), and NEt_3 (10.1 mL, 72.3 mmol). Chromatography (1:50; EtOAc: hexanes) afforded **3.43j** as an orange oil (1.33 g, 23%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.69 – 5.67 (m, 1H), 5.18 – 5.16 (m, 1H), 1.77 (dd, *J* = 7.5 Hz, 3.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.9, 113.6, 91.8, 66.8, 12.5; IR (thin film) 3029, 2986, 2930, 2224, 1965, 1738, 1453, 1439, 1391, 1372 cm-1; HRMS (EI) m/z calcd. for C_5H_5N $(M)^+$ 79.0421, observed 79.0422.

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APPENDICES

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Research Advisor: Dr. Youngkwan Ko
Project: Derivatizations for Isoxazolines for PPO (Protoporphyrinogen oxidase) Inhibitors

Researcher, Material Chemistry Institute Mar-July, 2011
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Project: Lineshape Analysis of DNMR Spectra of Thiocarbamates

Graduate Student (M.S), Chungnam National University 2009-2011
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Undergraduate Internship, Korean Research Institute of Chemical Technology July, 2008
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PUBLICATIONS & PATENT

- Son, J.; Reidl, T. W.; Kim, K. H.; Wink, D. J.; Anderson, L. L. 'Generation and Rearrangement of *N*,*O*-Dialkenylhydroxylamines for the Synthesis of 2-Aminotetrahydrofurans' *Angew. Chem., Int. Ed.* **2018**, *Accepted manuscript*
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PRESENTATIONS

- Chicago Organic Symposium, Chicago, IL, 2017
  Electrocyclizations of *N*-Vinylnitrones and Sigmatropic Rearrangements of *N*,*O*-Divinylhydroxylamines: Novel Access to Highly-Substituted Morpholines and Furans
- Heterocyclic Compounds, Gordon Research Conference, Newport, RI, 2017
  Electrocyclizations of *N*-Vinylnitrones and Sigmatropic Rearrangements of *N*,*O*-Divinylhydroxylamines: Novel Access to Highly-Substituted Morpholines and Furans
- Chicago Organic Symposium, Chicago, IL, 2016
  Rearrangement of *N–O* Bond Cleavage
- AbbVie Scholars Symposium, North Chicago, IL, 2016
  Rearrangement of *N–O* Bond Cleavage
- Chicago Organic Symposium, Chicago, IL, 2015
  6π- and 4π-Electrocyclizations of *N*-Alkenylnitrones
- American Chemical Society, San Diego, CA, 2013
  Synthesis and C–N Bond Rotation of 1,3,5-Triazine-2,4,6-triyltris(dibutylcarbamodithioate)
- Asia Pacific Conference on Ionic Liquids and Green Process, Dalian, China, 2010
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- Graduate College Student Presenters Award / GSC Travel Award, 2017
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