DEVELOPMENT OF HETEROATOM-CENTERED RADICAL APPROACHES TO SELECTIVE HYDROCARBON FUNCTIONALIZATION

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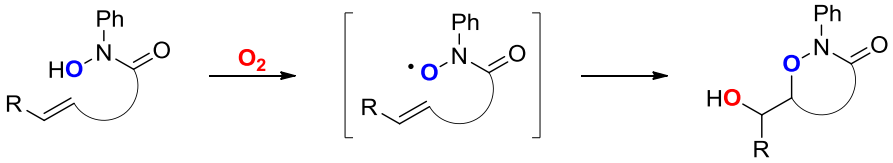
ABSTRACT

VALERIE ANNE SCHMIDT: Development of Heteroatom-Centered Radical Approaches to Selective Hydrocarbon Functionalization
(Under the direction of Erik J. Alexanian)

I. Alkene Difunctionalizations

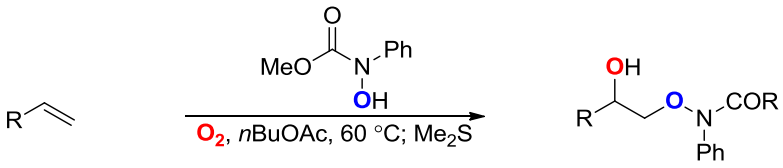
An overview of alkene difunctionalization reactions is presented. The current landscape of alkene dioxygenations, oxyaminations, and diaminations is discussed.

II. Aerobic Intramolecular Alkene Dioxygenations Using Hydroxamic Acids



In the presence of either oxygen or air as the sole oxidant and external oxygen-atom source, a variety of unsaturated hydroxamic acids afford cyclic hydroxamates that are readily converted into 1,2-diols, with the potential for high levels of reaction stereocontrol.

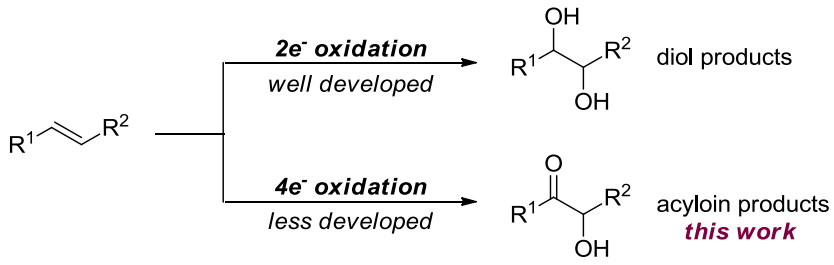
III. Aerobic Intermolecular Alkene Dioxygenations Using Hydroxamic Acids



The dioxygenation of alkenes using molecular oxygen and a simple hydroxamic acid derivative is described. The reaction system consists of readily prepared methyl *N*-hydroxy-*N*-phenylcarbamate and molecular oxygen with a radical initiator, offering an alternative to common dioxygenation processes catalyzed by precious transition metals. This transformation capitalizes on

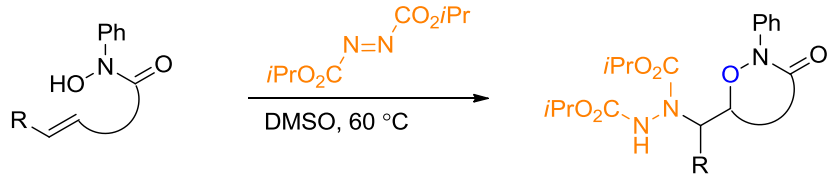
the unique reactivity profile of hydroxamic acid derivatives in radial-mediated alkene addition processes.

IV. Aerobic Alkene Ketooxygenations Using Hydroxamic Acids



A radical-mediated alkene ketooxygenation is described. This four-electron alkene oxidation delivers α-oxyketones directly from simple alkenes with high levels of regio- and stereocontrol.

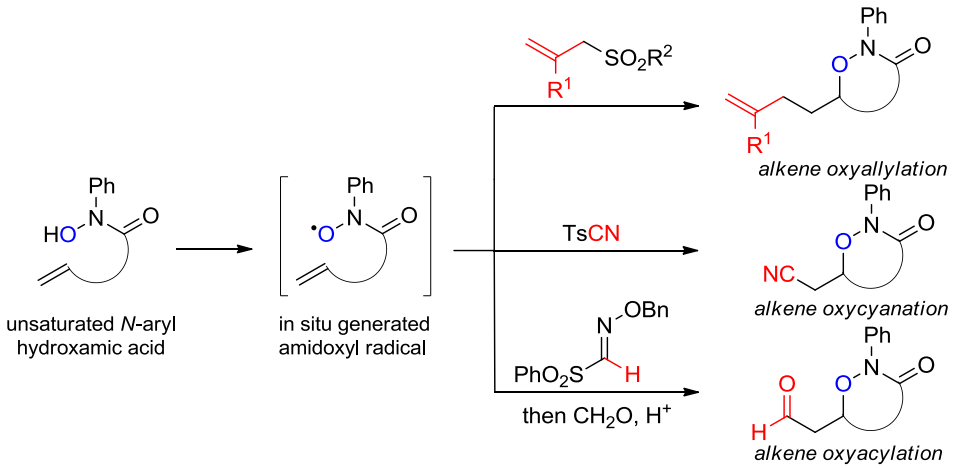
V. Radical-Mediated Alkene Oxyaminations Using Hydroxamic Acids



highly regio- and stereoselective alkene oxyaminations

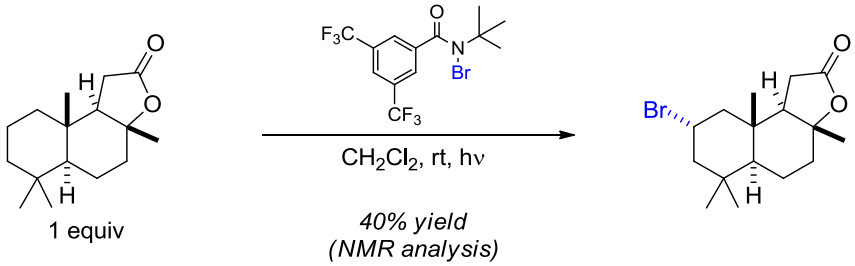
A radical-mediated approach to alkene oxyamination is described. This method capitalizes on the unique reactivity of the amidoxyl radical in alkene additions to furnish a general difunctionalization using simple diisopropyl azodicarboxylate (DIAD) as a radical trap. The intramolecular nature of the process provides single regioisomer products in all cases. Difunctionalizations of cyclic alkenes provide *trans* oxyamination products inaccessible using current methods with high levels of stereoselectivity, complementing *cis*-selective oxyamination processes.

VI. Radical-Mediated Alkene Carbooxygenations Using Hydroxamic Acids



A radical-mediated approach to alkene carbooxygenation using hydroxamic acids is described. These transformations represent rare examples of direct carbooxygenations, and deliver versatile functionality to the unsaturated substrate. Included in this study are alkene oxyallylation, oxycyanation, and formal oxyacylation processes.

VII. Heteroatom-Centered Radical Aliphatic C-H Halogenations



A site-selective approach to C-H halogenation using nitrogen-centered radicals is outlined. Developing predictably selective C-H functionalizations has the potential to revolutionize the way chemists construct molecules. Nitrogen-centered radicals have demonstrated promising steric and electronic selectivity in the bromination of alkane substrates under neutral conditions. Initial functionalization studies of complex molecules are also described.

ACKNOWLEDGEMENTS

There are a number of individuals that deserve mention in the longest document I've prepared to date. Firstly, I have to thank my advisor Erik Alexanian. From the earliest days of getting the lab set up, to seeing the first of that original class graduate, Erik has been a constant source of support and guidance to me. He has always believed in me, even in moments when I was not able to do that for myself. Mere words on paper could never adequately express my gratitude for all of this, and my only hope is that a more fitting expression is that I can one day make him proud to have trained me, and prove that I was worth all the effort.

Much of the work that I've accomplished over the past five years is a result of the combined effort of my fellow group members. I'd like to thank Andrew Brusoe, Benjamin Giglio, and Ryan Quinn who I've had the privilege of directly working with on projects. I'd also like to thank all group members, past and present and wish them luck and success in all their future endeavors: Kayla Bloome-Le, Brendan Lainhart, Njamkou Noucti, Dr. Rahul Edwankar, Caitlin McMahon, and Alex Venning.

In my years of schooling I have had many tremendous educators who have inspired me, challenged me, and taught me so much more than can be contained in books. For their years of dedication, I thank them. I'd also like to thank my friends and family for accepting me, allowing me to forge my own path, and for reminding me that they would always be there for me. I think that my most sincere sentiments can be summed up with a quote from *Wicked*, the musical that I will forever connect with my time at Carolina: "I've heard it said that people come into our lives for a reason, bringing something we must learn. Well, I don't know if I believe that's true, but I know I'm who I am today because I knew you."

To my family, and the little girl they raised who never would have believed she could accomplish what she has.

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LIST OF ABBREVIATIONS AND SYMBOLS

μ	micro
°C	degrees Celsius
$\Delta_f H°$	heat of formation
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
4 Å MS	4 angstrom molecular sieves
Ac	acetate
Ac_2O	acetic anhydride
acac	acetylacetone
AcOH	acetic acid
AD	asymmetric dihydroxylation
atm	atmospheres
Bn	benzyl
br s	broad singlet
BQ	benzoquinone
Bu	butyl
Bz	benzoyl
C-H	carbon-hydrogen bond
cat.	catalytic amount or catalyst
cm^{-1}	wavenumbers
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane

dd	doublet of doublets
ddd	doublet of doublet of doublets
DLP	dilauroyl peroxide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
e^-	electron
ee	enantiomeric excess
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
et al.	and others
etc.	et cetera
Et*N*iPr_2	*N*,*N*,*N*-diisopropyl-ethylamine
EtOAc	ethyl acetate
h	hours
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
hν	light
Hz	hertz
i.e.	in other words
iPr	iso-propyl

IR	infared spectroscopy
J	coupling constant
kcal	kilocalorie
k	rate
LDA	lithium diisopropylamide
LDE	lithium diethylamide
LRMS	low resolution mass spectroscopy
m	multiplet
Mbs	4-methoxybenzenesulfonyl
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
min	minute(s)
mg	milligram
mL	milliliter
mmol	millimole
modp	bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)
NBS	*N*-bromosuccinimide
nBuOAc	butyl acetate
NHC	*N*-heterocyclic carbene
nPrOH	butyl acetate
Ns	4-nitrobenezenesulfonyl
OTf	triflate, trifluoromethanesulfonate
Ph	phenyl
Phth	phthalimide

PPh_3	triphenyl phosphine
ppm	parts per million
PTFE	polytetrafluoroethylene, teflon
p-Tol	4-methyl phenyl
q	quartet
qd	quartet of doublets
quant	quantitative
R	generic organic group
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
tBu	*tert*-butyl
tBuOH	*tert*-butanol
td	triplet of doublets
TEMPO	tetramethylpiperidine-*N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPP	tetraphenylporphyrin
Ts	tosyl, 4-toluenesulfonyl
UVA	ultraviolet A light

1. CHAPTER ONE

Alkene Difunctionalizations

1.1 Introduction

Alkenes are a particularly attractive and versatile functional group for chemical synthesis. Simple alkenes are among the most widely available, naturally abundant, and diverse classes of starting materials for use in complex synthesis. They are excellent starting materials as they are derived from readily available chemical feedstocks and a plethora of synthetic methods exist for their selective preparation. Additionally, alkenes participate in a wide variety of different types of transformations including polar, radical, pericyclic, and organometallic pathways but remain unaffected by many harsh reaction conditions (i.e. strong bases, many oxidants, etc.). Synthetic methods that introduce useful functionality from readily available starting materials are extremely important to the development of new efficient pathways to materials, pharmaceuticals, and agrochemicals.

The interaction of heteroatom functionality of bioactive compounds with biological receptors is directly linked to the physiological responses they elicit. As a result, the ability to create highly functionalized, stereochemically dense molecules from simple, easily accessed starting materials is crucial to the development of small molecule therapeutics that modulate biological activity and have the potential to ultimately impact human health. Alkene difunctionalization, which is the addition of two functional groups (typically heteroatoms such as oxygen, nitrogen, halogens, etc.) across a carbon-carbon double bond, has emerged as one of the leading methods for the stereoselective introduction of heteroatomic functionality in synthesis. This added functionality may be necessary in the final product or used for subsequent manipulations.

1.2 Background

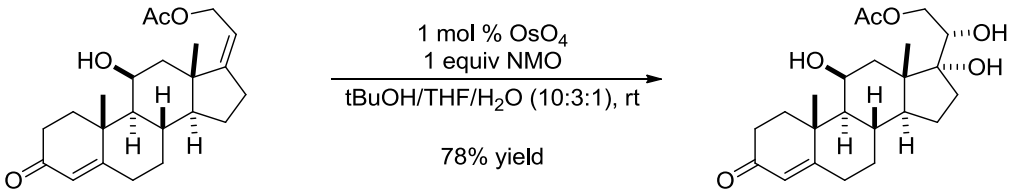
The first alkene difunctionalization protocol was reported by Makowka in 1908.[1] However, it was not until seminal work by Sharpless and coworkers nearly seventy years later that the utility of this type of transformation was realized. Vicinal diols, amino alcohols, and diamines are important motifs in synthetic chemistry, as they are found in a wide range of natural products and chiral reagents, and are used as intermediates in complex synthesis. Thus, developing efficient (high yielding, single step, atom economical, etc.) pathways to these prevalent motifs is highly valuable in chemical synthesis.

1.2.1 Dioxygenation

Alkene dioxygenation has been one of the most commonly developed classes of alkene difunctionalization. Dioxygenation is the addition of two oxygen based functional groups across a double bond, resulting in a formal two-electron oxidation of the alkene. However, alkene dioxygenation does not apply to epoxidation because two distinct oxygen-atom functionalities have not been added, and consequently is beyond the scope of the present discussion.

The formation of vicinal diols from simple starting materials like alkenes greatly facilitates the preparation of functionalized organic compounds. The discovery of the Upjohn process allowed for a catalytic amount of osmium tetroxide (OsO_4) to be used in conjunction with *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant (**Figure 1-1**).[2]

Figure 1-1. Os-Catalyzed Alkene Dihydroxylation: the Upjohn process

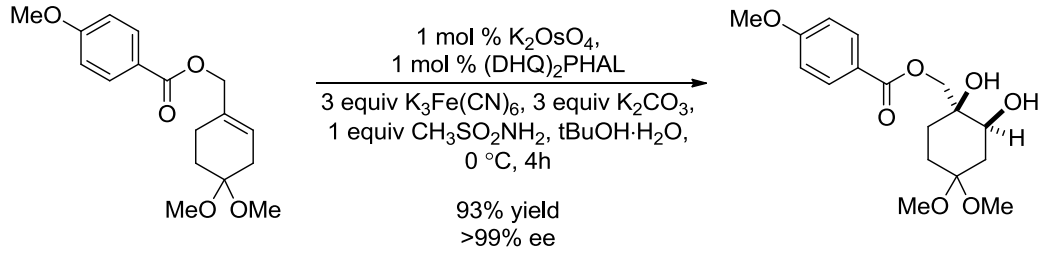


The development of this catalytic variant is responsible for elevating Os-catalyzed dihydroxylation to its current high status. Another significant advance in this area came with the

discovery of the ligand acceleration effect pyridine has on enhancing the rate of difunctionalizations. This important observation led to the development of asymmetric dihydroxylation protocols using low loadings of K_2OsO_4 and the chiral cinchona alkaloid based-$(DHQ)_2PHAL$ ligand.[2]

Commonly referred to as AD-mix-α or β (based on the chirality of the alkaloid ligand used), the Sharpless asymmetric dihydroxylation catalytic system has been applied in the synthesis of numerous important molecular targets, and serves as the benchmark from which all subsequent dioxygenations are measured (**Figure 1-2**).[3]

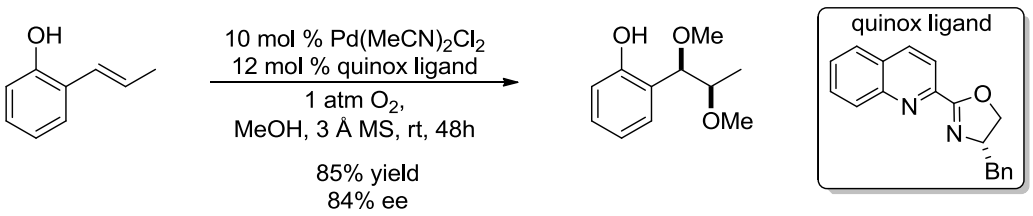
Figure 1-2. Sharpless Asymmetric Dihydroxylation in Total Synthesis



Corey *JACS* **1994**, 12109.

Although the Sharpless methods have proven general and robust, they rely on the use of expensive and highly toxic osmium salts that require removal and subsequent waste treatment. As a result, alternative methods have been explored and particular focus placed on the development of palladium catalysts for alkene dioxygenation. For example, Sigman and coworkers have developed a direct aerobic Pd(II)-catalyzed enantioselective dioxygenation of 2-propenylphenols using chiral quinoline oxazole ligands (**Figure 1-3**).[4]

Figure 1-3. Enantioselective Pd-Catalyzed Alkene Dialkoxylation

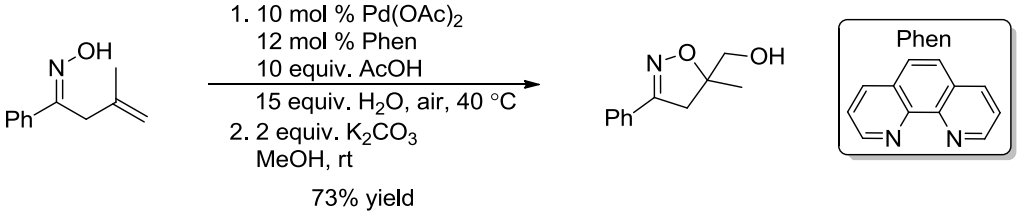


Sigman *JACS* **2007**, 3076.

Loh and co-workers have also developed a Pd-catalyzed dioxygenation of unsaturated oxime

substrates.[5] These reactions take advantage of facile nucleopalladation and specifically designed substrates where undesired β-hydride elimination is not feasible (**Figure 1-4**).

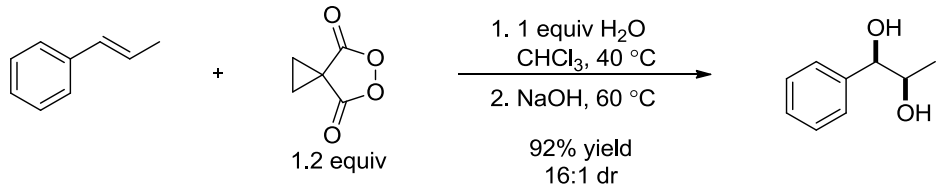
Figure 1-4. Pd-Catalyzed Oxime Assisted Intramolecular Dioxygenation



Loh *JACS* **2010**, 6284.

Dioxygenations have also been developed that require no transition metals at all.[6] Hypervalent iodine reagents are attractive because of the associated low toxicity, ready availability, and ease of handling. These reagents have received considerable attention in recent years and have found multiple uses in synthesis.[7,8] In 2008, Dong and co-workers reported a Pd-catalyzed alkene dioxygenation using (diacetoxyiodo)benzene ($PhI(OAc)_2$) as a stoichiometric oxidant.[9] Their proposed mechanism invokes a Pd(II)/(IV) pathway, promoted by $PhI(OAc)_2$, but notes the importance of the cationic Pd-catalyst ($Pd(dppp)(H_2O)_2(OTf)_2$). However, further studies by Gade indicate that this transformation is not catalyzed by palladium.[10] Gade provides evidence for a protiocatalytic pathway where the Pd-salt serves to produce triflic acid (TfOH) at the beginning of the reaction, which acts as the active catalyst. The need to generate a strong acid, like triflic acid, in situ thus explains why Dong required the use of a Pd-catalyst containing triflate as the counter-ion.

Figure 1-5. Alkene Syn Dihydroxylation with Malonoyl Peroxides

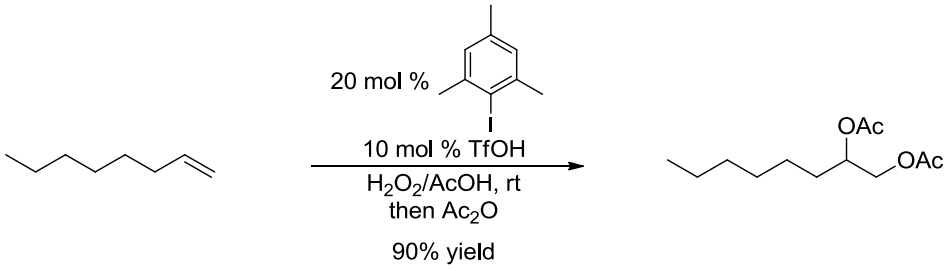


Tomkinson *JACS* **2010**, 14409.

Organic peroxides have received attention as capable reagents for alkene dioxygenationations owing to their high reactivity, and generally low cost and low toxicity of reagents and by-products. For example, malonyl peroxide has been used to achieve the *syn*-dihydroxylation of alkenes with high

levels of diastereoselectivity (**Figure 1-5**).[11] Phthaloyl peroxides[12–14] and inorganic peroxides such as Oxone[15–17] have also been successful for alkene dioxygenation. Recent studies have used peracids in conjunction with tetrabutylammonium iodide and *tert*-butyl hydroperoxide as oxygen-atom sources for alkene dioxygenations.[18] Meng and Li have developed an organocatalytic *syn* diacetoxylation of alkenes using readily available aryl iodides as catalysts (**Figure 1-6**).[19]

Figure 1-6. Organocatalytic Syn-Diacetoxylation of Alkenes

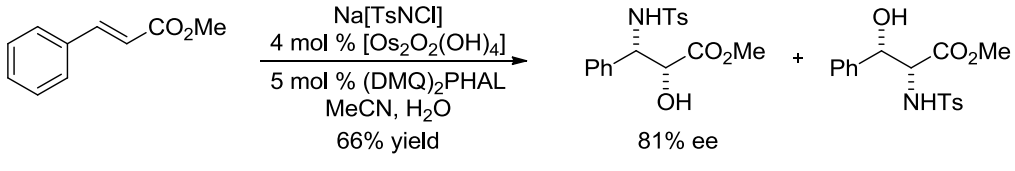


Meng and Li *Org, Lett.* **2012**, 3336.

1.2.2 Oxyaminations

The oxyamination of alkenes is the most developed method of vicinal aminofunctionalization.[20] Aminoalcohols are present in a wide array of biologically active molecules and natural products.[21] Again, Sharpless pioneered this class of alkene difunctionalizations showing that a stoichiometric monoimido osmate complex could affect the aminohydroxylation of styrenes with high levels of regioselectivity with the amino group favoring addition at the terminal position. A catalytic variant was later developed using chloramine-T trihydrate as a nitrene-based oxidant that doubles as the nitrogen-atom source.[22,23] An analogous asymmetric aminohydroxylation was finally reported in 1996 using chloramine-T and the Os-ligand combination used in the AD-mix reagent (**Figure 1-7**).[24]

Figure 1-7. Intramolecular Os-Catalyzed Aminohydroxylation of Olefins

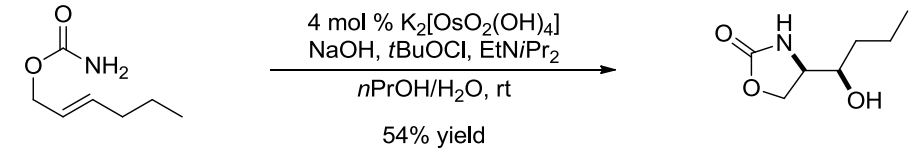


Sharpless *ACIE* **1996**, 451.

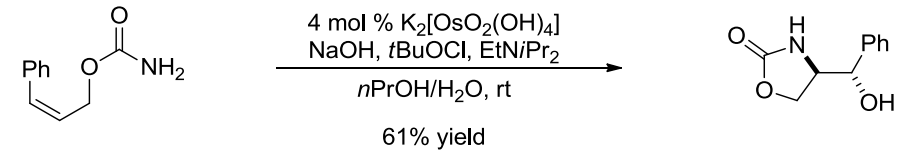
Subsequently, other nitrogen-atom sources have been developed.[25] However, these methods are

plagued by low regioselectivities of internal alkenes. One effective approach to solving this regioselectivity issue is to tether the alkene to the nitrogen-atom source. This strategy was first implemented by Donohoe using allylic carbamates to access a variety of hydroxyl oxazolidinones in moderate yields and as single regioisomers (**Figure 1-8**).[26, 27]

Figure 1-8. Intramolecular Os-Catalyzed Aminohydroxylation of Alllylic Carbamates



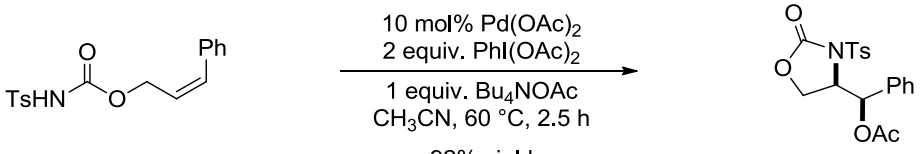
Donohoe *ChemComm.* **2001**, 2078.



Donohoe *Org. Biomol. Chem.* **2003**, 2025.

Palladium-catalyzed alkene oxyaminations have also been developed that are proposed to proceed via a Pd(II)/(IV) mechanism.[28–30] The use of Pd in alkene oxyamination reactions dates back to 1975 where stoichiometric Pd(II) compounds were used to activate the olefin towards nucleophilic attack by simple amines followed by oxidation of the C-Pd bond with lead tetraacetate.[31] A significant advancement appeared in 2005 where a catalytic amount of simple $Pd(OAc)_2$ was used in conjunction with stoichiometric $PhI(OAc)_2$ to achieve the aminoacetoxylation of unsaturated *N*-tosyl-carbamates (**Figure 1-9**).[28]

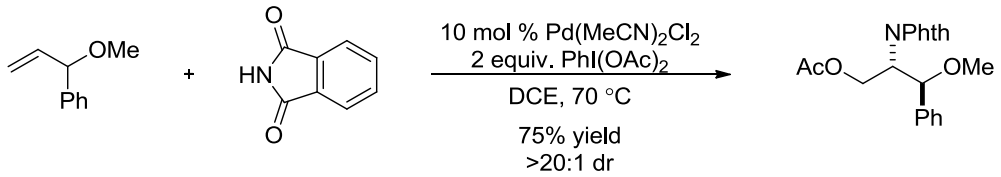
Figure 1-9. Pd-Catalyzed Intramolecular Aminoacetoxylation of Alkenes



Sorensen *JACS* **2005**, 7690.

The following year Stahl and coworkers used similar catalytic conditions to achieve an intermolecular alkene oxyamination using phthalimide as the nitrogen-atom source (Figure **1-10**).[29]

Figure 1-10. Regioselective Intermolecular Pd-Catalyzed Alkene Aminoacetoxylation

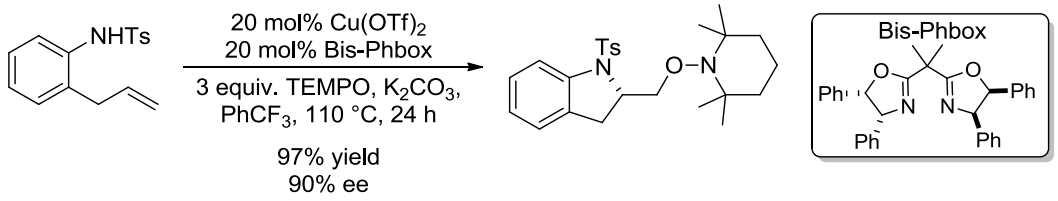


Stahl *JACS* **2006**, 7179.

While this method displays impressive regio- and diastereocontrol, the substrate scope is largely limited to terminal allylic ethers. Sanford subsequently reported another intramolecular variant of this chemistry using homoallylic alcohols and phthalimide.[30]

The first intramolecular Cu-catalyzed enantioselective oxyamination was reported in 2008 by Chemler and co-workers.[32] This report uses catalytic copper(II) triflate and stoichiometric 2,2′,6,6′-tetramethylpiperidine (TEMPO) to achieve oxyamination of unsaturated sulfonamides. Here TEMPO acts as both the oxygen-atom source as well as oxidant. The inclusion of a chiral bisoxazoline ligand (Bis-Phbox) leads to protected vicinal amino-alcohols with good to excellent enantiomeric excesses (**Figure 1-11**).

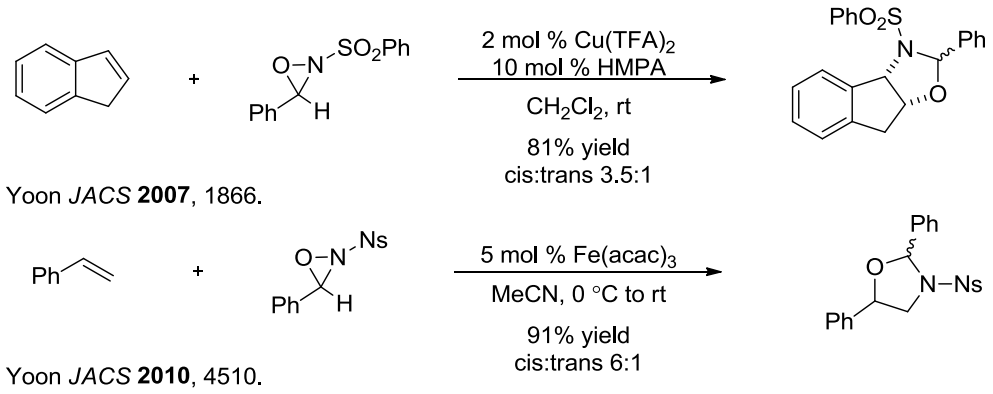
Figure 1-11. Enantioselective Cu-Catalyzed Alkene Oxyamination



Chemler *JACS* **2008**, 17638.

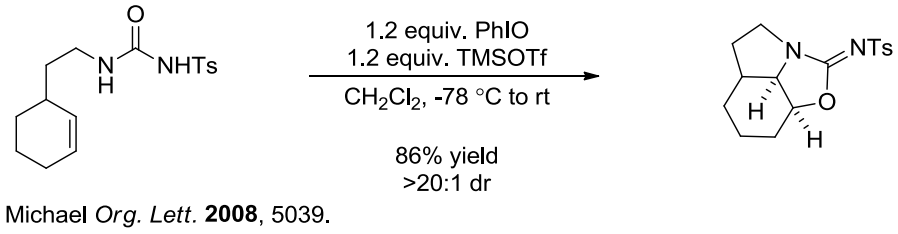
Yoon developed a pair of oxyamination protocols giving complementary regioselectivity by selecting either a Cu or Fe-catalyst (**Figure 1-12**). In these reactions *N*-sulfonyl oxaziridines are used as both the O-atom and N-atom sources where Cu-catalysts introduce oxygen-functionality at the terminal position[33] and Fe-catalysts places the nitrogen-functionality at the terminal position.[34]

Figure 1-12. Regioselective Alkene Aminooxygenation Using Cu- or Fe-Catalysts



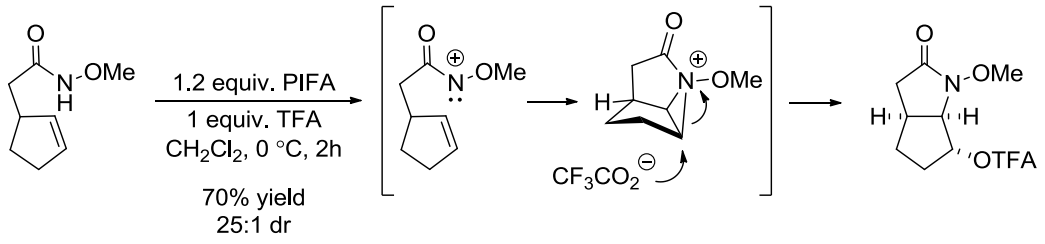
Similarly to alkene dioxygenation, there have been approaches to alkene oxyamination that do not require transition metals. An excellent example of intramolecular oxyamination comes from the Michael group where the oxidative cyclization of unsaturated sulfonylureas is mediated by iodosyl benzene and a Lewis or Brønsted acid (**Figure 1-13**).[35]

Figure 1-13. Hypervalent Iodine-Mediated Alkene Oxyamination



Additionally, Wardrop and coworkers have developed an intramolecular oxamidation reaction using *O*-alkyl hydroxamates and iodine(III) reagents (**Figure 1-14**).[36] In these reactions, it is proposed that the phenyliodine(III) bis(trifluoroacetate) (PIFA) oxidizes the substrate hydroxamate to the corresponding nitrenium ion, a process made possible due to the stabilizing effect of the adjacent *O*-alkyl group. This platform allows for the formation of multiple lactam ring sizes (i.e. 5–8) and is general to various types of alkene substitution. The usefulness of this nitrenium-mediated approach was further demonstrated by Wardrop in the total synthesis of (-)-swainsonine.[37]

Figure 1-14. Nitrenium-Mediated Intramolecular Oxamidation



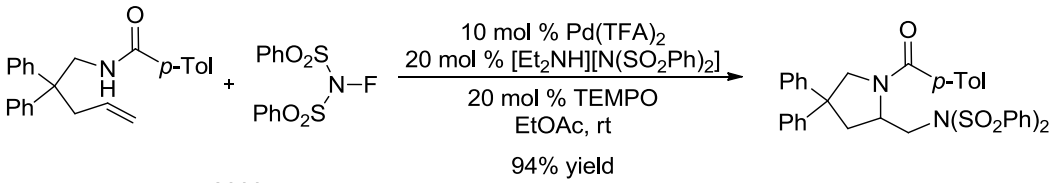
Wardrop *JACS* **2010**, 1188.

1.2.3 Diaminations

As with vicinal diols and amino-alcohols, vicinal diamines are ubiquitous in natural products, pharmaceutical agents, and organic reagents. The diamination of alkenes is the most direct and efficient approach to this important motif.

The earliest known examples of direct alkene diamination involve the addition reaction of nitrogen dioxide, providing di-nitro compounds that can be reduced to diamines.[38,39] And while many methods have been developed since that do not require nitrogen dioxide,[40] some of the most significant developments have surfaced over the last two decades.[41–45] For example, Michael and co-workers reported an intramolecular diamination using *N*-fluorobenzenesulfonamide (NFBS) as an electrophilic aminating reagent (**Figure 1-15**).[46] This is particularly interesting as NFBS is typically used as an electrophilic fluorine-atom source.

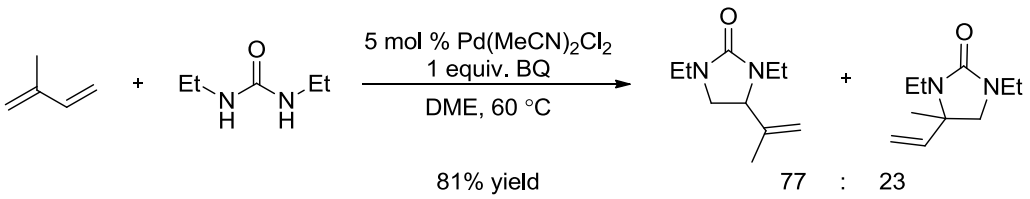
Figure 1-15. Pd-Catalyzed Alkene Diamination Using *N*-Fluorobenzenesulfonamide



Michael *Org. Lett.* **2009**, 1147.

Booker-Milburn developed an intermolecular diamination where 1,3-dienes are treated with *N*,*N*-diethylurea in the presence of catalytic bis(acetonitrile)palladium dichloride and *para*-benzoquinone (BQ) to form vinylic cyclic ureas (**Figure 1-16**).[47]

Figure 1-16. Pd-Catalyzed Diamination Using Dialkyl Ureas



Booker-Milburn *JACS* **2005**, 7308.

1.3 Summary and Outlook

Although the direct difunctionalization of alkenes has been known for over a century, recent success in this area has come from developments in metal-catalyzed and iodine(III)-mediated processes. Despite these advances, general methods that give high levels of stereo- and regiocontrol that are comparable Os-catalyzed protocols do not yet exist. This success inspires the continued development of improvements of these reactions (higher yielding, more efficient, more atom economical, etc.) as well as developing other types of alkene difunctionalizations that incorporate other useful functionality.

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2. CHAPTER TWO

Aerobic Intramolecular Alkene Dioxygenations Using Hydroxamic Acids

2.1 Introduction

The vicinal dioxygenation of alkenes has long been used in the preparation of functionalized organic compounds and tremendous progress has been made in the development of catalytic and asymmetric protocols.[1] However, the robust Sharpless dihydroxylation reaction requires Os-salts that are both expensive and highly toxic. Efforts over the past two decades have attempted to obviate the need of Os in favor of more environmentally friendly and inexpensive approaches (see **Chapter 1**).

2.2 Background

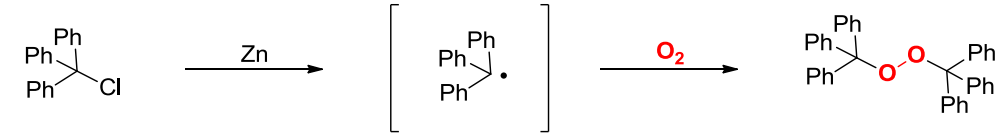
Alkene dioxygenation was the first class of alkene difunctionalization reported, and one of the most commonly developed types since. Dioxygenation is the addition of two oxygen based functional groups across a double bond, resulting in a formal two-electron oxidation of the alkene. See **Chapter 1.2.1** for an overview of alkene dioxygenation methods.

2.3 Reaction Development

Molecular oxygen can be considered to be an ideal oxidant for many reasons: (1) it is naturally abundant and renewable, (2) inexpensive, (3) highly atom-economical, and (4) environmentally benign.[2] As a result, there is significant motivation to develop processes that benefit from the use of O_2. There have been recent examples of Pd-catalyzed alkene dioxygenations, such as the work of Sigman[3] and Loh,[4] that use an atmosphere of O_2 as a stoichiometric oxidant. While dioxygen is an excellent oxidant in metal-catalyzed dioxygenations, it does not serve as an oxygen-atom source in either of these examples.

In general, molecular oxygen does not react with ground-state organic molecules and thus has not been used successfully as oxygen-atom source. This can be attributed to the spin forbidden reaction between dioxygen with a triplet, diradical ground-state and singlet ground-state organic molecules. However, carbon-centered radicals exist in a triplet state and their reaction with dioxygen is spin allowed. The reaction of O_2 with carbon-centered radicals dates back to the groundbreaking work Gomberg conducted with the first reported organic free-radical, triphenylmethyl radical (**Figure 2-1**).[5] In this work, Gomberg observed that generation of triphenylmethyl radical in the presence of O_2 resulted in the formation of the dimerized dialkyl peroxide product. Consequently, we hypothesized that the use of O_2 as an oxidant as well as an oxygen-atom source in an alkene dioxygenation process could be viable. In order to achieve this, we turned our attention to radical chemistry.

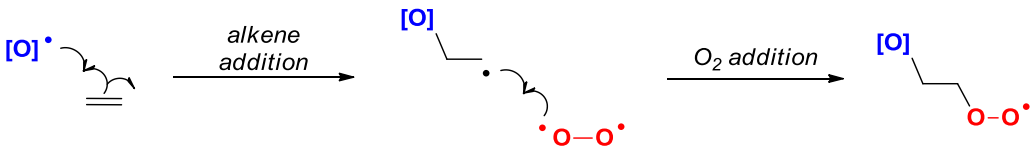
Figure 2-1. Pioneering Organic Free-Radical Studies



Gomberg *JACS* **1900**, 757.

We envisioned that a dioxygen-mediated alkene dioxygenation where an oxygen-centered (**Figure 2-2**). Since the trapping of a carbon-centered radical is a well precedented process, we turned our focus to the identification of a viable oxygen-centered radical for alkene addition.

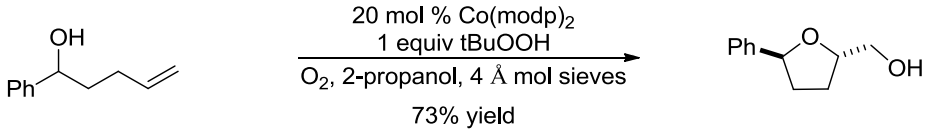
Figure 2-2. Proposed Approach to Aerobic Radical-Mediated Alkene Dioxygenations



Hydroxyl radicals are the simplest of oxygen-centered radicals, but are known for non-selective reactivity and are generally not used in synthesis.[6–9] Alkoxyl radicals, which are the simplest organic oxygen-centered radicals, are similarly known for their high reactivity and indiscriminate selectivity

causing H-atom abstraction and β-scission pathways to compete with alkene addition. This reactivity is typically attributed to the instability of the oxygen-centered radical derived from alcohols with O-H bond strengths of approximately 105 kcal/mol.[10] As a result, alkoxyl radicals have not found much utility in synthetic chemistry. One relatively rare example of a controlled alkoxyl radical addition to an alkene achieves a dioxygenation. This aerobic, Co-catalyzed homoallylic alcohol cyclization forms 2-hydroxymethyl tetrahydrofuran rings through the proposed formation of a Co-alkoxide which attenuates the otherwise expected unselective behavior of free alkoxy radicals (**Figure 2-3**).[11]

Figure 2-3. Intramolecular Co-Catalyzed Alkene Dioxygenation

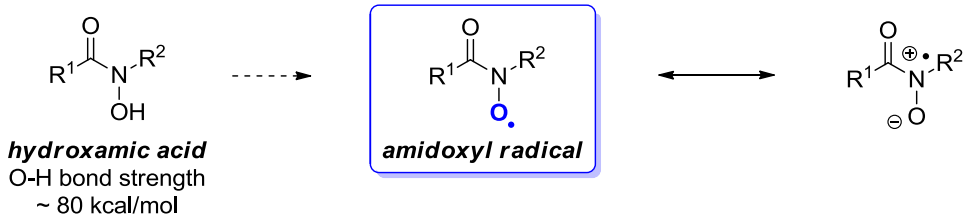


Mukaiyama *Chem. Lett*. **1990**, 67.

Conversely, relative to alkoxy radicals, nitroxyl radicals are stabilized by the presence of an adjacent nitrogen atom. These radicals are typified by the bench-stable, *N*-oxy-2,2,6,6-tetramethylpiperidinyl (TEMPO) radical. While nitroxyl radicals have found a useful place within oxidation protocols (i.e. oxidation of alcohols, sulfides, etc.) and living free-radical polymerizations, they do not find general use for efficient addition to alkenes.[12]

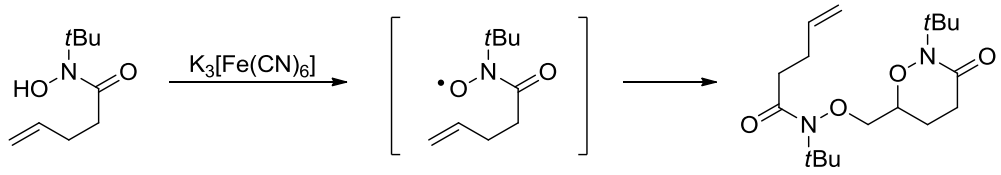
One strategy to destabilize a nitroxyl radical is through the substitution of an electron-donating alkyl group on nitrogen with a more electron-withdrawing acyl group. This hydroxylamine to hydroxamic acid shift has a dramatic effect of the O-H bond strengths in these compounds; increasing the bond strength from ~70 kcal/mol for TEMPO-H to approximately 80 kcal/mol for general hydroxamic acids (**Figure 2-4**).[10] With a bond dissociation energy between that of alcohols and hydroxylamines, we hypothesized that hydroxamic acids, the parents of amidoxyl radicals, might strike a suitable balance between reactivity and stability to offer a controlled reactivity profile for use in alkene dioxygenations.

Figure 2-4. Source of Amidoxyl Radical Reactivity



Studies of amidoxyl radicals have shown that they are capable of intramolecular benzylic hydrogen-atom abstraction, but attempts at allylic hydrogen-atom abstraction were unsuccessful and instead resulted in substrate dimerization following cyclization (**Figure 2-5**).[13]

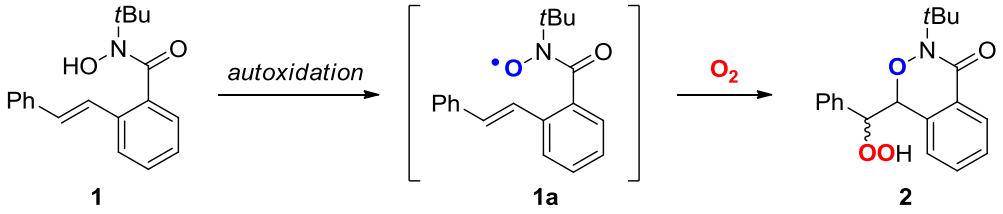
Figure 2-5. Unsaturated Hydroxamic Acid Dimerization Inititated by Single-Electron Oxidants



Perkins *Pure. & Appl. Chem.* **1990**, 195.

During their pioneering work on the fundamental reactivity of amidoxyl radicals and alkenes, Perkins and co-workers observed an amidoxyl radical cyclization followed by oxygenation. Isolation attempts of highly conjugated stilbene-substituted *N*-*tert*-butyl amidoxyl radical **1a** were unsuccessful, and the parent hydroxamic acid **1** underwent autoxidation, cyclization, and subsequent radical oxygenation to deliver alkyl hydroperoxide **2** (**Figure 2-6**).[13,14] However, this unique reactivity was never expanded to a general or synthetically relevant reaction manifold. We thus envisioned that a general approach to aerobic alkene dioxygenation could arise from the cyclization of an amidoxyl radical formed in situ from readily prepared hydroxamic acids, and subsequent reaction with molecular oxygen.

Figure 2-6. Unique Example of Aerobic Amidoxyl Radical Alkene Dioxygenation



1 1a 2

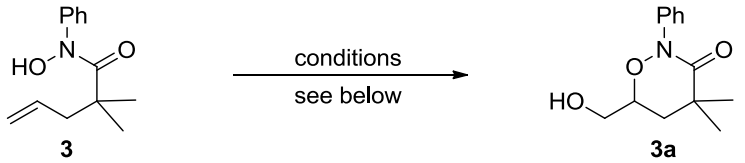
Perkins *ACIE* **1990**, 195.

2.3.1 Optimization

Our studies began with unsaturated *N*-phenyl hydroxamic acid **3**. To facilitate cyclization, initial experiments explored the catalytic use of simple, inexpensive cobalt salts, which are known to assist the formation of amidoxyl radicals and other oxygen-centered radicals under aerobic conditions.[11,15] Heating **3** with either 2 mol % $Co(OAc)_2$ or 2 mol % $Co(acac)_3$ under 1 atm of O_2 in acetic acid (AcOH) delivered the desired deoxygenated [1,2]-oxazinone **3a** in 55 and 54% yield, respectively (**Table 2-1, entries 1** and **2**). A control experiment without any added metal catalyst revealed that the dioxygenation proceeded under 1 atm O_2 alone, to afford **3a** in 80% yield following a mild reductive work up with 1 equivalent of PPh_3 (**Table 2-1, entry 3**). The use of a reductive work up was not necessary in the presence of either Co-salt investigated, as the cobalt species also served as an in situ reductant of the initially formed alkyl peroxide product.

A similar reduction was achieved without the use of added PPh_3 or Co-salt by substituting dimethyl sulfoxide (DMSO) for AcOH as solvent and increasing the temperature to 90 °C (**Table 2-1, entry 4**). The reducing capability of dimethyl sulfoxide at elevated temperatures is a result of the known disproportionation process that occurs, generating both dimethyl sulfone and dimethyl sulfide, which is active reducing agent of the hydroperoxide. This was confirmed not only by the pungent odor dectected, but also that the addition of 20 equivalents of dimethyl sulfide to the crude reaction mixture and gentle heating effects the same reduction as added PPh_3.

Table 2-1. Initial Aerobic Dioxygenation Studies



3 **3a**

entry	metal	solvent	conditions	T (°C)/ t (h)	% yield
1	2 % $Co(OAc)_2$	AcOH	1 atm O_2	60 / 4	55[a]
2	2% $Co(acac)_3$	AcOH	1 atm O_2	60 / 4	54[a]
3	none	AcOH	1 atm O_2	60 / 4	80[b]
4	none	DMSO	1 atm O_2	90 / 9	65[c]
5	none	AcOH	1 atm Ar	60 / 4	trace
6	none	AcOH	1 atm *Air*	60 / 4	77[b]

[a]Yield determined by GC analysis. [b]Yield of isolated product after PPh_3 workup.
[c]Yield of isolated product.

The use of an aerobic atmosphere proved crucial, as replacing the O_2 with Ar resulted in no reaction (**Table 2-1, entry 5**). However, only a slight decrease in yield was observed when the O_2 atmosphere was replaced with air, proving that the dioxygen present in air alone was sufficient to serve as the sole oxidant as well as the external oxygen-atom source in this reaction (**Table 2-1, entry 6**).

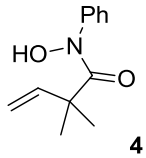
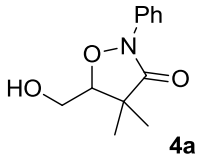
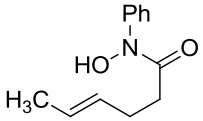
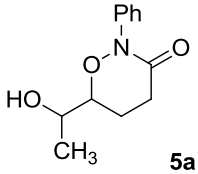
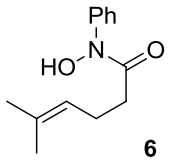
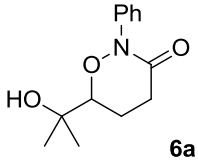
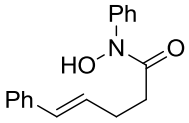
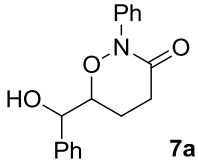
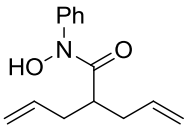
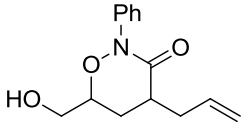
2.3.2 Substrate Scope

Encouraged by these initial results, we began to explore the generality of this radical-mediated alkene dioxygenation in a variety of synthetic contexts (**Table 2-2**). The choice of *N*-phenyl hydroxamic acids was made for practical reasons, as they are easily synthesized via two simple routes (See **2.5 Experimental**). While Perkins uses *N-tert*-butyl hydroxamic acids exclusively, methods reported for their synthesis were extremely challenging in our hands and required a more intensive synthetic pathway. We did however observe that alkene dioxygenation was successful using *N-tert*-butyl hydroxamic acids.

The difunctionalization of hydroxamic acid **4** by 5-*exo* ring closure proceeded well, delivering isoxazolinone **4a** in 88% yield (**Table 2-2, entry 1**). Further substitution of the alkene is well-tolerated as demonstrated by the successful reactions involving 1,2-disubstituted and trisubstituted

substrates **5** and **6** (**Table 2-2, entries 2 and 3**), as well as conjugated alkenes (**entry 4**). We prepared α-diallyl hydroxamic acid **8** to determine the potential for selective oxidation of diene substrates. We hypothesized that oxidation using a metal-catalyzed intermolecular protocol with this type of substrate would likely lead to mixtures of mono- and bis-dioxygenation products. However, as dictated by the intramolecular amidoxyl radical cyclization, we observe reaction at only one alkene to produce [1,2]-oxazinone **8a** in 75% yield (**Table 2-2, entry 5**).

Table 2-2. Aerobic Dioxygenations of Alkenyl *N*-Aryl Hydroxamic Acids

entry[a]	substrate	condition[b]	product	% yield[c,d]
1	 **4**	**A**	 **4a**	88
2	 **5**	**B**	 **5a**	66 55:45 dr
3	 **6**	**C**	 **6a**	79
4	 **7**	**B**	 **7a**	63 60:40 dr
5	 **8**	**B**	 **8a**	75 62:38 dr

[a]All reactions run 0.1M in specified solvent, 1 atm O_2, 3 - 40h. [b]Condition A: AcOH, 60 °C w/PPh_3 workup. Condition B: DMSO, 90 °C. Condition C: DMSO, 60 °C w/PPh_3 workup. [c]Yields of isolated product. [d]Diastereomeric ratios were determined by ^1H NMR spectroscopy of crude reaction mixtures.

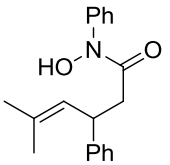
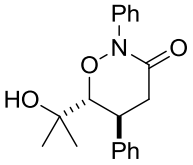
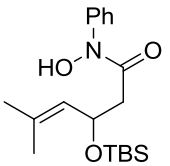
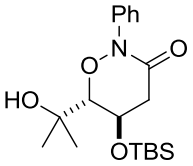
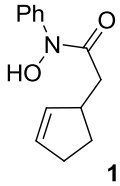
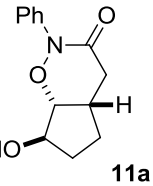
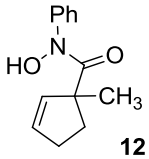
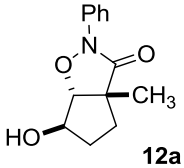
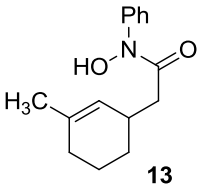
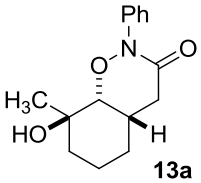
These results demonstrate the unique chemoselectivity of amidoxyl radicals in 6-*exo* alkene cyclization reactions. Oxygen-centered radicals are generally unable to provide access to six-

membered ring systems through alkene cyclizations because of their propensity to undergo side reactions such as 1,5-H-atom abstraction at the allylic position.[16,17] It is important to note that we observe no by-products resulting from these allylic oxidation pathways. We attribute this to the attenuated reactivity of amidoxyl radicals compared to alkoxy radicals.

To assess the potential for diastereocontrol in the dioxygenation process, we studied a number of different substrates (**Table 2-3**). Substrates **9** and **10**, possessing β-substituents, undergo highly stereoselective 6-*exo* cyclizations providing products **9a** and **10a** as a single diastereomers in good yields (**Table 2-3, entries 1** and **2**). Thus, β-silyloxy substrate **10**, effectively delivers a fully differentiated masked triol, **10a**. The differentiation of the oxygen functionality added across the alkene is a common feature of our radical-mediated dioxygenation approach as one oxygen-atom is always protected in the cyclic hydroxamate formed. This is noteworthy as this is not as easily achieved using intermolecular metal-catalyzed alkene dioxygenation methods. We also explored the potential of this process for reactions involving cyclic alkenes. Cyclopentenyl substrate **11** undergoes 6-*exo* cyclization to provide [5,6]-*cis*-fused product **11a** as a 78:22 mixture of β:α hydroxy diastereomers in excellent yield (**Table 2-3, entry 3**). The difunctionalization of other cyclic alkene substrates (**12** and **13**) also favor their respective *trans*-dioxygenation products (**Table 2-3, entries 4** and **5**). These results indicate that the aerobic dioxygenation of cyclic substrates favors *trans*-alkene difunctionalizations, complementing existing *cis*-selective metal-catalyzed processes.[1,3]

In several of these reactions, the radical-initiator dilauroyl peroxide (DLP) was used (**Table 2-3**). While not necessary, we found this to be a simple and practical way to increase reaction rates if they proved to be sluggish. Over the course of our subsequent studies we also found that, amidoxyl radicals could be formed in the absence of any added initiator or O_2. We attribute this background reactivity to small amounts of amidoxyl radical formed via autoxidation processes during the synthesis, purification, and storage of the parent hydroxamic acids.

Table 2-3. Studies of Alkene Dioxygenation Stereoselectivity

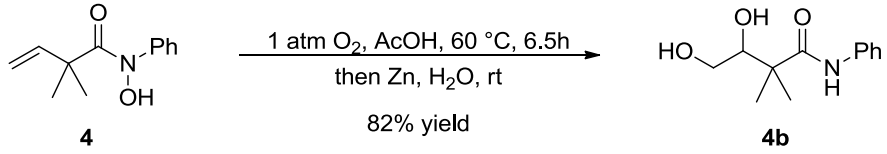
entry[a]	substrate	condition[b]	product	% yield[c,d]
1	 **9**	**A**	 **9a**	62 >95:5 dr
2	 **10**	**C**	 **10a**	69[e] >95:5 dr
3	 **11**	**A**	 **11a**	91[e] 78:22 dr β:α
4	 **12**	**A**	 **12a**	98 66:33 dr β:α
5	 **13**	**A**	 **13a**	64[e] 84:16 dr β:α

[a]All reactions run 0.1M in specified solvent, 1 atm O_2, 3 - 40h. [b]Condition A: AcOH, 60 °C w/PPh_3 workup. Condition B: DMSO, 90 °C. Condition C: DMSO, 60 °C w/PPh_3 workup. [c]Yields of isolated product. [d]Diastereomeric ratios were determined by ^1H NMR spectroscopy of crude reaction mixtures. [e]Reactions initiated with 10 mol % dilauroyl peroxide.

2.3.3 Post-Reaction Product Manipulation

Access to simple 1,2-diols from the alkene dioxygenation products is readily accomplished through the reduction of the N-O bond of the cyclic hydroxamate. We took advantage of the AcOH used as solvent to develop a one-pot alkene dihydroxylation reaction by adding Zn metal directly into the reaction mixture prior to work up. This protocol effectively achieves an aerobic alkene dihydroxylation of substrate **4** to produce diol **4b** in 82% yield (**Figure 2-7**).

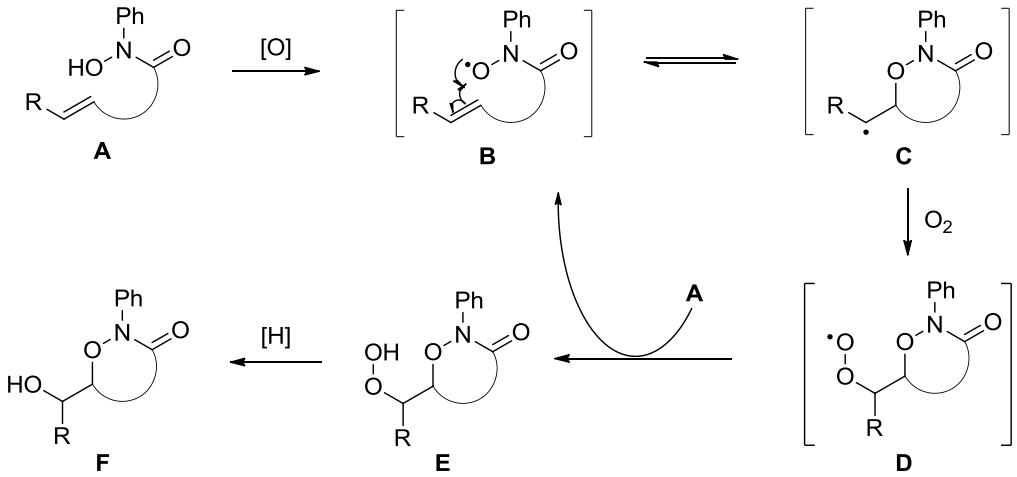
Figure 2-7. One-Pot Aerobic Alkene Dioxygenation



2.3.4 Proposed Mechanism

A plausible reaction mechanism is shown in **Figure 2-8**. Following initiation of the reaction via formation of the amidoxyl radical, a reversible cyclization produces carbon-centered radical **C**.[18] This intermediate reacts with molecular oxygen to provide alkylhydroperoxy radical **D**, which subsequently performs a hydrogen-atom abstraction from the substrate hydroxamic acid **A**,[19] generating amidoxyl radical **B** and affording alkylhydroperoxide **E**. Subsequent reduction by dimethyl sulfide or PPh_3, produces dioxygenation product **F**. We have verified the production of alkylhydroperoxides by isolating and characterizing the peroxide dioxygenation product of hydroxamic acid substrate **6** (see **2.5 Experimental**).

Figure 2-8. Proposed Radical-Mediated Alkene Dioxygenation



2.4 Summary

In conclusion, we have developed a radical-mediated, aerobic alkene dioxygenation using hydroxamic acids. This reaction avoids the use of precious transition-metal catalysts that are typically required in related difunctionalization processes and uses O_2 or air as readily available oxidants and

external oxygen-atom sources. The dioxygenation reaction is applicable to a wide range of unsaturated substrates and affords difunctionalized products with differentiated oxygen-atom functionality; a unique feature of this radical-mediated process. This method also exhibits the potential for high reaction stereoselectivity, and results in *trans* difunctionalizations with cyclic alkenes, complementing transition-metal-catalyzed *cis*-selective dioxygenation reactions. The mild reaction conditions, simple substrate preparation, and generality of this dioxygenation procedure are attractive aspects for organic synthesis.

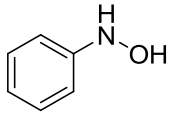
2.5 Experimental

2.5.1 General Methods

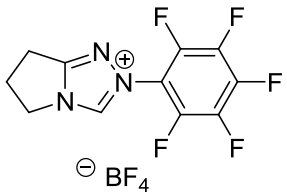
Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 500 or a Bruker AMX 300 (^{1}H NMR at 300 MHz, 400 MHz or 500 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.27 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, CD_2Cl_2 at 54.0 ppm, DMSO-d_6 at 39.5 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Thin layer chromatography (TLC) was performed on SiliaPlate 250µm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Hydroxamic acids can be visualized using a $FeCl_3$ solution in sulfuric acid. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 µm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Oxygen UHP 305CF was purchased from

National Specialty Gases, National Welders Supply Company. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

2.5.2 Compound Preparation



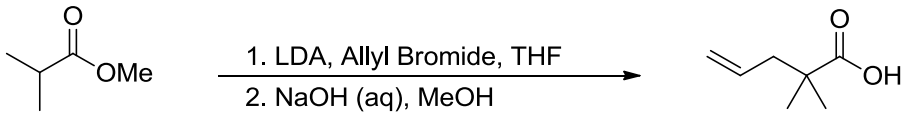
N-Phenylhydroxylamine was synthesized according to literature procedures.[20] To a vigorously stirring suspension of nitrobenzene (3.62 g, 29.4 mmol) and NH_4Cl (1.79 g, 33.5 mmol) in H_2O (56 mL) was added activated Zn powder (3.85 g, 58.8 mmol) portion-wise over the course of 10 min. The ZnO solids were filtered away after the suspension had cooled to rt, the solids were washed with 20 mL hot water, and the resultant filtrate extracted with CH_2Cl_2 (5x). The organic extracts were washed with brine and concentrated under reduced pressure to give a yellow woolen solid that was washed with warm hexanes and filtered to collect 2.13 g (66% yield) *N*-phenylhydroxylamine as an ivory woolen solid. *Note: hydroxylamine is stable for storage at -40 ºC for several weeks. Avoid inhaling; strongly irritating.* Physical and spectral data were in accordance with literature data.[21]



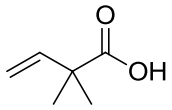
6,7-Dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate.[27] Trimethyloxonium tetrafluoroborate (2.60 g, 17.6 mmol) was added to pyrrolidinone (1.4 mL, 17.6 mmol) in CH_2Cl_2 (75 mL) and stirred overnight at rt under an Ar atmosphere. Pentafluorophenyl hydrazine (3.50 g, 17.6 mmol) was added and stirred at rt for 2.5 h. Solvent was removed under reduced pressure prior to heating to 110 ºC under active vacuum for 2 h. Triethylorthoformate (14.7 mL, 88.1 mmol) was added to the reaction mixture before heating to 110 ºC under Ar for 1 h. The resultant dark orange solution was diluted with toluene, filtered and the collected solid washed with MeOH and dried under vacuum to give 2.70 g (43% yield) of the title compound as shimmery pale

ivory crystals. All spectroscopic and physical data matched a commercially available sample purchased from Sigma Aldrich.

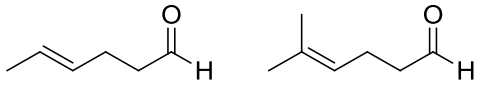
Figure 2-9. Synthesis of 2,2-Dimethylpent-4-enoic acid



2,2-Dimethylpent-4-enoic acid. Title compound was prepared using a procedure outlined by Trost *et. al*[22] followed by standard saponification of the alkylated ester. Physical and spectral data were in accordance with a commercially available sample.

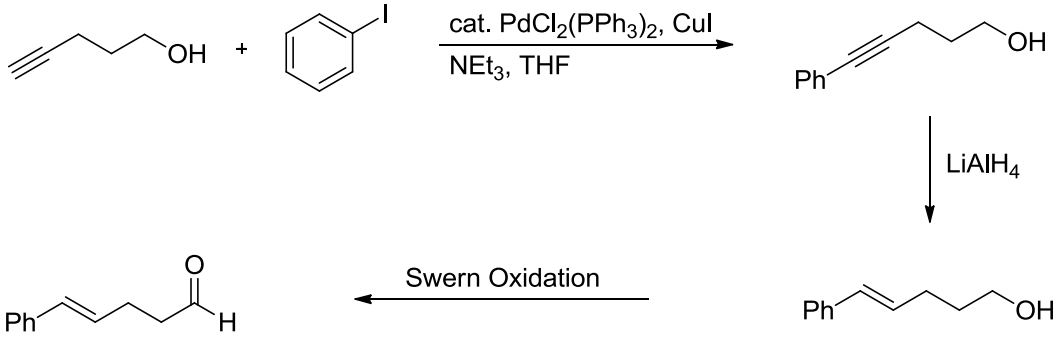


3,3-Dimethyl-but-3-enoic acid was prepared using literature procedures with physical and spectra data in agreement with those reported.[23]



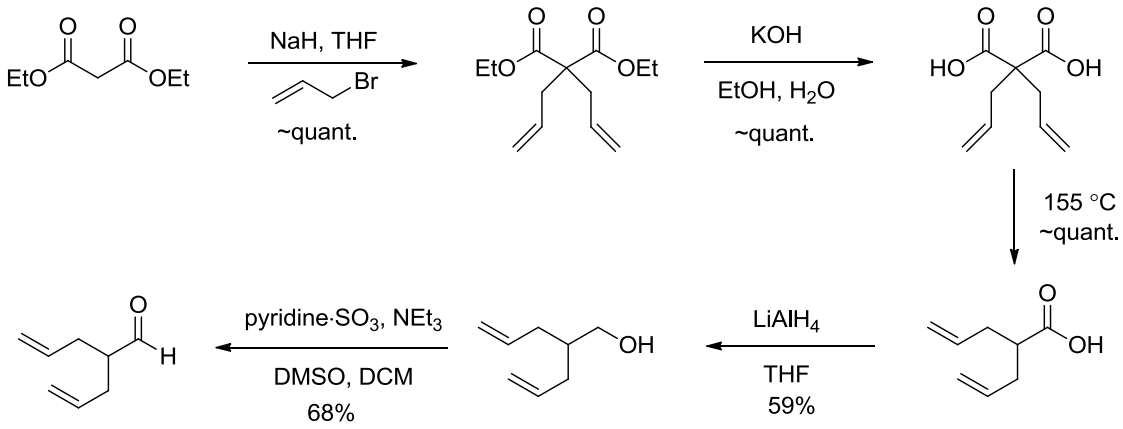
(*E*)-hex-4-enal and 5-methyl-4-enal were prepared via Claisen rearrangements following the procedure used by Kraus *et. al*.[24] Physical and spectral data were in accordance with literature data.[25]

Figure 2-10. Synthesis of (*E*)-5-phenylpent-4-enal



(*E*)-5-phenylpent-4-enal was synthesized according to literature Sonogashira procedures[26] followed by $LiAlH_4$ reduction[27] and Swern oxidation (**Figure 2-10**).[28] Physical and spectral data were in accordance with literature data.[29]

Figure 2-11. Synthesis of 2-Allylpent-4-enal

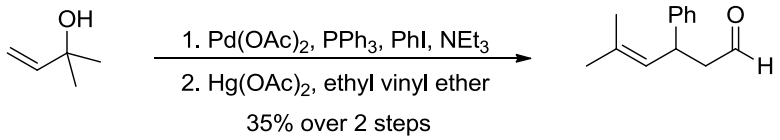


2-Allylpent-4-enal was synthesized according to the following stepwise procedure (**Figure 2-11**): To a 0 ºC suspension of 60% wt. NaH dispersion in oil (2.16 g, 58.5 mmol) in THF (100 mL) was added diethyl malonate (3.56 mL, 23.4 mmol) dropwise in THF (25 mL) under Ar. The reaction mixture was warmed to rt for 15 min and then treated with allyl bromide (3.96 mL, 46.8 mmol) and heated to reflux overnight. The reaction was quenched with NH_4Cl, extracted Et_2O (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 6.02 g (~quant.) diethyl 2,2-diallylmalonate as a yellow-orange liquid.

Crude diethyl 2,2-diallylmalonate (9.00 g, 37.5 mmol) was then dissolved in EtOH (23 mL), H_2O (14 mL), and KOH (4.62 g, 82.4 mmol) and heated to reflux under Ar overnight. Solvent was removed under reduced pressure, the resultant residue was taken up in H_2O, acidified to pH 1 with 6N HCl, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 6.88 g (~quant.) of 2,2-diallylmalonic acid as a peach solid. Neat, crude 2,2-diallylmalonic acid was heated at 155 ºC overnight to afford 5.45 g (~quant.) 2-allylpent-4-enoic acid as a dark amber liquid.

The crude acid (5.45 g, 38.9 mmol) was added dropwise as a solution in THF (30 mL) to a suspension of $LiAlH_4$ (2.21 g, 58.4 mmol) in THF (24 mL) at 0 ºC. The reaction mixture was warmed to rt before heating to reflux for 21 h. The reaction mixture was cooled to 0 ºC and quenched by slow sequential addition of H_2O (2.2 mL), 10% NaOH (4.4 mL), and H_2O (6.6 mL). After 20 min. of stirring at rt the suspension was filtered, the solid washed with Et_2O, the collected filtrate dried ($MgSO_4$), and concentrated *in vacuo* to give crude oil that was purified via flash chromatography (30% EtOAc/Hexanes) to give 2.91 g (59% yield) 2-allylpent-4-en-1-ol as a pale yellow liquid. To a 0 ºC solution of 2-allylpent-4-en-1-ol (1.50 g, 11.9 mmol) in CH_2Cl_2 (36 mL) was added triethylamine (6.6 mL, 47.4 mmol) followed by pyridine·SO_3 complex (5.7 g, 35.6 mmol) as a solution in DMSO (36 mL). The reaction solution was stirred at 0 ºC for 1 h before quenching with sat. $NaHCO_3$. The solution was then extracted with Et_2O (3x), the combined organics were washed successively with Na_2HPO_4, 1N HCl, brine and dried ($MgSO_4$) to give 1.01 g (68% yield) 2-allylpent-4-enal as a pale yellow liquid which was used without further purification. Physical and spectral data were in accordance with literature data.[30]

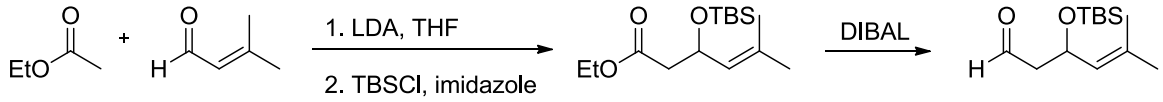
Figure 2-12. Synthesis of 5-Methyl-3-phenylhex-4-enal



5-Methyl-3-phenylhex-4-enal was synthesized through a two-step procedure (**Figure 2-12**). A mixture of 2-methylbut-3-en-2-ol (5.2 mL, 50.0 mmol), iodobenzene (4.4 mL, 40.0 mmol), $Pd(OAc)_2$ (27 mg, 0.12 mmol), and triphenylphosphine (63 mg, 0.24 mmol) in triethylamine (20 mL) was flushed with N_2 then heated to reflux overnight. The reaction mixture was diluted with Et_2O and H_2O and the layers separated. The organic layer was washed with H_2O (3x), brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified via distillation to give 5.74 g (*E*)-2-methyl-4-phenylbut-3-en-2-ol as a pale liquid. The alcohol (5.74 g, 35.4 mmol) was then combined in a sealed tube with $Hg(OAc)_2$ (562 mg, 1.76 mmol) and ethyl vinyl ether (25 mL). The mixture was flushed

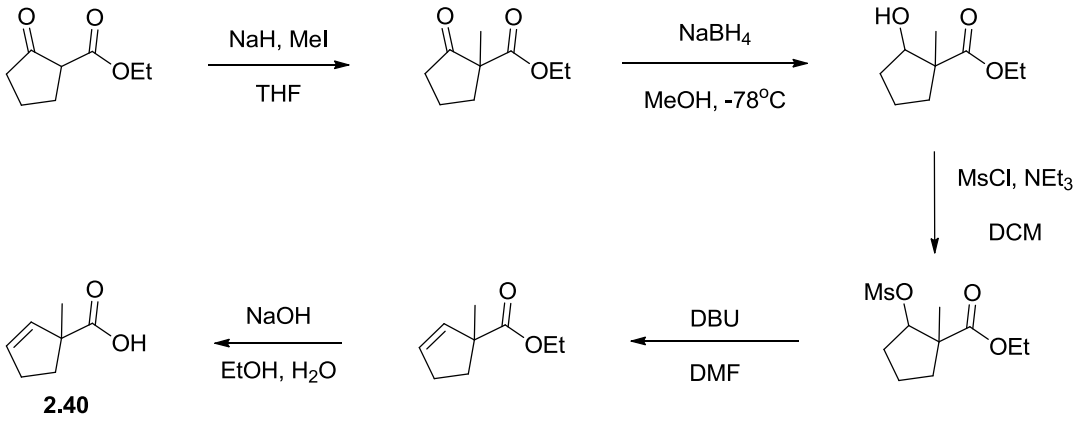
with Ar, sealed and heated to 50 ºC 24 h, then 120 ºC overnight, and 130 ºC for a second overnight to give a 1:1 mix of recoverable alcohol starting material: aldehyde by NMR. Excess ethyl vinyl ether was removed *in vacuo*, and the resultant liquid was purified via flash chromatography (15:1 Hexanes:EtOAc) to yield 3.25 g (35% over 2 steps) 5-methyl-3-phenylhex-4-enal as a greenish-yellow liquid. Physical and spectral data were in accordance with literature data.[31]

Figure 2-13. Synthesis of 3-(*tert*-butyldimethylsilyloxy)-5-methylhex-4-enal



3-(*tert*-butyldimethylsilyloxy)-5-methylhex-4-enal was synthesized by TBS protection of Aldol product of ethyl acetate and 3-methylcrotonaldehyde followed by standard DIBAL reduction using literature procedures (**Figure 2-13**).[32]

Figure 2-14. Synthesis of 1-Methylcyclopent-2-enecarboxylic acid

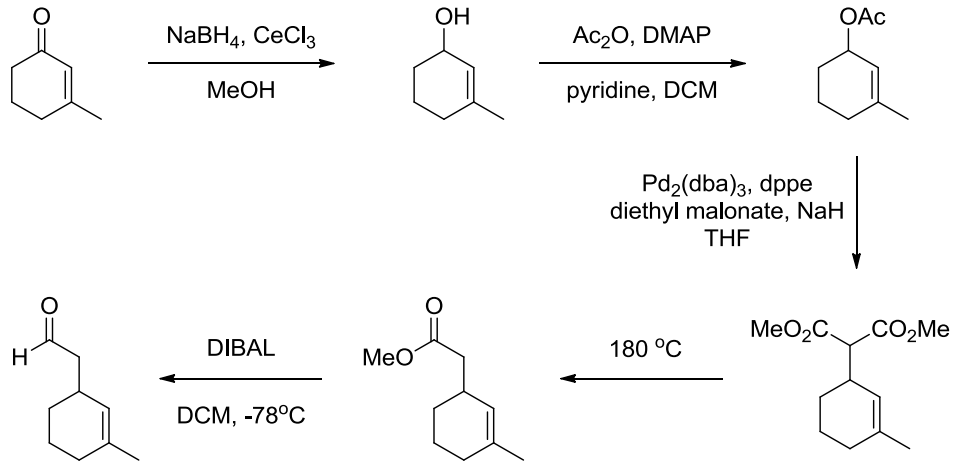


2.40

1-Methylcyclopent-2-enecarboxylic acid was synthesized according the procedure developed by Pichlmair *et. al* (**Figure 2-14**).[33] Procedure for the saponification of ethyl 1-methylcyclopent-2-enecarboxylate follows: The crude ester (1.16 g, 7.52 mmol) was heated to reflux in a solution of EtOH (8 mL) and NaOH (400 mg, 10 mmol) for 2 h. The reaction mixture was diluted with Et_2O and acidified with 1N HCl. The aqueous layer was extracted with Et_2O (4x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give crude acid product that was

purified via flash chromatography (20% EtOAc/Hexanes) to give 1-methylcyclopent-2-ene carboxylic acid (619 mg, 4.91 mmol, 65% yield) as a pale liquid. Physical and spectral data were in accordance with literature data.[34]

Figure 2-15. Synthesis of 2-(3-Methylcyclohex-2-enyl)acetaldehyde

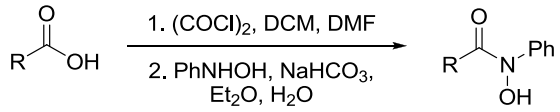


3-Methylcyclohex-2-enol was obtained from a Luche reduction of 3-methylcyclohex-2-enone, and the allylic alcohol was elaborated to 2-(3-Methylcyclohex-2-enyl)acetaldehyde using an analogous procedure to that used by Cossy *et. al*[35] to make 2-(cyclohex-2-enyl)acetaldehyde (**Figure 2-15**). Physical and spectral data were in accordance with literature data.[36]

2.5.3 General Procedures for the Preparation of Hydroxamic Acids

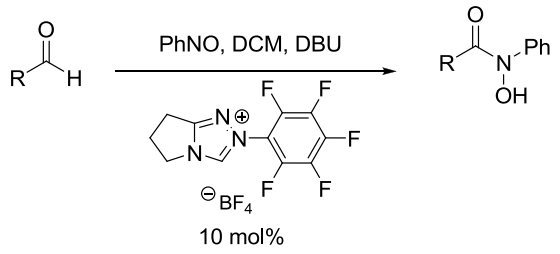
Note: All N-aryl hydroxamic acids should be purified promptly upon formation and stored neat at -40 ºC.

Method A[21]



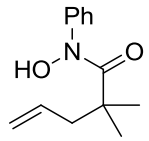
To a 0 ºC solution of carboxylic acid (1 mmol) in DCM (1.4 mL) and DMF (10 drops) was added oxalyl chloride (2 mmol) dropwise under an argon atmosphere. The solution was stirred at 0 ºC for 15 min. then warmed to room temperature overnight. The resultant yellow solution was evaporated almost to dryness under reduced pressure before sodium bicarbonate (2 mmol) was added and redissolved in H_2O/Et_2O (1 mL/2 mL). The solution was then again cooled to 0 ºC and phenylhydroxylamine (1 mmol) was added and the reaction was stirred at 0 ºC for 3.5 h. The layers were separated, the aqueous layer was acidified with citric acid and extracted with Et_2O (3x). The combined organic layers were then washed with brine, dried ($MgSO_4$), and concentrated to give an orange oil that was purified by flash chromatography to yield the corresponding *N*-phenyl hydroxamic acid.

Method B[37]



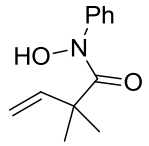
To a solution of aldehyde (1 mmol), nitrosobenzene (1 mmol), and triazolium salt (0.10 mmol) in CH_2Cl_2 (4.5 mL) under Ar was added DBU (0.10 mmol). The solution color rapidly changed from green-blue to amber over 15 min. stirring at rt. Upon TLC visualization of consumption of aldehyde, solvent was removed under reduced pressure and the resultant oil was purified via flash

chromatography to yield the corresponding *N*-phenyl hydroxamic acid. Note: this procedure was not effective for the synthesis of α-disubstituted *N*-aryl hydroxamic acids.



3

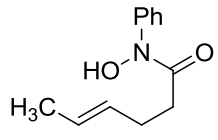
3 was synthesized via ***Method A*** in 79% yield as an orange oil that crystallizes upon scratching. Analytical data for **3**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.85 (br. s., 1 H) 7.44 (m, 5 H) 5.79 (m, 1 H) 5.09 (m, 2 H) 2.32 (d, *J*=7.33 Hz, 2 H) 1.10 (s, 6 H); ^{13}C NMR (126 MHz, chloroform-d) 173.9, 140.1, 134.3, 129.4, 129.2 (2 C), 128.2, 118.1 (2 C), 45.5, 42.4, 26.3 (2 C); IR (thin film, cm^{-1}) 3194, 2976, 1614, 1591, 1496, 1391, 1361, 1271, 1067, 997, 916, 761, 690; HRMS (ESI) Calcd. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.12, Found = 242.1154



4

4 was synthesized via ***Method A*** in 63% yield as a pale yellow solid.

Analytical data for **4**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.14 (br. s., 1 H) 7.47 (m, 2 H) 7.40 (m, 2 H) 7.34 (m, 1 H) 5.95 (m, 1 H) 4.97 (m, 2 H) 1.35 (s, 6 H); ^{13}C NMR (500 MHz, METHYLENE CHLORIDE-d_2) 174.3, 143.2, 141.1, 128.6 (2 C), 127.3, 124.8, 112.3 (2 C), 45.2, 25.4 (2 C); IR (thin film, cm^{-1}) 3216, 2978, 2931, 1945, 1622, 1592, 1495, 1384, 1355, 1235, 1184, 1084, 1068, 913, 759, 701; HRMS (ESI) Calcd. for $[C_{12}H_{15}NO_2+Na]^+$ = 228.10, Found = 228.1009.

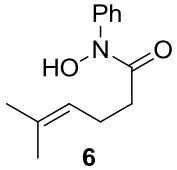


5

5 was synthesized via ***Method B*** in 25% yield as a yellow solid.

Analytical data for **5**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.19 (br. s., 1 H) 7.44 (m, 5 H) 5.42 (m, 2 H) 2.35 (m, 4 H) 1.64 (d, *J*=5.50 Hz, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) 172.7, 142.2, 130.8

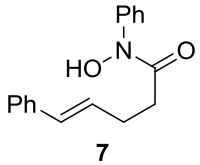
(2 C), 128.9, 125.5 (2 C), 125.0, 120.6, 34.0, 27.5, 18.2; IR (thin film, cm^{-1}) 3183, 3055, 2919, 1633, 1593, 1495, 1454, 1398, 1265, 967, 750, 704; HRMS (ESI) Calcd. for $[C_{12}H_{15}NO_2+Na]^+$ = 228.10, Found = 228.0993.



6

6 was synthesized via ***Method B*** in 67% yield as a pale orange solid.

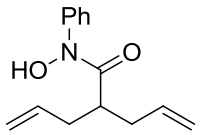
Analytical data for **6**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.09 (br. s., 1 H) 7.46 (m, 2 H) 7.41 (m, 3 H) 5.04 (m, 1 H) 2.35 (m, 4 H) 1.68 (s, 3 H) 1.58 (s, 3 H); ^{13}C NMR (500 MHz, chloroform-d) 167.9, 138.0, 133.5, 129.3 (2 C), 129.1, 126.6, 122.1 (2 C), 32.1, 25.7, 24.0, 17.6; IR (thin film, cm^{-1}) 3187, 2968, 2915, 1633, 1593, 1495, 1399, 1092, 1070, 757, 691; HRMS (ESI) Calcd. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.12, Found = 242.1155.



7

7 was synthesized via ***Method B*** in 38% yield as a pale yellow solid.

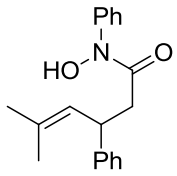
Analytical data for **7**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.25 (br. s., 1 H) 7.45 (m, 4 H) 7.33 (m, 5 H) 7.24 (d, *J*=6.87 Hz, 1 H) 6.41 (d, *J*=15.12 Hz, 1 H) 6.18 (m, 1 H) 2.58 (d, *J*=6.19 Hz, 2 H) 2.47 (m, 2 H); ^{13}C NMR (126 MHz, METHEYLENE CHLORIDE-d_2) δ ppm 206.7, 137.3, 130.8, 129.3, 129.1, 128.8, 128.5, 128.1, 127.1, 126.6, 125.9, 31.9, 28.5; IR (thin film, cm^{-1}) 3169, 2915, 1627, 1590, 1483, 1400, 1298, 1070, 963, 756, 738, 688; LRMS (ESI) Calcd. for $[C_{17}H_{17}NO_2+Na]^+$ = 290.11, Found = 290.11.



8

8 was synthesized via ***Method B*** in 59% yield as dark orange oil.

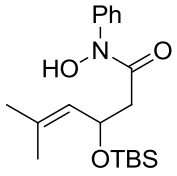
Analytical data for **8**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.19 (br. s., 1 H) 7.42 (m, 5 H) 5.64 (m, 2 H) 5.05 (m, 4 H) 2.59 (m, 1 H) 2.42 (m, 2 H) 2.20 (m, 2 H); ^{13}C NMR (126 MHz, chloroform-d) 169.1, 137.5, 134.9 (2 C), 129.4 (2 C), 129.3 (2 C), 127.7, 117.5 (2 C), 41.1, 36.7 (2 C); IR (thin film, cm^{-1}) 3180, 3077, 2979, 2912, 1625, 1593, 1495, 1442, 1402, 994, 916; HRMS (ESI) Calcd. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.12, Found = 254.1154.



9

9 was synthesized via ***Method B*** in 56% yield as a yellow-orange solid.

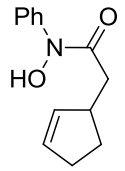
Analytical data for **9**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.20 (br. s., 1 H) 7.43 (m, 3 H) 7.28 (m, 3 H) 7.20 (m, 2 H) 7.12 (m, 2 H) 5.18 (m, 1 H) 4.17 (m, 1 H) 2.62 (m, 2 H) 1.71 (dd, *J*=7.33, 0.92 Hz, 6 H); ^{13}C NMR (126 MHz, chloroform-d) 166.3, 144.1, 137.8, 133.3, 129.2, 128.9, 128.5, 127.2, 126.8, 126.3, 122.4, 40.9, 39.3, 25.8, 18.1; IR (thin film, cm^{-1}) 3175, 3028, 2968, 2913, 1632, 1593, 1495, 1453, 1394, 1303, 1092, 1071, 757, 698; HRMS (ESI) Calcd. for $[C_{19}H_{21}NO_2+Na]^+$ = 318.15, Found = 318.1467.



10

10 was synthesized via ***Method B*** in 69% yield as an orange oil that crystallizes upon scratching. Analytical data for **10**: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.55 (m, 1 H) 7.60 (m, 2 H) 7.37 (t,

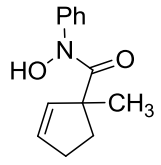
J=7.79 Hz, 5 H) 7.14 (m, 1 H) 5.16 (m, 3 H) 4.95 (m, 1 H) 2.83 (m, 1 H) 2.57 (m, 1 H) 1.66 (d, *J*=11.91 Hz, 6 H) 0.82 (s, 9 H) 0.01 (s, 6 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 169.9, 142.2, 131.9, 128.8, 128.7, 124.9, 120.5, 66.8, 43.8, 26.2, 25.9, 18.5, 18.3; IR (thin film, cm^{-1}) 3174, 2955, 2929, 2857, 1633, 1594, 1494, 1389, 1253, 1071, 834; LRMS (ESI) Calcd. for $[C_{19}H_{31}NO_3Si+Na]^+$ = 372.19, Found = 372.19.



11

11 was synthesized via ***Method A*** from commercially available 2-Cyclopentene-1-acetic acid in 83% yield as a pale yellow solid.

Analytical data for **11**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 9.44 (br. s., 1 H) 7.44 (m, 5 H) 5.75 (br. s., 1 H) 5.66 (m, 1 H) 3.17 (m, 1 H) 2.39 (m, 2 H) 2.29 (br. s., 2 H) 2.12 (m, 1 H) 1.39 (br. s., 1 H); ^{13}C NMR (126 MHz, chloroform-d) δ ppm 167.7, 138.3, 133.7, 131.6, 129.4, 129.2, 126.9, 42.3, 38.1, 31.8, 29.7; IR (thin film, cm^{-1}) 3164, 3058, 2937, 2851, 1631, 1592, 1495, 1393, 1095, 1070, 905, 756, 717, 690; LRMS (ESI) Calcd. for $[C_{13}H_{15}NO_2+Na]^+$ = 240.09, Found = 240.09.

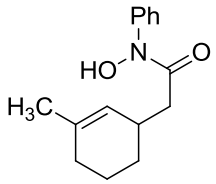


12

12 was synthesized via ***Method A*** in 75% yield as pale yellow solid.

Analytical data for **12**: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.53 (br. s., 1 H) 7.41 (m, 5 H) 5.56 (m, 1 H) 5.50 (m, 1 H) 2.39 (m, 1 H) 2.29 (m, 2 H) 1.70 (ddd, *J*=12.63, 7.58, 4.89 Hz, 1 H) 1.30 (s, 3 H); ^{13}C NMR (500 MHz, METHYLENE CHLORIDE-d_2) 175.5, 141.1, 135.6 (2 C) 130.3, 128.6 (2 C), 127.3, 124.8, 56.2, 35.7, 31.3, 24.5; IR (thin film, cm^{-1}) 3200, 2930, 2850, 1622, 1592,

1494, 1454, 1381, 1065, 921, 758, 694; HRMS (ESI) Calcd. for $[C_{13}H_{15}NO_2+Na]^+$ = 240.10, Found = 240.1002.



13

13 was synthesized via ***Method A*** in 69% yield as a yellow solid.

Analytical data for **13**: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 9.08 (br. s., 1 H) 7.45 (m, 5 H) 5.24 (s, 1 H) 2.69 (m, 1 H) 2.29 (m, 2 H) 1.85 (br. s., 2 H) 1.77 (m, 1 H) 1.63 (s, 3 H) 1.54 (m, 2 H) 1.12 (m, 1 H); ^{13}C NMR (126 MHz, chloroform-d) 167.3, 138.0, 135.5 (2 C), 129.4 (2 C), 129.1, 126.9, 124.2, 38.3, 32.8, 29.9, 28.4, 23.8, 21.2; IR (thin film, cm^{-1}) 3184, 2926, 1632, 1594, 1495, 1395, 1092, 1069, 757, 691; HRMS (ESI) Calcd. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.13, Found = 268.1313.

2.5.4 Dioxygenation Conditions

Caution! Alkylhydroperoxides are produced using the following conditions. While no problems were encountered in this work, alkylhydroperoxides are prone to rapid exothermic decomposition and appropriate care should be taken in their handling.

Condition A

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid and dissolved in glacial acetic acid to make a 0.1M solution. The vial was fitted with a PTFE-lined screw cap and oxygen was bubbled through the solution for 10 min. The reaction was allowed to stir under 1 atm oxygen at the specified temperature. Upon disappearance of the hydroxamic acid substrate, as indicated by TLC analysis, the reaction was cooled to rt and 1 equiv PPh_3 added to decompose any alkyl hydroperoxides in solution. This solution was diluted with CH_2Cl_2 (4 mL), washed with H_2O (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

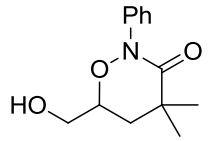
Condition B

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid and dissolved in dimethyl sulfoxide to make a 0.1M solution. The vial was fitted with a PTFE-lined screw cap and oxygen was bubbled through the solution for 10 min. The reaction was allowed to stir under 1 atm oxygen at the specified temperature. Upon disappearance of the hydroxamic acid substrate as indicated by TLC analysis, the solution was diluted with CH_2Cl_2 (4 mL), washed with H_2O (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

Condition C

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid and dissolved in dimethyl sulfoxide to make a 0.1M solution. The vial was fitted with a PTFE-lined screw cap and oxygen was bubbled through the solution for 10 min. The reaction was allowed to stir under 1 atm oxygen at the specified temperature. Upon disappearance of the hydroxamic acid substrate as indicated by TLC analysis, the reaction was cooled to rt and 1 equiv PPh_3 added to decompose any alkylhydroperoxides in solution. This solution was diluted with CH_2Cl_2 (4 mL), washed with H_2O (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

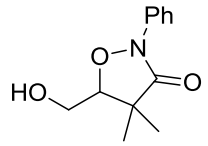
Note: Reactions requiring more than 1.5 mL solvent were conducted using new 20 mL scintillation vials, capped with rubber septa and sealed with PTFE tape.



3a

3a was prepared by ***Condition A*** using **3** (200.0 mg, 0.912 mmol) and HOAc (9.0 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h under O_2. Triphenylphosphine (240 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (40% EtOAc/hexanes) to afford **3a** (177.9 mg, 0.757 mmol, 83% yield) as a dark green oil.

Analytical data for **3a**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.72 (d, *J*=7.56 Hz, 2 H) 7.38 (t, *J*=8.02 Hz, 2 H) 7.18 (t, *J*=7.33 Hz, 1 H) 4.47 (qd, *J*=8.21, 3.09 Hz, 1 H) 3.74 (m, 2 H) 2.12 (br. s., 1 H) 2.03 (dd, *J*=13.52, 8.02 Hz, 1 H) 1.74 (dd, *J*=13.75, 8.71 Hz, 1 H) 1.41 (d, *J*=7.79 Hz, 6 H)); ^{13}C NMR (126 MHz, chloroform-d) 174.9, 139.7, 128.8 (2 C), 125.3, 119.5 (2 C), 81.1, 63.9, 39.1, 38.2, 27.0, 25.5; IR (thin film, cm^{-1}) 3060, 1625, 1494, 1449, 1386, 963, 921, 760, 691; HRMS (ESI) Calcd. for $[C_{13}H_{17}NO_3+H]^+$ = 236.13, Found = 236.1289.

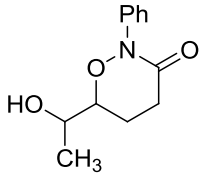


4a

4a was prepared by ***Condition A*** using **4** (20.0 mg, 0.0974 mmol) and HOAc (970 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 4 h under O_2. Triphenylphosphine (26 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **4a** (19.0 mg, 0.0859 mmol, 88% yield) as a pale yellow residue.

Analytical data for **4a**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.75 (dd, *J*=8.59, 1.03 Hz, 2 H) 7.40 (m, 2 H) 7.17 (m, 1 H) 4.41 (dd, *J*=7.79, 3.44 Hz, 1 H) 3.99 (m, 1 H) 3.87 (d, *J*=11.68 Hz, 1 H) 2.03 (br. s., 1 H) 1.38 (s, 3 H) 1.24 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 171.3, 136.9, 128.8 (2 C), 124.8, 116.6 (2 C), 87.6, 60.5, 45.4, 22.5, 17.6; IR (thin film, cm^{-1}) 3060, 1625, 1494, 1449,

1386, 963, 921, 760, 691; HRMS (ESI) Calcd. for $[C_{12}H_{15}NO_3+H]^+$ = 222.11, Found = 222.1126.

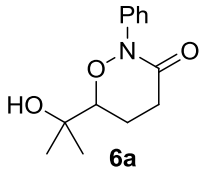


5a

5a was prepared by ***Condition B*** using **5** (40.0 mg, 0.195 mmol) and DMSO (2.00 mL). The reaction was completed, as indicated by TLC, after heating at 90 ºC for 14 h under O_2. The crude reaction mixture was worked up and purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **5a** (28.4 mg, 0.128 mmol, 66% yield) as a 55:45 mixture of diastereomers.

Analytical data for **5a major**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.72 (dd, *J*=9.0, 1.15 Hz, 2 H) 7.39 (m, 2 H) 7.19 (m, 1 H) 4.20 (m, 1 H) 4.14 (m, 1 H) 2.76 (m, 1 H) 2.63 (ddd, *J*=14.83, 6.01, 3.67 Hz, 1 H) 2.41 (m, 1 H) 2.12 (m, 1 H) 1.85 (d, *J*=4.35 Hz, 1 H) 1.30 (d, *J*=6.42 Hz, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 171.1, 138.9, 128.8 (2 C), 125.1, 118.7 (2 C), 83.4, 68.1, 30.8, 22.4, 18.5; IR (thin film, cm^{-1}) 3420, 2976, 2930, 1667, 1595, 1493, 1458, 1381, 1303, 1065, 756, 690; HRMS (ESI) Calcd. for $[C_{12}H_{15}NO_3+H]^+$ = 222.11, Found = 222.1123.

Analytical data for **5a minor**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.70 (dd, *J*=8.82, 1.03 Hz, 2 H) 7.41 (m, 2 H) 7.20 (t, *J*=7.45 Hz, 1 H) 4.07 (m, 1 H) 3.90 (m, 1 H) 2.68 (m, 2 H) 2.24 (m, 1 H) 2.23 (d, *J*=3.44 Hz, 1 H) 2.00 (m, 1 H) 1.29 (d, *J*=6.42 Hz, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 171.1, 139.2, 128.9 (2 C), 125.6, 119.1 (2 C), 84.9, 68.9, 30.4, 24.7, 18.1; IR (thin film, cm^{-1}) 3420, 2976, 2930, 1667, 1595, 1493, 1458, 1381, 1303, 1065, 756, 690; HRMS (ESI) Calcd. for $[C_{12}H_{15}NO_3+H]^+$ = 222.11, Found = 222.1124.

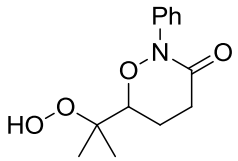


6a

6a was prepared by ***Condition C*** using **6** (20.0 mg, 0.0912 mmol) and DMSO (920 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 40 h under O_2. Triphenylphosphine

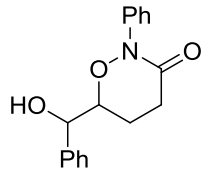
(12 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **6a** (17.0 mg, 0.0722 mmol, 79% yield) as a pale yellow residue.

Analytical data for **6a**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.72 (m, 2 H) 7.39 (m, 2 H) 7.18 (m, 1 H) 4.06 (dd, *J*=8.02, 7.56 Hz, 1 H) 2.74 (m, 1 H) 2.60 (m, 1 H) 2.39 (m, 1 H) 2.11 (dddd, *J*=13.43, 11.08, 8.25, 6.19 Hz, 1 H) 1.97 (s, 1 H) 1.41 (s, 3 H) 1.31 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 170.9, 139.0, 128.8 (2 C), 125.1, 118.7 (2 C), 86.2, 72.1, 30.9, 26.2, 25.0, 23.5; IR (thin film, cm^{-1}) 3425, 3067, 2978, 2360, 2246, 1668, 1596, 1494, 1459, 1379, 1305, 1065, 1036, 952, 756, 731, 690; HRMS (ESI) Calcd. for $[C_{13}H_{17}NO_3+Na]^+$ = 258.11, Found = 258.1096.



6c

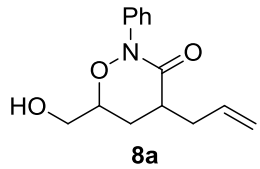
6c was isolated prior to the addition of PPh_3 in a reaction the same as described to isolate **6a**. Analytical data for **6c**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.86 (br. s., 1 H) 7.77 (dd, *J*=8.82, 1.03 Hz, 2 H) 7.39 (m, 2 H) 7.18 (m, 1 H) 4.41 (t, *J*=8.13 Hz, 1 H) 2.73 (m, 1 H) 2.63 (ddd, *J*=14.89, 6.42, 3.21 Hz, 1 H) 2.33 (m, 1 H) 2.15 (m, 1 H) 1.43 (s, 3 H) 1.34 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 170.9, 139.0, 128.8 (2 C), 125.0, 118.5 (2 C), 83.2, 82.9, 30.8, 23.4, 20.7, 20.2; IR (thin film, cm^{-1}) 3311, 3068, 2983, 2925, 2854, 2361, 2250, 1667, 1596, 1495, 1459, 1382, 1065, 953, 909, 757, 732, 690; HRMS (ESI) Calcd. for $[C_{13}H_{17}NO_4+Na]^+$ = 274.11, Found = 274.1055.



7a

7a was prepared by ***Condition C*** using **7** (20.0 mg, 0.0748 mmol) and DMSO (750 µL). The reaction was completed, as indicated by TLC, after stirring at 60 ºC for 25 h under O_2. Triphenylphosphine (20 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (2:1:1 Hexanes:CH_2Cl_2:Et_2O) to afford **7a** (13.3 mg, 0.0469 mmol, 63% yield) as a 60:40 mixture of diastereomers.

Analytical data for **7a major diastereomer** : ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.56 (d, *J*=8.02 Hz, 2 H) 7.42 (m, 4 H) 7.38 (m, 1 H) 7.33 (t, *J*=8.02 Hz, 2 H) 7.15 (t, *J*=7.45 Hz, 1 H) 5.09 (dd, *J*=4.24, 2.41 Hz, 1 H) 4.41 (td, *J*=7.62, 4.70 Hz, 1 H) 2.75 (m, 1 H) 2.60 (dd, *J*=6.19, 3.89 Hz, 1 H) 2.57 (dd, *J*=6.19, 3.89 Hz, 1 H) 2.47 (m, 1 H) 2.31 (d, *J*=2.98 Hz, 1 H) 2.04 (m, 1 H); ^{13}C NMR (126 MHz, chloroform-d) δ ppm 171.1, 139.4, 138.9, 128.7, 128.7, 128.4, 126.5, 124.9, 118.5, 83.3, 74.3, 30.7, 22.8; IR (thin film, cm^{-1}) 3409, 3063, 3030, 2923, 1665, 1594, 1491, 1455, 1379, 1064, 1029, 754, 701; LRMS (ESI) Calcd. for $[C_{17}H_{17}NO_3+Na]^+$ = 306.10, Found = 306.10.

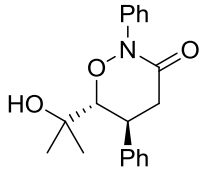


8a

8a was prepared by ***Condition B*** using **8** (40.0 mg, 0.173 mmol) and DMSO (1.70 mL). The reaction was completed, as indicated by TLC, after heating at 90 ºC for 12 h under O_2. The crude reaction mixture was worked up and purified by flash chromatography (3:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **8a** (31.9 mg, 0.128 mmol, 75% yield) as a 62:38 mixture of partially separable diastereomers. Analytical data for **8a major**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.75 (dd, *J*=8.59, 1.03 Hz, 2 H) 7.39 (m, 2 H) 7.18 (m, 1 H) 5.92 (m, 1 H) 5.15 (m, 2 H) 4.42 (m, 1 H) 3.87 (m, 2 H) 2.89 (m, 1 H)

2.76 (m, 1 H) 2.28 (m, 1 H) 2.18 (m, 1 H) 1.96 (t, *J*=6.19 Hz, 1 H) 1.86 (m, 1 H); ^{13}C NMR (126 MHz, chloroform-d) 172.3, 139.1, 135.7, 128.8 (2 C), 125.0, 118.4 (2 C), 117.2, 81.2, 64.1, 38.8, 33.2, 30.3; IR (thin film, cm^{-1}) 3434, 3075, 2958, 2925, 2853, 1682, 1595, 1494, 1458, 1380, 1299, 917, 755, 691; HRMS (ESI) Calcd. for $[C_{14}H_{17}NO_3+Na]^+$ = 270.11, Found = 270.1098.

Analytical data for **8a minor**: ^{1}H NMR (300 MHz, chloroform-d) δ ppm 7.77 (m, 2 H) 7.40 (m, 2 H) 7.19 (m, 1 H) 5.89 (m, 1 H) 5.15 (m, 2 H) 4.51 (qd, *J*=8.58, 3.23 Hz, 1 H) 3.69 (m, 1 H) 3.59 (m, 1 H) 2.88 (m, 1 H) 2.78 (m, 1 H) 2.42 (ddd, *J*=13.51, 8.60, 6.08 Hz, 1 H) 2.28 (m, 1 H) 1.72 (dd, *J*=7.76, 4.40 Hz, 1 H) 1.36 (m, 1 H); ^{13}C NMR (126 MHz, chloroform-d) 172.6, 139.9, 135.5, 128.9, 128.4, 125.2, 118.9 (2 C), 117.4, 81.6, 63.1, 39.1, 33.6, 29.2; IR (thin film, cm^{-1}) 3434, 3075, 2958, 2925, 2853, 1682, 1595, 1494, 1458, 1380, 1299, 917, 755, 691; HRMS (ESI) Calcd. for $[C_{14}H_{17}NO_3+Na]^+$ = 270.11, Found = 270.1099.

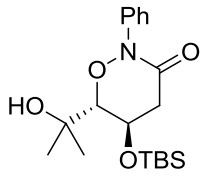


9a

9a was prepared by ***Condition A*** using **9** (20.0 mg, 0.0677 mmol) and HOAc (680 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 9 h under O_2. Triphenylphosphine (20 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **9a** (13.0 mg, 0.0417 mmol, 62% yield) as a single diastereomer.

Analytical data for **9a**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.83 (dd, *J*=8.71, 1.15 Hz, 2 H) 7.45 (m, 2 H) 7.32 (m, 2 H) 7.25 (m, 4 H) 4.23 (d, *J*=6.64 Hz, 1 H) 3.91 (m, 1 H) 3.13 (dd, *J*=14.43, 8.25 Hz, 1 H) 2.59 (dd, *J*=14.43, 2.52 Hz, 1 H) 1.96 (br. s., 1 H) 1.44 (s, 3 H) 1.28 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 170.1, 143.5, 138.9, 129.2 (2 C), 129.0 (2 C), 127.6 (2 C), 127.3, 125.2, 118.3 (2 C), 92.8, 72.6, 42.7, 39.8, 26.7, 25.7; IR (thin film, cm^{-1}) 3430, 3064, 3031, 2979, 2928, 1682, 1596, 1494, 1457, 1373, 1303, 971, 910, 754, 732, 701, 690; HRMS (ESI) Calcd. for

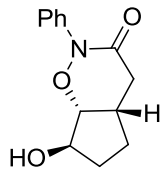
$[C_{19}H_{21}NO_3+Na]^+$ = 334.14, Found = 334.1418.



10a

10a was prepared by ***Condition C*** using **10** (40.0 mg, 0.114 mmol), dilauroyl peroxide (4.5 mg, 0.011 mmol) added in 10 mol% portions every 1.5h and DMSO (1.10 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 6 h under O_2. Triphenylphosphine (29.9 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **10a** (28.6 mg, 0.078 mmol, 69% yield) as a single diastereomer.

Analytical data for **10a**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.71 (m, 2 H) 7.39 (m, 2 H) 7.18 (m, 1 H) 4.74 (m, 1 H) 3.84 (d, *J*=2.98 Hz, 1 H) 2.87 (dd, *J*=14.43, 4.12 Hz, 1 H) 2.63 (dd, *J*=14.43, 2.52 Hz, 1 H) 1.84 (s, 1 H) 1.47 (s, 3 H) 1.37 (s, 3 H) 0.88 (s, 9 H) 0.19 (s, 3 H) 0.10 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) δ ppm 168.6, 138.8, 128.8, 124.9, 118.5, 93.8, 71.3, 69.7, 41.4, 26.4, 26.0, 25.6, 17.7, -4.1, -4.6; IR (thin film, cm^{-1}) 3440, 2955, 2930, 2857, 1679, 1596, 1492, 1378, 1303, 1252, 1172, 1082, 837, 778, 753; LRMS (ESI) Calcd. for $[C_{19}H_{31}NO_4Si+Na]^+$ = 388.18, Found = 388.18.

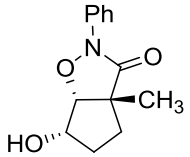


11a

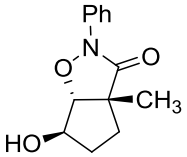
11a was prepared by ***Condition A*** using **11**(100.0 mg, 0.460 mmol) dilauroyl peroxide (18.3 mg, 0.046 mmol) added in 10 mol% portions every hour in HOAc (4.60 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h under O_2. Triphenylphosphine (120.6

mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **11a** (98.1 mg, 0.421 mmol, 91% yield) as a 78:22 mixture of β:α diastereomers.

Analytical data for **11a-β**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.23 (d, *J*=7.79 Hz, 2 H) 7.31 (m, 2 H) 7.03 (t, *J*=7.33 Hz, 1 H) 4.13 (dd, *J*=8.25, 2.98 Hz, 1 H) 3.94 (m, 1 H) 2.40 (m, 1 H) 2.15 (m, 2 H) 1.62 (m, 1 H) 1.52 (m, 1 H) 1.22 (m, 1 H) 1.03 (td, *J*=13.40, 6.42 Hz, 2 H); ^{13}C NMR (126 MHz, chloroform-d) 170.4, 139.2, 128.8, 125.0, 118.5, 91.4, 75.8, 37.7, 36.8, 32.4, 29.4; IR (thin film, cm^{-1}) 3380, 3066, 2929, 2869, 1682, 1594, 1492, 1457, 1370, 1024, 755; LRMS (ESI) Calcd. for $[C_{13}H_{15}NO_3+Na]^+$ = 234.14, Found = 234.14.



12a-α



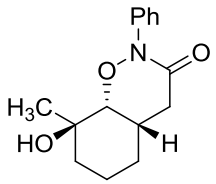
12a-β

12a was prepared by ***Condition A*** using **12** (40.0 mg, 0.184 mmol) and HOAc (1.80 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h under O_2. Triphenylphosphine (48 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (30% EtOAc/hexanes) to afford **12a** (42.2 mg, 0.181 mmol, 98% yield) as 66:33 mixture of β:α diastereomers.

Analytical data for **12a-β**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.73 (m, 2 H) 7.39 (m, 2 H) 7.17 (m, 1 H) 4.55 (m, 1 H) 4.48 (m, 1 H) 2.35 (m, 1 H) 2.02 (m, 3 H) 1.90 (m, 1 H) 1.56 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 170.5, 136.6, 128.8 (2 C), 124.9, 116.8 (2 C), 92.9, 77.8, 54.5, 35.9, 33.2, 22.3; IR (thin film, cm^{-1}) 3418, 3066, 2967, 2934, 2872, 1682, 1595, 1496, 1461, 1385, 754, 689; HRMS (ESI) Calcd. for $[C_{13}H_{15}NO_3+Na]^+$ = 256.10, Found = 256.0950.

Analytical data for **12a-α**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.77 (m, 2 H) 7.41 (m, 2 H) 7.20 (m, 1 H) 4.61 (d, *J*=4.81 Hz, 1 H) 4.27 (m, 1 H) 2.36 (ddd, *J*=13.52, 7.22, 1.95 Hz, 1 H) 2.27 (d, *J*=9.39 Hz, 1 H) 2.15 (m, 1 H) 1.74 (m, 1 H) 1.57 (ddd, *J*=13.57, 12.20, 6.53 Hz, 1 H) 1.49 (s, 3 H);

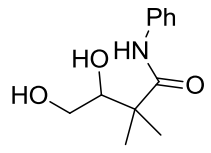
^{13}C NMR (126 MHz, chloroform-d) 170.1, 136.5, 128.9 (2 C), 125.1, 116.8 (2 C), 86.7, 75.3, 53.4, 34.1, 32.3, 21.9 ; IR (thin film, cm^{-1}) 3418, 3066, 2967, 2934, 2872, 1682, 1595, 1496, 1461, 1385, 754, 689; HRMS (ESI) Calcd. for $[C_{13}H_{15}NO_3+H]^+$ = 234.11, Found = 234.1137.



13a-β

13a was prepared by ***Condition A*** using **13** (20.0 mg, 0.0865 mmol), dilauroyl peroxide (3.4 mg, 0.008 mmol) and HOAc (860 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 10 h under O_2. Triphenylphosphine (22.6 mg, 1 equiv) was added to the crude reaction mixture and upon complete dissolution the mixture was worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **13a** (13.7 mg, 0.0554 mmol, 64% yield) as 84:16 mixture of β:α diastereomers.

Analytical data for **13a-β**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.02 (m, 2 H) 7.30 (m, 2 H) 7.05 (t, *J*=7.33 Hz, 1 H) 3.49 (s, 1 H) 2.71 (dd, *J*=18.21, 8.13 Hz, 1 H) 2.22 (d, *J*=18.33 Hz, 1 H) 2.10 (m, 1 H) 1.63 (m, 2 H) 1.41 (m, 2 H) 1.36 (m, 2 H) 1.31 (s, 3 H) 1.19 (d, *J*=13.29 Hz, 1 H); ^{13}C NMR (126 MHz, chloroform-d) 166.3, 139.3, 128.6 (2 C), 126.0, 121.5 (2 C), 84.1, 69.9, 36.9, 33.8, 30.8, 28.5, 27.2, 20.2; IR (thin film, cm^{-1}) 3418, 3064, 2934, 2863, 1643, 1594, 1494, 1457, 1371, 1306, 1272, 1174, 1064, 992, 899, 756, 689; HRMS (ESI) Calcd. for $[C_{15}H_{19}NO_3+Na]^+$ = 284.13, Found = 284.1273.



4b

4b was prepared by ***Condition A*** using **4** (40.0 mg, 0.195 mmol) and HOAc (1.90 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 4 h under O_2. Water (1.90 mL) and Zn (255.1 mg, 3.90 mmol) were added to the crude reaction mixture and allowed to stir overnight at rt.

At the complete consumption of **4**, CH_2Cl_2 (5 mL) was added, the mixture was filtered through celite, concentrated in vacuo and purified via flash chromatography (10% MeOH:CH_2Cl_2) to afford **4b** (35.2 mg, 0.158 mmol, 82% yield) as a pale yellow oil.

Analytical data for **4b**: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.72 (br. s., 1 H) 7.48 (d, *J*=7.79 Hz, 2 H) 7.31 (t, *J*=7.68 Hz, 2 H) 7.11 (t, *J*=6.87 Hz, 1 H) 4.43 (br. s., 1 H) 3.74 (d, *J*=10.31 Hz, 1 H) 3.67 (m, 1 H) 3.50 (t, *J*=9.85 Hz, 1 H) 3.37 (br. s., 1 H) 1.35 (s, 3 H) 1.18 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-d) 175.4, 137.7, 128.9 (2 C), 124.4, 120.4 (2 C), 77.5, 62.7, 44.7, 24.6, 21.5; IR (thin film, cm^{-1}) 3332, 2978, 2360, 1945, 1666, 1599, 1539, 1500, 1442, 1318, 1256, 1153, 1080, 1034, 753, 693; HRMS (ESI) Calcd. for $[C_{12}H_{17}NO_3+Na]^+$ = 246.11, Found = 246.1098.

2.6 References

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Synthesis of Halogenated Tetrahydrofurans by Stereoselective Alkoxyl Radical Ring Closures. *Eur. J. Org. Chem.* **2003**, *2003*, 4033–4052.

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3. CHAPTER THREE

Aerobic Intermolecular Alkene Dioxygenations Using Hydroxamic Acids

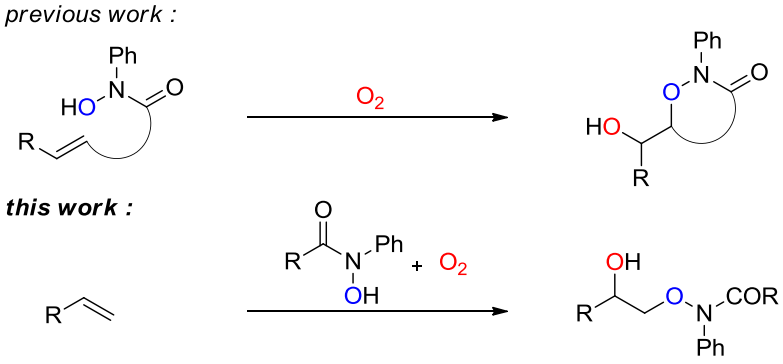
3.1 Introduction

Methods that achieve the vicinal dioxygenation of alkenes are valuable in the preparation of complex molecules. Significant progress has been made in the development of catalytic and asymmetric dioxygenations but many of these protocols require the use of expensive and/or highly toxic transition-metal catalysts (see **Chapter 1**).[1]

3.2 Background

See **Chapter 1.2.1**. Based on the success of our radical-mediated aerobic, intramolecular dioxygenation, we sought to expand the capabilities of amidoxyl radicals by developing a variant proceeding via an intermolecular radical addition as shown in **Figure 3-1** (see **Chapter 2** for our initial dioxygenation work). By disconnecting the alkene functionality from the hydroxamic acid moiety, the potential substrates available for dioxygenation are significantly more diverse with respect to the alkene component.

Figure 3-1. Aerobic Hydroxamic Acid-Mediated Alkene Dioxygenations

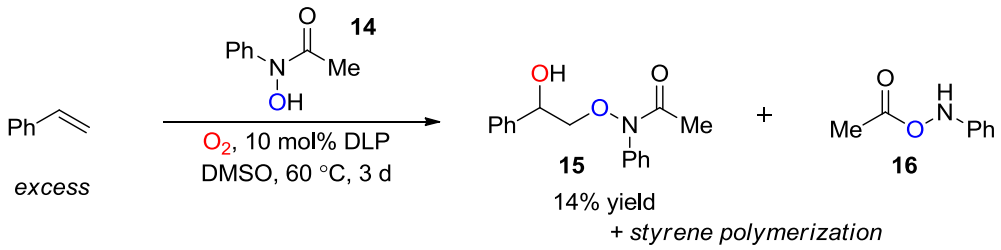


3.3 Reaction Development

In our continued quest to develop aerobic alkene dioxygenations, we sought to expand the intramolecular reactivity observed with amidoxyl radicals to intermolecular alkene additions. This would facilitate the direct dioxygenation of unsaturated hydrocarbons using molecular oxygen as the sole oxidant. In order to accomplish this, several challenges needed to be addressed. Firstly, there are no examples of general synthetic methods that proceed via intermolecular addition of oxygen-centered radicals to alkenes.[2,3] Secondly, such a process would have a greater activation entropy than the previously reported intramolecular dioxygenation.

We initially explored this intermolecular approach using simple *N*-phenylhydroxylamine derivatives such as *N*-hydroxy-*N*-phenyl acetamide **14** under conditions similar to those in our previous intramolecular studies. However, we quickly found that despite testing multiple simple *N*-phenyl hydroxamic acids, we had little to no success in identifying a viable dioxygenation reagent. In some cases, we did observe a small amount of dioxygenation product, **15**, but we also saw a significant amount of an isomerization product of the hydroxamic acid starting material (**Figure 3-2**).

Figure 3-2. Isomerization of Simple Hydroxamic Acids under Dioxygenation Conditions

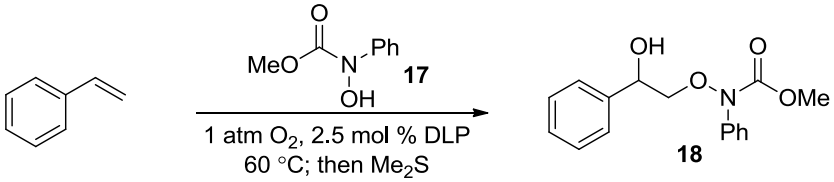


This isomerization is likely the result of homolytic bond cleavage of the acyl carbon-nitrogen bond, followed by recombination to form a carbon-oxygen bond to form the *O*-acetyl-*N*-phenylhydroxylamine **16**. We hypothesized that this undesired pathway could be minimized by making the acyl group less electrophilic. This was attempted by exploring the use of the simple hydroxamic acid derivative, *N*-hydroxy-*N*-phenylcarbamate **17**.

3.3.1 Initial Studies

We concentrated on assessing the viability of hydroxamic acid derivative **17**, with styrene as the alkene component in our dioxygenation studies. Optimization studies are highlighted in **Table 3-1**. Heating **17** with 1.2 equivalents of styrene, 2.5 mol % dilauroyl peroxide (DLP) to 60 °C in DMSO under 1 atmosphere of O_2, followed by a reductive work up with dimethyl sulfide (DMS, 20 equivalents) provided dioxygenated styrene **18** in 52% isolated yield (**Table 3-1, entry 1**). Changing the reaction solvent to AcOH, not only reduced the reaction time from 17 hours to 8, but also increased the reaction yield to 80% (**Table 3-1, entry 2**). Intrigued by this marked solvent effect, we screened a number of other possible reaction solvents, focusing on solvents with known high O_2 solubilities.[4] This screen identified *n*-butyl acetate (*n*BuOAc), a higher boiling alternative to ethyl acetate, as an excellent and convenient dioxygenation solvent. The dioxygenation of styrene in *n*BuOAc with DLP under 1 atm O_2 proceeds in 93% yield of **18** following reductive work up (**Table 3-1, entry 3**). In the absence of the radical initiator DLP, the dioxygenation still delivers **18** in 90% yield although the reaction rate was slightly decreased (**entry 4**). We attribute the reaction in the absence of added initiator to formation of a small amount of the carbamidoxyl radical of **17** via autoxidation processes.

Table 3-1. Optimization of Styrene Dioxygenation using **17**

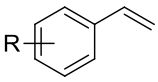
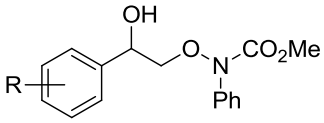
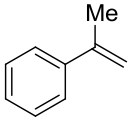
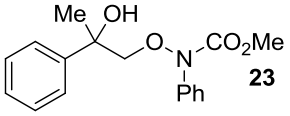
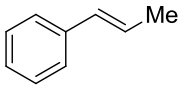
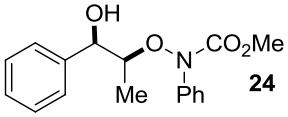
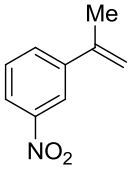
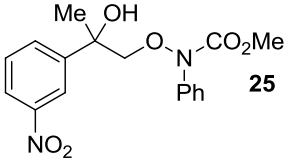
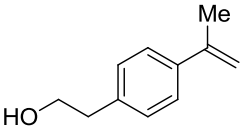
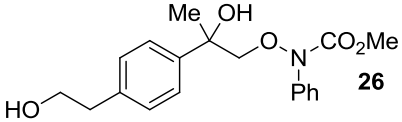
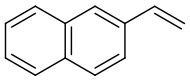
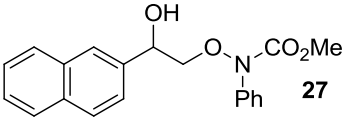
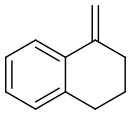
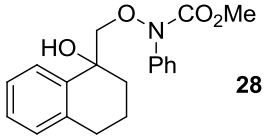
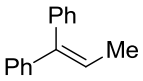
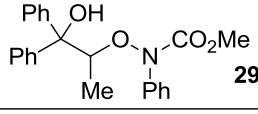


entry	conditions[a]	% yield[b]
1	DMSO as solvent, 17 h	52
2	AcOH as solvent, 8 h	80
3	*n*BuOAc as solvent, 17 h	93
4	no DLP, 25 h	90
5	1.0 equiv alkene instead of 1.2, 3 d	49
6	1.0 equiv alkene and 1.2 equiv **17**, 26 h	74

[a]All of the reactions were run using 1.0 equiv of **17** and 1.2 equiv of styrene.
[b]Yields of isolated products.

The use of only 1.0 equivalent of styrene with either 1.0 or 1.2 equivalents of **17** led to reduced yields (**Table 3-1, entries 5** and **6**), attributed to side reactions of styrene. Notably, the aerobic dioxygenation could be run on a 1.0 gram scale with no loss in reaction efficiency (92% isolated yield).

Table 3-2. Aerobic Dioxygenation of Styrenyl Alkenes

entry	substrate[a]	product		time (h)	% yield[b]
1		 R = 4-OMe	**19**	5	82
2		R = 4-Me	**20**	12	83
3		R = 2-Br	**21**	11	89
4		R = 4-CF_3	**22**	15	84
5			**23**	8.5	92
6			**24**	7.5	86 78:22 dr
7			**25**	5	83
8			**26**	5	78
9			**27**	24	89
10			**28**	3	79
11			**29**	5	87

[a]All reactions were run using 1.0 equiv of **17** and 1.2 equiv of substrate with 2.5 mol % DLP in *n*BuOAc at 60 °C, followed by 5 equiv Me_2S. [b]Yields of isolated products.

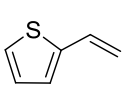
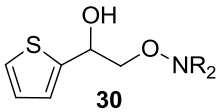
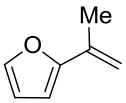
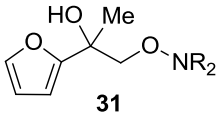
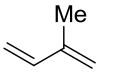
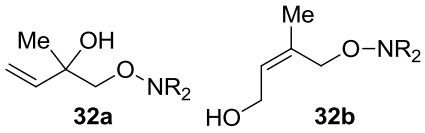
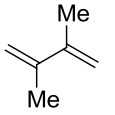
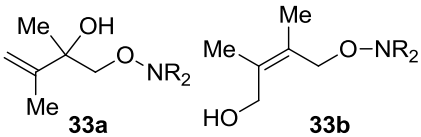
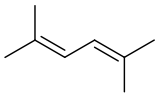
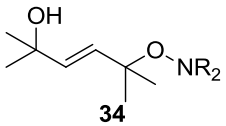
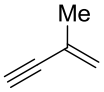
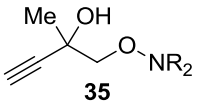
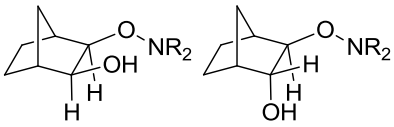
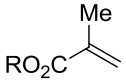
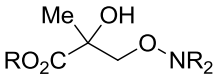
3.3.2 Substrate Scope – Styrenes

We next explored the alkene scope using our optimized dioxygenation protocol. Styrenes proved to be excellent substrates for aerobic dioxygenation (**Table 3-2**). Both electron-rich and electron-poor styrenes were dioxygenated in high yield (**entries 1 – 4**). Notably, these reactions all produced a single differentiated diol regioisomer as the product, as did all of the other substrates shown in **Table 3-2**. Styrenes containing alkyl substituents were also viable substrates (**entries 5 – 7**), with β-methylstyrene favoring the *anti* dioxygenation product with a moderate level of stereoselection (77:22 dr). The presence of easily abstracted, allylic C-H bonds in these substrates also demonstrates the high chemoselectivity of the attenuated carbamidoxyl radical derivative of **17** for alkene addition as opposed to abstraction. This aerobic, radical-mediated dioxygenation is also compatible with common functional groups that are susceptible to oxidation (**Table 3-2, entry 8**). More highly conjugated and trisubstituted styrenes also proved to be excellent substrates under these conditions (**entries 9 – 11**).

3.3.3 Substrate Scope – Non-Styrenes

We also explored the dioxygenation of a variety of other unsaturated hydrocarbons to define the scope of our current reaction system (**Table 3-3**). The heterocyclic substrates 2-vinylthiophene (**entry 1**) and 2-(prop-1-en-2-yl)furan (**entry 2**) yielded dioxygenation products in 84 and 48% yield, respectively. A number of reactions employing dienes were successful (**entries 3 – 5**), with the potential for both 1,2- and 1,4-dioxygenation. Enynes were viable substrates as well, displaying high chemoselectivity for difunctionalizations of the alkene (**Table 3-3, entry 6**). The dioxygenation of norbornene proceeded efficiently, delivering a 1.2:1 mixture of product diastereomers (**entry 7**). And reactions involving methacrylic acid (**entry 8**) and methyl methacrylate (**entry 9**) additionally demonstrated the ability of this system to dioxygenate electron-poor conjugated alkenes.

Table 3-3. Aerobic Dioxygenation of a Variety of Unsaturated Hydrocarbons

entry	substrate[a]	product	time (h)	% yield[b]
1		 **30**	7	84[c]
2		 **31**	2	48[c]
3		 **32a** **32b**	6	88[d] 2:1 **a:b**
4		 **33a** **33b**	3	88[d] 5.9:1 **a:b**
5		 **34**	2	59[c]
6		 **35**	7	68
7		 **36a** **36b**	6	77[d] 1.2:1 **a:b**
				
8		R = H **37**	7	45[d]
9		R = Me **38**	20	84[d]

R_2 = Ph, CO_2Me

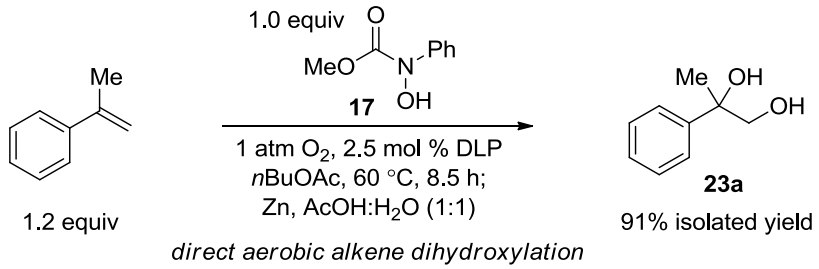
[a]All reactions were run using 1.0 equiv **17** and 1.2 equiv of substrate with 2.5 mol % DLP in *n*BuOAc at 60 °C, followed by 5 equiv Me_2S. [b]Yields of isolated products. [c]2.0 equiv of substrate used. [d]5.0 equiv of substrate used.

3.3.4 Post-Reaction Modification

We similarly developed a simple one-pot protocol for direct aerobic dihydroxylation of alkenes in this intermolecular context as the intramolecular variant (see **Chapter 2.3.3**). Following initial dioxygenation, direct reduction of the acyclic hydroxamate N-O bond and the hydroperoxide is easily accomplished using Zn metal as the reductant. For instance, the one-pot dihydroxylation of

α-methylstyrene yielded 2-phenylpropane-1,2-diol (**23a**) in 82% yield (**Figure 3-3**).

Figure 3-3. One-Pot Dihydroxylation of α-Methyl Styrene Using **17**



3.3.5 Proposed Mechanism

We postulate that an analogous intermolecular aerobic dioxygenation is operative as outlined in **2.3.4 Proposed Mechanism**.

3.4 Summary

In conclusion, we have developed an intermolecular, aerobic alkene dioxygenation method that uses a simple hydroxamic acid derivative and is applicable to a variety of alkenes. The reaction proceeds without the use of precious and/or toxic transition-metal catalysts common to related alkene difunctionalizations processes and uses molecular oxygen as the sole oxidant. This approach capitalizes on the synthetic versatility of the carbamidoxyl radical, which is formed under mild conditions from a simple hydroxamic acid derivative and can serve as a useful source of oxygen-centered radicals for synthesis. Harnessing this unique reactivity has led to the first example of a general synthetic transformation involving the intermolecular addition of an oxygen-centered radical to alkenes.

3.5 Experimental

3.5.1 General Methods

See **2.5 Experimental** for general methods.

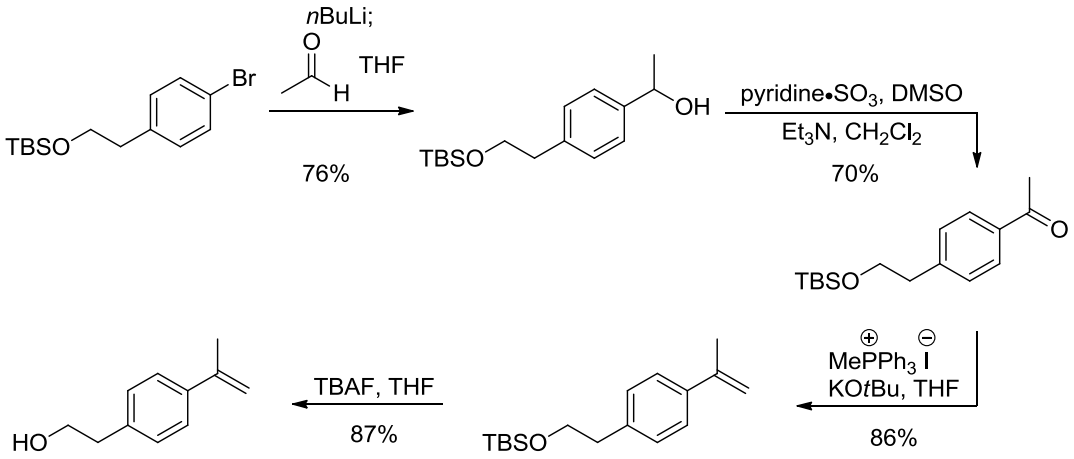
3.5.2 Substrate Preparation

Styrene, α-methylstyrene, β-methylstyrene, *para*-methylstyrene, *para*-methoxystyrene, 2-

bromostyrene, isoprene, 2,3-dimethyl-1,3-butadiene, 2,5-dimethyl-2,4-hexadiene, 2-methyl-1-buten-3-yne, methyl methacrylate, and methacrylic acid were purchased from commercial sources, purified by distillation, deoxygenated via multiple freeze-pump-thaw cycles, and stored at -35 °C under an inert atmosphere prior to use. Norbornene was purified by sublimation and stored under an inert atmosphere.

Para-trifluoromethylstyrene,[5,6] 3-nitro-α-methylstyrene,[7,8] 2-vinylnaphthalene,[8] 1-methylene-1,2,3,4-tetrahydronaphthalene,[9] 1,1-diphenylpropene[10] 2-vinylthiophene,[11] and 2-(prop-1-en-2-yl)furan[9,10] were prepared according to standard procedures. All physical and spectral data were in accordance with literature data.

Figure 3-4. Synthesis of 2-(4-(prop-1-en-2-yl)phenyl)ethanol



2-(4-(prop-1-en-2-yl)phenyl)ethanol was synthesized via the scheme outlined in **Figure 3-4** as follows: 1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanol was synthesized using the procedure outlined by Kellogg and coworkers.[12] To a chilled (-78 ^{o}C) solution of 2-(4-bromophenyl)-ethoxy-*tert*-butyl-dimethylsilane[13] (10.0 g, 31.7 mmol, 1.0 equiv) in THF (70 mL) was added *n*-butyllithium (2.5M solution in hexanes, 27.9 mL, 69.8 mmol, 2.2 equiv) dropwise. After stirring for 20 min, acetaldehyde (4.5 mL, 79.3 mmol, 2.5 equiv) was added in a single portion. After warming to room temperature, the reaction mixture was quenched with water and extracted three times with

EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (20% to 1:4 EtOAc/hexanes) to give 1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanol (6.78 g, 24.2 mmol, 76% yield) as a pale yellow oil, along with 2-hexanol as an inseparable byproduct.

Analytical data for 1-(4-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanol: **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.47 - 7.40 (m, 2 H), 7.24 - 7.17 (m, 2 H), 5.38 (dd, *J* = 0.9, 1.6 Hz, 1 H), 5.08 (q, *J* = 1.5 Hz, 1 H), 3.84 (t, *J* = 7.3 Hz, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H), 2.18 (dd, *J* = 0.8, 1.4 Hz, 3 H), 0.92 (s, 9 H), 0.04 (s, 6 H); **^{13}C NMR** (126 MHz, chloroform -*d*) 143.7, 138.4, 129.3, 125.3, 70.3, 64.5, 39.3, 25.9, 25.1, 18.4, -5.4; **IR** (thin film, cm^{-1}) 3376, 2929, 2857, 2361, 1513, 1471, 1255, 1095, 1006, 833, 776; **LRMS** (ESI) Calcd. for $[C_{16}H_{28}O_2Si+Na]^+$ = 303.18, Found = 303.15.

1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanol (3.5 g, 12.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 ^oC. Triethylamine (7 mL, 49.9 mmol, 4.0 equiv) was added, followed by a solution of pyridine sulfur trioxide complex (11.9 g, 74.5 mmol, 6.0 equiv) in DMSO (30 mL). The reaction was stirred at 0 ^oC until judged complete by TLC analysis. After completion, the reaction was quenched with saturated $NaHCO_3$(aq) solution (300 mL) and extracted three times with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc/hexanes) to give 1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanone (2.42 g, 8.69 mmol, 70% yield) as a clear, colorless liquid.

Analytical data for 1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanone: **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.93 - 7.86 (m, 2 H), 7.35 - 7.29 (m, 2 H), 3.85 (t, *J* = 6.6 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H), 2.60 (s, 3 H), 0.87 (s, 9 H), -0.02 (s, 6 H); **^{13}C NMR** (126 MHz, chloroform-*d*) 197.9, 145.3, 135.3, 129.4, 128.3, 63.8, 39.5, 26.6, 25.9, 18.3, -5.4; **IR** (thin film, cm^{-1}) 2954, 2366, 1684, 1608, 1359, 1267, 1100, 833; **LRMS** (ESI) Calcd. for $[C_{16}H_{26}O_2Si+Na]^+$ = 301.16, Found = 301.12.

tert-butyldimethyl(4-(prop-1-en-2-yl)phenethoxy)silane was synthesized using a procedure adapted

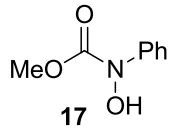
from that described by Chiba and Hui.[7] To a slurry of methyltriphenylphosphonium iodide (3.70 g, 9.08 mmol, 1.1 equiv) in THF (25 mL) was added potassium *tert*-butoxide (1.03 g, 9.16 mmol, 1.1 equiv) in a single portion. The slurry was stirred for 30 minutes. A solution of 1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)ethanone (2.30 g, 8.26 mmol, 1.0 equiv) in THF (5 mL) was added dropwise to the slurry, which was then refluxed for 1 h, cooled to room temperature, and filtered through Celite with hexanes. The filtrate was concentrated in vacuo, dry loaded onto silica, and purified via column chromatography (3% EtOAc/hexanes) to give *tert*-butyldimethyl(4-(prop-1-en-2-yl)phenethoxy)silane (1.97 g, 7.13 mmol, 86% yield) as a pale yellow liquid.

Analytical data for *tert*-butyldimethyl(4-(prop-1-en-2-yl)phenethoxy)silane : **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.47 - 7.40 (m, 2 H), 7.24 - 7.17 (m, 2 H), 5.38 (dd, *J* = 0.9, 1.6 Hz, 1 H), 5.08 (q, *J* = 1.5 Hz, 1 H), 3.84 (t, *J* = 7.3 Hz, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H), 2.18 (dd, *J* = 0.8, 1.4 Hz, 3 H), 0.92 (s, 9 H), 0.04 (s, 6 H); **^{13}C NMR** (126 MHz, chloroform-*d*) 143.1, 139.1, 138.4, 129.0, 125.4, 111.8, 64.5, 39.3, 26.0, 21.9, 18.4, -5.4; **IR** (thin film, cm^{-1}) 3086, 2929, 2857, 1628, 1514, 1471, 1255, 1098, 834, 775; **LRMS** (ESI) Calcd. for $[C_{17}H_{28}OSi+Na]^{+}$ = 299.18, Found = 299.15.

To a solution of *tert*-butyldimethyl(4-(prop-1-en-2-yl)phenethoxy)silane (1.0 g, 3.62 mmol, 1.0 equiv) in THF (30 mL) was added TBAF (1.0M solution in THF, 5.4 mL, 5.43 mmol, 1.5 equiv). The reaction was stirred at room temperature until judged complete by TLC analysis, quenched with saturated NH_4Cl(aq) (60 mL), and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (33% EtOAc/hexanes) to give 2-(4-(prop-1-en-2-yl)phenyl)ethanol (513.0 mg, 3.16 mmol, 87% yield) as a white solid.

Analytical data for 2-(4-(prop-1-en-2-yl)phenyl)ethanol: **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.46 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 5.38 (d, *J* = 0.9 Hz, 1 H), 5.09 (t, *J* = 1.3 Hz, 1 H), 3.89 (t, *J* = 6.5 Hz, 2 H), 2.90 (t, *J* = 6.6 Hz, 2 H), 2.17 (d, *J* = 0.6 Hz, 3 H), 1.49 (br. s., 1 H); **^{13}C NMR** (126 MHz, chloroform-*d*) 142.9, 139.5, 137.7, 128.9, 125.7, 112.1, 63.6, 38.8, 21.8; **IR** (thin film, cm^{-1}) 3352, 3086, 2942, 1626, 1514, 1437, 1374, 1045, 889, 825; **LRMS** (ESI) Calcd. for

$[C_{11}H_{14}O+H]^+$ = 163.11, Found = 163.10.



17

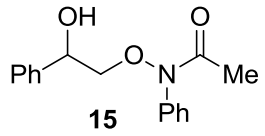
Synthesis of Methyl N-hydroxy(phenyl) carbamate (**17**)**:** To a 0 ºC solution of methyl chloroformate (1.6 mL, 20.2 mmol, 1.1 equiv) in Et_2O (40 mL) and a saturated aqueous solution of sodium bicarbonate (20 mL) was added *N*-phenylhydroxylamine (2.0 g, 18.3 mmol, 1.0 equiv). The solution was stirred at 0 ºC for 3 h, then warmed to room temperature. The layers were separated, the aqueous layer was acidified with 1 M $NaHSO_4$ and extracted with Et_2O (3 x). The combined organic layers were then washed with brine, dried ($MgSO_4$), and concentrated to give an oil that was purified by flash chromatography to give methyl *N*-hydroxy(phenyl)carbamate (2.92 g, 17.5 mmol, 95% yield) as an off-white solid. All spectra were in accordance with literature data.[14]

3.5.3 General Dioxygenation Conditions

Caution! Aerobic reactions in organic solvents may produce potentially explosive peroxides. Alkylhydroperoxides are produced using the following conditions. While no problems were encountered in this work, alkylhydroperoxides are prone to rapid exothermic decomposition and appropriate care should be taken in their handling.

A new 1-dram vial containing a magnetic stir bar was charged with **17** (50.0 mg, 0.299 mmol, 1.0 equiv), dilauroyl peroxide (DLP, 3.0 mg, 0.007 mmol, 2.5 mol%), alkene (1.2 equiv) and dissolved in nBuOAc (300 μL, to make a 1M solution). The vial was fitted with a PTFE-lined screw cap and the reaction mixture was degassed with O_2 for 3 minutes. The reaction was allowed to stir under an atmosphere of oxygen at 60 °C. Upon disappearance of **17**, as indicated by TLC analysis, reaction solvent was removed under a stream of argon. The crude reaction mixture was then taken up in CH_2Cl_2 (300 μL) and dimethyl sulfide (DMS, 110 μL, 5.0 equiv) added. The reaction was tightly capped and heated to 40 °C until disappearance of the initially formed hydroperoxide was observed

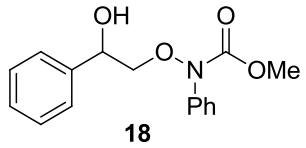
by TLC analysis (typically no longer than 1 h). The reaction mixture was then concentrated under reduced pressure and subsequently purified by flash chromatography using the specified solvent system to yield the resultant dioxygenation product.



15

15 was prepared using styrene (22.7 µL, 0.359 mmol) under the standard conditions substituting DMSO for nBuOAc as solvent. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 days. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **15** (6.3 mg, 0.0231 mmol, 14% yield) as a clear, colorless residue.

Analytical data for **15**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.50 - 7.43 (m, 2 H), 7.43 - 7.33 (m, 7 H), 7.33 - 7.29 (m, 1 H), 4.99 (dd, *J* = 2.7, 9.3 Hz, 1 H), 4.00 (dd, *J* = 2.8, 11.0 Hz, 1 H), 3.83 (br. s., 1 H), 2.13 (br. s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 169.7, 139.3, 138.8, 129.5, 128.9, 128.8, 128.5, 127.9, 126.2, 119.9, 79.8, 70.8, 21.8; **IR** (thin film, cm^{-1}) 3404, 3063, 3031, 2932, 2876, 1660, 1594, 1493, 1375, 1067, 759; **LRMS** (ESI) Calcd. for $[C_{16}H_{17}NO_3+Na]^+$ = 294.11, Found = 294.12.

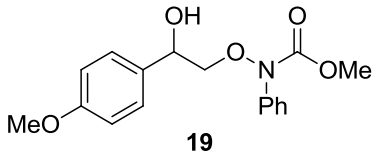


18

18 was prepared using styrene (41.1 µL, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 17 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **18** (79.8 mg, 0.278 mmol, 93% yield) as a clear, colorless residue.

Analytical data for **18**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.44 - 7.27 (m, 10 H), 5.07 (dd, *J* =

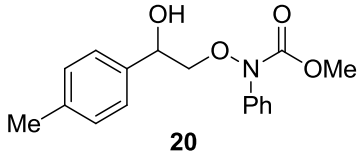
2.5, 9.8 Hz, 1 H), 4.49 (br. s, 1 H), 4.05 (dd, *J* = 2.8, 11.3 Hz, 1 H), 3.88 (s, 3 H), 3.86 - 3.83 (m, 1 H); **^{13}C NMR** (126 MHz, chloroform-d) 156.4, 139.5, 134.0, 129.0, 128.5, 127.9, 127.1, 126.2, 123.6, 80.6, 70.7, 54.0; **IR** (thin film, cm^{-1}) 3443, 30.63, 3031, 2955, 2928, 1715, 1595, 1494, 1440, 1348, 1117, 754, 697; **LRMS** (ESI) Calcd. for $[C_{16}H_{17}NO_4+Na]^+$ = 310.11, Found = 310.10.



19

19 was prepared using *para*-methoxy styrene (48.0 µL, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (33% EtOAc/hexanes) to afford **19** (77.7 mg, 0.245 mmol, 82% yield) as a clear, colorless residue.

Analytical data for **19**: **^{1}H NMR** (500 MHz, benzene-d_6) δ = 7.45 (d, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.17 (t, *J* = 7.7 Hz, 2 H), 7.07 - 6.98 (m, 1 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 5.20 (d, *J* = 9.5 Hz, 1 H), 4.91 (br. s., 1 H), 4.00 (dd, *J* = 1.9, 11.0 Hz, 1 H), 3.91 - 3.81 (m, 1 H), 3.38 (s, 6 H); **^{13}C NMR** (126 MHz, chloroform-d) 159.3, 156.3, 139.5, 131.0, 128.9, 127.0, 123.5, 113.9, 80.5, 70.2, 55.3, 54.0; **IR** (thin film, cm^{-1}) 3449, 3065, 3004, 2956, 2838, 1714, 1612, 1597, 1514, 1494, 1441, 1347, 1250, 1030, 833, 753, 694; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_5+Na]^+$ = 340.12, Found = 340.11.

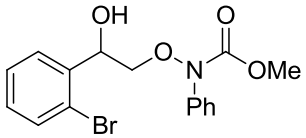


20

20 was prepared using *para*-methyl styrene (47.0 µL, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (1:4 to 1:3 EtOAc/hexanes) to afford **20** (74.4 mg, 0.247 mmol, 83% yield) as a clear, colorless residue.

Analytical data for **20**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.46 - 7.39 (m, 4 H), 7.32 - 7.27 (m, 3 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 5.04 (dd, *J* = 2.0, 9.6 Hz, 1 H), 4.45 (br. s, 1 H), 4.03 (dd, *J* = 2.5, 11.3

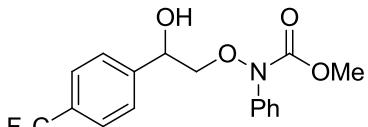
Hz, 1 H), 3.88 (s, 3 H), 3.88 - 3.82 (m, 1 H), 2.36 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 156.3, 139.5, 137.6, 136.0, 129.1, 129.0, 127.0, 126.2, 123.5, 80.6, 70.5, 54.0, 21.2; **IR** (thin film, cm^{-1}) 3446, 3027, 2955, 2924, 2872, 1714, 1595, 1494, 1441, 1347, 1117, 816, 753; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.13.



21

21 was prepared using 2-bromostyrene (45.0 µL, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20-25% EtOAc/hexanes) to afford **21** (96.7 mg, 0.264 mmol, 89% yield) as a clear, colorless residue.

Analytical data for **21**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.73 (dd, *J* = 1.6, 7.9 Hz, 1 H), 7.52 - 7.27 (m, 6 H), 7.16 (dt, *J* = 1.9, 7.7 Hz, 1 H), 5.43 (dd, *J* = 2.2, 9.5 Hz, 1 H), 4.75 (br. s, 1 H), 4.18 (dd, *J* = 2.4, 11.5 Hz, 1 H), 3.88 (s, 3 H), 3.62 (dd, *J* = 9.5, 11.7 Hz, 1 H); **^{13}C NMR** (126 MHz, chloroform-d) 156.7, 139.4, 138.1, 132.5, 129.3, 129.0, 128.2, 127.9, 127.4, 124.2, 121.7, 78.4, 69.6, 54.1; **IR** (thin film, cm^{-1}) 3438, 2955, 1714, 1595, 1494, 1441, 1347, 1118, 1025, 911, 755, 694; **LRMS** (ESI) Calcd. for $[C_{16}H_{16}BrNO_4+Na]^+$ = 388.02, Found = 388.00.

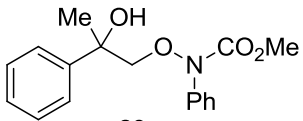


22

22 was prepared using para-trifluoromethylstyrene (61.8 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **22** (88.9 mg, 0.250 mmol, 84% yield) as a clear, colorless residue.

Analytical data for **22**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.62 (d, *J* = 8.3 Hz, 2 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.47 - 7.38 (m, 4 H), 7.32 (tt, *J* = 1.6, 6.9 Hz, 1 H), 5.12 (d, *J* = 9.4 Hz, 1 H), 4.77 (br. s,

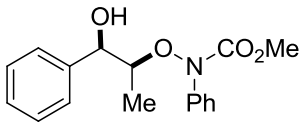
1 H), 4.07 (dd, *J* = 2.6, 11.7 Hz, 1 H), 3.88 (s, 3 H), 3.82 (dd, *J* = 9.4, 11.7 Hz, 1 H); **^{13}C NMR** (151 MHz, chloroform-d) 156.6, 143.1, 139.4, 129.0, 127.3, 126.5, 125.42, 125.39, 125.36, 125.34, 123.8, 80.3, 70.2, 54.1; **IR** (thin film, cm^{-1}) 3435, 3068, 3044, 2958, 1714, 1620, 1326, 1123, 1017, 845, 755; **LRMS** (ESI) Calcd. for $[C_{17}H_{16}F_3NO_4+Na]^+$ = 378.09, Found = 378.11.



23

23 was prepared using α-methylstyrene (46.6 µL, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 8.5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **23** (83.2 mg, 0.276 mmol, 92% yield) as a clear, colorless residue.

Analytical data for **23**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.53 - 7.46 (m, 2 H), 7.42 - 7.18 (m, 8 H), 4.38 (br. s, 1 H), 4.24 (d, *J* = 10.1 Hz, 1 H), 4.07 (d, *J* = 10.4 Hz, 1 H), 3.80 (s, 3 H), 1.56 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.4, 144.8, 139.4, 128.8, 128.2, 127.0, 126.5, 125.0, 122.8, 83.3, 73.2 53.7, 27.0; **IR** (thin film, cm^{-1}) 3425, 3061, 3029, 2979, 2955, 2934, 2249, 1953, 1882, 1714, 1595, 1495, 1442, 1348, 1119, 912, 763, 697; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.10.



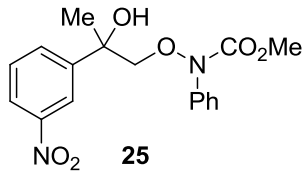
24

24 was prepared using β-methylstyrene (46.6 µL, 0.359 mmol,), under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 7.5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (15-20% EtOAc/hexanes gradient) to afford **24**as a mixture of diastereomers (56.0 mg major and 21.7 mg minor, 0.258 mmol total, 86% yield) as a clear, colorless residue.

Analytical data for **24 major**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.40 - 7.52 (m, 4 H), 7.21 - 7.37 (m, 6 H), 5.21 (d, *J* = 2.51 Hz, 1 H), 4.15 - 4.44 (m, 1 H), 4.05 (dd, *J* = 6.53, 2.51 Hz, 1 H), 3.88 (s, 3 H), 1.03 (d, *J* = 6.53 Hz, 3 H); **^{13}C NMR** (101 MHz, chloroform-d) 156.2, 139.9, 139.3, 129.0, 128.2, 127.2, 127.1, 125.8, 123.8, 83.8, 71.2, 54.1, 11.2; **IR** (thin film, cm^{-1}) 3455, 3063, 3030, 2989, 2955, 2925, 2854, 2250, 1954, 1884, 1714, 1595, 1494, 1441, 1337, 1117, 1067, 913, 747, 699; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.12.

Analytical data for **24 minor**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.40 - 7.26 (m, 10 H), 5.04 (br. s., 1 H), 4.65 (dd, *J* = 1.60, 5.20 Hz, 1H), 4.21 (m, 1H), 3.84 (s, 3H), 0.938 (d, *J* = 4.00 Hz, 3H); **^{13}C NMR** (101 MHz, chloroform-d) 157.0, 141.44, 140.3, 128.7, 128.4, 127.9, 127.0, 126.9, 123.9, 88.5, 54.0, 16.6; **IR** (thin film, cm^{-1}) 3420, 3031, 2981, 2925, 1714, 1595, 1494, 1441, 1341, 1114, 1041, 761, 698; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.12.

The stereochemistry of **24** was determined by reductive cleavage of the N-O bond using Zn (using an analogous procedure to that used in the 1-pot, direct dihydroxylation of α-methylstyrene reported below). Literature values for the anti diol report a 4.61 ppm (m, 1H), matching that obtained from reductive cleavage of **24 major**, while the corresponding syn diol is shifted upfield at 4.28 ppm (m, 1H).[15]

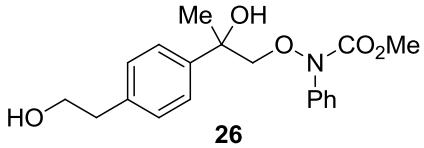


25

25 was prepared (58.6 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **25** (85.4 mg, 0.247 mmol, 83% yield) as a clear, colorless residue.

Analytical data for **25**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 8.37 (t, *J* = 2.0 Hz, 1 H), 8.16 (ddd, *J* = 0.9, 2.4, 8.0 Hz, 1 H), 7.87 (qd, *J* = 0.9, 7.8 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.40 - 7.33 (m, 2 H), 7.28 - 7.24 (m, 1 H), 7.23 - 7.19 (m, 2 H), 4.84 (br. s, 1 H), 4.32 (d, *J* = 10.7 Hz, 1 H), 4.11 (d, *J* =

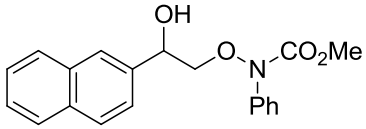
10.7 Hz, 1 H), 3.79 (s, 3 H), 1.56 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.6, 148.3, 147.5, 139.2, 131.5, 129.2, 128.9, 127.0, 123.1, 122.1, 120.4, 83.0, 73.1, 53.9, 27.0; **IR** (thin film, cm^{-1}) 3417, 3090, 2981, 2875, 1695, 1595, 1531, 1349, 909; **LRMS** (ESI) Calcd. for $[C_{17}H_{18}N_2O_6+Na]^+$ = 369.11, Found = 369.10.



26

26 was prepared using 2-(4-(prop-1-en-2-yl)phenyl)ethanol (58.2 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (50% EtOAc/hexanes) to afford **26** (80.5 mg, 0.233 mmol, 78% yield) as a clear, colorless residue.

Analytical data for **26**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.46 - 7.42 (m, 2 H), 7.39 - 7.34 (m, 2 H), 7.29 - 7.22 (m, 5 H), 4.35 (br. s, 1 H), 4.23 (d, *J* = 10.1 Hz, 1 H), 4.05 (d, *J* = 10.4 Hz, 1 H), 3.88 (t, *J* = 6.6 Hz, 2 H), 3.80 (s, 3 H), 2.89 (t, *J* = 6.6 Hz, 2 H), 1.54 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.4, 143.0, 139.4, 137.2, 128.8, 128.7, 126.6, 125.3, 122.8, 83.4, 73.1, 63.7, 53.7, 38.8, 26.9; **IR** (thin film, cm^{-1}) 3418, 3061, 2954, 2876, 1713, 1595, 1494, 1349, 1048, 751; **LRMS** (ESI) Calcd. for $[C_{19}H_{23}NO_5+Na]^+$ = 368.15, Found = 368.15.

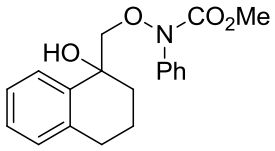


27

27 was prepared using 2-vinylnaphthalene (55.4 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 24 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **27** (89.5 mg, 0.265 mmol, 89% yield) as a clear, colorless residue.

Analytical data for **27**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.92 (s, 1 H), 7.88 - 7.81 (m, 3 H), 7.54 - 7.40 (m, 7 H), 7.34 - 7.27 (m, 1 H), 5.25 (dd, *J* = 2.4, 9.6 Hz, 1 H), 4.66 (br. s, 1 H), 4.16 (dd, *J*

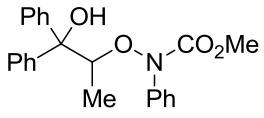
= 2.6, 11.3 Hz, 1 H), 3.95 (dd, *J* = 9.8, 11.3 Hz, 1 H), 3.90 (s, 3 H); **^{13}C NMR** (151 MHz, chloroform-d) 156.5, 139.5, 136.4, 133.3, 133.1, 129.0, 128.2, 127.9, 127.7, 127.1, 126.2, 126.0, 125.2, 124.1, 123.6, 80.5, 70.8, 54.1; **IR** (thin film, cm^{-1}) 3437, 3060, 2955, 1714, 1595, 1494, 1348, 1122, 750; **LRMS** (ESI) Calcd. for $[C_{20}H_{19}NO_4+Na]^+$ = 360.12, Found = 360.13.



28

28 was prepared using 1-methylene-1,2,3,4-tetrahydronaphthalene (51.8 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **28** (76.6 mg, 0.234 mmol, 78% yield) as a clear, colorless residue.

Analytical data for **28**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.65 - 7.56 (m, 1 H), 7.48 - 7.34 (m, 4 H), 7.30 - 7.17 (m, 3 H), 7.14 - 7.05 (m, 1 H), 4.20 (d, *J* = 9.8 Hz, 1 H), 4.03 (d, *J* = 9.8 Hz, 1 H), 3.89 (s, 3 H), 3.80 (br. s., 1 H), 2.93 - 2.82 (m, 1 H), 2.81 - 2.71 (m, 1 H), 2.42 - 2.31 (m, 1 H), 2.04 - 1.91 (m, 2 H), 1.89 - 1.74 (m, 1 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.4, 139.8, 138.0, 137.5, 128.9, 128.8, 127.7, 126.9, 126.4, 126.2, 122.6, 81.5, 71.8, 53.7, 33.5, 29.4, 19.9; **IR** (thin film, cm^{-1}) 3434, 3063, 3025, 2940, 2872, 2839, 2249, 1714, 1595, 1494, 1442, 1348, 1119, 911, 735, 693; **LRMS** (ESI) Calcd. for $[C_{19}H_{21}NO_4+Na]^+$ = 350.14, Found = 350.13.

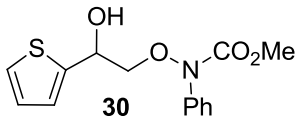


29

29 was prepared using 1,1-diphenylpropene (61.8 mg, 0.359 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (10% EtOAc/hexanes) to afford **29** (98.2 mg, 0.260 mmol, 87% yield) as a clear, colorless residue.

Analytical data for **29**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.70 - 7.61 (m, 2 H), 7.49 (dd, *J* =

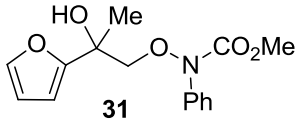
1.1, 8.4 Hz, 2 H), 7.44 - 7.39 (m, 2 H), 7.37 - 7.32 (m, 2 H), 7.30 - 7.23 (m, 6 H), 7.19 - 7.14 (m, 1 H), 5.11 (q, *J* = 6.3 Hz, 1 H), 4.72 (br. s., 1 H), 3.64 (s, 3 H), 1.19 (d, *J* = 6.3 Hz, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.5, 145.8, 144.5, 139.8, 128.7, 128.2, 127.8, 126.6 126.4, 126.0, 125.4, 123.0, 82.9, 78.5, 53.6, 14.1; **IR** (thin film, cm^{-1}) 3515, 3396, 3060, 3031, 3000, 2954, 2852, 2250, 1953, 1882, 1714, 1595, 1494, 1441, 1344, 1190, 910, 732, 696; **LRMS** (ESI) Calcd. for $[C_{23}H_{23}NO_4+Na]^+$ = 400.15, Found = 400.13.



30

30 was prepared using 2-vinylthiophene (65.9 mg, 0.598 mmol, 2.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **30** (73.6 mg, 0.251 mmol, 84% yield) as a clear, colorless residue.

Analytical data for **30**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.43 (d, *J* = 4.1 Hz, 2 H), 7.33 - 7.27 (m, 2 H), 7.02 - 6.98 (m, 2 H), 5.32 (td, *J* = 2.4, 9.5 Hz, 1 H), 4.66 (br. s, 1 H), 4.12 (dd, *J* = 2.8, 11.5 Hz, 1 H), 3.98 (dd, *J* = 9.4, 11.7 Hz, 1 H), 3.88 (s, 3 H); **^{13}C NMR** (151 MHz, chloroform-d) 155.5, 142.2, 139.4, 129.0, 127.2, 126.7, 125.0, 124.3, 123.7, 80.1, 67.1, 54.1; **IR** (thin film, cm^{-1}) 3433, 2360, 1714, 1493, 1440, 1348, 1116, 753, 694; **LRMS** (ESI) Calcd. for $[C_{14}H_{15}NO_4S+Na]^+$ = 316.06, Found = 316.03.

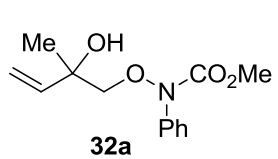


31

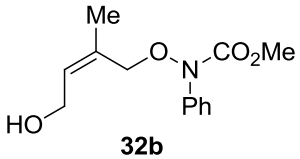
31 was prepared using 2-(prop-1-en-2-yl)furan (64.7 mg, 0.598 mmol, 2.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 2.5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **31** (41.4 mg, 0.142 mmol, 48% yield) as a clear, colorless residue.

Analytical data for **31**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.40 - 7.35 (m, 3 H), 7.32 - 7.29 (m,

2 H), 7.27 - 7.23 (m, 1 H), 6.41 - 6.34 (m, 2 H), 4.53 (br. s, 1 H), 4.32 (d, *J* = 10.2 Hz, 2 H), 3.98 (d, *J* = 10.5 Hz, 1 H), 3.80 (s, 3 H), 1.55 (s, 3 H); **^{13}C NMR** (151 MHz, chloroform-d) 157.3, 155.6, 141.7, 139.4, 128.8, 126.7, 123.0, 110.3, 105.4, 81.0, 70.5, 53.8; **IR** (thin film, cm^{-1}) 3411, 2984, 2955, 1714, 1595, 1447, 1349, 1015, 751; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_5+Na]^+$ = 314.10, Found = 314.06.



32a

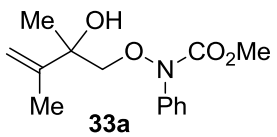


32b

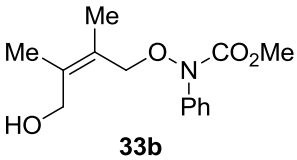
32 was prepared using isoprene (150.0 µL, 1.50 mmol, 5.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **32** as a mixture of isomers (44.0 mg, 0.175 mmol, 59% yield of the kinetic isomer a and 21.9 mg, 0.087 mmol, 29% yield of the thermodynamic isomer b) as a clear, colorless residue.

Analytical data for **32a**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.44 - 7.38 (m, 4 H), 7.28 - 7.25 (m, 1 H), 5.93 (dd, *J* = 10.7, 17.1 Hz, 1 H), 5.43 (dd, *J* = 1.3, 17.1 Hz, 1 H), 5.18 (dd, *J* = 1.3, 10.7 Hz, 1 H), 3.95 (d, *J* = 9.8 Hz, 1 H), 3.87 - 3.85 (m, 1 H), 3.84 (s, 3 H), 1.31 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.4, 141.6, 139.5, 128.9, 128.8, 127.0, 126.6, 123.4, 122.8, 113.7, 112.6, 82.4, 78.5, 72.1, 71.8, 53.8, 24.5; **IR** (thin film, cm^{-1}) 3434, 2978, 2956, 2876, 1714, 1595, 1348, 1119, 751; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_4+Na]^+$ = 274.11, Found = 274.10.

Analytical data for **32b**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.50 - 7.43 (m, 2 H), 7.42 - 7.36 (m, 2 H), 7.27 - 7.19 (m, 1 H), 5.75 - 5.66 (m, 1 H), 4.51 and 4.20 (d, *J* = 7.2 and 6.8 Hz, 2 H), 4.32 and 4.04 (s, 2 H), 3.87 and 3.85 (d, *J* = 1.1 and 0.8 Hz, 3 H), 1.75 and 1.72 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.3, 140.1, 133.0, 130.4, 128.7, 126.1, 125.9, 122.7, 122.1, 117.4, 80.5, 70.5, 67.7, 59.1, 53.4, 14.6, 13.9; **IR** (thin film, cm^{-1}) 3422, 2955, 2863, 1714, 1595, 1494, 1349, 1114, 752; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_4+Na]^+$ = 274.11, Found = 274.10.



33a

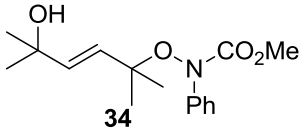


33b

33 was prepared using 2,3-dimethyl-1,3-butadiene (169.7 µL, 1.50 mmol, 5.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **33** as a mixture of isomers (59.2 mg, 0.223 mmol, 75% yield of the kinetic isomer a and 10.0 mg, 0.038 mmol, 13% yield of the thermodynamic isomer b) as a clear, colorless residue.

Analytical data for **33a**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.45 - 7.36 (m, 4 H), 7.28 - 7.23 (m, 1 H), 5.23 - 5.16 (m, 1 H), 4.98 - 4.92 (m, 1 H), 4.17 (d, *J* = 9.8 Hz, 1 H), 3.87 - 3.81 (m, 4 H), 1.81 (s, 3 H), 1.31 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.4, 127.8, 139.7, 128.9, 126.5, 122.7, 111.1, 81.5, 74.1, 53.7, 24.0, 19.4; **IR** (thin film, cm^{-1}) 3441, 3066, 2977, 2855, 1714, 1596, 1347, 1119, 905; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_4+Na]^+$ = 288.12, Found = 288.12.

Analytical data for **33b**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.51 - 7.44 (m, 2 H), 7.44 - 7.35 (m, 2 H), 7.26 - 7.18 (m, 1 H), 4.46 (s, 2 H), 4.17 (s, 2 H), 3.87 (s, 3 H), 1.90 - 1.84 (m, 3 H), 1.84 - 1.79 (m, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 155.2, 140.2, 136.7, 128.8, 128.6, 126.2, 126.1, 125.9, 122.5, 122.1, 75.9, 75.0, 63.6, 63.4, 53.6, 53.4, 18.7, 17.7, 17.1, 16.5; **IR** (thin film, cm^{-1}) 3425, 2954, 2924, 1715, 1596, 1494, 1349, 1107, 750; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_4+Na]^+$ = 288.12, Found = 288.12.

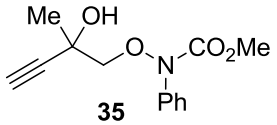


34

34 was prepared using 2,5-dimethyl-2,4-hexadiene (85.3 µL, 0.598 mmol, 2.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 2 h.

The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **34** (52.0 mg, 0.177 mmol, 59% yield) as a clear, colorless residue.

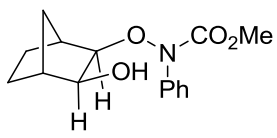
Analytical data for **34**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.43 - 7.36 (m, 2 H), 7.36 - 7.27 (m, 2 H), 7.22 - 7.09 (m, 1 H), 5.66 - 5.52 (m, 2 H), 3.77 (s, 3 H), 1.44 - 1.31 (m, 6 H), 1.11 (s, 6 H); **^{13}C NMR** (101 MHz, chloroform-d) 157.1, 144.1, 137.8, 130.9, 128.2, 125.8, 123.7, 84.4, 70.1, 53.4, 29.2; **IR** (thin film, cm^{-1}) 3456, 3030, 2977, 2933, 1723, 1595, 1364, 1133, 769; **LRMS** (ESI) Calcd. for $[C_{16}H_{23}NO_4+Na]^+$ = 316.15, Found = 316.16.



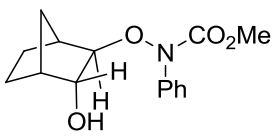
35

35 was prepared using 2-methyl-1-buten-3-yne (140.0 µL, 1.50 mmol) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **35** (50.6 mg, 0.203 mmol, 68% yield) as a clear, colorless residue.

Analytical data for **35**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.48 - 7.39 (m, 4 H), 7.31 - 7.26 (m, 1 H), 4.69 (br. s, 1 H), 4.08 (d, *J* = 10.8 Hz, 1 H), 3.85 (s, 3 H), 3.82 (d, *J* = 10.5 Hz, 1 H), 2.50 (s, 1 H), 1.50 (s, 3 H); **^{13}C NMR** (101 MHz, chloroform-d) 155.8, 139.2, 128.9, 126.9, 123.2, 85.5, 82.0, 71.6, 65.8, 53.9, 25.9; **IR** (thin film, cm^{-1}) 3414, 3286, 2956, 1714, 1594, 1494, 1441, 1348, 1305, 1119, 1026, 751, 694; **LRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_4+Na]^+$ = 272.09, Found = 272.09.



36a



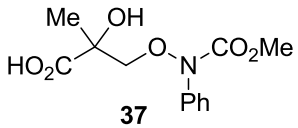
36b

36 was prepared using norbornene (141.0 mg, 1.50 mmol, 5.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (15-20%

EtOAc/hexanes gradient) to afford **36** as a mixture of diastereomers (35.2 mg, 0.127 mmol, 42% yield **36a** and 28.8 mg, 0.104 mmol, 35% yield **36b**) as a clear, colorless residue.

Analytical data for **36a**: **^{1}H NMR** (600 MHz, benzene-d_6) δ = 7.40 - 7.33 (m, 2 H), 7.11 - 7.03 (m, 2 H), 6.95 - 6.87 (m, 1 H), 4.71 (br. s., 1 H), 3.91 (d, *J* = 5.6 Hz, 1 H), 3.71 (dd, *J* = 1.5, 5.6 Hz, 1 H), 3.26 (s, 3 H), 2.32 (d, *J* = 4.5 Hz, 1 H), 2.19 (td, *J* = 1.7, 10.1 Hz, 1 H), 2.13 (d, *J* = 4.1 Hz, 1 H), 1.15 - 1.06 (m, 1 H), 1.06 - 0.99 (m, 1 H), 0.93 - 0.89 (m, 1 H), 0.69 (ddd, *J* = 2.1, 4.1, 11.9 Hz, 1 H), 0.56 - 0.50 (m, 1 H); **^{13}C NMR** (151 MHz, benzene-d_6) 155.9, 141.0, 128.6, 128.0, 126.5, 123.6, 90.2, 76.2, 53.0, 43.3, 41.2, 32.8, 25.0, 23.7; **IR** (thin film, cm^{-1}) 3432, 2961, 2874, 1708, 1646, 1493, 1341, 756; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_4+Na]^+$ = 300.12, Found = 300.12.

Analytical data for **36b**: **^{1}H NMR** (600 MHz, benzene-d_6) δ = 7.55 (d, *J* = 7.5 Hz, 2 H), 7.11 (t, *J* = 8.1 Hz, 2 H), 6.94 - 6.88 (m, 1 H), 4.19 (d, *J* = 3.8 Hz, 1 H), 3.88 (s, 1 H), 3.38 (s, 3 H), 2.67 (br. s, 1 H), 2.28 (d, *J* = 5.3 Hz, 1 H), 2.17 - 2.11 (m, 1 H), 1.89 - 1.82 (m, 1 H), 1.75 (d, *J* = 10.2 Hz, 1 H), 1.33 - 1.25 (m, 1 H), 1.13 - 1.05 (m, 1 H), 1.04 - 0.99 (m, 1 H), 0.99 - 0.94 (m, 1 H); **^{13}C NMR** (151 MHz, benzene-d_6) 156.0, 142.0, 128.5, 128.0, 125.8, 123.0, 94.5, 77.7, 52.7, 41.7, 40.8, 34.2, 24.9, 19.7; **IR** (thin film, cm^{-1}) 3428, 2958, 2876, 1712, 1440, 1341, 1107, 758; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_4+Na]^+$ = 300.12, Found = 300.11.

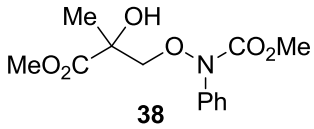


37

37 was prepared using methacrylic acid (130.0 µL, 1.50 mmol, 5.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (3% MeOH/CH_2Cl_2) to afford **37** (36.5 mg, 0.136 mmol, 45% yield) as a clear, colorless residue.

Analytical data for **37**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.43 - 7.39 (m, 2 H), 7.38 - 7.35 (m, 2 H), 7.32 - 7.29 (m, 1 H), 4.49 (d, *J* = 10.9 Hz, 1 H), 3.87 (d, *J* = 10.9 Hz, 1 H), 3.83 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR** (151 MHz, chloroform-d) 176.6, 156.6, 139.0, 129.0, 127.5, 123.7, 80.0, 73.8,

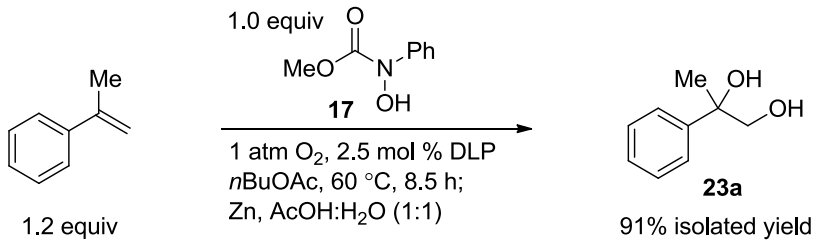
54.3, 22.4; **IR** (thin film, cm^{-1}) 3449, 2957, 1723, 1493, 1442, 1349, 1349, 754, 695; **LRMS** (ESI) Calcd. for $[C_{12}H_{15}NO_6+Na]^+$ = 292.08, Found = 292.05.



38

38 was prepared using methyl methacrylate (160.0 µL, 1.50 mmol, 5.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 22 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (133-50% EtOAc/hexanes) to afford **38** (70.9 mg, 0.250 mmol, 84% yield) as a clear, colorless residue. Analytical data for **38**: **^{1}H NMR** (500 MHz, chloroform-d) δ = 7.41 - 7.35 (m, 4 H), 7.27 - 7.22 (m, *J* = 3.2, 5.7, 5.7 Hz, 1 H), 4.36 (br. s., 1 H), 4.29 (d, *J* = 10.1 Hz, 1 H), 3.89 (d, *J* = 10.1 Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 1.39 (s, 3 H); **^{13}C NMR** (126 MHz, chloroform-d) 174.9, 155.6, 139.5, 128.8, 126.7, 122.8, 80.4, 73.8, 53.8, 52.8, 22.3; **IR** (thin film, cm^{-1}) 3447, 2996, 2955, 1732, 1595, 1494, 1441, 1349, 759, 695; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_6+Na]^+$ = 306.10, Found = 306.10.

Figure 3-5. One-Pot, Direct Dihydroxylation Procedure



23a was prepared using α-methylstyrene (77.8 μL, 0.598 mmol, 2.0 equiv) under the standard conditions. The reaction was completed, as indicated by TLC, after heating at 60 ºC for 8.5 h. The crude reaction mixture was concentrated, taken up in AcOH (1 mL) before water (1 mL) and Zn powder (391.0 mg, 5.98 mmol, 20 equiv) was added. The reaction was completed, as indicated by TLC, after heating at 40 ºC for 3 h. The crude reaction mixture was taken up in CH_2Cl_2, filtered through Celite, dried ($MgSO_4$) and concentrated under reduced pressure prior to purification by flash chromatography (50% EtOAc/hexanes) to afford **23a** (41.5 mg, 0.273 mmol, 91% yield) as a clear, colorless residue. Physical and spectral data were in accordance with literature values.[16]

3.6 References

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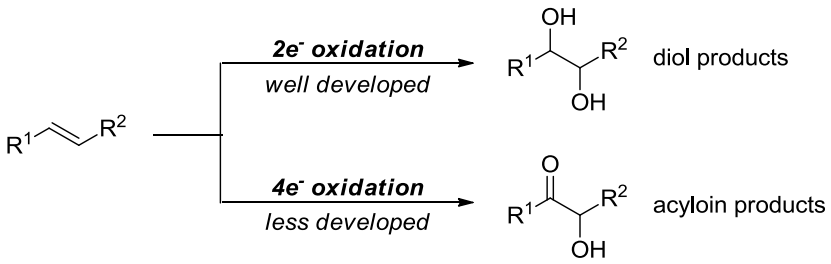
4. CHAPTER FOUR

Aerobic Alkene Ketooxygenations Using Hydroxamic Acids

4.1 Introduction

Acyloins, or α-ketols, are an important structural motif commonly found in biologically active small molecules and natural products, and are versatile intermediates in chemical synthesis. Common synthetic approaches to these compounds include acyloin and benzoin condensation reactions,[1] α-oxidations of carbonyl compounds,[2–5] and the reduction of 1,2-diketones.[6–8] Alternatively, the direct synthesis of acyloins from alkenes via multiple-electron oxidation (ketooxygenation) provides efficient access to these compounds (**Figure 4-1**).[9–11]

Figure 4-1. Alkene Difunctionalizations Using Hydroxamic Acids



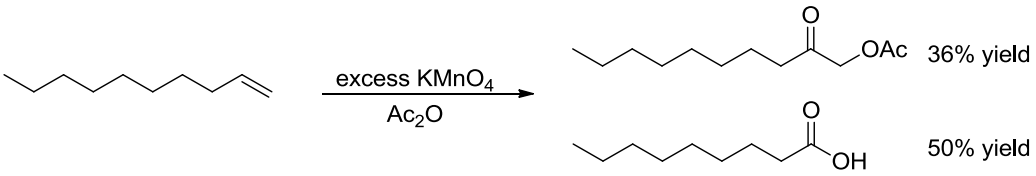
4.2 Background

Alkene difunctionalizations typically focus on pathways that achieve 2-electron oxidations, such as dihydroxylation, oxyamination, and diamination (see **Chapter 1**). Methods that achieve a higher degree of oxidation (i.e. 4-electron oxidations), are comparatively underdeveloped owing to several major challenges. For example, the oxidative conditions must be precisely controlled to avoid diol, diketone, or oxidative C-C bond cleavage products. High regioselectivity is also notoriously difficult to achieve, particularly when the substrate alkene is symmetrically substituted and/or electronically unbiased. Furthermore, most methods utilize precious and/or toxic transition-metal

catalysts (e.g. Ru, Os), and involve strongly oxidizing conditions that are not amenable to complex synthesis.

An early report of direct alkene ketooxygenation from Sharpless exemplifies many of these challenges (**Figure 4-2**). Highly oxidizing potassium permanganate ($KMnO_4$) was required for the dioxygenation to proceed and the major product is the result of oxidative C-C bond cleavage.[12]

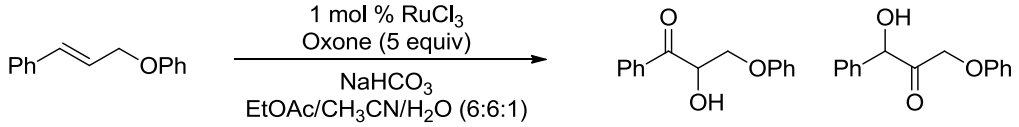
Figure 4-2. Mn-Promoted Alkene Ketooxygenations



Sharpless *JACS* **1971**, 3303.

Significant advances in multi-electron alkene oxidations were made by Plietker (**Figure 4-3**).[13] These studies focused on Ru-catalyzed protocols that use Oxone as the terminal oxidant. While efficient, especially with low catalytic loadings of $RuCl_3$, the regioselectivity is modest.

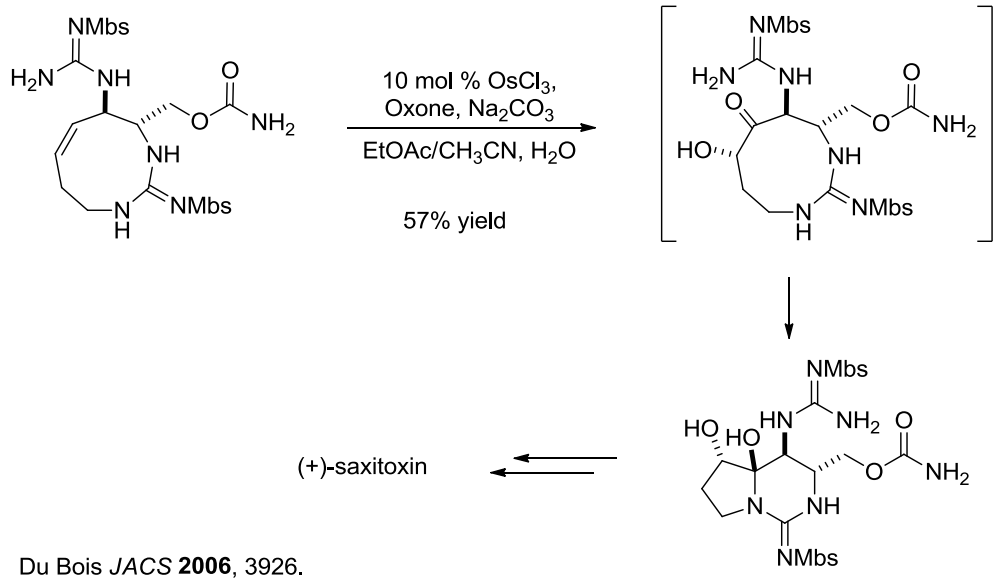
Figure 4-3. Ru-Catalyzed Alkene Ketooxygenation



Plietker *JOC* **2004**, 8287.

Additionally, the potential for alkene ketooxygenations in complex molecule synthesis is well demonstrated in DuBois's total synthesis of (+)-saxitoxin (**Figure 4-4**).[14] However, the high level of regioselectivity displayed in this example is highly substrate controlled and not generally applicable.

Figure 4-4. Os-Catalyzed Ketooxygenation in the Total Synthesis of (+)-Saxitoxin



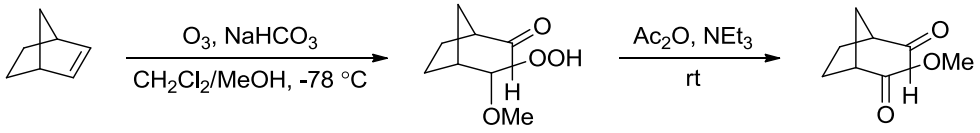
Du Bois *JACS* **2006**, 3926.

Herein, we report a metal-free approach to alkene ketooxygenation using easily prepared *N*-aryl hydroxamic acids with molecular oxygen as an environmentally benign and inexpensive oxidant. This mild, radical-mediated approach avoids the strongly oxidizing conditions of transition-metal-catalyzed ketooxygenations, while offering the potential for high levels of reaction regio- and stereocontrol.

4.3 Reaction Development

Our successes in using hydroxamic acids as convenient sources of amidoxyl radicals for aerobic alkene dioxygenations prompted us to further explore this reactivity in other contexts. Noting that in these previous dioxygenation methods, the products formed initially are alkylhydroperoxides that are subjected to a reductive work up, we considered that instead of sacrificing this oxidation state to reduction, it could be harnessed to provide the analogous four-electron ketooxygenation product. We were inspired by ozonolysis work up conditions of α-alkoxy hydroperoxides used by Schreiber. These reactions treat alkylhydroperoxides with base and acetic anhydride in order to facilitate a dehydration reaction to obtain ester products (**Figure 4-5**).[15,16]

Figure 4-5. Hydroperoxide Dehydration Promoted by Acetylation



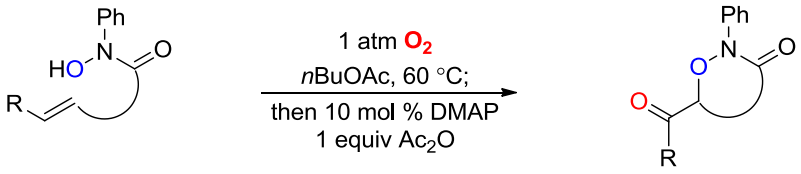
90% yield
2 steps

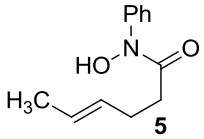
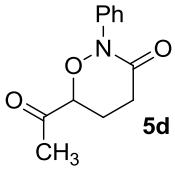
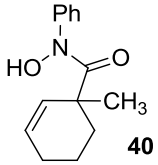
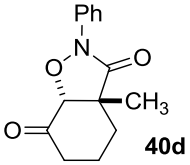
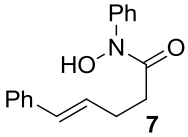
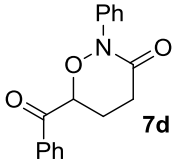
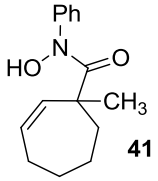
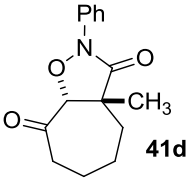
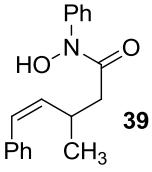
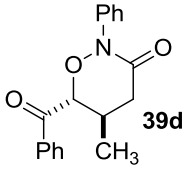
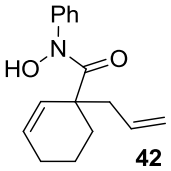
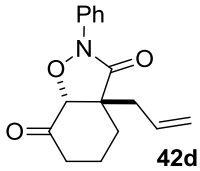
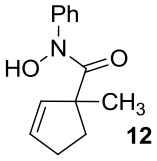
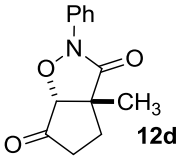
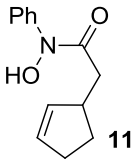
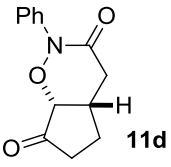
Schreiber *Tet. Lett.* **1987**, 3867.

4.3.1 Substrate Scope – Intramolecular Ketooxygenations

We commenced our studies with unsaturated *N*-aryl hydroxamic acid **5** as it proved an excellent substrate for our previous dioxygenation protocol (**Table 4-1, entry 1**).

Table 4-1. Ketooxygenations of Unsaturated *N*-Aryl Hydroxamic Acids



entry	substrate	product	% yield[a,b]	entry	substrate	product	% yield[a,b]
1	 **5**	 **5d**	80[c]	5	 **40**	 **40d**	88 >95:5 dr
2	 **7**	 **7d**	72[c]	6	 **41**	 **41d**	75 >95:5 dr
3	 **39**	 **39d**	72 >95:5 dr	7	 **42**	 **42d**	84 >95:5 dr
4	 **12**	 **12d**	81 >95:5 dr	8	 **11**	 **11d**	84[c] >95:5 dr

[a]Yields of isolated product. [b]The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [c]Reactions were initiated using 10 mol % dilauroyl peroxide (DLP).

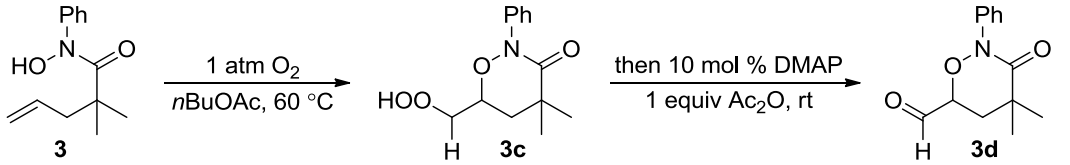
Following amidoxyl radical cyclization and hydroperoxide formation, addition of 10 mol % 4-(dimethylamino)pyridine (DMAP) and 1 equivalent acetic anhydride to the reaction mixture afforded the desired ketooxygenation product **5d** in 80% isolated yield. Further studies determined that conjugated alkenes as well as cycloalkenes also react efficiently under these conditions (**Table 4-1, entries 2 - 8**). The reaction of β-methyl-substituted hydroxamic acid **39** proceeded via a highly stereoselective 6-*exo* cyclization, providing [1,2]-oxazinone **39d** as a single diastereomer in 72% yield (**entry 3**). The direct ketooxygenation of a variety of cycloalkenyl substrates also provided α-oxyketones with high diastereoselectivities (**entries 4 – 8**). We observed in our previous dioxygenation studies that the reaction of O_2 with the putative carbon-centered radical intermediate formed upon cyclization is only moderately stereoselective (see **Chapter 2, Table 2-3**). However, this dehydration work up step eliminates the stereocenter created upon non-selective radical trapping, effectively converging the diastereomers formed.

The intramolecular nature of the ketooxygenation also permits chemoselective, single difunctionalization of diene substrates as demonstrated by the reaction of hydroxamic acid **42** (**entry 7**). Ketooxygenation of similar diene substrates using highly oxidizing, intermolecular metal-catalyzed protocols would likely result in a mixture of mono- and bis-difunctionalization. The ketooxygenation of the symmetrically substituted and electronically unbiased cyclopentenyl hydroxamic acid **11** highlights the high regio- and stereoselectivity of this approach as dictated by the amidoxyl radical cyclization step (**Table 4-1, entry 8**).

Notably absent from the results in **Table 4-1** are hydroxamic acids containing terminal alkenes. This substrate type was tested using hydroxamic acid **3**. Analysis of the crude reaction mixture confirms that the corresponding alkylhydroperoxide **3c** as well as the aldehyde ketooxygenation product **3d** were successfully formed (**Figure 4-6**). However, attempts at the isolation of **3d** failed, resulting in decomposition of the aldehyde product, likely a result from the instability of α-oxy aldehydes. Typically, protocols that generate this motif rely on a reductive work up to transform the aldehyde to a primary alcohol. For purposes of developing a direct alkene ketooxygenation, this

reductive strategy is unproductive and was therefore not pursued.

Figure 4-6. Aerobic Ketooxygenation of a Terminal Alkene

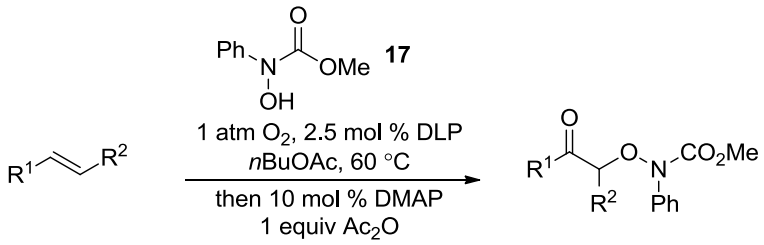


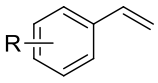
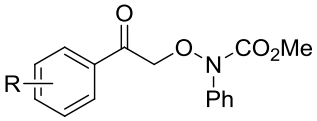
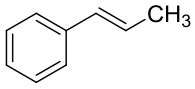
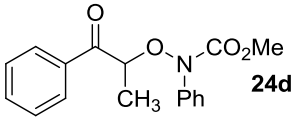
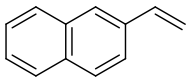
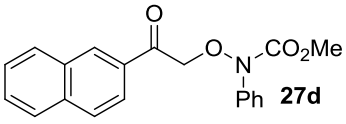
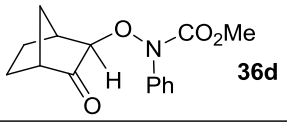
no yield obtained

4.3.2 Substrate Scope – Intermolecular Ketooxygenations

We have also established the utility of the ketooxygenation in intermolecular contexts using readily prepared methyl *N*-hydroxy-*N*-phenylcarbamate **17** (see **Chapter 3**).

Table 4-2. Intermolecular Radical-Mediated Alkene Ketooxygenations



entry	substrate[a]	product	% yield[b,c]
			
1	R = H	**18d**	88[d]
2	R = 4-OMe	**19d**	77
3	R = 2-Br	**21d**	76
4	R = 4-CF_3	**22d**	72
5		 **24d**	94
6		 **27d**	82
7		 **36d**	77[e] >95:5 dr

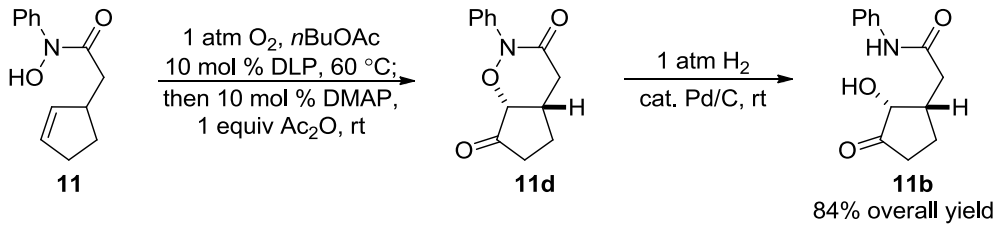
[a]1.2 equiv substrate used in all reactions. [b]Yields of isolated product. [c]The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d]EtOAc was used as solvent. [e]5.0 equiv substrate used.

The success of this strategy is demonstrated by the efficient ketooxygenation of a variety of electron-rich and electron-poor styrenes (**Table 4-2, entries 1 – 6**). Notably, these reactions all produce a single regioisomer as product. Additionally, difunctionalization of norbornene demonstrates the utility of this method with non-conjugated, albeit highly strained, alkene substrates (**entry 7**).

4.3.3 Post-Ketooxygenation Modification

Simple reductive N-O bond cleavage of the cyclic hydroxamate **11d** yielded α-ketol **11b** in good yield as a single regioisomer and diastereomer (**Figure 4-7**). Such a selective multiple-electron alkene oxidation would be very challenging using other known transition-metal-catalyzed methods.

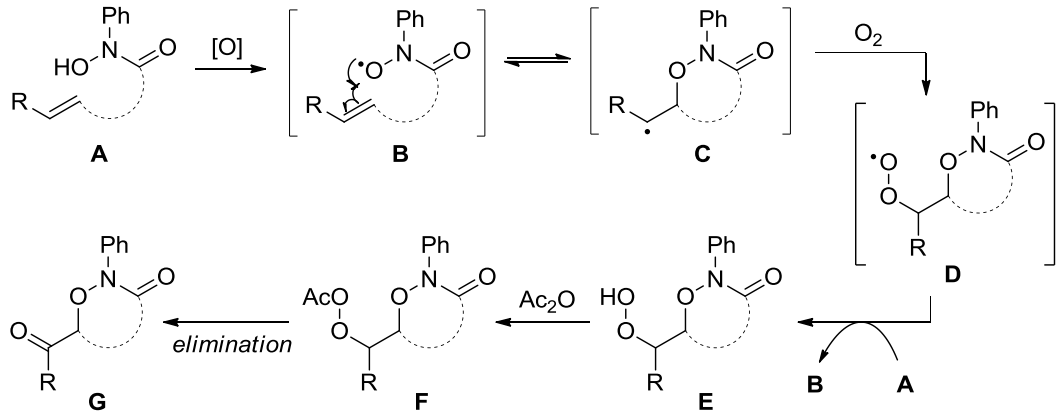
Figure 4-7. Regioselective Alkene Ketohydroxylation



4.3.4 Proposed Mechanism

We postulate that an analogous aerobic dioxygenation is operative as outlined in **2.3.4 Proposed Mechanism**, however the reaction is intercepted at the hydroperoxide stage (**Figure 4-8**).

Figure 4-8. Proposed Radical-Mediated Aerobic Alkene Ketooxygenation



The addition of Ac_2O and catalytic DMAP to the crude reaction mixture effects the acetylation

of the terminal oxygen-atom of the hydroperoxide. Elimination then affords the desired ketooxygenation product **G**.

4.4 Summary

We have developed a radical-mediated, aerobic alkene ketooxygenation using *N*-phenyl hydroxamic acids. This difunctionalizations proceeds without the use of transition-metal catalysts and highly oxidizing conditions that are common to current multiple-electron alkene oxidation processes. This protocol is applicable to a wide range of alkene substrates and demonstrates excellent regioselectivity in all cases, which is a major challenge using current metal-catalyzed methods. This approach capitalizes on the ability of amidoxyl radicals, formed in situ under mild conditions, to serve as a synthetically useful source of oxygen-centered radicals.

4.5 Experimental

4.5.1 General Methods

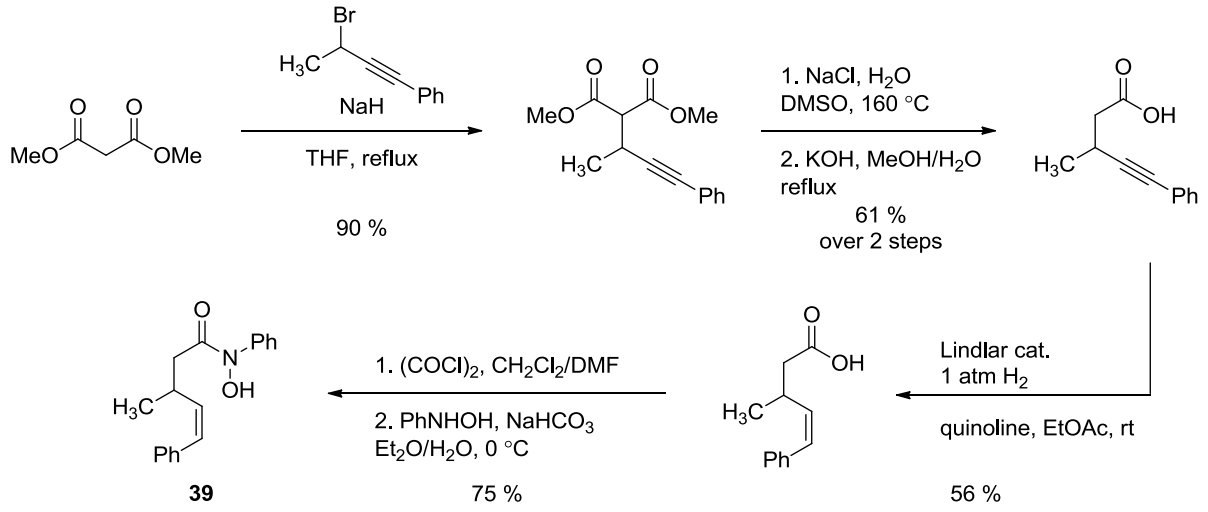
See **2.5 Experimental** for general methods and substrate prep.

4.5.2 Substrate Preparation

Styrene, β-methylstyrene, *p*-methoxystyrene, *o*-bromostyrene were purchased from commercial sources, purified by distillation, deoxygenated via multiple freeze-pump-thaw cycles, and stored at -35 °C under an inert atmosphere prior to use. Norbornene was purified by sublimation and stored under an inert atmosphere.

Para-trifluoromethylstyrene[17,18] and 2-vinylnaphthalene[19] were prepared according to standard procedures. All physical and spectral data were in accordance with literature data.

Figure 4-9. Synthesis of **39**



Dimethyl 2-(4-phenylbut-3-yn-2-yl)malonate was prepared via dropwise addition of dimethylmalonate (1.64 mL, 14.3 mmol, 3.0 equiv) to a 0 ºC suspension of NaH (210.0 mg of a 60 % dispersion in mineral oil, 5.26 mmol, 1.1 equiv). Stirring cold for 5 minutes was followed by dropwise addition of (3-bromobut-1-yn-yl)benzene (1.00 g, 4.78 mmol, 1.0 equiv). The reaction mixture was then heated to reflux for 10 h, cooled to rt and quenched with a saturated NH_4Cl (aq) solution. The mixture was extracted with Et_2O (4x), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude alkylation product was then purified via flash chromatography (17.5% EtOAc/hexanes) to give dimethyl 2-(4-phenylbut-3-yn-2-yl)malonate (1.12 g, 4.30 mmol, 90% yield) as a colorless oil.

Analytical data for dimethyl 2-(4-phenylbut-3-yn-2-yl)malonate: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 7.44 - 7.35 (m, 2 H), 7.33 - 7.25 (m, 3 H), 3.80 (s, 6 H), 3.56 (d, *J* = 9.3 Hz, 1 H), 3.53 - 3.44 (m, 1 H), 1.38 (d, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 168.0, 167.9, 131.6, 128.2, 128.0, 123.2, 89.9, 82.5, 57.6, 52.7, 52.6, 27.0, 19.0 ppm; **IR** (thin film, cm^{-1}) 3055, 3033, 2980, 2953, 2879, 2845, 1956, 1757, 1739, 1490, 1436, 1339, 1243, 1069, 1018, 759, 693; **LRMS** (ESI) Calcd. for $[C_{15}H_{16}O_4+H]^+$ = 261.12, Found = 261.07.

3-Methyl-5-phenylpent-4-ynoic acid was prepared using a 2 step, decarboxylation and hydrolysis route. A round-bottom flask was charged with dimethyl 2-(4-phenylbut-3-yn-2-yl)malonate (1.12 g, 4.30 mmol, 1.0 equiv), NaCl (251.0 mg, 4.30 mmol, 1.0 equiv), water (155.0 µL, 8.60 mmol, 2.0 equiv) and DMSO (30 mL). The reaction was observed to be complete after heating at 160 ºC for 8 h. The crude mixture was cooled to rt, diluted with water (30 mL), extracted with CH_2Cl_2 (4x) then the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow liquid. This crude ester (609.0 mg, 3.01 mmol, 1 equiv) was taken up into MeOH (9 mL) and water (5 mL) and KOH (372.0 mg, 6.62 mmol, 2.2 equiv) added. The mixture was heated to reflux for 2 h, cooled to rt then acidified to pH 1 using 6N HCl. The cloudy solution was then extracted with Et_2O (4x), the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 3-methyl-5-phenylpent-4-ynoic acid (492.0 mg, 2.61 mmol, 60 % yield over 2 steps) as a yellow oil that did not require further purification.

Analytical data for 3-methyl-5-phenylpent-4-ynoic acid: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 10.66 (br. s., 1H), 7.44 - 7.39 (m, 2 H), 7.33 - 7.28 (m, 3 H), 3.21 (sxt, *J* = 7.0 Hz, 1 H), 2.75 (dd, *J* = 7.0, 16.1 Hz, 1 H), 2.58 (dd, *J* = 7.5, 15.6 Hz, 1 H), 1.38 (d, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 177.7, 131.6, 128.2, 127.8, 123.4, 92.1, 81.3, 41.4, 23.2, 20.8 ppm; **IR** (thin film, cm^{-1}) 3418, 2976, 2934, 1711, 1599, 1490, 1442, 1291, 1230, 915, 757, 691; **LRMS** (ESI) Calcd. for $[C_{12}H_{12}O_2+H]^+$ = 189.09, Found = 189.00.

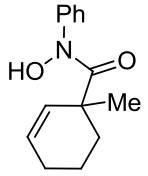
3-Methyl-5-phenylpent-4-ynoic acid (492.0 mg, 2.61 mmol, 1 equiv) was added to a flask containing Lindlar catalyst (5% Pd on $CaCO_3$, 261 mg catalyst, 0.131 mmol Pd) and quinoline (772.0 µL, 6.53 mmol, 2.51 equiv) in EtOAc (60 mL). The flask was evacuated and refilled with H_2 four times, and then allowed to stir rt under 1 atm H_2 for 2 h. The reaction mixture was then filtered through Celite, washed with EtOAc, and concentrated. The crude residue was purified via flash chromatography (15% EtOAc/Hex) to give (*Z*)-3-methyl-5-phenylpent-4-enoic acid (277.0 mg, 1.46 mmol, 56 % yield) as a clear, colorless oil.

Analytical data for (*Z*)-3-Methyl-5-phenylpent-4-enoic acid: **^{1}H NMR** (chloroform-d, 400 MHz): δ =

11.66 - 9.30 (br. s., 1 H), 7.41 - 7.19 (m, 5 H), 6.45 (d, *J* = 11.5 Hz, 1 H), 5.52 (t, *J* = 10.9 Hz, 1 H), 3.41 - 3.27 (m, 1 H), 2.50 - 2.34 (m, 2 H), 1.20 - 1.14 (m, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 178.4, 137.2, 136.1, 128.8, 128.6, 128.3, 126.8, 41.7, 29.4, 20.8 ppm; **IR** (thin film, cm^{-1}) 3056, 2966, 2929, 2874, 1947, 1882, 1708, 1494, 1446, 1412, 1291, 1072, 917, 798, 769, 699; **LRMS** (ESI) Calcd. for $[C_{12}H_{14}O_2+Na]^+$ = 213.09, Found = 213.17.

39 was synthesized via ***Method A*** (outlined in **2.5 Experimental**) using (*Z*)-3-methyl-5-phenylpent-4-enoic acid in 75% yield (146.7 mg) as an off-white solid.

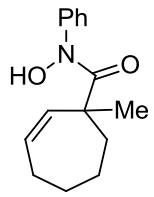
Analytical data for **39**: **^{1}H NMR** (chloroform-d, 500 MHz): δ = 9.05 (br. s., 1 H), 7.41 (br. s., 3 H), 7.38 - 7.22 (m, 7 H), 6.39 (d, *J* = 11.3 Hz, 1 H), 5.42 - 5.29 (m, 1 H), 3.33 (m, 1 H), 2.38 (br. s., 2 H), 1.07 (d, *J* = 5.0 Hz, 3 H); **^{13}C NMR** (chloroform-d, 126 MHz) 166.9, 138.3, 137.1, 136.3, 136.2, 129.2, 128.5, 128.4, 128.2, 127.0, 126.7, 126.0, 39.4, 29.8, 20.7 ppm; **IR** (thin film, cm^{-1}) 3398, 2964, 2928, 2959, 1953, 1637, 1494, 1393, 1069, 916; **LRMS** (ESI) Calcd. for $[C_{18}H_{19}NO_2+H]^+$ = 282.15, Found = 282.17.



40

The corresponding carboxylic acid of **40** was synthesized via the same route as **12** beginning with the cyclohexane analog. **40** was synthesized via ***Method A*** (outlined in **2.5 Experimental**) in 80% yield (790.0 mg) as an off-white solid.

Analytical data for **40**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 8.74 (br. s, 1 H), 7.32 - 7.45 (m, 5 H), 5.44 (m, 1 H), 5.10 - 5.39 (m, 1 H), 2.26 - 2.37 (m, 1 H), 1.80 - 1.97 (m, 2 H), 1.56 - 1.68 (m, 2 H), 1.38 (ddd, *J*=12.8, 8.4, 4.2 Hz, 1 H), 1.29 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 174.0, 140.2, 130.9, 128.8, 128.6, 127.4, 127.2, 43.4, 33.9, 26.4, 24.5, 19.5 ; **IR** (thin film, cm^{-1}) 3205, 3036, 2933, 2871, 2834, 1615, 1591, 1491, 1452, 1355, 1306, 1066, 758, 695; **LRMS** (ESI) Calcd. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.12, Found = 254.14.



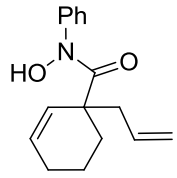
41

The corresponding carboxylic acid of **41** was synthesized via the same route as **12** beginning with the cycloheptane analog.

Spectral data for 1-methylcyclohept-2-enecarboxylic acid : **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 10.94 - 12.90 (m, 1 H), 5.84 (dt, *J*=11.7, 6.0 Hz, 1 H), 5.61 (dd, *J*=11.7, 0.6 Hz, 1 H), 2.14 - 2.21 (m, 2 H), 2.02 - 2.11 (m, 1 H), 1.77 - 1.84 (m, 2 H), 1.50 - 1.75 (m, 3 H), 1.38 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 101MHz): 183.8, 134.4, 132.3, 48.4, 37.0, 28.1, 27.4, 27.1, 25.8 ppm.

41 was synthesized via ***Method A*** (outlined in **2.5 Experimental**) in 61% yield (544.0 mg) as an off-white solid.

Analytical data for **41**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 7.30 - 7.60 (m, 5 H), 5.45 (br. s., 1 H), 4.91 - 5.28 (m, 1 H), 2.27 (ddd, *J*=13.5, 5.7, 3.6 Hz, 1 H), 1.72 - 2.09 (m, 4 H), 1.43 - 1.65 (m, 3 H), 1.32 - 1.39 (m, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 182.2, 174.4, 171.7, 171.2, 170.7, 140.6, 136.5, 136.0, 134.6, 132.2, 131.0, 128.7, 127.9, 126.0, 125.0, 124.7, 117.1, 117.0, 116.8, 87.5, 85.5, 85.4, 84.0, 51.0, 49.0, 48.5, 48.3, 47.7, 38.3, 37.4, 37.1, 34.8, 31.9, 30.7, 29.5, 28.3, 28.1, 27.4, 27.2, 27.1, 26.5, 26.3, 25.9, 23.8, 23.7 ppm (*Note*: Due to the high reactivity of this hydroxamic acid, it was only able to be isolated in 90% purity; therefore oxyamination reactions were performed immediately following isolation); **IR** (thin film, cm^{-1}) 3237, 3019, 2927, 2860, 1698, 1668, 1623, 1593, 1495, 1453, 1373, 1352, 757, 690; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.13, Found = 268.15.



42

The corresponding carboxylic acid of **42** was synthesized via the same route as **40** using allyl bromide instead of iodomethane. **42** was synthesized ***Method A*** (outlined in **2.5 Experimental**) in 76% yield (588.0 mg) as an off-white solid.

Analytical data for **42**: **^{1}H NMR** (chloroform-d, 500 MHz): δ = 9.07 (br. s., 1 H), 7.50 – 7.29 (m, 5 H), 5.89 - 5.66 (m, 1 H), 5.45 - 5.28 (m, 1 H), 5.26 - 4.99 (m, 3 H), 2.51 (br. s., 1 H), 2.42 - 2.18 (m, 2 H), 1.85 (br. s., 2 H), 1.72 - 1.48 (m, 2 H), 1.36 (br. s., 1 H); **^{13}C NMR** (chloroform-d, 126 MHz) 172.0, 139.8, 133.7, 129.2, 128.7, 128.2, 118.2, 46.9, 44.4, 32.7, 24.7, 19.4 ppm; **IR** (thin film, cm^{-1}) 3412, 3036, 2936, 2870, 2834, 1621, 1591, 1490, 1452, 1362, 955, 914; **LRMS** (ESI) Calcd. for $[C_{16}H_{19}NO_2+H]^+$ = 258.15, Found = 258.16.

4.5.3 General Dioxygenation Conditions

Caution! Aerobic reactions in organic solvents may produce potentially explosive peroxides. Alkylhydroperoxides are produced using the following conditions. While no problems were encountered in this work, alkylhydroperoxides are prone to rapid exothermic decomposition and appropriate care should be taken in their handling.

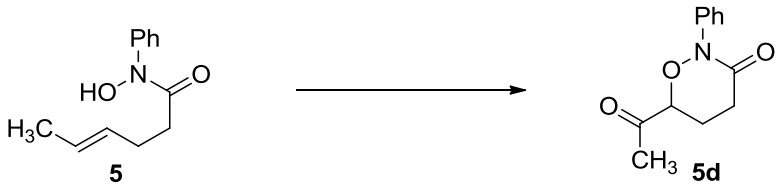
For Intramolecular Ketooxygenations

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and dissolved in *n*BuOAc to make a 0.1M solution. The vial was fitted with a PTFE-lined screw cap and O_2 was bubbled through the solution for 10 min. The reaction was allowed to stir under 1 atm O_2 at 60 ºC. Upon disappearance of the hydroxamic acid substrate, as indicated by TLC analysis, the reaction mixture was cooled to rt and 4-(dimethylamino)pyridine (DMAP, 10 mol %)

and acetic anhydride (Ac_2O, 1 equiv) were added under Ar. Upon completion of the elimination, as indicated by TLC analysis, the crude reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (2 x 5 mL) then brine, dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

For Intermolecular Ketooxygenations

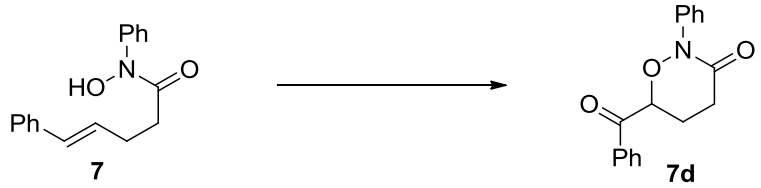
A new 1-dram vial containing a magnetic stir bar was charged with **17** (50.0 mg, 0.299 mmol, 1.0 equiv), dilauroyl peroxide (DLP, 3.0 mg, 0.007 mmol, 2.5 mol %), alkene (0.359 mmol, 1.2 equiv) and dissolved in *n*BuOAc (300 µL, 1.0M). The vial was fitted with a PTFE-lined screw cap and O_2 was bubbled through the solution for 5 minutes. The reaction was allowed to stir under 1 atm O_2 at 60 °C. Upon disappearance of **17**, as indicated by TLC analysis, the reaction mixture was cooled to rt, nBuOAc (300 µL; dilute by a factor of 2), 4-(dimethylamino)pyridine (DMAP, 3.7 mg, 0.030 mmol, 10 mol %) and acetic anhydride (Ac_2O, 28.2 µL, 0.299 mmol, 1 equiv) were added under Ar. Upon completion of the elimination, as indicated by TLC analysis, the crude reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (2 x 5 mL) then brine, dried ($MgSO_4$), and concentrated. The resulting hydroxamate was purified by flash chromatography using the specified solvent system.



5d was prepared using **5** (60.0 mg, 0.292 mmol), DLP (11.7 mg, 0.029 mmol) in nBuOAc (2.70 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 24 h. The crude reaction mixture was cooled to rt, DMAP (3.6 mg, 0.029 mmol) and Ac_2O (27.6 µL, 0.292 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **5d** (50.9 mg, 0.233 mmol, 80% yield) as a clear residue.

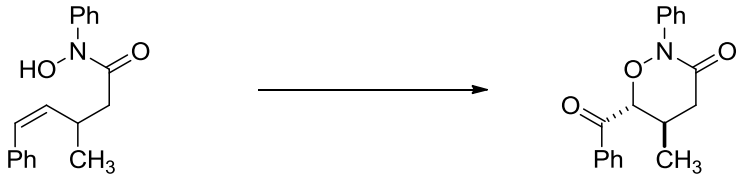
Analytical data for **5d**: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 7.67 - 7.60 (m, 2 H), 7.44 - 7.36 (m,

2 H), 7.25 - 7.18 (m, 1 H), 4.63 (dd, *J* = 7.3, 9.3 Hz, 1 H), 2.77 - 2.62 (m, 2 H), 2.54 - 2.44 (m, 1 H), 2.44 - 2.32 (m, 1 H), 2.30 (s, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 205.0, 171.1, 138.7, 128.8, 125.7, 119.7, 83.1, 29.9, 27.1, 23.5 ppm; **IR** (thin film, cm^{-1}) 3069, 3044, 2959, 2925, 2250, 1954, 1721, 1683, 1595, 1493, 1362, 1179, 1065, 756; **LRMS** (ESI) Calcd. for $[C_{12}H_{13}NO_3+H]^+$ = 220.10, Found = 220.03.



7d was prepared using **7** (60.0 mg, 0.224 mmol), DLP (8.0 mg, 0.022 mmol; a second portion was added after 24 h of heating) in nBuOAc (2.20 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 48 h. The crude reaction mixture was cooled to rt, DMAP (2.7 mg, 0.022 mmol) and Ac_2O (21.0 µL, 0.224 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **7d** (45.2 mg, 0.161 mmol, 72% yield) as a clear residue.

Analytical data for **7d**: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 8.02 - 7.89 (m, 2 H), 7.68 - 7.54 (m, 3 H), 7.53 - 7.44 (m, 2 H), 7.36 - 7.24 (m, 2 H), 7.20 - 7.06 (m, 1 H), 5.57 (dd, *J* = 6.6, 9.3 Hz, 1 H), 2.91 - 2.64 (m, 3 H), 2.55 - 2.41 (m, 1 H); **^{13}C NMR** (chloroform-d, 126 MHz) 194.2, 170.9, 138.7, 134.5, 134.0, 128.9, 128.8, 128.6, 125.5, 119.7, 79.4, 30.1, 23.9 ppm; **IR** (thin film, cm^{-1}) 3064, 2930, 2359, 2341, 1692, 1596, 1494, 1368, 755, 690; **LRMS** (ESI) Calcd. for $[C_{17}H_{15}NO_3+Na]^+$ = 304.10, Found = 304.10.

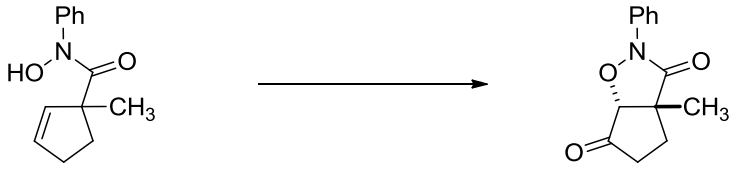


39 **39d**

39d was prepared using **39** (75.1 mg, 0.267 mmol) in nBuOAc (2.50 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 9 h. The crude reaction mixture was cooled to rt, DMAP (3.3 mg, 0.027 mmol) and Ac_2O (25.2 µL, 0.267 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **39d** (56.8 mg, 0.192 mmol, 72% yield) as a clear residue.

Analytical data for **39d**: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 8.01 - 7.94 (m, 2 H), 7.66 - 7.59 (m, 1 H), 7.52 - 7.45 (m, 4 H), 7.28 - 7.22 (m, 2 H), 7.15 - 7.08 (m, 1 H), 5.06 (d, *J* = 6.5 Hz, 1 H), 3.13 (td, *J* = 6.7, 13.4 Hz, 1 H), 2.93 (dd, *J* = 6.1, 14.7 Hz, 1 H), 2.56 (dd, *J* = 7.0, 14.6 Hz, 1 H), 1.28 (d, *J* = 7.0 Hz, 4 H); **^{13}C NMR** (chloroform-d, 151 MHz) 194.5, 170.5, 138.5, 135.1, 134.0, 129.1, 128.8, 128.6, 125.4, 119.7, 85.8, 38.2, 30.1, 19.9 ppm; **IR** (thin film, cm^{-1}) 3064, 2966, 2931, 2874, 1682, 1596, 1494, 1449, 1361, 1304, 754, 689; **LRMS** (ESI) Calcd. for $[C_{18}H_{17}NO_3+H]^+$ = 296.13, Found = 296.12.

Stereochemistry was determined by 2-D NMR analysis.



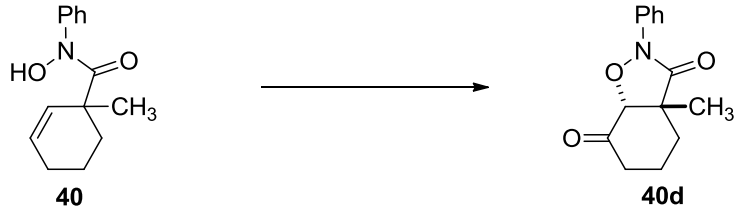
12 **12d**

12d was prepared using **12** (60.0 mg, 0.276 mmol) in nBuOAc (2.50 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 8 h. The crude reaction mixture was cooled to rt, DMAP (3.4 mg, 0.028 mmol) and Ac_2O (26.0 µL, 0.276 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 10 h. The mixture was then worked up and

purified by flash chromatography (33% EtOAc/hexanes) to afford **12d** (51.9 mg, 0.224 mmol, 81% yield) as a clear residue.

Analytical data for **12d**: **^{1}H NMR** (chloroform-d, 600 MHz): δ = 7.75 - 7.70 (m, 2 H), 7.42 - 7.36 (m, 2 H), 7.22 - 7.16 (m, 1 H), 4.37 (s, 1 H), 2.67 (ddd, *J* = 2.8, 10.2, 13.4 Hz, 1 H), 2.58 - 2.50 (m, 1 H), 2.41 - 2.31 (m, 1 H), 2.02 - 1.93 (m, 1 H), 1.60 (s, 3 H); **^{13}C NMR** (chloroform-d, 151 MHz) 213.5, 168.3, 136.3, 128.9, 125.6, 117.2, 84.6, 51.7, 36.1, 29.0, 20.3 ppm; **IR** (thin film, cm^{-1}) 3068, 2969, 2934, 2873, 1758, 1695, 1594, 1496, 1381, 994, 755, 689; **LRMS** (ESI) Calcd. for $[C_{13}H_{13}NO_3+Na]^+$ = 254.08, Found = 254.07.

Stereochemistry was determined by 2-D NMR analysis.

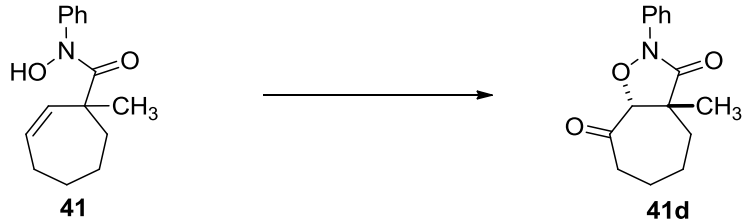


40 **40d**

40d was prepared using **40** (60.0 mg, 0.259 mmol) in nBuOAc (2.50 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was cooled to rt, DMAP (3.2 mg, 0.026 mmol) and Ac_2O (24.5 µL, 0.259 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 2 h. The mixture was then worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **40d** (55.7 mg, 0.227 mmol, 88% yield) as a white solid.

Analytical data for **40d**: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 7.87 - 7.75 (m, 2 H), 7.46 - 7.35 (m, 2 H), 7.25 - 7.14 (m, 1 H), 4.51 - 4.45 (m, 1 H), 2.68 - 2.57 (m, 1 H), 2.45 - 2.31 (m, 2 H), 2.08 - 1.97 (m, 1 H), 1.81 - 1.70 (m, 2 H), 1.56 - 1.49 (m, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 204.9, 168.1, 136.6, 128.8, 125.4, 117.4, 86.7, 52.1, 40.1, 31.1, 22.7, 22.2 ppm; **IR** (thin film, cm^{-1}) 2970, 2933, 2871, 1703, 1682, 1647, 1496, 1458, 1363, 999, 755; **LRMS** (ESI) Calcd. for $[C_{14}H_{15}NO_3+Na]^+$ = 268.10, Found = 268.04.

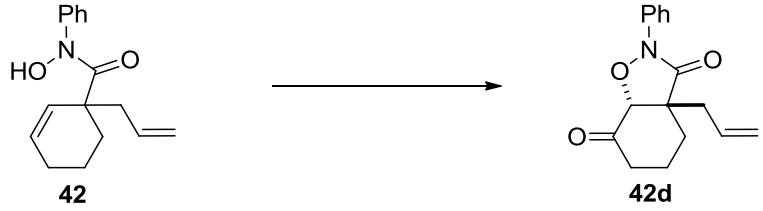
Stereochemistry was determined by 2-D NMR analysis.



41d was prepared using **41** (60.0 mg, 0.245 mmol) in nBuOAc (2.00 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 2 h. The crude reaction mixture was cooled to rt, DMAP (3.0 mg, 0.025 mmol) and Ac_2O (23.0 µL, 0.245 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **41d** (47.6 mg, 0.184 mmol, 75% yield) as a clear residue.

Analytical data for **41d**: **^{1}H NMR** (chloroform-d, 400 MHz): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 7.3 Hz, 2 H), 7.26 - 7.17 (m, 1 H), 4.83 (s, 1 H), 3.02 - 2.90 (m, 1 H), 2.55 - 2.45 (m, 1 H), 2.15 - 2.04 (m, 1 H), 2.02 - 1.92 (m, 1 H), 1.91 - 1.81 (m, 1 H), 1.71 - 1.52 (m, 3 H), 1.47 (s, 3 H); **^{13}C NMR** (chloroform-d, 101 MHz) 206.4, 168.8, 136.3, 128.9, 125.3, 117.1, 90.2, 48.4, 39.1, 35.8, 25.6, 23.0, 22.7 ppm; **IR** (thin film, cm^{-1}) 2935, 2867, 1702, 1595, 1496, 1385, 1012, 754, 690; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_3+Na]^+$ = 282.11, Found = 282.09.

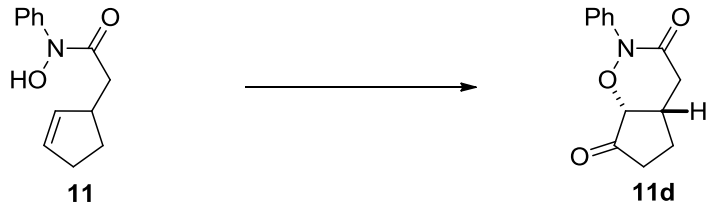
Stereochemistry was determined by 2-D NMR analysis.



42d was prepared using **42** (43.2 mg, 0.168 mmol) in nBuOAc (1.70 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 4 h. The crude reaction mixture was cooled to rt, DMAP (2.1 mg, 0.017 mmol) and Ac_2O (15.9 µL, 0.168 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and

purified by flash chromatography (20% EtOAc/hexanes) to afford **42d** (38.2 mg, 0.141 mmol, 84% yield) as a clear residue.

Analytical data for **42d**: **^{1}H NMR** (chloroform-d, 500 MHz): δ =7.84 - 7.75 (m, 2 H), 7.44 - 7.37 (m, 2 H), 7.23 - 7.16 (m, 1 H), 5.91 (tdd, *J* = 7.5, 9.9, 17.0 Hz, 1 H), 5.31 - 5.22 (m, 2 H), 4.62 (s, 1 H), 2.65 - 2.53 (m, 3 H), 2.39 - 2.28 (m, 2 H), 2.10 - 2.00 (m, 1 H), 1.89 - 1.78 (m, 1 H), 1.78 - 1.65 (m, 1 H); **^{13}C NMR** (chloroform-d, 126 MHz) 205.3, 167.1, 136.5, 131.6, 128.8, 125.5, 120.8, 117.5, 84.1, 55.5, 40.1, 40.0, 28.6, 21.8 ppm; **IR** (thin film, cm^{-1}) 3077, 2928, 2871, 1731, 1698, 1594, 1496, 1371, 1309, 1003, 754, 689; **LRMS** (ESI) Calcd. for $[C_{16}H_{17}NO_3+Na]^+$ = 294.11, Found = 294.10. Stereochemistry was determined by 2-D NMR analysis.



11 **11d**

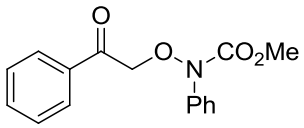
11d was prepared using **11** (300.0 mg, 1.38 mmol), DLP (55.0 mg, 0.138 mmol) in nBuOAc (13.0 mL). The dioxygenation reaction was completed, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was cooled to rt, DMAP (16.8 mg, 0.138 mmol) and Ac_2O (130.0 µL, 1.38 mmol) were added, and the mixture stirred at rt under an Ar atmosphere for 3 h. The mixture was then worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **11d** (267.2 mg, 1.16 mmol, 84% yield) as a white solid.

Analytical data for **11d**: **^{1}H NMR** (chloroform-d, 600 MHz): δ = 7.80 - 7.67 (m, 2 H), 7.38 (t, *J* = 7.9 Hz, 2 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 4.59 (d, *J* = 9.4 Hz, 1 H), 3.27 - 3.14 (m, 1 H), 2.92 (dd, *J* = 6.0, 14.7 Hz, 1 H), 2.67 (dd, *J* = 5.8, 14.5 Hz, 1 H), 2.48 - 2.40 (m, 2 H), 2.39 - 2.32 (m, 1 H), 1.91 - 1.80 (m, 1 H); **^{13}C NMR** (chloroform-d, 101 MHz) 212.0, 170.2, 138.7, 128.7, 125.7, 119.4, 81.4, 36.7, 36.4, 34.4, 25.9 ppm; **IR** (thin film, cm^{-1}) 3066, 2970, 1754, 1688, 1594, 1493, 1365, 757, 690; **LRMS** (ESI) Calcd. for $[C_{13}H_{13}NO_3+Na]^+$ = 254.08, Found = 254.06.

Stereochemistry was determined by 2-D NMR analysis.

For Intermolecular Ketooxygenations

A new 1-dram vial containing a magnetic stir bar was charged with **17** (50.0 mg, 0.299 mmol, 1.0 equiv), dilauroyl peroxide (DLP, 3.0 mg, 0.007 mmol, 2.5 mol %), alkene (0.359 mmol, 1.2 equiv) and dissolved in *n*BuOAc (300 µL, 1.0M). The vial was fitted with a PTFE-lined screw cap and O_2 was bubbled through the solution for 3 minutes. The reaction was allowed to stir under 1 atm O_2 at 60 °C. Upon disappearance of **17**, as indicated by TLC analysis, the reaction mixture was cooled to rt, nBuOAc (300 µL; dilute by a factor of 2), 4-(dimethylamino)pyridine (DMAP, 3.7 mg, 0.030 mmol, 10 mol %) and acetic anhydride (Ac_2O, 28.2 µL, 0.299 mmol, 1 equiv) were added under Ar. Upon completion of the elimination, as indicated by TLC analysis, the crude reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (2 x 5 mL) then brine, dried ($MgSO_4$), and concentrated. The resulting hydroxamate was purified by flash chromatography using the specified solvent system.

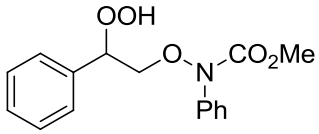


18d

18d was prepared using styrene (49.4 µL, 0.431 mmol), under the standard conditions using **17** (60.0 mg, 0.359 mmol), DLP (14.3 mg, 0.036 mmol, 10 mol %) in EtOAc (360 µL; optimization proved that for this substrate only, EtOAc was a more efficient solvent than *n*BuOAc). **17** was consumed, as indicated by TLC, after heating at 60 ºC for 12 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **18d** (90.2 mg, 0.316 mmol, 88% yield) as a white solid.

Analytical data for **18d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 8.02 - 7.89 (m, 2 H), 7.66 - 7.57 (m, 1 H), 7.55 - 7.43 (m, 4 H), 7.42 - 7.34 (m, 2 H), 7.28 - 7.20 (m, 1 H), 5.21 (s, 2 H), 3.85 (s, 3 H);

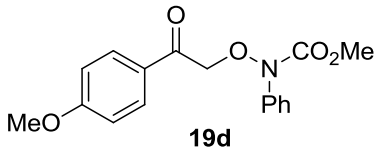
^{13}C NMR (chloroform-*d*, 101 MHz) 193.2, 155.2, 139.6, 134.5, 133.7, 128.7, 18.6, 128.1, 126.4, 122.7, 76.9, 53.5 ppm; **IR** (thin film, cm^{-1}) 2955, 2852, 1730, 1701, 1647, 1598, 1494, 1440, 1348, 1231, 970; **LRMS** (ESI) Calcd. for $[C_{16}H_{15}NO_4+Na]^+$ = 308.09, Found = 308.09.



18c

18c was prepared as above but isolated prior to the dehydration step to support the intermediacy of alkyl hydroperoxides in an intermolecular context.

Analytical data for **18c**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 9.90 (br. s., 1 H), 7.47 - 7.33 (m, 9 H), 7.31 - 7.24 (m, 1 H), 5.28 (t, *J* = 5.7 Hz, 1 H), 4.32 (d, *J* = 5.4 Hz, 2 H), 3.88 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 126 MHz) 155.7, 139.5, 136.0, 128.9, 128.8, 128.7, 127.2, 126.8, 123.1, 84.5, 76.7, 53.9 ppm; **IR** (thin film, cm^{-1}) 3419, 2957, 2089, 1645, 1494, 1441, 1348, 751; **LRMS** (ESI) Calcd. for $[C_{16}H_{17}NO_5+Na]^+$ = 326.10, Found = 326.10.

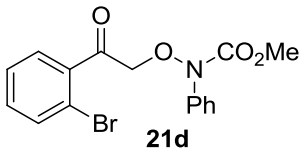


19d

19d was prepared using *p*-methoxystyrene (48.2 mg, 0.359 mmol), under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 48 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (2:1:1 Hexanes:CH_2Cl_2:Et_2O) to afford **19d** (73.0 mg, 0.231 mmol, 77% yield) as a pale yellow solid.

Analytical data for **19d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 8.01 - 7.92 (m, 2 H), 7.53 - 7.45 (m, 2 H), 7.42 - 7.34 (m, 2 H), 7.27 - 7.19 (m, 1 H), 6.99 - 6.92 (m, 2 H), 5.14 (s, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 101 MHz) 191.8, 164.0, 155.3, 139.7, 130.7, 128.8, 127.8, 126.5, 122.8, 113.9, 76.9, 55.5, 53.6 ppm; **IR** (thin film, cm^{-1}) 3067, 3009, 2955, 2843, 2252, 2044, 1953, 1714, 1683, 1602, 1513, 1494, 1440, 1346, 1242, 1174, 1026, 973, 835, 694; **LRMS** (ESI) Calcd. for

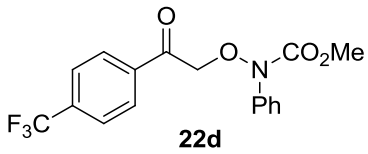
$[C_{17}H_{17}NO_5+Na]^+$ = 338.10, Found = 338.08.



21d

21d was prepared using *o*-bromostyrene (65.7 mg, 0.359 mmol) under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 18 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **21d** (82.3 mg, 0.226 mmol, 76% yield) as a waxy white solid.

Analytical data for **21d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 7.63 - 7.28 (m, 8 H), 7.27 - 7.19 (m, 1 H), 5.10 (s, 2 H), 3.82 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 101 MHz) 197.7, 155.5, 139.8, 138.3, 133.8, 132.5, 129.7, 128.7, 127.4, 126.7, 123.0, 119.5, 78.5, 53.7 ppm; **IR** (thin film, cm^{-1}) 3065, 2955, 2910, 2359, 1945, 1730, 1588, 1494, 1439, 1347, 1258, 1104, 1027, 757, 693; **LRMS** (ESI) Calcd. for $[C_{16}H_{14}BrNO_4+Na]^+$ = 386.00, Found = 385.99.

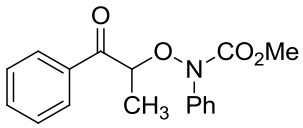


22d

22d was prepared using *p*-trifluoromethylstyrene (61.8 mg, 0.359 mmol), under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 48 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (15% EtOAc/10% CH_2Cl_2 in hexanes) to afford **22d** (76.0 mg, 0.215 mmol, 72% yield) as a white solid.

Analytical data for **22d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 8.08 (d, *J* = 8.3 Hz, 2 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 7.46 - 7.40 (m, 2 H), 7.39 - 7.31 (m, 2 H), 7.28 - 7.21 (m, 1 H), 5.18 (s, 2 H), 3.83 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 101 MHz) 193.0, 155.4, 139.6, 137.4, 135.1, 134.7, 128.8, 127.0, 125.8, 125.7, 125.6, 124.8, 123.3, 122.1, 77.3, 53.7 ppm; **IR** (thin film, cm^{-1}) 3071, 2958, 2927, 2854,

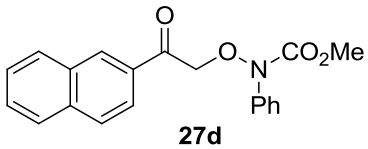
1946, 1731, 1712, 1442, 1327, 1171, 1066, 846, 753; **LRMS** (ESI) Calcd. for $[C_{17}H_{14}F_3NO_4+Na]^+$ = 376.08, Found = 376.00.



24d

24d was prepared using *trans*-β-methylstyrene (46.6 µL, 0.359 mmol) under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 20 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **24d** (84.3 mg, 0.287 mmol, 94% yield) as a pale yellow solid.

Analytical data for **24d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 8.04 - 7.91 (m, 2 H), 7.62 - 7.54 (m, 1 H), 7.49 - 7.41 (m, 2 H), 7.40 - 7.30 (m, 4 H), 7.27 - 7.15 (m, 1 H), 5.44 (q, *J* = 6.8 Hz, 1 H), 3.77 (s, 3 H), 1.58 (d, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (chloroform-*d*, 101 MHz) 197.3, 156.3, 141.0, 135.0, 133.5, 129.0, 128.6, 126.8, 123.9, 82.2, 53.6, 16.8 ppm; **IR** (thin film, cm^{-1}) 3064, 2990, 2954, 2853, 1966, 1731, 1693, 1597, 1493, 1440, 1337, 1103, 965, 759; **LRMS** (ESI) Calcd. for $[C_{17}H_{17}NO_4+Na]^+$ = 322.11, Found = 322.08.

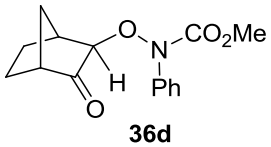


27d

27d was prepared using 2-vinylnaphthalene (55.4 mg, 0.359 mmol) under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 36 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **27d** (82.1 mg, 0.245 mmol, 82% yield) as a pale yellow solid.

Analytical data for **27d**: **^{1}H NMR** (chloroform-*d*, 600 MHz): δ = 8.51 (s, 1 H), 8.00 (dd, *J* = 1.5, 8.7 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 1 H), 7.93 - 7.88 (m, 2 H), 7.65 (dt, *J* = 1.3, 7.4 Hz, 1 H), 7.61 - 7.57

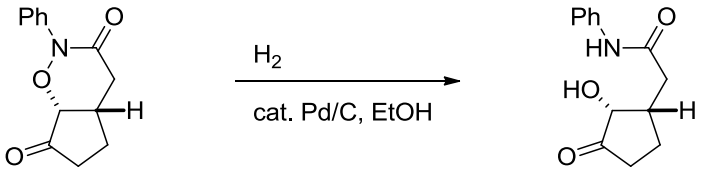
(m, 1 H), 7.54 - 7.49 (m, 2 H), 7.41 - 7.36 (m, 2 H), 7.27 - 7.22 (m, 1 H), 5.34 (s, 2 H), 3.87 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 151 MHz) 193.3, 155.4, 139.7, 135.9, 132.4, 130.4, 129.7, 128.9, 128.8, 128.7, 127.9, 127.0, 126.6, 123.5, 122.9, 77.1, 53.7 ppm; **IR** (thin film, cm^{-1}) 3060, 2955, 2023, 2851, 1731, 1696, 1627, 1596, 1494, 1439, 1348, 1191, 822, 750, 693; **LRMS** (ESI) Calcd. for $[C_{20}H_{17}NO_4+Na]^+$ = 358.11, Found = 358.12.



36d

36d was prepared using norbornene (141.0 mg, 1.50 mmol, 5.0 equiv) under the standard conditions. **17** was consumed, as indicated by TLC, after heating at 60 ºC for 40 h, and the elimination was complete after 3 h at rt. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **36d** (63.1 mg, 0.229 mmol, 77% yield) as a waxy white solid.

Analytical data for **36d**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 7.49 – 7.47 (m, 2 H), 7.41 – 7.37 (m, 2 H), 7.26 – 7.22 (m, 1 H), 3.81 (s, 3 H), 3.74 (d, *J* = 2.4 Hz, 1 H), 2.72 (s, 1 H), 2.65 (s, 1 H), 2.38 (d, *J* = 10.8 Hz, 1 H), 1.86 – 1.79 (m, 2 H), 1.59 (d, *J* = 10.4 Hz, 1 H), 1.50 – 1.47 (m, 1 H), 1.34 – 1.30 (m, 1 H); **^{13}C NMR** (chloroform-*d*, 101 MHz) 211.1, 155.4, 139.8, 128.7, 126.5, 123.2, 84.2, 53.5, 48.4, 39.4, 34.4, 24.6, 23.2 ppm; **IR** (thin film, cm^{-1}) 3064, 2956, 2879, 1756, 1731, 1595, 1494, 1440, 1349, 1192, 909, 755; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_4+H]^+$ = 276.13, Found = 276.06. Stereochemistry was determined by 2-D NMR analysis.



11d **11b**

11b was prepared by charging a flask with **11d** (75.0 mg, 0.324 mmol), 10 % Pd on carbon (20.0 mg) in EtOH (13 mL). The flask was evacuated and refilled with H_2 four times, and then allowed to stir rt

under 1 atm H_2 for 1.5 h. The reaction mixture was then filtered through Celite and concentrated. The residue was taken up in CH_2Cl_2, dried ($MgSO_4$) and concentrated to give **11b** in quantitative yield (75.3 mg) as a white solid.

Analytical data for **11b**: **^{1}H NMR** (methanol-d_4, 600 MHz): δ = 7.60 - 7.52 (m, 2 H), 7.36 - 7.27 (m, 2 H), 7.12 - 7.09 (m, 1 H), 5.52 (s, 1 H), 4.26 (d, *J* = 7.2 Hz, 1 H), 2.91 (tdd, *J* = 3.1, 6.6, 9.7 Hz, 1 H), 2.64 (dd, *J* = 5.5, 14.9 Hz, 1 H), 2.34 - 2.24 (m, 2 H), 2.18 (dd, *J* = 9.4, 14.7 Hz, 1 H), 2.14 - 2.06 (m, 1 H), 1.92 (m, 1 H); **^{13}C NMR** (methanol-d_4, 101 MHz) 217.6, 172.0, 138.4, 128.4, 123.8, 119.9, 76.2, 37.5, 34.4, 31.7, 21.7 ppm; **IR** (thin film, cm^{-1}) 3434, 2524, 2089, 1645, 1498, 1443, 1119; **LRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_3+H]^+$ = 234.12, Found = 234.10.

This reduction was also attempted using our previously reported N-O bond cleavage conditions of cyclic hydroxamates. Zn/Acetic acid and Raney Nickel reductions resulted in various undesired byproducts, presumably involving over reduction.

4.6 References

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5. CHAPTER FIVE

Radical-Mediated Alkene Oxyaminations Using Hydroxamic Acids

5.1 Introduction

Vicinal amino alcohols are highly valuable compounds in chemical synthesis, comprising a multitude of biologically active compounds and natural products.[1] Alkene oxyamination enables the direct synthesis of 1,2-aminoalcohols from simple unsaturated hydrocarbons and is therefore, a useful synthetic transformation for accessing this important motif.[2–4] There are a number of synthetic methods capable of facilitating alkene oxyamination; however, these processes commonly rely on the use of precious and/or toxic transition metal catalysts[5–16] or hypervalent iodine(III)-based oxidants.[17–19] In addition, the control of oxyamination regioselectivity is often a major challenge using metal-catalyzed intermolecular difunctionalizations protocols.

5.2 Background

See **Chapter 1.2.2.**

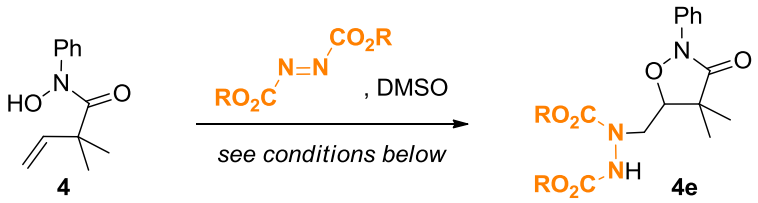
5.3 Reaction Development

Readily prepared *N*-aryl hydroxamic acids are easily converted to amidoxyl radicals upon exposure to mild oxidants or radical initiators.[20] These reactive species are then capable of selective addition to alkenes, producing an intermediate carbon-centered radical. We have previously shown that interception of this carbon-centered radical with molecular oxygen provides a radical based approach to alkene dioxygenation (see **Chapters 2 - 4**).[21–23] We hypothesized that substitution of molecular oxygen for a nitrogen-atom radical trap could provide the analogous oxyamination product.

We commenced our studies using azodicarboxylates as a nitrogen-atom source, as these readily

available compounds have demonstrated ability as carbon-centered radical traps.[24,25] We began by exploring the oxyamination of unsaturated hydroxamic acid **4**. Heating this substrate in DMSO at 60 °C in the presence of 1 equivalent of diisopropyl azodicarboxylate (DIAD) delivered the isoxazolidinone oxyamination product **4e** in 88% isolated yield (**Table 5-1, entry 1**). While the reaction utilizing 1 equivalent of DIAD was successful, using an excess of DIAD (3 equivalents) proceeded in higher yield (94%, **entry 2**) and a much shorter reaction time.

Table 5-1. Survey of Azodicarboxylates as *N*-Atom Sources in Alkene Oxyaminations

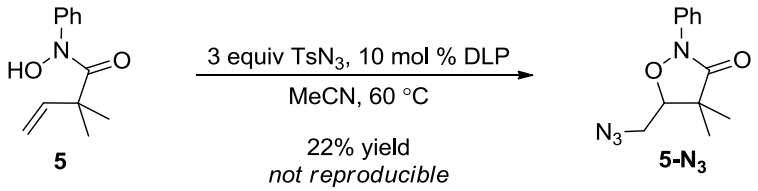


entry	azodicarboxylate	temp.(°C)/ time(h)	% yield
1	1 equiv DIAD, R= *i*Pr	60 / 27	88
2	3 equiv DIAD, R= *i*Pr	60 / 5	94
3	3 equiv DEAD, R= Et	60 / 3	93
4	3 equiv DTAD, R= *t*Bu	60 / 2	68
5	3 equiv DBAD, R= Bn	60 / 2	complex mixture
6	3 equiv TCEAD, R= CH_2CCl_3	60 / 5	complex mixture

Oxyaminations of substrate **4** using other simple, commonly used azodicarboxylates such as diethyl azodicarboxylate (DEAD) and di-*tert*-butyl azodicarboxylate (DTAD) were also successful, delivering the corresponding difunctionalized products in 93% and 68% yield, respectively (**Table 5-1, entries 3** and **4**). Other simple azodicarboxylates such as di-benzyl (DBAD, **entry 5**) and di-trichloroethyl (TCEAD, **entry 6**) produced only a complex mixture of unidentified products and no desired oxyamination product. Notably, this alkene difunctionalization proceeds without any additional reagents. We attribute this reactivity to the formation of a small amount of amidoxyl radical (autoxidation) prior to the start of the reaction, capable of initiating the radical chain process. It is also possible that the azodicarboxylate could contribute to the initiation of the oxyamination process, similar to the common radical initiator AIBN, but this typically requires elevated reaction temperatures beyond those used in our study.[26] We also explored the possibility of using sulfonyl

azides (tosyl azide and ethyl sulfonyl azide) as *N*-atom sources.[25] An initial reaction with hydroxamic acid **5** and tosyl azide (TsN_3) generated oxyazidation product **5-N$_3$** in 22% yield (**Figure 5-1**). However, this result was not reproducible under any set of oxyazidation conditions, therefore sulfonyl azides were not investigated further.

Figure 5-1. Anomalous Alkene Oxyazidation Result

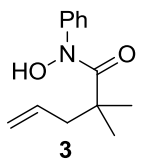
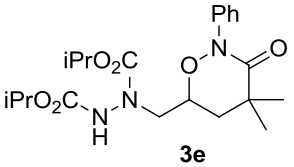
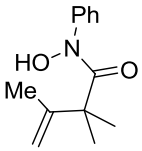
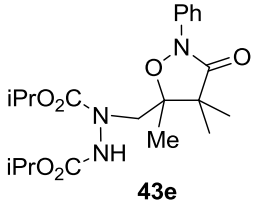
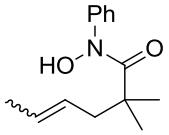
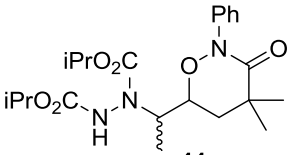
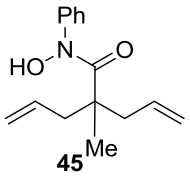
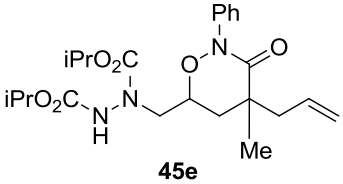
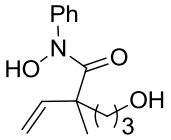
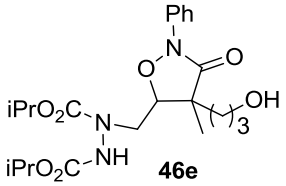


5.3.1 Substrate Scope – Acyclic Alkenes

We next explored the scope of this metal-free alkene oxyamination utilizing a variety of unsaturated hydroxamic acids as substrates (**Table 5-2**). The difunctionalization of hydroxamic acid **3** involving 6-*exo* ring closure proceeded efficiently, affording oxazinone **3e** in 83% yield (**entry 1**). This reaction was initiated by the addition of commercially available, low temperature radical initiator V-65 (2,2′-azobis(2,4-dimethyl valeronitrile)), as reaction without added initiator was slow. Although not necessary in reactions with most substrates, we found this to be a simple way to increase reaction rates, as desired. The use of V-65 was preferred over other radical initiators as it allowed for the reaction to take place at 40 °C instead of 60 °C and minimized non-productive side reactions.

Reactions involving 1,1- and 1,2-disubstituted alkenes were also successful, as demonstrated by the reactions of substrates **43** and **44**, respectively (**Table 5-2, entries 2** and **3**). Substrate hydroxamic acids containing a trisubstituted alkene however, were not viable under these conditions. To date, we have not developed a strategy to incorporate this important substrate class as the trapping azodicarboxylate is too sterically bulky to attack the putative tertiary carbon-centered radical.

Table 5-2. Oxyamination of Alkenyl *N*-Aryl Hydroxamic Acids

entry	substrate[a]	product	% yield[b,c]
1	 **3**	 **3e**	83[d]
2	 **43**	 **43e**	74
3	 **44**	 **44e**	86 1.8:1 dr
4	 **45**	 **45e**	59 1:1 dr
5	 **46**	 **46e**	64

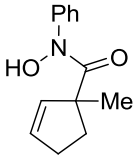
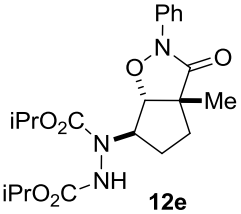
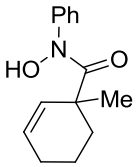
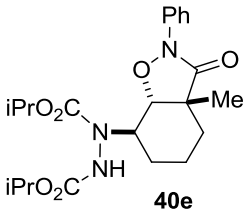
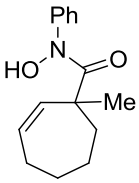
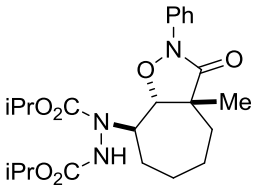
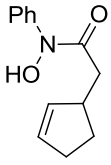
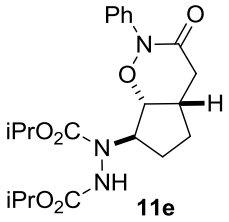
[a]All reactions run 0.5M in DMSO with 3 equiv. DIAD at 60 °C. [b]Yields of isolated product. [c]Diastereomeric ratio of isolated diastereomers. [d]10 mol % V-65

The intramolecular nature of the oxyamination process also permits chemoselective single difunctionalizations of diene substrates, as demonstrated by the reaction of α-diallyl hydroxamic acid **45** (**Table 5-2, entry 4**). The utilization of common intermolecular oxyamination protocols would likely lead to mixtures of mono- and bis-difunctionalized products. Reaction of **46** afforded isoxazolidinone **46e** in 64% yield, demonstrating the mildness of this radical-mediated protocol towards functional groups susceptible to oxidation (**entry 5**).

5.3.2 Substrate Scope – Cyclic Alkenes

In contrast to the variety of methods available for *cis*-selective oxyamination, there are few methods capable of the direct, stereoselective *trans* oxyamination of cycloalkenes.[27] An intramolecular oxyamination process using unsaturated *O*-alkyl hydroxamates and stoichiometric quantities of hypervalent iodine(III) reagents by Wardrop is a notable exception.[18] In order to assess the stereoselectivity of the oxyamination process using cycloalkenes, we studied the oxyamination of a number of cycloalkenyl hydroxamic acids (**Table 5-3**).

Table 5-3. Stereoselective Oxyaminations of Cycloalkenes

entry	substrate[a]	product	% yield[b,c]
1	 **12**	 **12e**	80 >95:5 dr β:α
2	 **40**	 **40e**	92 >95:5 dr β:α
3	 **41**	 **41e**	89 >95:5 dr β:α
4	 **11**	 **11e**	52 >95:5 dr β:α

[a]All reactions run 0.5M in DMSO with 3 equiv. DIAD at 60 °C. [b]Yields of isolated product. [c]Diastereomeric ratio of isolated diastereomers.

Our studies began with the study of cyclopentenyl substrate **12**, which delivered *trans* oxyamination product **12e** as a single diastereomer in 80% yield (**Table 5-3, entry 1**). Both cyclohexenyl hydroxamic acid **40** and cycloheptenyl substrate **41** also produced *trans* difunctionalization products in high yield as single diastereomers (**Table 5-3, entries 2 - 3**). The difunctionalizations of cyclic substrates is also not limited to 5-*exo* cyclizations, as cyclopentenyl substrate **11** reacted to provide product **11e** as a single diastereomer, albeit in lower yield (52%, **Table 5-3, entry 4**).

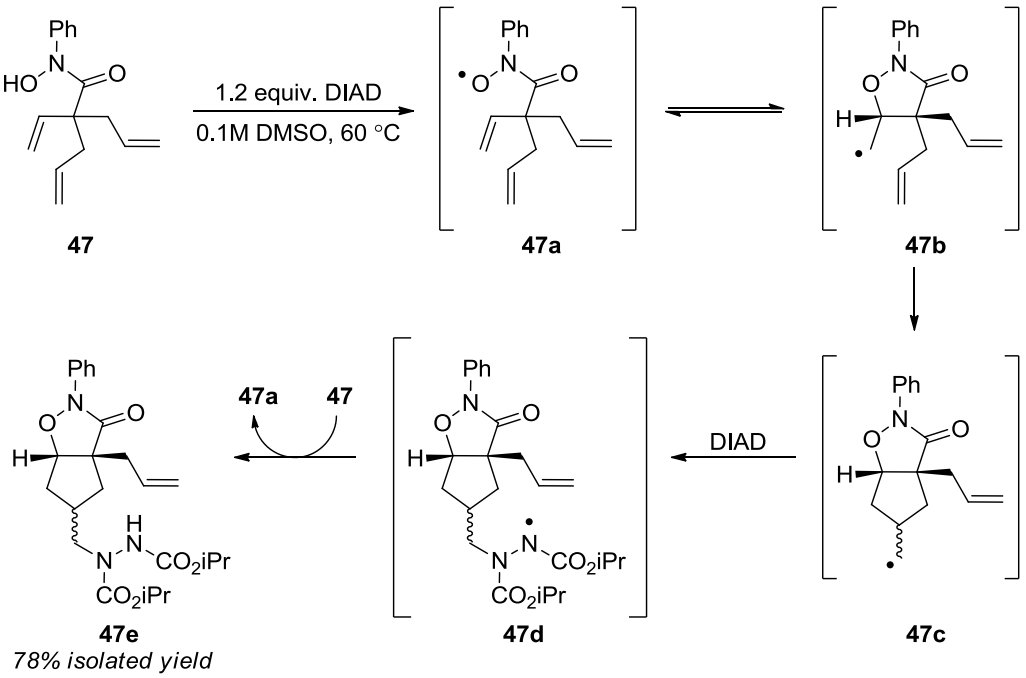
This highly *trans*-selective radical-mediated oxyamination of cycloalkenes complements *cis*-selective transition-metal-catalyzed protocols. In addition, the tethered nature of the difunctionalization processes described in **Tables 5-2** through **5-3** facilitates the formation of single regioisomers of the alkene difunctionalization products, which is an important advantage of this present method. Control of oxyamination regioselectivity using sterically or electronically unbiased alkenes is major challenge using common transition-metal-catalyzed processes.[28] Furthermore, current methods for intramolecular alkene oxyamination involve cyclizations of *N*-atom functionality. This oxyamination using unsaturated hydroxamic acids involves initial *O*-atom alkene addition, providing access to products of opposite regioselectivity.

5.3.3 Radical Cascade Reactions

Radical-mediated cascade reactions of polyunsaturated compounds have long served as outstanding synthetic platforms for the rapid generation of molecular complexity. As the oxyamination protocol involves carbon-centered radicals as intermediates, we hypothesized that it may be possible to perform cascade-type sequences by inserting a C-C bond-forming step prior to final carbon-centered radical trapping by the azodicarboxylate. Our studies have initially focused on triene hydroxamic acid substrate **47**. Upon heating **47** to 60 °C in DMSO in the presence of 1.2 equivalents of DIAD, desired *cis*-fused bicyclic isoxazolidinone **47e** was isolated in good yield. A mechanistic proposal is shown in **Figure 5-2**. Following amidoxyl radical formation, reversible

alkene cyclization produces isoxazolidinone **47e**. Intermediate **47b** is well positioned for a subsequent C-C bond-forming cyclization step, which is followed by azodicarboxylate addition to deliver **47e**.

Figure 5-2. Cascade Cyclization of Triene Substrate **47**



rare example of a C-O/C-C/C-N bond forming radical cascade process

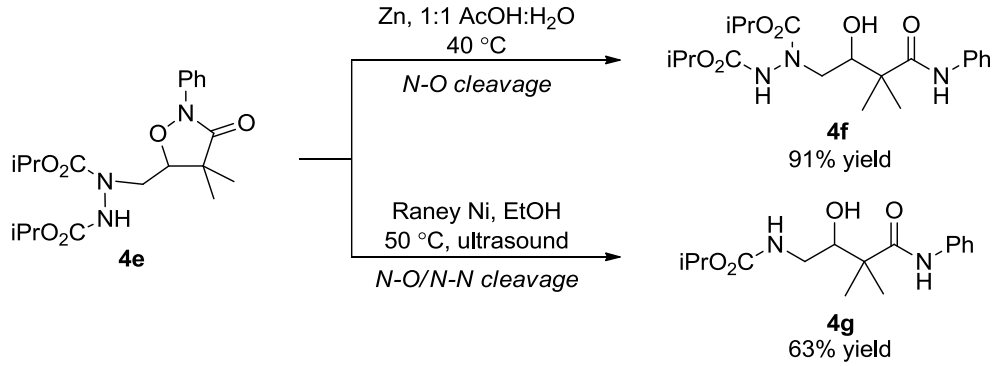
Notably, this cascade process is a rare example of a synthetic transformation capable of the construction of three distinct bond types in a single reaction: C-O, C-C, and C-N. The ability of our radical-based oxyamination approach to generate functionalized, complex products via cascade sequences is a useful feature uncommon to transition-metal-mediated or ionic oxyamination processes.[29] We view the controlled reactivity of amidoxyl radicals in alkene additions, particularly in light of the facile formation of these species from simple hydroxamic acids, as a promising approach that harnesses the potential of oxygen-centered radicals for synthesis.

5.3.4 Post-Reaction Modifications

Following the oxyamination process, direct reductive cleavage of the N-O or N-N bonds present in the reaction products, is easily accomplished to provide the acyclic difunctionalization

products (**Figure 5-3**). For example, selective mild reduction of the isoxazolidinone N-O bond of **4e** proceeds using Zn in a 1:1 AcOH/H_2O solvent mixture. Reduction using Raney Ni under ultrasonic conditions[30] results in one-pot cleavage of the N-O and N-N bond of **4e**, delivering **4g** in 63% yield.

Figure 5-3. Selective Reduction of Difunctionalization Products



5.4 Summary

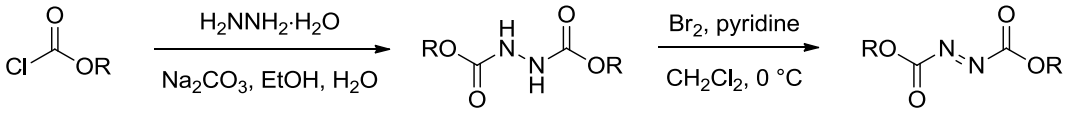
In conclusion, we have developed a radical-mediated approach to alkene oxyamination using hydroxamic acids and simple, commercially available azodicarboxylates. These reactions proceed without the use of transition-metal catalysts and/or hypervalent iodine(III) reagents common to related alkene difunctionalizations processes. This tethered oxyamination reaction is applicable to a wide range of unsaturated substrates, delivering single regioisomers in all cases, which is often a challenge using intermolecular protocols. In addition, this process exhibits high *trans*-stereoselectivity using cycloalkenyl substrates, complementing transition-metal-catalyzed *cis*-selective oxyaminations.

5.5 Experimental

5.5.1 General Methods

See **2.5 Experimental** for general methods and substrate preparation.

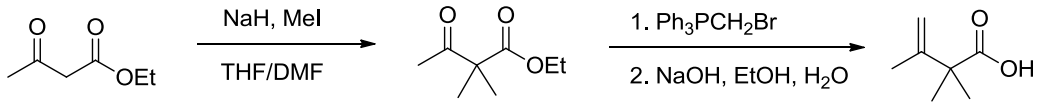
Figure 5-4. Synthesis of Azodicarboxylates



R = Bn or CH_2CCl_3

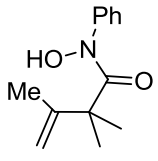
Dibenzyl and ditrichloroethyl azodicarboxylates were synthesized according to literature procedures via the scheme above.[31] Diisopropyl, diethyl, and di-*tert*-butyl azodicarboxylates were purchased from commercial sources and used without further purification.

Figure 5-5. Synthesis of 2,2,3-trimethylbut-3-enoic acid



The corresponding carboxylic acid of **43** was synthesized via dimethylation of ethyl acetoacetate followed by a methylene Wittig reaction and base hydrolysis.

The procedure is as follows: Dimethylformamide (3 mL, DMF) was added to a 0 ºC suspension of NaH (4.26 g, 106.4 mmol, 60% wt. dispersion in oil, 1.05 equiv) and ethyl acetoacetate (12.8 mL, 101.3 mmol, 1.0 equiv) in THF (250 mL) to solubilize the generated enolate. Methyliodide (7.88 mL, 126.6 mmol, 1.25 equiv) was added dropwise, the reaction mixture warmed to rt and then heated to reflux for 2 h. The reaction mixture was then cooled to 0 ºC, NaH (4.26 g, 106.4 mmol, 60% wt. dispersion in oil, 1.05 equiv) was added followed by methyliodide (7.88 mL, 126.6 mmol, 1.25 equiv). The mixture was refluxed overnight before being quenched with water, extracted with CH_2Cl_2 (x 4), washed with water then brine, dried ($MgSO_4$) and concentrated *in vacuo* to give ethyl 2,2-dimethylacetoacetate (18.2 g) as a yellow liquid. The crude ester was used immediately in a methylene Wittig reaction reported by Gansauer *et al.*[32] followed by base hydrolysis.

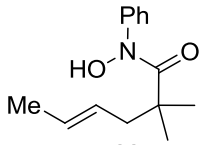


43

43 was synthesized via ***Method A*** (see **2.5 Experimental**) in 9% yield (70.0 mg) as a pale yellow

solid.

Analytical data for **43**: **^{1}H NMR** (chloroform-*d*, 600 MHz): δ = 7.12 - 7.62 (m, 5 H), 4.55 - 5.10 (m, 2 H), 1.81 (s, 3 H), 1.30 - 1.40 (s, 6 H) ppm; **^{13}C NMR** (chloroform-*d,* 126 MHz) 181.8, 149.3, 147.2, 140.6, 128.6, 127.2, 111.1, 110.1, 48.3, 47.5, 29.7, 25.4, 24.5, 20.0, 19.9; **IR** (thin film, cm^{-1}) 3224, 3088, 2976, 2943, 1622, 1593, 1495, 1383, 1355, 1083, 1067, 887, 759; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.12, Found = 242.14.



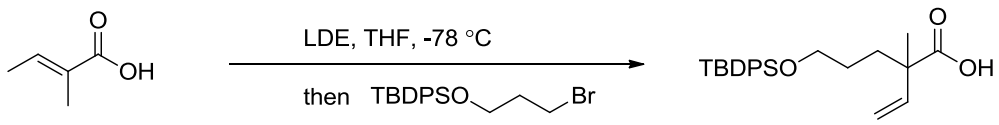
44

The corresponding carboxylic acid of **44** was synthesized via an alkylation of methyl isobutyrate with crotyl bromide followed by base hydrolysis using literature procedures as with **3** (see **2.5 Experimental**).

44 was synthesized via ***Method A*** (**2.5 Experimental**) in 78% yield (1.02 g) as an orange oil that crystallizes upon scratching.

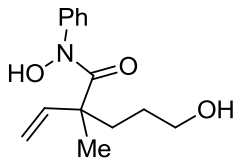
Analytical data for **44**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 8.68 - 9.08 (m, 1 H), 7.31 - 7.43 (m, 5 H), 5.43 - 5.63 (m, 1 H), 5.32 - 5.42 (m, 1 H), 2.21 - 2.35 (m, 2 H), 1.54 - 1.70 (m, 3 H), 1.04 - 1.15 (m, 6 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 174.7, 140.6, 128.8, 128.4, 126.9, 126.7, 126.6, 125.8, 43.7, 42.9, 42.8, 37.5, 25.9, 25.8, 18.0, 13.0; **IR** (thin film, cm^{-1}) 3189, 2969, 2930, 1613, 1591, 1494, 1390, 1360, 1067, 968, 760, 701; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_2+Na]^+$ = 256.13, Found = 256.15.

Figure 5-6. Synthesis of 5-((*tert*-butyldiphenylsilyl)oxy)-2-methyl-2-vinylpentanoic acid



The corresponding carboxylic acid of **46** was synthesized via an alkylation of tiglic acid with allyl bromide as previously described with **4** (see **2.5 Experimental**).

The procedure is as follows: Under a gentle stream of Ar, Hexanes was removed from a commercially available solution of n-BuLi (36.8 mL of a 1.52M solution, 55.9 mmol). The nearly dry mixture was cooled to -78 ºC, and taken up in THF (18 mL). Diethylamine (5.5 mL, 53.6 mmol, 2.1 equiv) was added to the cold solution, the resultant mixture was warmed to 0 ºC and stirred 15 min. The reaction mixture was cooled again to -78 ºC, tiglic acid (2.52 g, 25.2 mmol, 1.0 equiv) was added as a solution in THF (25 mL) before warming to 0 ºC and stirring for 30 min. The reaction mixture was cooled again to -78 ºC and a solution of (3-bromopropoxy)(*tert*-butyl)diphenylsilane (9.0 g, 25.2 mmol, 1.0 equiv) in THF (50 mL) was added. The reaction mixture was allowed to come to rt, stirred 1 h and then quenched by slow addition of water. The reaction mixture was extracted with EtOAc (3 x), the combined organic layers discarded; the aqueous layer was acidified using 1N HCl until cloudiness persisted, extracted with EtOAc (4 x), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude acid product was purified via flash chromatography (15% EtOAc/Hexanes) to afford 5-((*tert*-butyldiphenylsilyl)oxy)-2-methyl-2-vinylpentanoic acid (4.20 g, 42%) as a pale yellow oil.

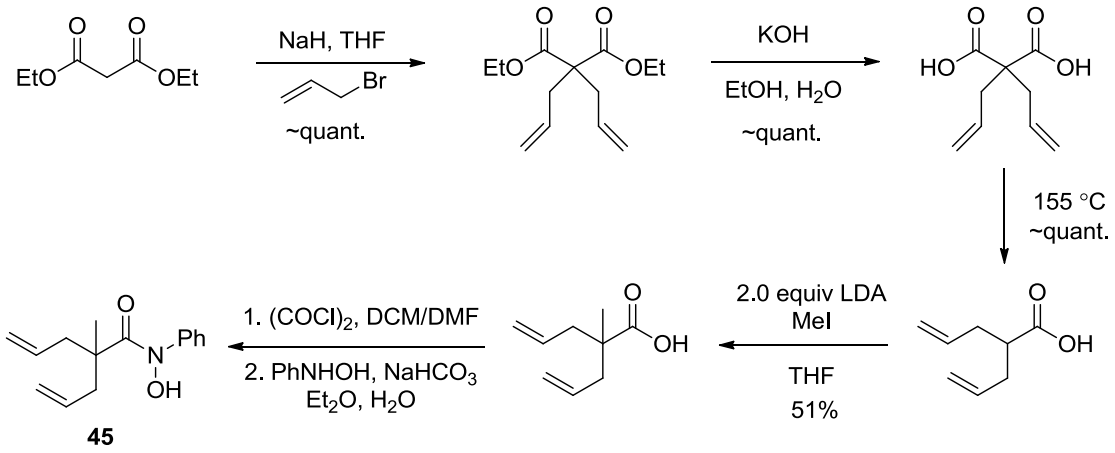


46

46 was synthesized via ***Method A*** (**2.5 Experimental**), immediately followed by TBAF deprotection of the silyl ether to give **46** in 21% yield (149.1 mg) over 2 steps as an orange oil.

Analytical data for **46**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 8.18 - 8.96 (br. s, 1 H), 7.48 (d, *J*=7.8 Hz, 2 H), 7.36 (t, *J*=7.8 Hz, 2 H), 7.22 - 7.28 (m, 1 H), 6.05 (m, 1 H), 4.93 - 5.10 (m, 2 H), 3.59 (m, 2 H), 2.50 - 3.22 (m, 1 H), 2.06 (d, *J*=5.3 Hz, 1 H), 1.58 - 1.73 (m, 2 H), 1.51 (br. s., 1 H), 1.30 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 173.5, 142.2, 141.0, 128.6, 127.1, 124.3, 113.0, 62.7, 48.9, 34.7, 27.4, 23.0 ppm; **IR** (thin film, cm^{-1}) 3216, 2937, 1624, 1592, 1491, 1454, 1376, 1066, 916, 759, 700; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_3+Na]^+$ = 272.13, Found = 272.14.

Figure 5-7. Synthesis of **45**

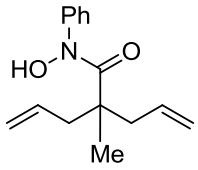


The corresponding carboxylic acid of **45** was synthesized according to the following stepwise procedure: To a 0 ºC suspension of NaH (2.16 g, 58.5 mmol, 60% wt dispersion in oil) in THF (100 mL) was added diethyl malonate (3.56 mL, 23.4 mmol) dropwise as a solution in THF (25 mL) under Ar. The reaction mixture was warmed to rt for 15 min and then treated with allyl bromide (3.96 mL, 46.8 mmol) and heated to reflux overnight. The reaction was quenched with NH_4Cl, extracted with Et_2O (x 3) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 6.02 g (~quant.) diethyl 2,2-diallylmalonate as a yellow-orange liquid.

Crude diethyl 2,2-diallylmalonate (9.00 g, 37.5 mmol) was then dissolved in EtOH (23 mL), H_2O (14 mL), and KOH (4.62 g, 82.4 mmol) and heated to reflux under Ar overnight. Solvent was removed under *in vacuo*, the resultant residue was taken up in H_2O, acidified to pH 1 with 6N HCl, and extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 6.88 g (~quant.) of 2,2-diallylmalonic acid as a peach solid. Neat, crude 2,2-diallylmalonic acid was heated at 155 ºC overnight to afford 5.45 g (~quant.) 2-allylpent-4-enoic acid as a dark amber liquid.

The crude acid (500.0 mg, 3.57 mmol) was added dropwise to a solution of LDA (7.63 mmol, 2.14 equiv) in THF (5.10 mL) at 0 ºC. The reaction mixture was warmed to rt for 1 h before cooling to -78 ºC followed by the addition of methyliodide (223 µL, 3.57 mmol). The reaction mixture was

allowed to slowly come to rt overnight followed by quenching with 3 N HCl. The reaction mixture was extracted with CH_2Cl_2 (x 3), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude methylated product that was purified via flash chromatography (15% EtOAc/Hexanes) to give 278.0 mg of the carboxylic acid (51%) as a clear, pale yellow liquid.



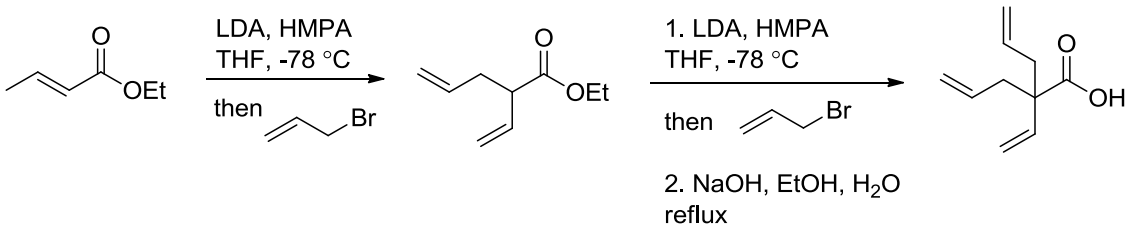
45

45 was synthesized via ***Method A*** (**2.5 Experimental**) in 55% yield (243.6 mg) as a white solid.

Analytical data for **45**: **^{1}H NMR** (chloroform-*d*, 600 MHz): δ = 8.57 (s, 1 H), 7.34 - 7.51 (m, 5 H), 5.73 - 5.86 (m, 2 H), 5.06 - 5.15 (m, 4 H), 2.54 (dd, *J*=13.6, 6.8 Hz, 2 H), 2.17 (dd, *J*=13.6, 7.9 Hz, 2 H), 0.99 (br. s., 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 172.6, 140.1, 133.9, 133.6, 129.1, 127.8, 118.3, 46.0, 43.8, 23.0; **IR** (thin film, cm^{-1}) 3181, 3076, 2978, 2934, 1611, 1590, 1485, 1453, 1379, 1068, 995, 015, 761, 690; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_2+Na]^+$ =268.13, Found = 268.15.

Figure 5-8. Synthesis of 2-allyl-2-vinylpent-4-enoic acid

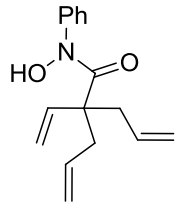
The corresponding carboxylic acid of **25** was synthesized via an alkylation of ethyl crotonate with



allyl bromide according to literature procedures described by Yamada *et. al*[33] followed by base hydrolysis (**Figure 5-9**).

The procedure is as follows: A 2.5M solution of n-BuLi in Hexanes (9.6 mL, 24.1 mmol, 1.1 equiv) was added to a -78 ºC solution of diisopropylamine (3.4 mL, 24.1 mmol, 1.1 equiv) in THF (11 mL). The resultant solution was warmed to 0 ºC for 15 min, then cooled to -78 ºC and HMPA (4.2 mL, 24.1 mmol, 1.1 equiv) added dropwise and stirred cold 1 h. A solution of ethyl crotonate

(2.7 mL, 21.9 mmol, 1.0 equiv) in THF (2 mL) was added to the LDA/HMPA mixture and allowed to stir -78 ºC for 30 min. Allyl bromide (2.5 mL, 28.5 mmol, 1.3 equiv) was added as a solution in THF (2 mL) to the -78 ºC reaction mixture, stirred cold for 30 min and then warmed to rt. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and diluted with Et_2O. The layers were separated, the aqueous was extracted with Et_2O (x 2), the combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide ethyl 2-vinylpent-4-enoate (1.85 g) as a yellow liquid. A second alkylation with allyl bromide using the same procedure afforded ethyl 2-allyl-2-vinylpent-4-enoate which was then subsequently converted to the corresponding carboxylic acid by base hydrolysis.



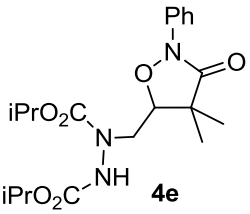
47

47 was synthesized via ***Method A*** (**2.5 Experimental**) in 47% yield (219.0 mg) as a pale yellow solid.

Analytical data for **47**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.46 (d, *J* = 7.9 Hz, 2 H), 7.40 - 7.34 (m, 2 H), 7.33 - 7.24 (m, 1 H), 6.04 - 5.82 (m, 1 H), 5.81 - 5.68 (m, 2 H), 5.31 - 4.91 (m, 6 H), 2.78 - 2.53 (m, 2 H), 2.53 - 2.44 (m, 2 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 178.8, 172.0, 140.7, 138.7, 133.6, 133.3, 128.6, 127.6, 124.9, 118.6, 118.5, 115.7, 114.6, 51.8, 39.4, 38.9 ppm; **IR** (thin film, cm^{-1}) 3221, 3077, 2979, 2923, 1619, 1592, 1493, 1364, 1086, 915; **LRMS** (ESI) Calcd. for $[C_{16}H_{19}NO_2+Na]^+$ = 280.13, Found = 280.13.

5.5.2 General Oxyamination Conditions

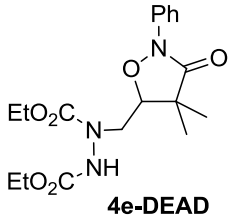
A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and diisopropyl azodicarboxylate (DIAD, 3.0 equiv) and dissolved in dimethyl sulfoxide (DMSO) to make a 0.5M solution. The vial was fitted with a PTFE-lined screw cap and argon was bubbled through the solution for 20 min. The reaction was allowed to stir under 1 atm argon at the specified temperature. Upon disappearance of the hydroxamic acid substrate, as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (8 mL), washed with H_2O (2 x 10 mL) then brine, dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.



4e

4e was prepared using **4** (250.0 mg, 1.22 mmol), DIAD (725 µL, 3.65 mmol) in DMSO (2.70 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **4e** (466.1 mg, 1.14 mmol, 94% yield) as a white foam.

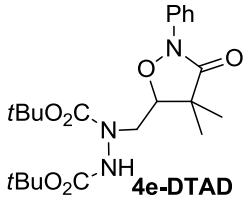
Analytical data for **4e**: **^{1}H NMR** (chloroform-*d*, 500 MHz, at 320 K): δ = 7.66 - 7.72 (m, 2 H), 7.35 (t, *J*=8.0 Hz, 2 H), 7.13 (t, *J*=7.4 Hz, 1 H), 6.46 - 6.81 (m, 1 H), 4.98 (m, *J*=19.0, 6.3 Hz, 2 H), 4.51 (d, *J*=6.9 Hz, 1 H), 3.59 - 4.16 (m, 2 H), 1.33 (s, 3 H), 1.25 - 1.30 (m, 12 H), 1.23 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K) 171.1, 155.7, 137.0, 128.7, 124.7, 116.6, 85.1, 70.8, 70.2, 70.1, 69.9, 48.7, 45.6, 22.0, 21.9, 21.9, 21.7, 21.5, 17.4 ppm; **IR** (thin film, cm^{-1}) 3298, 2981, 2937, 2878, 1714, 1596, 1496, 1469, 1268, 1180, 1146, 1109, 920, 754, 737, 690; **LRMS** (ESI) Calcd. for $[C_{20}H_{29}N_3O_6+Na]^+$ = 430.20, Found = 430.18.



4e-DEAD

4e-DEAD was prepared using **4** (50.0 mg, 0.244 mmol), DEAD (115 µL, 0.731 mmol) in DMSO (540 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was worked up and purified by flash chromatography (40% EtOAc/hexanes) to afford **4e-DEAD** (86.4 mg, 0.228 mmol, 93% yield) as a white foam.

Analytical data for **4e-DEAD**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.69 (d, *J* = 7.9 Hz, 2 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.19 - 7.13 (m, 1 H), 6.78 (br. s., 1 H), 4.51 (m, 1 H), 4.30 - 4.15 (m, 4 H), 4.10 (br. s., 2 H), 1.35 (s, 3 H), 1.33 - 1.25 (m, 6 H), 1.24 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 171.0, 156.1, 136.9, 128.8, 124.7, 116.5, 85.2, 84.5, 63.0, 62.4, 49.0, 45.7, 21.9, 21.5, 17.4, 14.4 ppm; **IR** (thin film, cm^{-1}) 3293, 2980, 2936, 2252, 1710, 1595, 1497, 1367, 1061; **LRMS** (ESI) Calcd. for $[C_{18}H_{25}N_3O_6+Na]^+$ = 402.16, Found = 402.27.

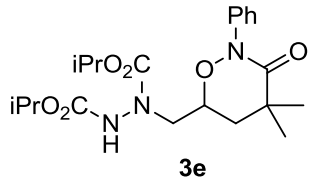


4e-DTAD

4e-DTAD was prepared using **4** (60.0 mg, 0.292 mmol), DTAD (201.9 mg, 0.877 mmol) in DMSO (640 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 2 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **4e-DTAD** (85.9 mg, 0.197 mmol, 68% yield) as a white foam.

Analytical data for **4e-DTAD**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.72 (d, *J* = 8.2 Hz, 2 H), 7.37 (t, *J* = 7.7 Hz, 2 H), 7.19 - 7.10 (m, 1 H), 6.60 - 6.21 (m, 1 H), 4.56 - 4.42 (m, 1 H), 4.07 - 3.55 (m, 2 H), 1.50 (s, 9 H), 1.49 (s, 9 H), 1.34 (s, 3 H), 1.23 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 171.2, 155.7, 155.2, 154.9, 136.9, 128.7, 124.6, 116.5, 85.3, 85.0, 82.3, 81.9, 81.5, 49.3, 48.3,

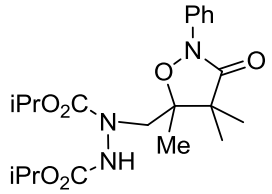
45.6, 28.2, 28.1, 28.0, 21.4, 17.4 ppm; **IR** (thin film, cm^{-1}) 3312, 2979, 2934, 2253, 1713, 1596, 1497, 1368, 1154, 915; **LRMS** (ESI) Calcd. for $[C_{22}H_{33}N_3O_6+Na]^+$ = 458.23, Found = 458.13.



3e

3e was prepared using **3** (20.0 mg, 0.0912 mmol), DIAD (54.2 µL, 0.274 mmol), 10 mol% V-65 (2.3 mg, 0.009 mmol x3) was added in portions in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 40 ºC for 18 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **3e** (31.9 mg, 0.076 mmol, 83% yield) as a pale yellow residue.

Analytical data for **3e**: **^{1}H NMR** (chloroform-*d*, 500 MHz at 320 K): δ = 7.60 (d, *J*=8.2 Hz, 2 H), 7.31 (t, *J*=7.5 Hz, 2 H), 7.12 (t, *J*=7.2 Hz, 1 H), 6.60 (br. s., 1 H), 4.87 - 4.96 (m, *J*=11.9, 5.7 Hz, 2 H), 4.48 - 4.63 (m, 1 H), 3.74 (br. s., 2 H), 2.07 (dd, *J*=13.5, 7.3 Hz, 1 H), 1.74 - 1.87 (m, 1 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.23 (d, *J*=5.9 Hz, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 174.9, 155.7, 139.8, 128.5, 125.1, 119.7, 77.7, 70.6, 69.9, 53.3, 40.0, 39.0, 26.9, 25.7, 21.9, 21.8 ppm; **IR** (thin film, cm^{-1}) 3294, 2981, 2936, 2875, 1714, 1595, 1495, 1388, 1109, 757, 690; **LRMS** (ESI) Calcd. for $[C_{21}H_{31}N_3O_6+Na]^+$ = 444.21, Found = 444.22.

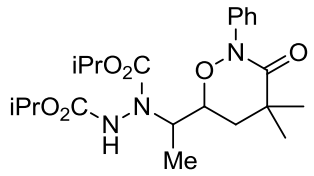


43e

43e was prepared using **43** (15.0 mg, 0.068 mmol), DIAD (41.0 µL, 0.205 mmol) in DMSO (150 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 4 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **43e**

(21.3 mg, 0.051 mmol, 74% yield) as an orange residue.

Analytical data for **43e**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.70 (d, *J*=7.9 Hz, 2 H), 7.37 (t, *J*=7.6 Hz, 2 H), 7.10 - 7.18 (m, 1 H), 6.35 - 6.69 (br. m, 1 H), 4.76 - 5.05 (m, 2 H), 3.41 - 4.19 (m, 2 H), 1.40 (s, 3 H), 1.17 - 1.28 (m, 15 H), 1.03 (br. s., 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 171.4, 171.2, 156.6, 156.1, 154.7, 137.2, 128.8, 124.5, 116.2, 88.7, 88.2, 71.1, 70.7, 69.8, 69.6, 60.4, 52.2, 51.7, 48.8, 31.6, 29.7, 21.9, 21.7, 20.2, 17.6, 16.1, 14.2 ppm; **IR** (thin film, cm^{-1}) 3304, 2981, 2937, 2252, 1714, 1596, 1497, 1375, 1109, 1040, 914, 752, 733; **LRMS** (ESI) Calcd. for $[C_{21}H_{31}N_3O_6+Na]^+$ = 444.21, Found = 444.20.



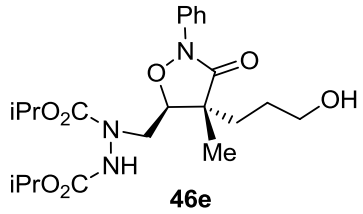
44e

44e was prepared using **44** (60.0 mg, 0.257 mmol), DIAD (150.0 µL, 0.772 mmol) in DMSO (570 µL). The reaction was completed, as indicated by TLC, after heating at 40 ºC for 10 h. The crude reaction mixture was worked up and purified by flash chromatography (16% EtOAc/hexanes) to afford **44e** as a 55:45 mixture of separable diastereomers (63.0 mg major and 33.6 mg minor, 0.222 mmol, 86% yield) as a pale yellow residue.

Analytical data for **44e major**: **^{1}H NMR** (chloroform-*d*, 500 MHz at 320 K): δ = 7.63 (d, *J*=7.8 Hz, 2 H), 7.36 (t, *J*=8.0 Hz, 2 H), 7.12 - 7.19 (m, 1 H), 6.29 (br. s., 1 H), 4.83 - 5.06 (m, *J*=6.0 Hz, 2 H), 4.12 - 4.54 (m, 2 H), 2.01 - 2.30 (m, 2 H), 1.44 (s, 3 H), 1.35 - 1.38 (m, *J*=3.2, 3.2 Hz, 6 H), 1.27 (d, *J*=6.2 Hz, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 175.2, 156.4, 155.3, 139.6, 128.5, 125.1, 119.8, 81.2, 70.6, 70.1, 56.6, 55.9, 39.9, 39.1, 26.8, 25.8, 22,9, 21.9, 21.9, 21.7 ppm; **IR** (thin film, cm^{-1}) 3286, 2981, 2935, 2875, 1713, 1595, 1495, 1469, 1387, 1302, 1231, 1180, 1109, 1039, 1018, 757, 691; **LRMS** (ESI) Calcd. for $[C_{22}H_{33}N_3O_6+Na]^+$ = 458.23, Found = 458.23.

Analytical data for **44e minor**: **^{1}H NMR** (chloroform-*d*, 400 MHz at 320 K): δ = 7.59 (d, *J*=6.6 Hz, 2 H), 7.35 (t, *J*=7.9 Hz, 2 H), 7.13 - 7.19 (m, 1 H), 6.08 (br. s, 1 H), 4.78 - 5.04 (m, 2 H), 4.12 - 4.64

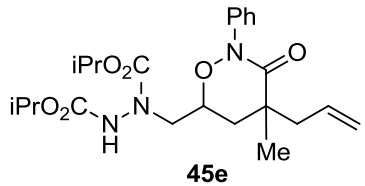
(m, 2 H), 2.04 (dd, *J*=13.6, 7.2 Hz, 1 H), 1.89 (br. s., 1 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.20 - 1.31 (m, 15 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 175.0, 156.4, 155.2, 139.7, 128.6, 125.2, 119.8, 119.1, 80.2, 79.8, 70.6, 70.0, 56.9, 40.0, 39.2, 29.7, 27.4, 25.8, 25.3, 22.0, 21.9, 21.8, 13.6 ppm; **IR** (thin film, cm^{-1}) 3286, 2981, 2935, 2875, 1713, 1595, 1495, 1469, 1387, 1302, 1231, 1180, 1109, 1039, 1018, 757, 691; **LRMS** (ESI) Calcd. for $[C_{22}H_{33}N_3O_6+Na]^+$ = 458.23, Found = 458.23.



46e

46e was prepared using **46** (20.0 mg, 0.080 mmol), DIAD (47.7 µL, 0.241 mmol), and V-65 (2.0 mg, 0.008 mmol, 10 mol%) in DMSO (180 µL). The reaction was completed, as indicated by TLC, after heating at 40 ºC for 12 h. The crude reaction mixture was worked up and purified by flash chromatography (75% EtOAc/hexanes) to afford a 75:25 diastereomer mix of **46e** (23.2 mg, 0.051 mmol, 64% yield) as a pale yellow residue.

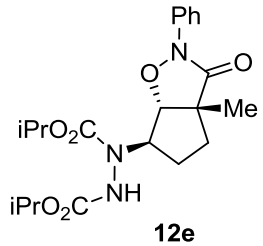
Analytical data for **46e**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 7.67 (d, *J*=8.2 Hz, 2 H), 7.34 (t, *J*=7.8 Hz, 2 H), 7.09 - 7.17 (m, 1 H), 6.91 (br. s., 1 H), 4.95 (ddt, *J*=19.0, 12.5, 6.0 Hz, 2 H), 4.65 (br. s., 1 H), 3.70 - 4.22 (m, 2 H), 3.63 (dt, *J*=10.9, 5.3 Hz, 2 H), 2.10 – 2.30 (br. s., 3 H), 1.53 - 1.86 (m, 4 H), 1.24 (dd, *J*=10.6, 4.7 Hz, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 170.7, 170.3, 155.7, 136.9, 128.7, 124.8, 124.7, 116.7, 116.6, 86.0, 82.6, 70.8, 70.1, 62.6, 62.4, 49.1, 48.7, 48.3, 31.6, 28.1, 27.2, 27.1, 22.0, 21.9, 21.9, 19.5, 16.2 ppm; **IR** (thin film, cm^{-1}) 3485, 3296, 3061, 2981, 2938, 2878, 1695, 1596, 1496, 1374, 1108, 1056, 920, 754; **LRMS** (ESI) Calcd. for $[C_{22}H_{33}N_3O_7+Na]^+$ = 474.22, Found = 474.20.



45e

45e was prepared using **45** (20.0 mg, 0.082 mmol), DIAD (50.0 µL, 0.245 mmol), in DMSO (180 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 9 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford a 50:50 diastereomer mix of **45e** (21.5 mg, 0.048 mmol, 59% yield) as a pale yellow residue.

Analytical data for **45e**: **^{1}H NMR** (chloroform-*d*, 500 MHz at 320 K): δ = 7.61 (t, *J*=6.3 Hz, 2 H), 7.30 - 7.40 (m, 2 H), 7.15 (t, *J*=7.3 Hz, 1 H), 6.52 (br. s., 1 H), 5.73 - 5.98 (m, 1 H), 5.14 (d, *J*=14.8 Hz, 2 H), 4.88 - 5.00 (m, 2 H), 4.56 (m, 1 H), 3.76 (br. s., 2 H), 1.68 - 2.66 (m, 4 H), 1.38 (s, 3 H; 2 singlets from diastereomers), 1.25 (d, *J*=5.7 Hz, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 173.9, 173.6, 155.7, 139.7, 139.6, 133.9, 133.5, 129.7, 128.8, 128.6, 125.3, 125.2, 120.0, 119.8, 118.8, 118.7, 116.5, 78.0, 70.6, 70.0, 53.3, 43.8, 42.5, 42.2, 42.1, 37.3, 37.1, 25.1, 23.9, 22.0, 21.9, 21.8, 21.6 ppm; **IR** (thin film, cm^{-1}) 3295, 3076, 2981, 2936, 2876, 2252, 1714, 1595, 1495, 1179, 1108, 1032, 918, 756, 734; **LRMS** (ESI) Calcd. for $[C_{23}H_{33}N_3O_6+Na]^+$ = 470.23, Found = 470.23.

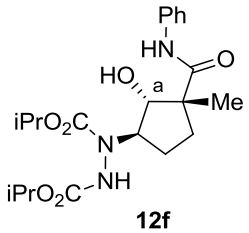


12e

12e was prepared using **12** (200.0 mg, 0.921 mmol), DIAD (547.0 µL, 2.76 mmol) in DMSO (2.0 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **12e** (308.9 mg, 0.736 mmol, 80% yield) as a single diastereomer as a white, foamy solid.

Analytical data for **12e**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.76 (d, *J*=7.8 Hz, 2 H), 7.38 (t,

J=7.9 Hz, 2 H), 7.16 (t, *J*=7.3 Hz, 1 H), 6.59 (br. s., 1 H), 4.93 - 5.07 (m, 2 H), 4.61 - 4.90 (m, 2 H), 2.26 - 2.34 (m, 1 H), 1.91 - 2.09 (m, 2 H), 1.79 - 1.87 (m, 1 H), 1.47 (s, 3 H), 1.31 (d, *J*=6.2 Hz, 6 H), 1.26 (d, *J*=6.2 Hz, 6 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz): 170.4, 156.8, 155.1, 136.7, 128.6, 124.8, 116.8, 90.8, 70.5, 70.1, 64.8, 53.4, 34.5, 27.1, 21.9, 21.8, 20.6 ppm; **IR** (thin film, cm^{-1}) 3290, 2981, 2936, 2875, 2252, 1714, 1596, 1496, 1385, 1304, 1243, 1108, 913, 754, 734; **LRMS** (ESI) Calcd. for $[C_{21}H_{29}N_3O_6+Na]^+$ = 442.20, Found = 442.19.



12f

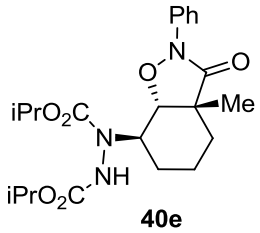
To confirm the relative stereochemistry of **12e**, the N-O bond was reductively cleaved using Raney Ni. **12f** was prepared by treating **12e** (31.6 mg, 0.0753 mmol) with Raney Ni (430 mg of 50% wt slurry in water) in EtOH (500 µL) and heating under Ar at 80 ºC. Upon completion at 5 h, as indicated by TLC, the crude reaction mixture was filtered through a Buchner funnel and washed sequentially with water (50 mL), MeOH (100 mL), and CH_2Cl_2 (25 mL). *Caution!: Raney Ni should never be left without solvent in order to prevent a spontaneous and highly exothermic reaction from occurring.* The filtrate was then concentrated, extracted with CH_2Cl_2 (25 mL x 10), dried ($MgSO_4$) and concentrated. The resultant residue was purified by flash chromatography (40% EtOAc/hexanes) to afford **12f** (31.0 mg, 0.0735 mmol, 97% yield) as a clear residue.

Note: While reductive cleavage of both N-O and N-N bonds of **4e** was achieved using Raney Ni and sonication, Raney Ni without sonication may be used in place of Zn/AcOH to obtain selective N-O bond cleavage.

Analytical data for **12f**: **^{1}H NMR** (chloroform-*d*, 500 MHz at 230 K): δ = 9.72 - 9.91 (m, 1 H), 7.57 (dd, *J*=15.1, 7.9 Hz, 2 H), 7.34 (q, *J*=8.4 Hz, 2 H), 7.05 - 7.20 (m, 1 H), 6.79 - 6.93 (m, 1 H), 4.84 - 5.10 (m, 2 H), 4.43 - 4.73 (m, 1 H), 3.58 - 3.78 (2 d resulting from 'freezing' out the rotamers at low

temp, *J*=10.4 Hz, 1 H, H_a), 2.59 - 2.76 (m, 1 H), 1.69 - 1.94 (m, 1 H), 1.06 - 1.49 ppm (m, 16 H); **^{13}C NMR** (chloroform-*d*, 151 MHz): 174.1, 173.9, 159.7, 159.0, 156.1, 155.4, 155.3, 138.6, 128.8, 123.8, 120.4, 120.1, 78.4, 78.0, 71.4, 71.1, 70.4, 61.5, 60.6, 49.1, 48.8, 31.9, 31.6, 30.1, 30.0, 29.7, 29.5, 29.4, 25.1, 24.9, 22.7, 22.0, 21.8, 20.9, 20.6, 20.3, 14.2 ppm; **IR** (thin film, cm^{-1}) 3286, 2981, 2929, 2872, 2251, 1714, 1600, 1550, 1308, 1267, 1109, 910, 755, 734; **LRMS** (ESI) Calcd. for $[C_{21}H_{31}N_3O_6+Na]^+$ = 444.20, Found = 444.19.

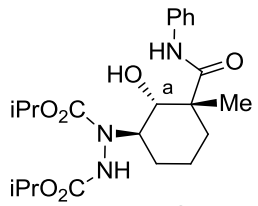
The observed coupling constant for H_a of **12f**, 10.4 Hz, suggests a *trans* relationship with the adjacent amino group. The lack of an observable NOESY between H_a and the α-Me group also suggests that, similarly to our dioxygenation findings, the 5,5-ring junction is *cis*.



40e

40e was prepared using **40** (200.0 mg, 0.865 mmol), DIAD (514.0 µL, 2.59 mmol) in DMSO (1.90 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **40e** (343.6 mg, 0.793 mmol, 92% yield) as a single diastereomer as a white, foamy solid.

Analytical data for **40e**: **^{1}H NMR** (chloroform-*d*, 500 MHz at 320 K): δ = 7.62 - 7.75 (m, 2 H), 7.35 (dt, *J*=8.9, 7.9 Hz, 2 H), 7.10 - 7.17 (m, 1 H), 6.51 (br. s., 1 H), 4.83 - 5.05 (m, 2 H), 4.13 - 4.45 (m, 2 H), 2.29 (d, *J*=13.7 Hz, 1 H), 1.53 - 2.07 (m, 5 H), 1.39 (s, 3 H), 1.26 - 1.34 (m, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K): 169.7, 156.9, 155.1, 137.3, 128.7, 124.7, 117.0, 116.7, 85.0, 84.0, 70.6, 70.1, 69.7, 57.6, 48.4, 30.8, 29.3, 27.1, 23.9, 21.9, 21.6, 16.6 ppm; **IR** (thin film, cm^{-1}) 3291, 2980, 2937, 2871, 1709, 1595, 1496, 1459, 1384, 1293, 1108, 754; **LRMS** (ESI) Calcd. for $[C_{22}H_{31}N_3O_6+Na]^+$ = 456.21, Found = 456.23.



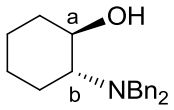
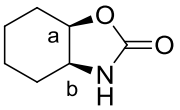
40f

To confirm the relative stereochemistry of **40e**, the N-O bond was reductively cleaved using Raney Ni.

40f was prepared by treating **40e** (76.1 mg, 0.176 mmol) with Raney Ni (1.01 g of 50% wt slurry in water) in EtOH (1.0 mL) and heating under Ar at 80 ºC. Upon completion at 15 h, as indicated by TLC, the crude reaction mixture was filtered through a Buchner funnel and washed sequentially with water (50 mL), MeOH (100 mL), and CH_2Cl_2 (25 mL). *Caution!: Raney Ni should never be left without solvent in order to prevent a spontaneous and highly exothermic reaction from occurring.* The filtrate was then concentrated, extracted with CH_2Cl_2 (25 mL x 10), dried ($MgSO_4$) and concentrated. The resultant residue was purified by flash chromatography (33% EtOAc/hexanes) to afford **40f** (44.3 mg, 0.102 mmol, 58% yield) as a clear residue.

Analytical data for **40f**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 9.95 (2 s, 1 H), 7.53 - 7.69 (m, 2 H), 7.32 (t, *J*=7.7 Hz, 2 H), 7.08 (t, *J*=7.4 Hz, 1 H), 6.38 (s, 1 H), 5.72 - 6.00 (2 s, 1 H), 4.88 - 5.12 (m, 2 H), 4.24 (2 m, 1 H), 3.41 (dd, *J*=10.4, 2.8 Hz, 1 H, H_a), 2.47 (m, 1 H), 1.59 - 1.69 (m, 3 H), 1.44 (s, 3 H), 1.35 (d, *J*=6.0 Hz, 6 H), 1.25 - 1.30 (m, 4 H), 1.02 - 1.17 (m, 4 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz): 173.7, 173.6, 159.7, 159.2, 156.1, 155.1, 138.7, 128.8, 123.7, 120.6, 120.0, 75.8, 71.6, 71.3, 71.2, 70.4, 59.8, 58.3, 48.5, 48.4, 35.7, 35.5, 31.6, 29.7, 28.5, 28.4, 26.1, 22.7, 22.1, 22.0, 21.9, 21.8, 21.7, 21.4, 14.1 ppm; **IR** (thin film, cm^{-1}) 3278, 2981, 2935, 2871, 1714, 1666, 1598, 1550, 1308, 1254, 1107, 756; **LRMS** (ESI) Calcd. for $[C_{22}H_{33}N_3O_6+Na]^+$ = 458.23, Found = 458.20.

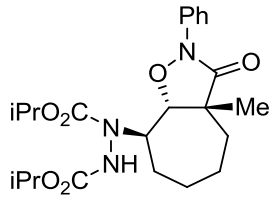
Table 5-4. Literature examples of *J* values for *trans* vs. *cis* O- and N-functionality on cyclohexanes

	 *trans* 2-(dibenzylamino)cyclohexanol	 *cis* hexahydrobenzo[*d*]oxazol-2(*3H*)-one
H_a	3.52 ppm, 1H (dt, *J* = 3.7, 9.3 Hz)	4.6 ppm, 1H (dt, *J* = 6 Hz)
H_b	2.36 ppm, 1H (dt, *J* = 3.0, 10.1 Hz)	3.70 ppm, 1H (q, *J* = 6 Hz)

The reported values of H_a and H_b for *trans*-2-(dibenzylamino)cyclohexanol[34] show that a large coupling constant (~10 Hz) suggests a *trans* substitution pattern.

Conversely, *cis*-hexahydrobenzo[*d*]oxazol-2(*3H*)-one[35] demonstrates that a smaller coupling constant (~6 Hz) would be evidence of a *cis* substitution pattern.

Thus, the observed coupling constant for H_a of **40f** is 10.6 Hz strongly suggests a *trans* relationship with the adjacent amino group. The lack of an observable nOe between H_a and the α-Me group also suggests that, similarly to our dioxygenation findings, the 5,6-ring junction is *cis*.

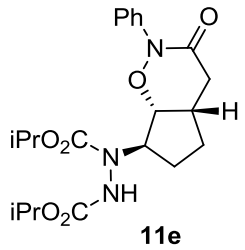


41e

41e was prepared using **41** (60.0 mg, 0.245 mmol), DIAD (145.0 µL, 0.734 mmol) in DMSO (540 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford **41e** (97.4 mg, 0.218 mmol, 89% yield) as a single diastereomer as a white solid.

Analytical data for **41e**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 7.54 - 7.81 (m, 2 H), 7.30 - 7.44 (m,

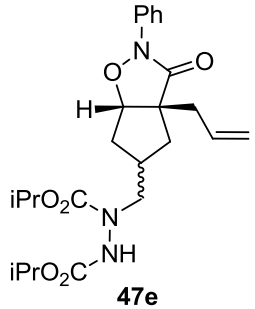
2 H), 7.08 - 7.20 (m, 1 H), 6.16 - 6.64 (m, 1 H), 4.79 - 5.22 (m, 2 H), 4.08 - 4.77 (m, 2 H), 2.23 (d, *J*=8.2 Hz, 2 H), 1.53 - 2.55 (m, 4 H), 1.39 - 1.52 (m, 3 H), 0.98 - 1.36 ppm (m, 14 H); **^{13}C NMR** (chloroform-*d*, 126 MHz): 170.7, 157.2, 156.3, 155.9, 154.8, 136.7, 128.8, 128.6, 124.9, 124.6, 116.9, 116.6, 115.9, 90.3, 89.1, 87.1, 85.5, 83.9, 71.0, 70.4, 70.1, 69.9, 69.7, 57.7, 57.2, 56.4, 49.4, 48.9, 48.4, 38.0, 37.6, 32.4, 30.7, 28.4, 27.4, 23.3, 22.0, 21.7 ppm; **IR** (thin film, cm^{-1}) 3290, 3062, 2980, 2932, 2861, 2359, 2341, 1704, 1595, 1497, 1463, 1385, 1304, 1109, 1038, 964, 754; **LRMS** (ESI) Calcd. for $[C_{23}H_{33}N_3O_6+Na]^+$ = 470.23, Found = 470.23. *Trans* stereochemical assignment is based on analogy to **12e** and **40e**.



11e

11e was prepared using **11** (300.0 mg, 1.38 mmol), DIAD (821 µL, 4.14 mmol) in DMSO (3.0 mL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 24 h. The crude reaction mixture was worked up and purified by flash chromatography (33% EtOAc/hexanes) to afford **11e** (303.6 mg, 0.724 mmol, 52% yield) as a single diastereomer as a pale yellow residue.

Analytical data for **11e**: **^{1}H NMR** ^{1}H NMR (chloroform-*d*, 500 MHz): δ = 7.77 (d, *J*=6.9 Hz, 2 H), 7.34 (t, *J*=7.9 Hz, 2 H), 7.13 (t, *J*=7.3 Hz, 1 H), 6.48 (br. s., 1 H), 4.88 - 5.03 (m, 2 H), 4.77 (br. s., 1 H), 4.56 - 4.66 (m, 1 H), 2.69 - 2.79 (m, 2 H), 2.47 - 2.56 (m, 1 H), 2.04 - 2.12 (m, 1 H), 1.99 (br. s., 1 H), 1.70 - 1.83 (m, 1 H), 1.46 - 1.58 (m, 1 H), 1.21 - 1.35 (m, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 170.3, 156.8, 155.2, 139.4, 128.6, 124.8, 118.6, 86.4, 70.6, 70.2, 62.7, 37.4, 37.1, 29.9, 27.5, 21.9 (2C); **IR** (thin film, cm^{-1}) 3291, 2981, 2937, 2876, 2251, 1714, 1595, 1494, 1468, 1374, 1304, 1239, 1108, 915, 755, 733; **LRMS** (ESI) Calcd. for $[C_{21}H_{29}N_3O_6+Na]^+$ = 442.20, Found = 442.21. Stereochemistry assigned based on 2-D NMR data.

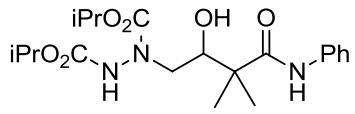


47e

47e was prepared using **47** (30.0 mg, 0.117 mmol), DIAD (27.7 µL, 0.140 mmol, 1.2 equiv) in DMSO (1.20 mL, 0.1 M). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 2 h. The crude reaction mixture was worked up and purified by flash chromatography (25% EtOAc/hexanes) to afford a 60:40 diastereomer mix of **47e** (40.7 mg, 0.0886 mmol, 76% yield) as a white foamy solid.

Analytical data for **47e**: **^{1}H NMR** (chloroform-*d*, 400 MHz): δ = 7.74 (dd, *J* = 4.6, 7.2 Hz, 2 H), 7.38 (t, *J* = 7.9 Hz, 2 H), 7.21 - 7.10 (m, 1 H), 6.76 - 6.29 (m, 1 H), 5.93 - 5.74 (m, 1 H), 5.26 - 5.11 (m, 2 H), 5.03 - 4.90 (m, 2 H), 4.89 - 4.77 (m, 1 H), 3.72 - 3.35 (m, 2 H), 2.76 - 1.42 (m, 7 H), 1.25 (d, *J* = 6.5 Hz, 12 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz) 170.2, 169.1, 155.9, 137.0, 136.6, 132.7,132.6, 128.7, 128.6,128.5, 124.8, 124.7,119.6, 116.9, 86.8, 85.3, 70.1, 69.9, 59.2, 58.3, 54.7, 53.2,40.5, 39.3, 39.1, 38.6, 37.0, 36.8, 36.5, 22.0, 21.97, 21.91 ppm; **IR** (thin film, cm^{-1}) 3294, 2980, 2935, 2251, 1697, 1595, 1496, 1375, 1109, 920; **LRMS** (ESI) Calcd. for $[C_{24}H_{33}N_3O_6+Na]^+$ = 482.23, Found = 482.23. Stereochemistry assigned based on 2-D NMR data. See included spectra for rationales.

5.5.3 Product Manipulations

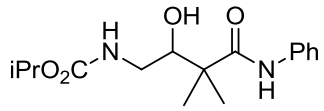


4f

4f was prepared by treatment of **4e** (30.0 mg, 0.074 mmol) with activated Zinc powder (187.0 mg, 2.95 mmol) in a mixture of AcOH/H_2O (740 µL/740 µL). The reaction was completed, as indicated

by TLC, after heating at 40 ºC for 11 h. The crude reaction mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (2 x 10 mL), washed with brine, dried ($MgSO_4$), and concentrated. The resultant residue was purified by flash chromatography (33% EtOAc/hexanes) to afford **4f** (27.6 mg, 0.067 mmol, 91% yield) as a clear residue.

Analytical data for **4f**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 9.09 - 9.44 (m, 1 H), 7.56 (d, *J*=7.9 Hz, 2 H), 7.31 (t, *J*=7.9 Hz, 2 H), 7.08 (t, *J*=7.4 Hz, 1 H), 6.76 (br. s., 1 H), 5.35 - 5.72 (m, 1 H), 5.02 (br. s., 1 H), 4.75 - 4.96 (m, 1 H), 3.47 - 3.95 (m, 3 H), 1.43 (br. s., 2 H), 1.32 (d, *J*=5.7 Hz, 6 H), 1.10 - 1.28 (m, 10 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz): 174.8, 174.6, 159.2, 157.9, 155.9, 138.5, 128.8, 123.7, 120.1, 119.9, 74.4, 73.6, 71.2, 70.8, 53.6, 45.0, 25.3, 24.9, 21.9, 21.8 ppm; **IR** (thin film, cm^{-1}) 3299, 2982, 2937, 2879, 2251, 1714, 1599, 1539, 1443, 1282, 1243, 1180, 1146, 1108, 1078, 1032, 916, 754, 733; **LRMS** (ESI) Calcd. for $[C_{20}H_{31}N_3O_6+Na]^+$ = 432.21, Found = 432.22.

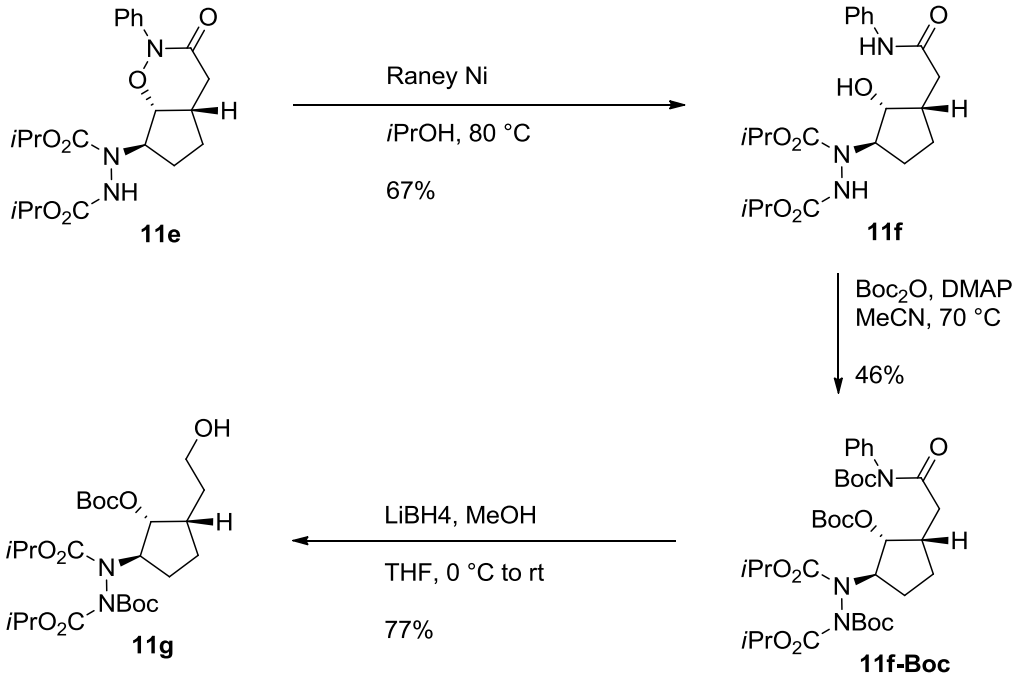


4g

4g was prepared by treatment of **4e** (32.0 mg, 0.079 mmol) with Raney Ni, 50% activated catalyst in H_2O (1 mL, Sigma Aldrich) in EtOH (700 µL). The reaction vial was immersed in an ultrasonic cleaner filled with water (bath temperature was measured at 50 ºC), and sonicated for 3 days. As the reaction progressed, additional portions of Raney Ni (300 µL x 5) were added to the reaction mixture. Upon completion, as indicated by TLC, the crude reaction mixture was filtered through a Buchner funnel and washed sequentially with water (50 mL), MeOH (100 mL), and CH_2Cl_2 (25 mL). *Caution!: Raney Ni should never be left without solvent in order to prevent a spontaneous and highly exothermic reaction from occurring.* The filtrate was then concentrated, extracted with CH_2Cl_2 (25 mL x 10), dried ($MgSO_4$) and concentrated. The resultant residue was purified by flash chromatography (33% EtOAc/hexanes) to afford **4g** (15.3 mg, 0.049 mmol, 63% yield) as a clear residue.

Analytical data for **4g**: **^{1}H NMR** (chloroform-*d*, 500 MHz): δ = 8.66 (br. s., 1 H), 7.47 - 7.57 (m, 2 H), 7.29 - 7.36 (m, 2 H), 7.10 (t, *J*=7.4 Hz, 1 H), 5.28 (br. s., 1 H), 5.00 (d, *J*=3.5 Hz, 1 H), 4.70 - 4.85 (m, 1 H), 3.63 - 3.74 (m, 1 H), 3.52 (ddd, *J*=14.7, 6.9, 2.4 Hz, 1 H), 3.17 - 3.29 (m, 1 H), 1.42 (s, 3 H), 1.26 (s, 3 H), 1.18 (d, *J*=6.0 Hz, 3 H), 1.08 (d, *J*=6.0 Hz, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 126 MHz): δ = 175.1, 158.4, 137.9, 128.9, 124.2, 120.1, 78.7, 69.1, 45.1, 43.6, 25.0, 22.0, 21.9, 21.8 ppm; **IR** (thin film, cm^{-1}) 3329, 2980, 2936, 2249, 1692, 1599, 1538, 1442, 1387, 1374, 1255, 1112, 920; **LRMS** (ESI) Calcd. for $[C_{16}H_{24}N_2O_4+Na]^+$ = 331.16, Found = 331.17.

Figure 5-9. Transformation of *N*-Phenyl amide via Boc-activation (unoptimized conditions)



11f was prepared by subjecting **11e** (190.5 mg, 0.454 mmol) to Raney Ni 50% wt slurry in H_2O (3.0 mL) in *i*PrOH (3.0 mL) and heating to 80 ºC under Ar. The reaction was completed as determined by TLC analysis at 2 h and was then cooled to rt, filtered through a Buchner funnel, washed successively with water, MeOH, and CH_2Cl_2. The layers were separated and the aqueous was extracted using CH_2Cl_2 (x 5), the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was then purified via flash chromatography (50% EtOAc in Hexanes) to give **11f** (128.2 mg, 67% yield) as a pale yellow, foamy solid.

Analytical data for **11f**: **^{1}H NMR** ^{1}H NMR (chloroform-*d*, 500 MHz at 320 K): δ = 8.79 (br. s., 1 H), 7.53 (d, *J* = 7.9 Hz, 2 H), 7.31 - 7.23 (m, 2 H), 7.10 - 7.00 (m, 1 H), 6.99 - 6.68 (m, 1 H), 5.01 - 4.87 (m, 2 H), 4.43 - 4.11 (m, 3 H), 2.75 (d, *J* = 9.1 Hz, 1 H), 2.54 (br. s., 1 H), 2.32 (br. s., 1 H), 2.02 - 1.78 (m, 2 H), 1.67 - 1.41 (m, 2 H), 1.31 - 1.16 (m, 12 H); **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K) 171.7, 157.7, 156.2, 138.5, 128.8, 123.8, 119.9, 74.3, 70.5, 70.3, 66.4, 39.6, 38.9, 37.2, 29.6, 28.0, 27.7, 24.8, 21.9, 21.8; **IR** (thin film, cm^{-1}) 3435, 2982, 2360, 1653, 1543, 1108, 908; **LRMS** (ESI) Calcd. for $[C_{21}H_{31}N_3O_6+Na]^+$ = 444.21, Found = 444.20.

11f-Boc was prepared by subjecting **11f** (123.3 mg, 0.293 mmol) to di-*tert*-butyl dicarbonate (Boc_2O, 958 mg, 4.39 mmol, 15.0 equiv), DMAP (107.2 mg, 0.878 mmol, 3.0 equiv) in MeCN (3.0 mL) and heating to 70 ºC under Ar. The reaction was completed as determined by TLC analysis at 15 min. The crude reaction mixture was then concentrated under reduced pressure and purified via flash chromatography (20% EtOAc in Hexanes) to give **11f-Boc** (98.3 mg, 46% yield) as a pale yellow solid.

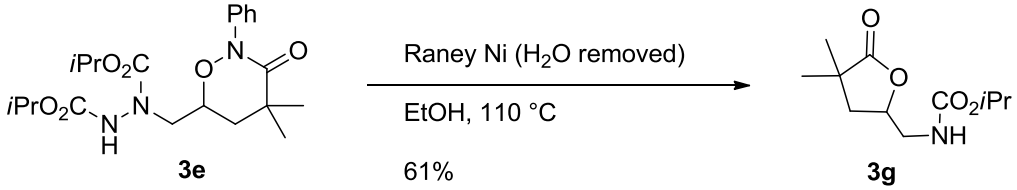
Analytical data for **11f-Boc**: **^{1}H NMR** ^{1}H NMR (chloroform-*d*, 500 MHz): δ = 7.41 - 7.34 (m, 2 H), 7.31 (d, *J* = 7.3 Hz, 1 H), 7.13 - 7.07 (m, 2 H), 5.45 - 5.30 (m, 1 H), 5.06 - 4.90 (m, 2 H), 4.34 - 4.19 (m, 1 H), 3.20 - 3.10 (m, 1 H), 2.92 - 2.82 (m, 1 H), 2.82 - 2.63 (m, 1 H), 2.14 - 2.05 (m, 1 H), 2.05 - 1.97 (m, 1 H), 1.86 - 1.71 (m, 1 H), 1.54 - 1.50 (m, 18 H), 1.37 (s, 8 H), 1.35 - 1.27 (m, 10 H), 1.21 (br. s., 4 H); **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K) 174.0, 154.1, 153.8, 152.9, 152.6, 151.7, 151.6, 150.5, 150.3, 139.2, 128.7, 128.3, 127.5, 84.1, 83.8, 82.7, 81.9, 81.6, 71.8, 71.6, 70.8, 69.8, 67.3, 67.1, 38.9, 38.7, 38.6, 37.3, 37.0, 28.8, 27.9, 27.8, 27.1, 26.8, 21.9, 21.6; **IR** (thin film, cm^{-1}) 3434, 2090, 1645, 1254, 523, 507; **LRMS** (ESI) Calcd. for $[C_{36}H_{55}N_3O_{12}+Cs]^+$ = 854.28, Found = 854.26.

11g was prepared by slow addition of $LiBH_4$ (78 µL, 3.0 equiv, 2 M in THF) to a solution of **11f-Boc** (37.5 mg, 0.052 mmol) in THF (520 µL) followed by MeOH (6 µL) at 0 ºC. The reaction was warmed to rt and stirred. The reaction was completed as determined by TLC analysis at 1 h. The

reaction was quenched at 0 ºC by the slow addition of 1M HCl, the mixture was then diluted up in water and extracted several times with Et_2O and CH_2Cl_2. The combined organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction mixture was purified via flash chromatography (50% EtOAc in Hexanes) to give **11g** (21.2 mg, 77% yield) as a colorless residue.

Analytical data for **11g**: **^{1}H NMR** ^{1}H NMR (chloroform-*d*, 500 MHz at 320 K): δ = 5.38 - 5.29 (m, 1 H), 5.03 (td, *J* = 6.2, 8.4 Hz, 2 H), 4.60 - 4.17 (m, 1 H), 3.75 - 3.62 (m, 2 H), 2.37 - 1.98 (m, 2 H), 1.95 - 1.65 (m, 3 H), 1.57 - 1.45 (m, 21 H), 1.37 - 1.28 (m, 6 H), 1.28 - 1.18 (m, 6 H); **^{13}C NMR** (chloroform-*d*, 126 MHz at 320 K) 153.1, 150.4, 84.1, 83.9, 82.1, 81.7, 71.7, 70.8, 69.9, 69.8, 67.6, 66.7, 61.7, 61.5, 39.5, 39.4, 31.5, 29.9, 29.6, 28.9, 28.1, 27.9, 27.8, 27.7, 26.9, 26.8, 22.0, 21.9, 21.7, 21.6; **IR** (thin film, cm^{-1}) 3434, 2084, 1638, 1369, 1252, 1157, 1100, 507; **LRMS** (ESI) Calcd. for $[C_{25}H_{44}N_2O_{10}+Cs]^+$ = 665.21, Found = 665.17.

Figure 5-10. Direct N-O and N-N cleavage concomitant with γ-lactone formation



3g was prepared by adding **3e** (60.0 mg, 0.142 mmol) as a solution in EtOH (1.0 mL) to Raney Ni (4.5 mL slurry, from which the water had been removed) in a sealed tube. The reaction was flushed with Ar, capped tightly and heated to 110 ºC for 20 h. The reaction was then cooled to rt, filtered through a Buchner funnel, washed successively with water, MeOH, and CH_2Cl_2. The layers were separated and the aqueous was extracted using CH_2Cl_2 (x 5), the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was then purified via flash chromatography (33% EtOAc in Hexanes) to give **3g** (20.0 mg, 61% yield) as a pale yellow, foamy solid.

Analytical data for **3g**: **^{1}H NMR** ^{1}H NMR (chloroform-*d*, 500 MHz): δ = 5.03 (br. s., 1 H), 4.97 -

4.85 (m, 1 H), 4.60 - 4.50 (m, 1 H), 3.63 (dd, *J* = 6.5, 14.3 Hz, 1 H), 3.29 - 3.20 (m, 1 H), 2.14 (dd, *J* = 6.1, 12.8 Hz, 1 H), 1.85 - 1.76 (m, 1 H), 1.31 - 1.26 (m, 6 H), 1.24 (d, *J* = 5.4 Hz, 6 H); **^{13}C NMR** (chloroform-*d*, 126 MHz) 181.5, 156.4, 76.0, 68.6, 44.4, 40.4, 39.7, 24.9, 24.6, 22.1; **IR** (thin film, cm^{-1}) 3434, 2359, 2341, 2085, 1646, 1260, 1108, 510; **LRMS** (ESI) Calcd. for $[C_{11}H_{19}NO_4+Na]^+$ = 252.12, Found = 252.14.

5.6 References

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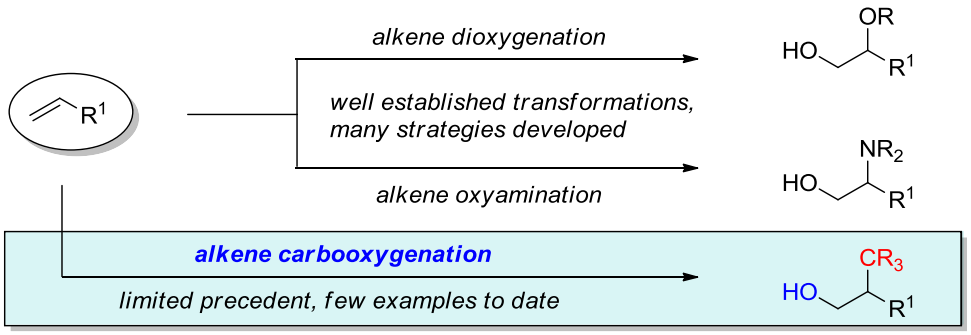
6. CHAPTER SIX

Radical-Mediated Alkene Carbooxygenations Using Hydroxamic Acids

6.1 Introduction

Alkene difunctionalizations have undoubtedly emerged as valuable synthetic methods for the efficient preparation of highly functionalized small molecules. While a diverse set of useful protocols for direct alkene dioxygenation[1–7] and oxyamination[8] exist, approaches for direct alkene carbooxygenation remain scarce (**Figure 6-1**). See **Chapter 1** for an in-depth discussion of alkene difunctionalizations.

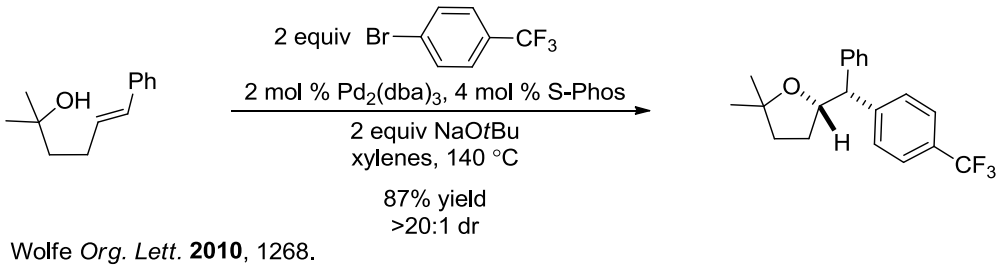
Figure 6-1. Alkene Carbooxygenation: An Underdeveloped Class of Difunctionalization



6.2 Background

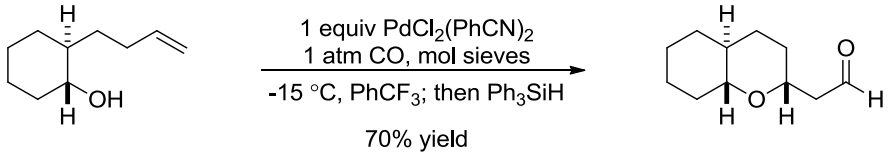
Although useful transition-metal-catalyzed alkene carbooxygenations have been developed, they often deliver a limited set of oxygen- and carbon-based functionality, and are restricted in alkene scope.[9–12] For example, Wolfe and co-workers developed a Pd-catalyzed carboetherification, but the substrates are limited to homoallylic alcohols and aryl bromides (**Figure 6-2**).[9] Additionally, Lambert has developed a Pd-mediated oxidative formylation, which is formally an alkene carbooxygenation.[13] This approach uses carbon monoxide as the external carbon-atom source, which greatly expands the carbon-functionality accessible but requires a full equivalent of $PdCl_2(PhCN)_2$ (**Figure 6-3**).

Figure 6-2. Diastereoselective Pd-Catalyzed Alkene Carboetherification



Wolfe *Org. Lett.* **2010**, 1268.

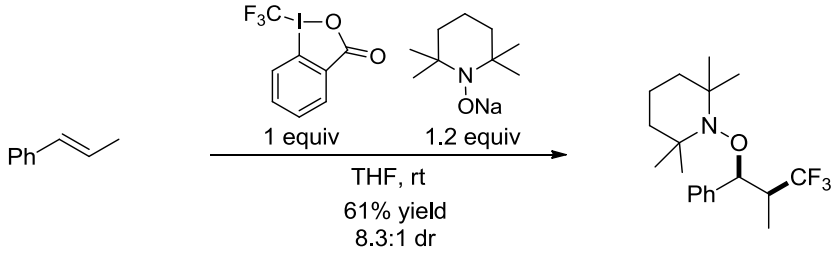
Figure 6-3. Oxidative Alkene Formylation



Lambert *Synthesis* **2010**, 870.

Alternatively, radical-mediated approaches to carbooxygenation have been successfully developed to achieve a number of important processes including alkene oxyarylation and oxytrifluoromethylation.[14–17] These transformations involve the addition of carbon-centered radicals to alkenes followed by radical trapping by the persistent nitroxide radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl). Despite the utility of these radical-mediated approaches to carbooxygenation, they are inherently limited to transformations involving carbon-atom functionality that efficiently undergo radical addition to alkenes. This is exemplified by the alkene trifluoromethylaminoxylation developed by Studer (**Figure 6-4**).[17] Their approach uses commercially available Togni reagent as a convenient source of trifluoromethyl radical, and the sodium salt of TEMPO serves as the oxygen-atom source in the difunctionalization.

Figure 6-4. Radical-Mediated Alkene Oxytrifluoromethylation



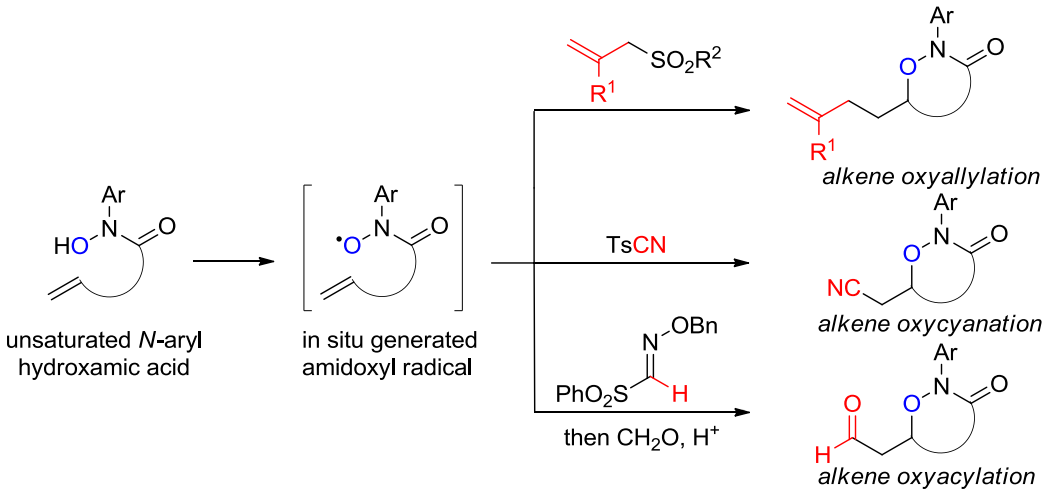
Studer *ACIE* **2012**, 8221.

6.3 Reaction Development

We postulated that a complementary approach to radical-mediated alkene carbooxygenation proceeding by initial addition of oxygen-centered radicals with subsequent carbon-carbon bond formation would enable a variety of unique transformations of alkenes. Such a strategy, which introduces the carbon-atom functionality in the second bond-forming step, capitalizes on the wealth of well-established radical-mediated methods available to form C-C bonds.[18,19] Herein, we report our successful implementation of this strategy using *N*-aryl hydroxamic acids as an in situ source of oxygen-centered radicals, enabling the development of a number of valuable carbooxygenation processes – alkene oxyallylation, oxycyanation, and oxyacylation– using readily available radical traps.

Based on our success using amidoxyl radicals in alkene dioxygenations (see **Chapters 2 – 4**)[20–22] and oxyaminations (see **Chapter 5**),[23] we envisioned that following cyclization, subsequent reaction with allyl sulfones, tosyl, cyanide, or sulfonyl oximes would facilitate direct alkene oxyallylation, oxycyanation, or oxyacylation respectively (**Figure 6-5**). These traps were specifically chosen based on their known ability to trap carbon-centered radicals.[24–33] While there are limited examples of transition-metal-catalyzed oxycyanation[11] and oxyacylation,[13] catalytic oxyallylation of alkenes are unknown.

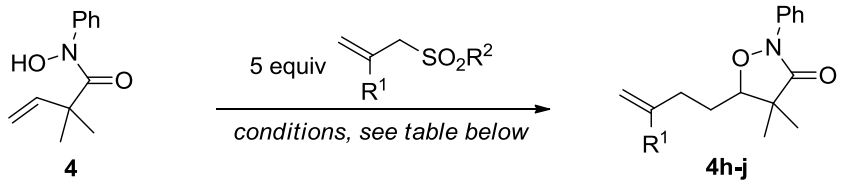
Figure 6-5. Proposed Alkene Oxyallylation, Oxycyantion, and Oxyacylations



6.3.1 Substrate Scope – Oxyallylations

Our oxyallylation studies commenced with *N*-aryl hydroxamic acid **4** and ethyl allyl sulfone as a radial trap. We initially surveyed a variety of non-polar and polar solvents suitable for radical reactions, including those used in our previous alkene difunctionalization studies (**Table 6-1, entries 1 - 4**). The reaction of substrate **4** in the presence of ethyl allyl sulfone (5 equivalents) at 60 °C in PhCN delivered allylated isoxazolidinone **4h**, albeit in low yield (**entry 1**). Increasing the temperature and switching to more polar solvents resulted in a modest increase in both reaction rate and yield (**entries 2 - 4**). In these initial experiments, conversions were moderate even with prolonged reaction times. In order to address this issue, we attempted an oxyallylation in the presence of AIBN as a radical initiator (**entry 5**). Radical initiators have proven useful in increasing reaction rates in other alkene difunctionalizations using hydroxamic acids. In this case, while increased rates were observed upon the addition of AIBN, numerous unidentified byproducts were formed and there was no increase in yield of the desired product.

Table 6-1. Initial Oxyallylation Studies



4 **4h-j**

entry	R^1, R^2	additive	solvent	temp (^oC)/time (h)	% yield[a]
1	H, Et	none	PhCN	60/50	15
2	H, Et	none	PhCN	80/36	26
3	H, Et	none	AcOH	80/24	20
4	H, Et	none	DMSO	80/48	37
5	H, Et	AIBN[b]	DMSO	80/24	34
6	H, Et	$PhSO_2NH_2$[c]	DMSO	85/36	53
7	CO_2Et, Et	$PhSO_2NH_2$[c]	DMSO	85/36	56
8	SO_2Ph, Ph	none	DMSO	85/48	77
9	***SO_2Ph, Ph***	***$PhSO_2NH_2$[c]***	***DMSO***	***85/36***	***95***

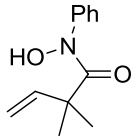
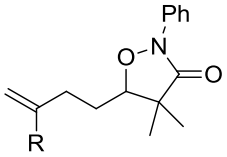
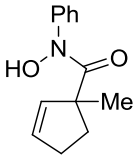
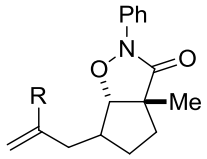
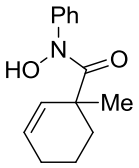
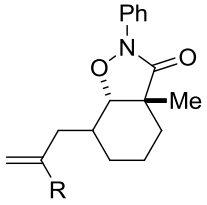
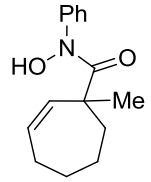
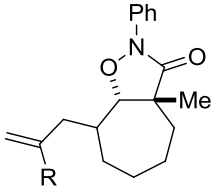
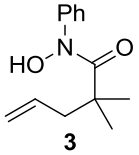
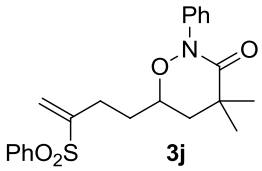
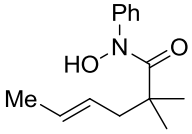
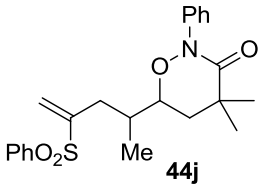
[a]Isolated yield of product. [b]10 mol % added every 2-3 h until full conversion. [c]50 mol % added.

With limited success in our early studies, we became intrigued by the possibility of a hydrogen-bond donor facilitating the oxyallylation process. We speculated that such a reagent could increase the efficiency of the reaction by two potential pathways: increasing the reactivity of the amidoxyl radical, or influencing the conformation of the substrate to favor reactivity. Recently, Lewis-acids have been shown to greatly increase the reactivity of nitroxide radicals (e.g. TEMPO),[34] supporting the possibility of generating a more reactive amidoxyl radical through hydrogen bonding. In addition, hydroxamic acids are known to form inter- and intramolecular hydrogen bonds,[35] which could serve to lower rates of the difunctionalizations. While the specific mode of activation remains to be identified and will be the subject of future investigations, the addition of 50 mol % of $PhSO_2NH_2$ afforded significant increases in reaction efficiency (**Table 6-1, entry 6**).

Substituting ethyl allyl sulfone for more electron–poor allylating agents further increased yields (**Table 6-1, entries 7 – 9**). The oxyallylation of substrate **4** with the 2-SO_2Ph-substituted allyl sulfone (**entry 8**) proceeds in 95% isolated yield, and is in fact more efficient than either the previously reported dioxygenation or oxyamination of that substrate. While these reactions do require an excess of allylating agent due to the slow reaction rates, recovery of the unreacted sulfone is trivial.

Upon identifying a suitable protocol for oxyallylation, we next investigated the reaction substrate scope using a variety of hydroxamic acid substrates (**Table 6-2**). Oxyallylations involving 5-*exo* cyclizations proceeded in moderate to high yield with both cyclic and acyclic substrates, with reaction efficiencies consistently higher with electron-poor allyl sulfones. The oxyallylation of cyclopentenyl-, cyclohexenyl-, and cycloheptenyl-substituted hydroxamic acids all delivered bicyclic isoxazolidinone products in moderate to good yields (**entries 2 – 4**). While the difunctionalizations of cyclopentenyl substrate **12** proceeded with good diastereoselectivity to provide the *trans* oxyallylation product **12h**, reactions of substrates **40** and **41** proved relatively unselective. The reactions of acyclic substrates **3** and **44** demonstrate that oxyallylation involving 6-*exo* cyclizations are also viable, albeit in moderate yield (**entries 5** and **6**).

Table 6-2. Oxyallylation of Unsaturated Hydroxamic Acids

entry	substrate	product	% yield[a-c]
1	 **4**		**4h** 53 (R=H) **4i** 56 (R=CO_2Et) **4j** 95 (R=SO_2Ph)[d]
2	 **12**		**12h** 30 (R=H) (91:9 dr β:α) **12i** 55 (R=CO_2Et) (90:10 dr β:α) **12j** 65 (R=SO_2Ph)[e] (90:10 dr β:α)
3	 **40**		**40i** 69 (R=CO_2Et) (58:42 dr) **40j** 84 (R=SO_2Ph)[d] (52:48 dr)
4	 **41**		**41i** 63 (R=CO_2Et) (69:31 dr β:α) **41j** 86 (R=SO_2Ph)[d] (72:28 dr β:α)
5	 **3**	 **3j**	37[e] (82)[f]
6	 **44**	 **44j**	41[e] (50:50 dr)

[a]All reactions run 0.5M in DMSO with 5 equiv allyl sulfone at 85 °C. [b]Yields of isolated product. [c]Diastereomeric ratio based on ^{1}H NMR analysis. [d]3.5 equiv sulfone added. [e]NMR yield. [f]Yield based on recovered starting material.

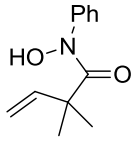
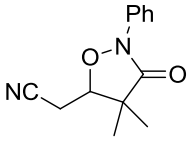
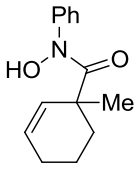
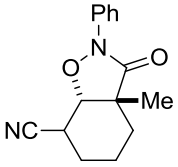
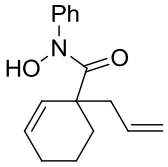
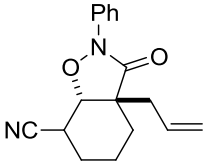
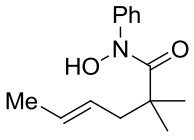
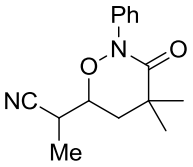
The decreased efficiency of these reactions is due to the relatively low conversions of substrate involving the slower 6-*exo* cyclization step – the oxyallylation of substrate **3** delivers [1,2]-oxazinone **3j** in good yield based on recovered starting material. All attempts to further increase reaction conversion in these cases with the use of radical initiators (or single-electron oxidants)

were unsuccessful.

6.3.2 Substrate Scope – Oxycyanations and Oxyacylations

Substituting tosyl cyanide (TsCN) for the allyl sulfone reagent under slightly modified conditions leads to a radical-mediated alkene oxycyanation protocol that proceeds with similar efficiencies (**Table 6-3**). For example, the reaction of substrate 4 with 3 equivalents of TsCN in EtCN at 60 °C in the presence of 10 mol % dilauroyl peroxide (DLP) provided oxycyanation product **4k** in 61% isolated yield (**entry 1**). The diastereoselectivity of the oxycyanation process was similar to that of the oxyallylation process, as reactions of cyclohexenyl substrates **40** and **42** both favored *trans* difunctionalizations to a small degree (**Table 6-3, entries 2 – 4**).

Table 6-3. Oxycyanation of *N*-Aryl Unsaturated Hydroxamic Acids

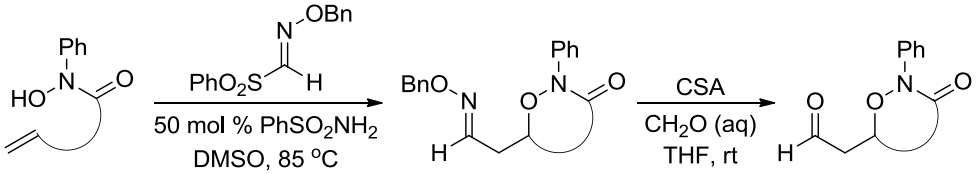
entry	substrate	product	% yield[a-c]
1	 **4**	 **4k**	61[d]
2	 **40**	 **40k**	57[d] (60:40 dr β:α)
3	 **42**	 **42k**	52[d] (68:32 dr β:α)
4	 **44**	 **44k**	54[e] (50:50 dr)

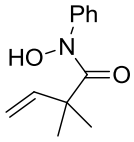
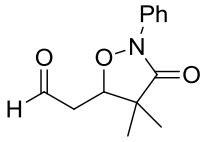
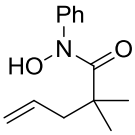
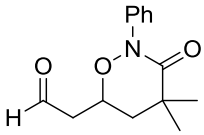
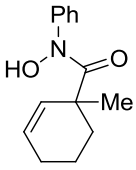
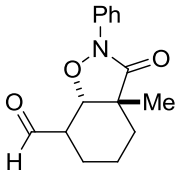
[a]All reactions run 0.5M in EtCN with 3 equiv TsCN at 60 °C. [b]Yields of isolated product. [c]Diastereomeric ratio based on 1H NMR analysis.

Notably, substrate **42** undergoes mono-difunctionalization under these conditions, likely resulting

from the kinetic preference of 5-*exo* over 6-*exo* cyclization (**entry 3**). The oxycyanation of substrate **44** delivers cyano-substituted [1,2]-oxazinone **44k** in moderate yield, demonstrating the ability of the oxycyanation to proceed via 6-*exo* ring-closure (**Table 6-3, entry 4**).

Table 6-4. Oxyacylation of *N*-Aryl Hydroxamic Acids



entry	substrate	product	% yield[a-c]
1	 **4**	 **4l**	71 (two steps)
2	 **3**	 **3l**	34[f] (two steps)
3	 **40**	 **40l**	54 (60:40 dr β:α) (two steps)

[a]All reactions run 0.5M in DMSO with 5 equiv oxime at 85 °C. [b]Yields of isolated product. [c]Diastereomeric ratio based based on ^{1}H NMR analysis. [d]NMR yield.

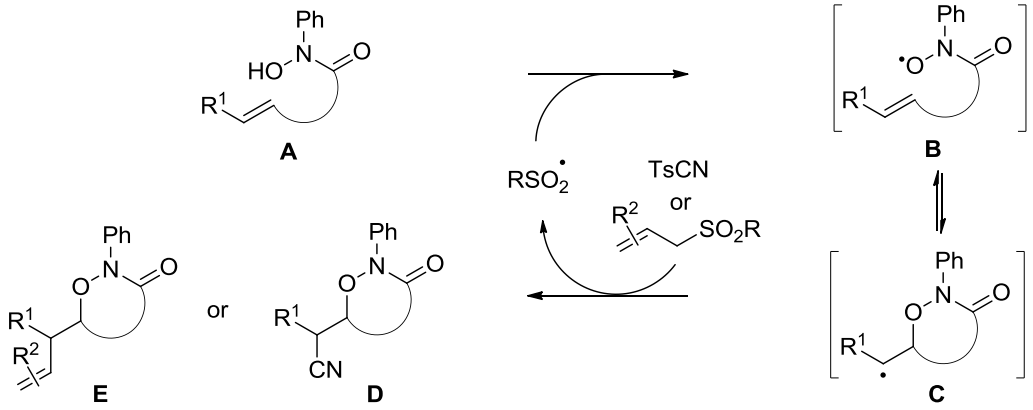
A third carbooxygenation variant that we targeted during these studies was a radical-mediated alkene oxyacylation. We viewed this transformation as particularly attractive due to the versatility of the aldehyde product for post reaction modification, as well as the construction of the valuable β-alkoxy aldehyde motif. Our approach to this process was inspired by the innovative work of Kim and co-workers,[33] who demonstrated the utility of phenylsulfonyl oximes to deliver formal acylation products. We envisioned that further hydrolysis of the initial oxime products would deliver the desired aldehydes (**Table 6-4**).[36] For example, the reaction of acyclic substrate **4** delivered isoxazolidinone aldehyde **4l** in good yield (71%) over the cyclization/hydrolysis sequence (**Table 6-4,**

entry 1). Oxyacylation of substrate **3** involving a less kinetically facile 6-*exo* ring closure did provide the desired [1,2]-oxazinone product **3l**, albeit in reduced yield (**entry 2**), as previously observed in the oxyallylation of **3** (**Table 6-4, entry 2**). The oxyacylation displayed similar levels of diastereoselectivity as the oxycyanation, as demonstrated by the reactions of cyclohexenyl substrate **40** (**entry 3**).

6.3.3 Proposed Mechanism

We envision the carbooxygenation process involving similar mechanisms as the dioxygenation and oxyamination reactions (**Figure 6-6**). Following the formation of the amidoxyl radical **8**, a reversible cyclization step provides carbon-centered radical **C**. This intermediate then reacts with the respective sulfone, delivering the carbooxygenation product and generating a sulfonyl radical. This species then facilitates hydrogen-atom abstraction from the starting material to continue the chain process.

Figure 6-6. Proposed Radical-Mediated Mechanism for Carbooxygenation



6.4 Summary

In conclusion, we have developed a radical-mediated approach to an under-developed class of alkene difunctionalizations: carbooxygenations. The transformations described include direct alkene oxyallylation, oxycyanation, and oxyacylation using unsaturated hydroxamic acids. These examples deliver highly functionalized, synthetically versatile small molecules from readily accessible

compounds. In the course of studies, we have also discovered the utility of hydrogen-bond donors in facilitating reactions of hydroxamic acids. These studies increase the capabilities of hydroxamic acids in enabling unique, radical-mediated alkene difunctionalizations.

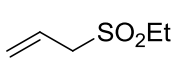
6.5 Experimental

6.5.1 General Methods

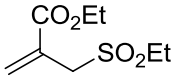
See **2.5 Experimental** for general methods and substrate preparation.

6.5.2 General Oxyallylation Conditions

Method A (Sulfones i and ii)



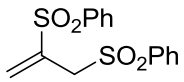
i



ii

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and sulfone (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85 ˚C. Upon disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

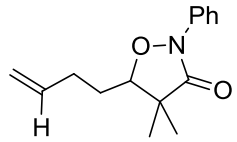
Method B (Sulfone iii)



iii

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and sulfone (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then

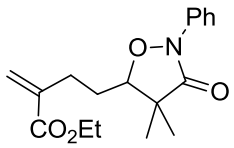
brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85 ˚C. Upon disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting crude mixture was dissolved in EtOH (1-2 mL) and cooled to 0˚C to induce precipitation of unreacted sulfone. The sulfone was then filtered off, and the filtrate was concentrated under reduced pressure. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.



4h

4h was prepared via ***Method A*** using **4** (20.1 mg, 0.098 mmol), sulfone i (65.8 mg, 0.490 mmol), benzene sulfonamide (7.75 mg, 0.049 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **4h** (12.7 mg, 0.052 mmol, 53% yield) as a clear oil.

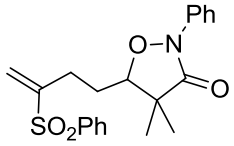
Analytical data for **4h**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.75 (d, *J* = 8.5 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 5.90 (tdd, *J* = 6.7, 10.3, 17.0 Hz, 1 H), 5.19 - 5.04 (m, 2 H), 4.23 (dd, *J* = 3.3, 9.8 Hz, 1 H), 2.48 - 2.35 (m, 1 H), 2.28 (qd, *J* = 7.2, 14.5 Hz, 1 H), 1.96 - 1.82 (m, 1 H), 1.77 - 1.64 (m, 1 H), 1.29 (s, 3 H), 1.21 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 172.1, 137.2, 128.7, 124.4, 116.3, 115.8, 86.9, 46.2, 29.9, 27.1, 21.3, 17.7 ppm; **IR** (thin film, cm^{-1}) 3076, 2972, 1704, 1641, 1595, 1496, 1389, 1306, 1180, 914, 752; **LRMS (ESI)** Calcd. for $[C_{15}H_{19}NO_2+H]^+$ = 246.14, Found = 246.13.



4i

4i was prepared via ***Method A*** using **4** (20.3 mg, 0.098 mmol), sulfone ii (98.1 mg, 0.490 mmol), benzene sulfonamide (7.8 mg, 0.049 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **4i** (17.3 mg, 0.054 mmol, 56% yield) as a clear oil.

Analytical data for **4i**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.74 (d, *J* = 8.5 Hz, 2 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 1.0 Hz, 1 H), 6.27 (s, 1 H), 5.68 (s, 1 H), 4.30 - 4.19 (m, 3 H), 2.73 - 2.61 (m, 1 H), 2.53 (ddd, *J* = 6.5, 8.7, 14.7 Hz, 1 H), 2.01 - 1.79 (m, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.21 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 100 MHz) 171.9, 166.8, 136.9, 139.6, 137.2, 128.7, 125.7, 124.4, 116.3, 87.0, 60.8, 46.2, 28.6 , 26.8, 21.3, 17.7, 14.2 ppm; **IR** (thin film, cm^{-1}) 2972, 2932, 1710, 1631, 1594, 1495, 1388, 1362, 1306, 1177, 1025, 753, 690; **LRMS (ESI)** Calcd. for $[C_{18}H_{23}NO_4+H]^+$ = 318.16, Found = 318.23.

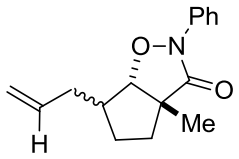


4j

4j was prepared via ***Method B*** using **4** (20.4 mg, 0.098 mmol), sulfone iii (112.1.6 mg, 0.340 mmol, 3.5 equiv), benzene sulfonamide (7.75 mg, 0.049 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **4j** (35.8 mg, 0.093 mmol, 95% yield) as a grey white residue.

Analytical data for **4j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.93 (d, *J* = 7.3 Hz, 2 H), 7.66 (d, *J* =

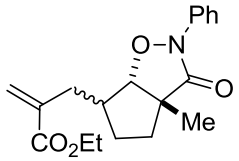
8.8 Hz, 3 H), 7.57 (t, *J* = 1.0 Hz, 2 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 6.47 (s, 1 H), 5.86 (s, 1 H), 4.11 (dd, *J* = 3.0, 10.0 Hz, 1 H), 2.70 - 2.58 (m, 1 H), 2.47 (td, *J* = 8.2, 16.0 Hz, 1 H), 1.96 - 1.76 (m, 3 H), 1.22 (s, 3 H), 1.13 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 171.6, 149.4, 138.6, 137.0, 133.8, 129.4, 128.8, 128.3, 124.6, 124.5, 116.3, 86.2, 46.1, 26.4, 26.2, 21.3, 17.6 ppm; **IR** (thin film, cm^{-1}) 2973, 2252, 2090, 1643, 1494, 1364, 1305, 1137, 1081, 909; **LRMS (ESI)** Calcd. for $[C_{21}H_{23}NO_4S+H]^+$ = 386.13, Found = 386.21.



12h

12h was prepared via ***Method A*** using **12** (20.0 mg, 0.092 mmol), sulfone i (65.1 mg, 0.460 mmol), benzene sulfonamide (7.6 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **12h** (7.8 mg, 0.052 mmol, 30% yield) as a clear oil.

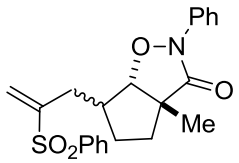
Analytical data for **12h**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.42 - 7.36 (m, *J* = 7.5, 8.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 5.91 - 5.79 (m, 1 H), 5.16 - 5.08 (m, 2 H), 4.39 (d, *J* = 3.0 Hz, 1 H), 2.45 - 2.36 (m, 1 H), 2.36 - 2.21 (m, 2 H), 2.21 - 2.11 (m, 1 H), 2.01 (qd, *J* = 7.6, 13.1 Hz, 1 H), 1.79 (td, *J* = 7.7, 13.4 Hz, 1 H), 1.64 - 1.52 (m, 2 H), 1.48 (s, 2 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): 171.1, 137.1, 136.0, 128.7, 124.6, 116.7, 93.3, 55.0, 45.8, 36.6, 35.9, 29.6, 21.7 ppm; **IR** (thin film, cm^{-1}) 3073, 2961, 2931, 2871, 1697, 1594, 1495, 1458, 1376, 1307, 994, 915, 753, 690 ; **LRMS (ESI)** Calcd. for $[C_{16}H_{19}NO_2+H]^+$ = 258.14, Found = 258.12.



12i

12i was prepared via ***Method A*** using **12** (20.0 mg, 0.092 mmol), sulfone ii (94.8 mg, 0.460 mmol), benzene sulfonamide (7.6 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **12i** (16.6 mg, 0.050 mmol, 55% yield) as a clear yellow oil.

Analytical data for **12i**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.74 (d, *J* = 7.8 Hz, 2 H), 7.38 (t, *J* = 1.0 Hz, 2 H), 7.15 (t, *J* = 1.0 Hz, 1 H), 6.30 (s, 0 H), 5.65 (s, 1 H), 4.38 (d, *J* = 3.3 Hz, 1 H), 4.28 - 4.17 (m, 2 H), 2.60 - 2.47 (m, 2 H), 2.47 - 2.37 (m, 1 H), 2.32 (td, *J* = 7.0, 13.7 Hz, 1 H), 2.06 - 1.92 (m, 1 H), 1.81 (td, *J* = 7.4, 13.6 Hz, 1 H), 1.56 (td, *J* = 6.7, 13.4 Hz, 1 H), 1.49 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 171.0, 166.9, 138.8, 137.0, 128.7, 126.3, 124.6, 116.7, 93.3, 60.9, 54.8, 45.3, 35.6, 34.6, 29.6, 21.9, 14.2 ppm; **IR** (thin film, cm^{-1}) 2961, 2872, 1710, 1630, 1594, 1494, 1459, 1375, 1306, 1189, 1155, 1024, 952, 734, 690; **LRMS (ESI)** Calcd. for $[C_{16}H_{23}NO_4+H]^+$ = 330.16, Found = 330.32.

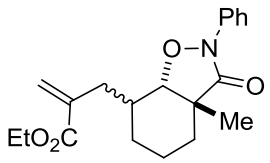


12j

12j was prepared via ***Method B*** using **12j** (20.1 mg, 0.092 mmol), sulfone iii (148.1 mg, 0.460 mmol, 5 equiv), benzene sulfonamide (7.2 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **12j** as a mixture with some residual sulfone. The yield was determined by NMR using 2,4,6 trimethoxybenzene as an

internal standard.

Analytical data **12j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.59 - 7.52 (m, 4 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 1.0 Hz, 1 H), 6.52 (s, 1 H), 5.89 (s, 1 H), 4.22 (d, *J* = 2.8 Hz, 1 H), 2.56 - 2.40 (m, 2 H), 2.39 - 2.20 (m, 2 H), 2.04 - 1.90 (m, *J* = 7.5, 13.3 Hz, 1 H), 1.68 (td, *J* = 7.5, 13.6 Hz, 1 H), 1.50 - 1.39 (m, 2 H), 1.37 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): 170.5, 148.6, 138.8, 136.9, 133.8, 129.4, 128.8, 128.3, 124.8, 124.6, 116.7, 92.9, 54.9, 44.3, 52.5, 31.9, 29.7, 21.6 ppm; **IR** (thin film, cm^{-1}) 3065, 2927, 2251, 1694, 1593, 1494, 1449, 1379, 1305, 1139, 1081, 912, 750, 690; **LRMS (ESI)** Calcd. for $[C_{22}H_{23}NO_4S+H]^+$ = 398.13, Found = 398.20



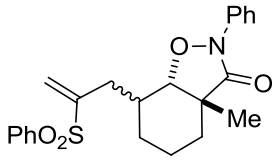
40i

40i was prepared via ***Method A*** using **40** (20.3 mg, 0.086 mmol), sulfone ii (88.6 mg, 0.430 mmol), benzene sulfonamide (6.5 mg, 0.043 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **40i** (20.9 mg, 0.059 mmol, 69% yield) as a clear oil. **40i** was isolated as a 58:42 mixture of inseparable diastereomers.

Analytical data for **40i**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.74 (t, *J* = 7.7 Hz, 2 H), 7.39 (dt, *J* = 4.8, 8.0 Hz, 2 H), 7.15 (dt, *J* = 4.4, 7.3 Hz, 1 H), 6.28 (dd, *J* = 1.4, 12.9 Hz, 1 H), 5.77 - 5.49 (m, 1 H), 4.25 (q, *J* = 7.0 Hz, 1 H), 4.18 - 3.95 (dd, *cis J*=2.8, *trans J*=8.4 Hz, 1 H), 4.15-4.01 (m, 1H), 2.80 - 2.44 (m, 2 H), 2.42 - 2.22 (m, 1 H), 2.05 - 1.83 (m, 1 H), 1.76 (dd, *J* = 3.4, 9.7 Hz, 1 H), 1.70 - 1.57 (m, 3 H), 1.40 - 1.30 (m, 4 H), 1.26 (s, 2 H), 1.19 (t, *J* = 7.0 Hz, 2 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): 172.6, 170.5, 167.0, 166.9, 138.8, 137.7, 137.6, 137.5, 128.8, 128.7, 127.4, 126.7, 124.3, 116.3, 116.2, 88.7, 84.5, 60.8, 60.7, 47.6, 45.6, 37.7, 37.0, 34.9, 34.3, 31.4, 29.9, 29.7, 28.2, 26.8, 23.7, 21.8, 20.8, 16.7, 14.2, 14.1 ppm; **IR** (thin film, cm^{-1}) 2934, 2863, 1710, 1629, 1594, 1495, 1457,

1363, 1303, 1213, 1159, 1024, 967, 753, 690; **LRMS (ESI)** Calcd. for $[C_{20}H_{25}NO_4+H]^+$ = 343.18, Found = 343.20.

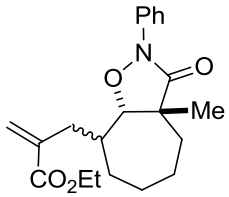
Based on the coupling constants reported for *trans* and *cis* aminoalcohols of cyclohexanes as well as with analogous compounds previously reported by our group,[20,23] the diastereomer exhibiting the greater coupling constant suggests a *trans* relationship for substituted 6-membered rings.



40j

40j was prepared via ***Method B*** using **40** (20.0 mg, 0.086 mmol), sulfone iii (96.9 mg, 0.300 mmol, 3.5 equiv), benzene sulfonamide (6.8 mg, 0.043 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **40j** (29.7 mg, 0.072 mmol, 84% yield) as a grey white residue. **40j** was isolated as a 52:48 mixture of inseparable diastereomers.

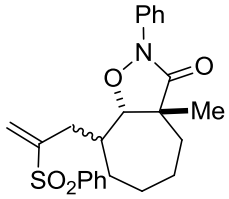
Analytical data for **40j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.96 - 7.90 (m, 1 H), 7.77 - 7.54 (m, 5 H), 7.48 - 7.32 (m, 3 H), 7.23 - 7.09 (m, 1 H), 6.53 - 6.44 (m, 1 H), 5.96 - 5.69 (m, 1 H), 4.09 - 3.77 (dd, 1H, *cis J*=2.8, *trans J*=8.4), 2.93 - 2.31 (m, 2 H), 2.29 - 1.90 (m, 1 H), 1.77 - 1.46 (m, 4 H), 1.44 - 1.20 (m, 4 H), 1.18 (s, 2 H) ppm; **^{13}C NMR** (100 MHz, chloroform-*d*): 172.3, 170.0, 147.7, 147.3, 138.9, 138.7, 137.5, 137.3, 133.8, 133.6, 129.4, 129.2, 128.9, 128.8, 128.3, 128.2, 128.1, 126.8, 126.7, 126.0, 125.9, 124.6, 124.5, 116.2, 116.1, 88.5, 88.4, 83.7, 83.6, 47.6, 45.4, 36.7, 34.4, 33.7, 32.9, 31.2, 29.7, 27.0, 26.8, 23.8, 23.7, 21.6, 20.6, 16.6, 16.5 ppm; **IR** (thin film, cm^{-1}) 3064, 2935, 2862, 1703, 1594, 1496, 1458, 1447, 1381, 1363, 1304, 1142, 1081, 968, 914, 750, 689; **LRMS (ESI)** Calcd. for $[C_{23}H_{25}NO_4S+H]^+$ = 412.15, Found = 412.24.



41i

41i was prepared via ***Method A*** using **41** (21.6 mg, 0.088 mmol), sulfone ii (90.6 mg, 0.440 mmol), benzene sulfonamide (6.9 mg, 0.044 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **41i** (20.8 mg, 0.055 mmol, 63% yield) as a clear oil. **41i** was isolated as a 69:31 mixture of inseparable diastereomers.

Analytical data for **41i**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.85 - 7.70 (m, 2 H), 7.45 - 7.34 (m, 2 H), 7.21 - 7.11 (m, 1 H), 6.29 (s, 1 H), 5.68 - 5.56 (m, 1 H), 4.27 - 4.16 (m, 2 H), 4.39 and 4.09-4.07 (s, indicates *cis* and d, *J*=8.4 Hz indicates *trans*, 1 H), 2.91 - 2.46 (m, 2 H), 2.36 - 2.04 (m, 2 H), 2.03 - 1.51 (m, 5 H), 1.50 - 1.20 (m, 10 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): 171.6, 166.9, 138.8, 138.7, 136.9, 128.7, 128.6, 127.2, 126.6, 124.6, 124.4, 116, 7, 116.4, 91.3, 88.9, 91.3, 88.9, 60.8, 60.7, 50.6, 50.3, 40.1, 39.0, 37.6, 37.1, 36.9, 31.7, 30.1, 29.5, 28.4, 28.2, 24.6, 24.1, 23.3, 22.8, 14.2, 14.1 ppm; **IR** (thin film, cm^{-1}) 2927, 2857, 1710, 1594, 1495, 1367, 1304, 1187, 1157, 1025, 952, 753, 690; **LRMS (ESI)** Calcd. for $[C_{21}H_{27}NO_4+H]^+$ = 358.19, Found = 358.25.

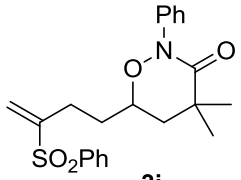


41j

41j was prepared via ***Method B*** using **41** (20.2 mg, 0.081 mmol), sulfone iii (91.9 mg, 0.290 mmol, 3.5 equiv), benzene sulfonamide (6.4 mg, 0.041 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **41j** (29.7 mg, 0.069

mmol, 86% yield) as a grey white residue. **41j** was isolated as a 72:28 mixture of inseparable diastereomers.

Analytical data for **41j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.96 - 7.33 (m, 9 H), 7.23 - 7.13 (m, 1 H), 6.55 - 6.45 (m, 1 H), 5.87 - 5.74 (m, 1 H), 4.21 and 3.90-3.78 (s, and d, *J*=8.8 Hz, 1 H), 2.86 - 2.42 (m, 2 H), 2.19 - 2.02 (m, 2 H), 1.88 - 1.55 (m, 4 H), 1.54 - 1.43 (m, 1 H), 1.42 - 1.26 (m, 2 H), 1.23 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 171.2, 148.7, 138.8, 136.8, 133.8133.5, 129.4, 129.2, 128.8, 128.7, 128.3, 126.1, 124.7, 126.6, 115.7, 116.4, 91.1, 88.1, 50.5, 50.2, 38.6, 37.4, 36.8, 36.4, 34.2, 31.6, 29.7, 29.0, 28.2, 28.0, 24.7, 24.0, 23.4, 23.5 ppm; **IR** (thin film, cm^{-1}) 3065, 2929, 2857, 2251, 1696, 1593, 1494, 1449, 1385, 1306, 1145, 1081, 957, 913, 749, 690; **LRMS (ESI)** Calcd. for $[C_{24}H_{27}NO_4S+H]^+$ = 426.14, Found = 426.22.

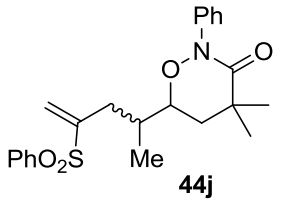


3j

3j was prepared via ***Method B*** using **3** (20.3 mg, 0.091 mmol), sulfone iii (296.1 mg, 0.910 mmol, 10 equiv), benzene sulfonamide (6.8 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **3j** as a mixture with some residual sulfone. The yield (37%) was determined by NMR using 2,4,6 trimethoxybenzene as an internal standard.

Analytical data for **3j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.89 (d, *J* = 8.0 Hz, 1 H), 7.71 - 7.63 (m, 1 H), 7.62 - 7.52 (m, 4 H), 7.35 (t, *J* = 8.0 Hz, 2 H), 7.22 - 7.12 (m, 1 H), 6.38 (s, 1 H), 5.71 (s, 1 H), 4.28 - 4.16 (m, 1 H), 2.58 - 2.33 (m, 2 H), 2.04 (dd, *J* = 7.3, 13.6 Hz, 1 H), 1.99 - 1.80 (m, 2 H), 1.76 (dd, *J* = 8.5, 13.8 Hz, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): 174.7, 149.6, 139.6, 138.7, 133.7, 129.3, 128.6, 128.3, 125.1, 124.1, 119.6, 79.1, 42.7, 39.1, 33.3, 27.2, 26.1, 25.9 ppm; **IR** (thin film, cm^{-1}) 3065, 2967, 2930, 2870, 1677, 1593, 1490, 1448, 1390,

1354, 1305, 1144, 1081, 954, 913, 750, 690, 573; **LRMS (ESI)** Calcd. for $[C_{22}H_{25}NO_4S+H]^+$ = 400.15, Found = 400.19



44j

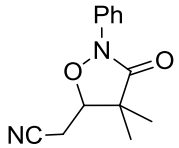
44j was prepared via ***Method B*** using **44** (20.5 mg, 0.085 mmol), sulfone iii (276.1 mg, 0.850 mmol, 10 equiv), benzene sulfonamide (6.8 mg, 0.043 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **44j** as a mixture with some residual sulfone. The yield (41%) was determined by NMR using 2,4,6 trimethoxybenzene as an internal standard.

Analytical data for **44j**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.88 (t, *J* = 7.7 Hz, 2 H), 7.64 (t, *J* = 7.3 Hz, 2 H), 7.59 - 7.51 (m, 3 H), 7.41 - 7.30 (m, 2 H), 7.21 - 7.12 (m, 1 H), 6.44 (d, *J* = 18.1 Hz, 1 H), 5.72 (d, *J* = 10.8 Hz, 1 H), 4.11 - 3.89 (m, 1 H), 2.81 - 2.44 (m, 1 H), 2.38 - 2.01 (m, 3 H), 2.00 - 1.85 (m, 2 H), 1.41 (s, 4 H), 1.34 (s, 3 H), 1.02 - 0.89 (m, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100MHz): δ = 174.6, 174.5, 148.4, 148.2, 139.5, 139.4, 138.7, 133.7, 133.6, 129.7, 129.6, 129.3, 129.2, 128.8, 128.6, 128.4, 128.3, 127.9, 125.8, 125.3, 125.1, 119.6, 83.9, 82.9, 40.6, 40.6, 40.3, 39.0, 38.9, 35,.8, 35.44, 33.6, 33.1, 27.8, 27.7, 26.2, 26.1, 14.5, 14.0 ppm; **IR** (thin film, cm^{-1}) 3065, 2971, 2932, 1676, 1593, 1490, 1449, 1390, 1354, 1304, 1142, 1081, 961, 912, 751, 690, 571; **LRMS (ESI)** Calcd. for $[C_{23}H_{27}NO_4S+H]^+$ = 414.17, Found = 414.24.

6.5.3 General Oxycyanation Conditions

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and *p*-toluenesulfonyl cyanide (TsCN, 3.0 equiv) and dissolved in specified nitrile solvent to make a 0.5M solution. While not necessary for reactivity, the addition of specified radical initiators in some reactions resulted in improved product yields and reaction times, and is indicated

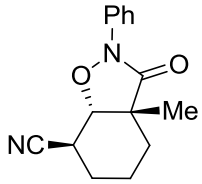
below when used. The vial was fitted with a PTFE-lined screw cap and argon was bubbled through the solution for 5-8 min. The reaction was allowed to stir under 1 atm argon at the specified temperature. Upon disappearance of the hydroxamic acid substrate, as indicated by TLC analysis, the solvent was removed under reduced pressure. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.



4k

4k was prepared using **4** (20.0 mg, 0.0974 mmol), TsCN (53.0 mg, 0.292 mmol), DLP (10 mol %, 3.9 mg, 0.0097 mmol) in EtCN (210 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 21 h. The solvent was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (33% EtOAc/hexanes) to afford **4k** (13.7 mg, 0.0595 mmol, 61 % yield) as a clear, colorless oil.

Analytical data for **4k**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.76 - 7.68 (m, 2 H), 7.47 - 7.35 (m, 2 H), 7.24 - 7.15 (m, 1 H), 4.56 (dd, *J* = 5.8, 7.8 Hz, 1 H), 2.87 (dd, *J* = 8.0, 17.1 Hz, 1 H), 2.75 (dd, *J* = 5.8, 16.8 Hz, 1 H), 1.45 - 1.40 (m, 3 H), 1.29 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 169.92, 136.56, 128.92, 125.19, 116.58, 115.47, 82.15, 46.35, 21.98, 17.77, 17.51 ppm; **IR** (thin film, cm^{-1}) 3068, 2974, 2932, 2254, 1708, 1594, 1494, 1392, 1361, 1308, 1180, 1149, 1083, 1051, 910, 754, 690; **LRMS (ESI)** Calcd. for $[C_{13}H_{14}N_2O_2+H]^+$ = 231.11, Found = 230.97.



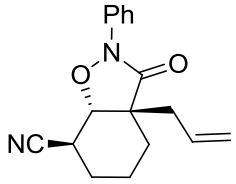
40k

40k was prepared using **40** (20.0 mg, 0.0.865 mmol), TsCN (47.0 mg, 0.0.259 mmol) in MeCN (200 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 22 h. The solvent

was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (20% EtOAc/hexanes) to afford **40k** as a 60:40 mixture of diastereomers (less polar spot 7.7 mg, 0.0300 mmol, and more polar spot 5.0 mg, 0.0194 mmol, total 57% yield) as a colorless oil.

Analytical data for **40k major** *:* **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.76 - 7.68 (m, 2 H), 7.45 - 7.37 (m, 2 H), 7.24 - 7.16 (m, 1 H), 4.48 (d, *J* = 7.8 Hz, indicates *trans*, 1 H), 2.91 (ddd, *J* = 4.1, 7.7, 10.5 Hz, 1 H), 2.26 - 2.17 (m, 1 H), 2.16 - 2.06 (m, 1 H), 1.83 - 1.64 (m, 2 H), 1.55 - 1.37 (m, 2 H), 1.46 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 169.13, 136.99, 128.96, 125.15, 119.83, 116.47, 83.36, 46.93, 30.16, 30.01, 26.18, 22.26, 20.51 ppm; **IR** (thin film, cm^{-1}) 3067, 2935, 2869, 2246, 1833, 1710, 1594, 1494, 1455, 1363, 1306, 1180, 1142, 1014, 973, 912, 754, 688; **LRMS (ESI)** Calcd. for $[C_{15}H_{16}N_2O_2+H]^+$ = 257.13, Found = 257.12.

Analytical data for **40k minor***:* **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.81 - 7.74 (m, 2 H), 7.47 - 7.37 (m, 2 H), 7.24 - 7.15 (m, 1 H), 4.44 (d, *J* = 3.3 Hz, indicates *cis*, 1 H), 2.98 (ddd, *J* = 3.3, 5.0, 12.3 Hz, 1 H), 2.12 - 1.95 (m, 2 H), 1.91 - 1.81 (m, 1 H), 1.81 - 1.68 (m, 2 H), 1.50 - 1.37 (m, 1 H), 1.36 - 1.30 (m, 3 H)) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 170.42, 136.86, 128.87, 125.03, 118.32, 116.53, 80.51, 44.99, 28.88, 28.17, 24.64, 19.63, 16.96 ppm; **IR** (thin film, cm^{-1}) 2928, 2867, 2246, 1707, 1593, 1495, 1458, 1364, 1305, 1154, 980, 903, 754, 691; **LRMS (ESI)** Calcd. for $[C_{15}H_{16}N_2O_2]^+$ = 257.13, Found = 257.12.



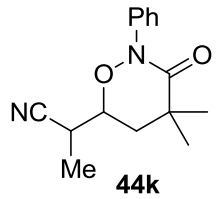
42k

42k was prepared using **42** (60.0 mg, 0.233 mmol), TsCN (126.8 mg, 0.699 mmol), DLP (10 mol %, 9.4 mg, 0.023 mmol) in EtCN (500 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 36 h. The solvent was removed from the crude reaction mixture under reduced

pressure and the crude material was purified by flash chromatography (gradient of 15-20-25% EtOAc/hexanes) to afford **42k** as a 68:32 mixture of diastereomers (less polar spot 23.2 mg, 0.0822 mmol, and more polar spot 10.8 mg, 0.0383, total 52% yield) as a colorless oil.

Analytical data for **42k major**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.77 - 7.70 (m, 2 H), 7.46 - 7.39 (m, 2 H), 7.25 - 7.17 (m, 1 H), 5.92 - 5.77 (m, 1 H), 5.30 - 5.21 (m, 2 H), 4.62 (d, *J* = 8.3 Hz, indicates *cis*, 1 H), 2.88 (ddd, *J* = 4.3, 8.2, 11.4 Hz, 1 H), 2.56 - 2.51 (m, 2 H), 2.24 - 2.16 (m, 1 H), 2.15 - 2.07 (m, 1 H), 1.85 - 1.74 (m, 1 H), 1.68 - 1.50 (m, 3 H), 1.45 - 1.30 (m, 1 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 167.89, 136.85, 131.37, 128.95, 125.21, 120.71, 119.99, 116.52, 80.93, 50.53, 39.54, 30.42, 27.84, 26.22, 20.67 ppm; **IR** (thin film, cm^{-1}) 3076, 2927, 2865, 2246, 1703, 1593, 1494, 1455, 1368, 1307, 1206, 1142, 1082, 987, 919, 754, 689; **LRMS (ESI)** Calcd. for $[C_{17}H_{18}N_2O_2+H]^+$ = 283.15, Found = 283.15.

Analytical data for **42k minor***:* **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.81 - 7.72 (m, 2 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.25 - 7.16 (m, 1 H), 5.95 - 5.79 (m, 1 H), 5.28 - 5.15 (m, 2 H), 4.63 (d, *J* = 3.3 Hz, indicates *cis*, 1 H), 2.94 (ddd, *J* = 3.3, 5.3, 11.8 Hz, 1 H), 2.64 (dd, *J* = 6.1, 14.2 Hz, 1 H), 2.39 (dd, *J* = 8.7, 14.4 Hz, 1 H), 2.11 - 1.96 (m, 2 H), 1.90 - 1.71 (m, 3 H), 1.59 (s, 3 H), 1.56 - 1.45 (m, 1 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 169.09, 136.69, 132.19, 128.83, 125.07, 119.84, 118.38, 116.57, 77.43, 48.09, 36.03, 28.31, 27.95, 24.13, 19.57 ppm; **IR** (thin film, cm^{-1}) 3075, 2925, 2857, 2247, 1832, 1705, 1594, 1494, 1456, 1365, 1305, 1177, 1143, 988, 914, 754, 690; **LRMS (ESI)** Calcd. for $[C_{17}H_{18}N_2O_2+H]^+$ = 283.15, Found = 283.15.



44k

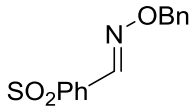
44k was prepared using **44** (25.0 mg, 0.107 mmol), TsCN (58.3 mg, 0.321 mmol), (*t*BuON)$_2$ (1.9 mg, 0.011 mmol, 10 mol % x3) in EtCN (250 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 28 h. The solvent was removed from the crude reaction mixture under

reduced pressure and the crude material was purified by flash chromatography (20% EtOAc/hexanes) to afford **44k** (less polar spot 6.6 mg, 0.0255 mmol and more polar spot 8.4 mg, 0.0325 mmol, 54% combined yield) as clear, colorless oils.

Analytical data for **44k TS**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.61 (d, *J* = 8.7 Hz, 2 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.26 - 7.17 (m, 1 H), 4.36 (q, *J* = 7.9 Hz, 1 H), 3.04 (quin, *J* = 7.1 Hz, 1 H), 2.28 (dd, *J* = 7.3, 13.7 Hz, 1 H), 2.11 (dd, *J* = 8.7, 13.9 Hz, 1 H), 1.48 (s, 3 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 151 MHz) 174.70, 139.07, 128.70, 125.66, 119.94, 119.47, 79.50, 40.02, 39.03, 30.58, 27.01, 25.33, 14.66 ppm; **IR** (thin film, cm^{-1}) 3064, 2926, 2244, 1679, 1594, 1491, 1391, 1355, 1300, 1177, 1059, 965, 755, 692; **LRMS (ESI)** Calcd. for $[C_{15}H_{18}N_2O_2+H]^+$ = 259.14, Found = 259.12.

Analytical data for **44k LS**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.73 (d, *J* = 8.7 Hz, 2 H), 7.44 - 7.38 (m, 2 H), 7.23 - 7.17 (m, 1 H), 4.38 - 4.33 (m, 1 H), 2.93 (quin, *J* = 7.1 Hz, 1 H), 2.16 (dd, *J* = 7.5, 13.9 Hz, 1 H), 2.01 (dd, *J* = 9.0, 13.9 Hz, 1 H), 1.49 (s, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.42 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 151 MHz) 174.33, 139.16, 128.73, 125.47, 119.50, 79.78, 40.56, 39.11, 30.63, 27.34, 25.54, 14.31 ppm; **IR** (thin film, cm^{-1}) 3064, 2926, 2244, 1679, 1594, 1491, 1391, 1355, 1300, 1177, 1059, 965, 755, 692; **LRMS (ESI)** Calcd. for $[C_{15}H_{18}N_2O_2+H]^+$ = 259.14, Found = 259.12.

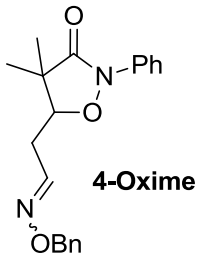
6.5.4 General Oxyacylation Conditions



iv

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv), sulfone iv (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85 ˚C. Upon

disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting crude mixture was dissolved in EtOH (1-2 mL) and cooled to 0˚C to induce precipitation of the unreacted sulfone which was removed by filtration. The filtrate was then concentrated under reduced pressure, dissolved in THF (1-3mL) and camphorsulfonic acid (4.0 equiv) and aqueous formaldehyde (37%, 10.0 equiv) were added. The reaction was stirred at room temperature, overnight. The mixture was then diluted with Et_2O (10 mL), washed with $NaHCO_3$ (5 mL), and extracted with Et_2O (2 x 10mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified using column chromatography in the specified solvent system

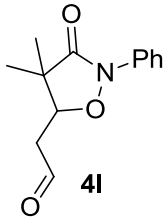


4-Oxime

4-Oxime was prepared according to the general procedure (but isolated prior to hydrolysis) using **4** (20.0 mg, 0.0981 mmol), sulfone iv (134.7 mg, 0.492 mmol), benzene sulfonamide (50 mol %, 7.1 mg, 0.050 mmol) in DMSO (210 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude material was purified by flash chromatography (16% hexanes/DCM) to afford **4-Oxime** as a 50:50 mixture of E/Z isomers (26.3 mg, 0.075 mmol, 76 % yield) as a clear, grey residue.

Analytical data for **4-Oxime**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.76 - 7.66 (m, 2 H), 7.60 (dd, *J* = 5.3, 6.8 Hz, 0.5 H), 7.45 - 7.32 (m, 7 H), 7.20 - 7.12 (m, 2 H), 6.94 (t, *J* = 5.3 Hz, 0.5 H), 5.18 (s, 1H), 5.13 (2, 1 H), 4.43 (ddd, *J* = 4.6, 9.1, 11.6 Hz, 1 H), 2.88 - 2.73 (m, 1 H), 2.69 (ddd, *J* = 5.5, 9.3, 14.9 Hz, 0.5 H), 2.64 - 2.54 (m, 0.5 H), 1.29 (d, *J* = 11.4 Hz, 3 H), 1.22 (d, *J* = 3.7 Hz, 3 H); **^{13}C**

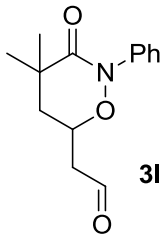
NMR (chloroform-*d*, 150MHz): 171.3, 171.2, 146.3, 146.2, 137.5, 137.4, 136.9, 136.8, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 124.7, 124.6, 116.4, 116.3, 84.9, 84.6, 76.2, 75.9, 46.3, 28.8, 25.2, 21.4, 21.3, 17.7, 17.6 ppm; **IR** (thin film, cm^{-1}) 3064, 3032, 2970, 2930, 2875, 1702, 1594, 1494, 1459, 1388, 1361, 1307, 1180, 1021, 902, 752, 659; **LRMS (ESI)** Calcd. for $[C_{20}H_{22}N_2O_3+H]^+$ = 339.16, Found = 339.07



4l

4l was prepared from the hydrolysis of **4-Oxime** (36.0 mg, 0.106 mmol), using CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.1mL µL). The reaction was completed, as indicated by TLC, after stirring at rt overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **4l** (23.1 mg, 0.098 mmol, 93 % yield, 71% over 2 steps) as a clear oil.

Analytical data for **4l**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 9.93 (s, 1 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.39 (t, *J* = 7.9 Hz, 2 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 4.84 (dd, *J* = 3.9, 9.0 Hz, 1 H), 2.97 (ddd, *J* = 1.8, 9.2, 17.2 Hz, 1 H), 2.75 (ddd, *J* = 1.1, 3.7, 17.6 Hz, 1 H), 1.34 (s, 3 H), 1.22 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 150MHz): 197.8, 179.9, 136.8, 128.8, 124.8, 116.4, 81.8, 46.0, 42.2, 21.3, 18.0ppm; **IR** (thin film, cm^{-1}) 2975, 2875, 2733, 1726, 1701, 1593, 1494, 1464, 1388, 1360, 1308, 1041, 918, 754; **LRMS (ESI)** Calcd. for $[C_{13}H_{15}NO_3+H+MeOH]^+$ = 266.13, Found = 266.04.

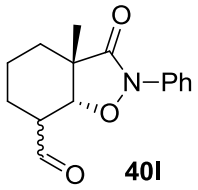


3l

3l was prepared according to the general procedure using **3** (20.3. mg, 0.091 mmol), sulfone iv (246.2.4 mg, 0.912 mmol), benzene sulfonamide (50 mol %, 6.8 mg, 0.046 mmol) in DMSO (210

μL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The reaction was worked up according to the general procedure and the crude product was subjected to the hydrolysis conditions: CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.2 mL μL). The reaction was completed, as indicated by TLC, after stirring at rt overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **3l** (7.9 mg, 0.031 mmol, 34% over 2 steps) as a clear oil.

Analytical data for **3l**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 9.85 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 2 H), 7.38 (t, *J* = 8.1 Hz, 2 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 4.91 (dq, *J* = 5.1, 7.9 Hz, 1 H), 3.03 (ddd, *J* = 1.7, 8.1, 17.8 Hz, 1 H), 2.80 - 2.74 (m, 1 H), 2.25 (dd, *J* = 7.3, 13.9 Hz, 1 H), 1.87 (dd, *J* = 8.4, 13.9 Hz, 1 H), 1.45 (s, 3 H), 1.41 (s, 3 H); **^{13}C NMR** (chloroform-*d*, 150MHz): 200.7, 174.4, 139.2, 128.7, 125.5, 119.5, 115.9, 74.8, 41.4, 39.1, 26.8, 25.3, 23.2 ppm; **IR** (thin film, cm^{-1}) 2925, 2360, 1725, 1676, 1592, 1489, 1353, 1302, 1059, 754, 690; **LRMS (ESI)** Calcd. for $[C_{14}H_{17}NO_3 + H + MeOH]^+$ = 280.15, Found = 380.02.



40l

40l was prepared according to the general procedure using **40** (31.2. mg, 0.134 mmol), sulfone iv (177.4 mg, 0.671 mmol), benzene sulfonamide (50 mol %, 10.3 mg, 0.067 mmol) in DMSO (210 μL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The reaction was worked up according to the general procedure and the crude product was subjected to the hydrolysis conditions: CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.2 mL). The reaction was completed, as indicated by TLC, after stirring at rt overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **40l** as a 60:40 mixture of diastereomers (19.1 mg, 0.074 mmol, 54% over two steps) as a clear oil. The diastereomers were later separated by additional flash chromatography (7% Et_2O/Pentanes).

Analytical data for **40l Major**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 9.82 (s, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.40 (t, *J* = 7.9 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 4.70 (d, *J* = 6.6 Hz, 1 H; indicates *trans*), 2.77 - 2.71 (m, 1 H), 2.27 - 2.21 (m, 1 H), 2.10 - 2.04 (m, 1 H), 1.74 - 1.68 (m, 1 H), 1.47 - 1.38 (m, 6 H) ppm; **^{13}C NMR** (chloroform-*d*, 150 MHz): 200.7, 170.1, 137.3, 128.9, 124.8, 116.3, 81.5, 50.3, 46.9, 30.8, 22.9, 22.4, 20.9 ppm; **IR** (thin film, cm^{-1}) 2928, 2858, 1705, 1594, 1494, 1458, 1380, 1362, 1303, 975, 754; **LRMS (ESI)** Calcd. for $[C_{15}H_{17}NO_3 + H + MeOH]^+$ = 292.15, Found = 292.07.

Analytical data for **40l Minor**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 9.91 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 4.75 (d, *J* = 2.9 Hz, 1 H indicates *cis*), 2.64 (td, *J* = 3.8, 12.7 Hz, 1 H), 2.03 - 1.97 (m, 1 H), 1.93 - 1.87 (m, 1 H), 1.81 (dq, *J* = 3.5, 13.1 Hz, 1 H), 1.76 - 1.72 (m, 2 H), 1.47 - 1.42 (m, 1 H), 1.35 (s, 3 H) ppm; **^{13}C NMR** (chloroform-*d*, 150 MHz): 200.6, 171.3, 137.1, 128.9, 128.8, 124.8, 116.4, 116.3, 81.6, 48.5, 45.4, 29.6, 20.4, 19.6, 16.6 ppm; **IR** (thin film, cm^{-1}) 3001, 2985, 1706, 1592, 1493, 1461, 1384, 1359, 1300, 975, 754; **LRMS (ESI)** Calcd. for $[C_{15}H_{17}NO_3 + H + MeOH]^+$ = 292.15, Found = 292.07.

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7. CHAPTER SEVEN

Heteroatom-Centered Radical Aliphatic C-H Halogenations

7.1 Introduction

Hydrocarbons, particularly saturated aliphatic hydrocarbons, are the major constituents of oil and natural gas and are the feedstocks of the chemical industry. However, because alkanes are made up of strong C-H and C-C bonds which contain no low energy empty orbitals or high energy filled orbitals that could easily participate in reactions, aliphatic molecules devoid of functionality are generally unreactive.

Traditionally, organic synthesis has relied on the transformation of functional groups which can often be plagued by low atom- and step-economy. Thus the creation of new bonds requires the presence of either a heteroatom (i.e. O, N, halogen, etc.) or an unsaturation (olefin), but C-H bonds are not usually viewed as viable functional groups for use in synthesis. However, introducing functionality directly through C-H bond transformations has the potential to revolutionize the way synthetic chemists construct molecules. This approach holds promise to streamline the synthesis of all types of molecules from agrochemicals to pharmaceuticals.

Enzymes are known catalysts of selective C-H functionalizations and have inspired generations of chemists to attempt to reproduce such reactivity in situ. However, enzymes are by design, limited to functionalization at specific sites on a specific substrate or set of substrates, making it challenging to apply this strategy in a general setting.[1,2]

7.2 Background

Efforts to develop selective, aliphatic C-H functionalization have been most successful using directing group strategies.[3] However, the use of a directing-group approach still requires pre-existing

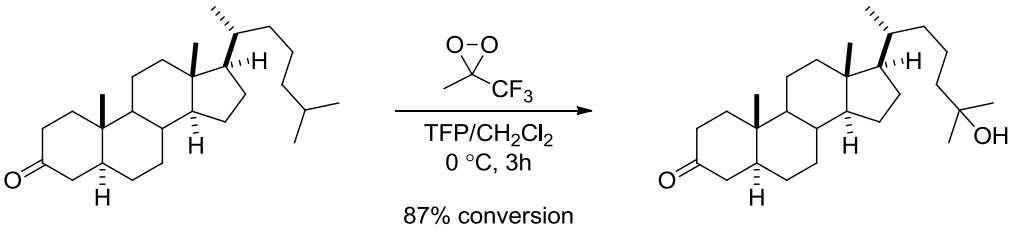
functionality in order to achieve a transformation of an aliphatic C-H bond, and it limits the potential substrates that can be functionalized. For purposes herein, focus will be directed only at intermolecular processes that do not require directing groups.

7.2.1 C-H Functionalization – Hydroxylation

The oxidation of C-H bonds has a long history and has been at the forefront of developing research in chemistry for several decades. Nature employs a group of enzymes, cytochrome P-450's, to metabolize a diverse array of small molecules, typically through the oxidation of aliphatic C-H bonds or epoxidation of alkenes.[2] Knowledge of this reactivity has inspired numerous research endeavors to approximate this reactivity without enzymes and the accompanying restrictions. A major challenge that has been encountered with alkane C-H oxidations has been less about developing catalytic systems that are reactive enough to activate these typically unreactive C-H bonds, but rather being able to activate them selectively and controllably.

Among some of the earliest selective C-H oxidation reagents are those of dioxiranes (**Figure 7-1**).[4] Curci and others have demonstrated that strained electrophilic heterocycles, such as trifluoromethyldioxirane (TFDO), are useful in aliphatic C-H oxidation. However, dioxiranes are suboptimal reagents to work with for practical purposes as they are unstable to ambient light and heat, and generally must be prepared in situ. These systems display good selectivity in some cases but in addition to their rapid decomposition, dioxiranes are reactive towards alkenes, resulting in epoxidation and further limiting their application to functionalized substrates.

Figure 7-1. Trifluoromethyldioxirane C-H Hydroxylation

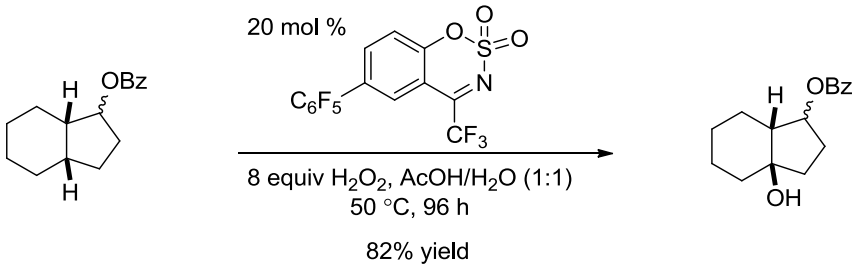


Curci *JOC* **1992**, 2182.

Oxaziridines are far more stable than their dioxirane analogs, making them more practical for use in

synthesis. Recently, Du Bois has developed benzoxathiazine-mediated C-H hydroxylation reactions that are highly selective for tertiary, methine C-H bond oxidation (**Figure 7-2**).[5–7]

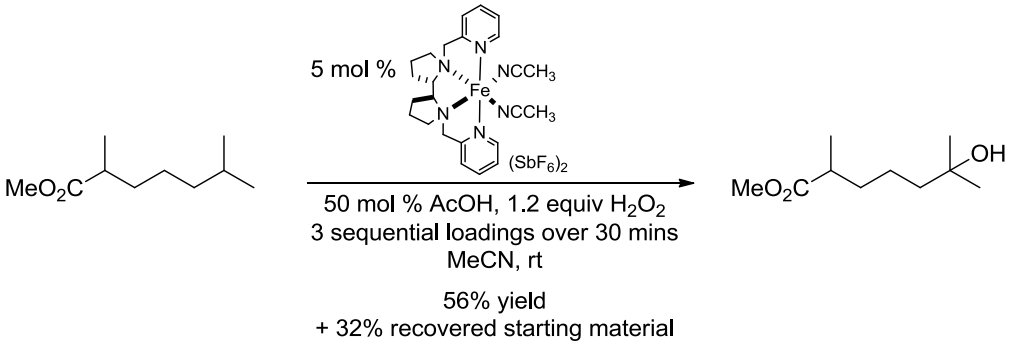
Figure 7-2. Tertiary Selective C-H Hydroxylations Using Benzoxathiazines



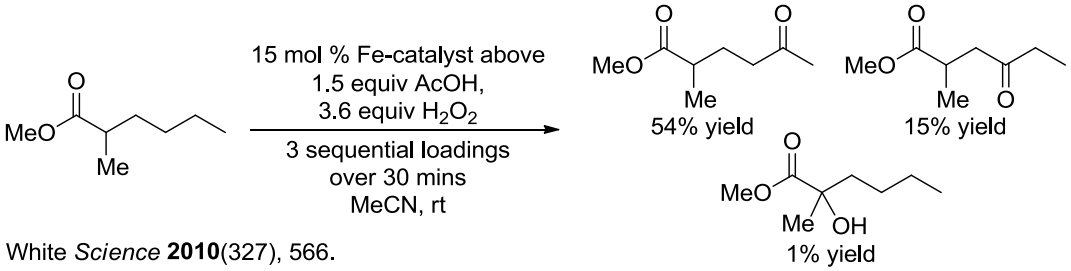
Du Bois *ACIE* **2009**, 4513.

Significant advances in the area of intermolecular, aliphatic C-H oxidation came with successive publications by White (**Figure 7-3**).[8,9] This biomimetic, Fe-catalyzed approach is successful at selectively functionalizing diverse C-H bonds based on steric, electronic, or substrate directivity factors. Under these oxidative conditions, methylene C-H oxidations are possible, though often result in over-oxidation to ketone products.

Figure 7-3. Fe-Catalyzed Aliphatic C-H Oxidations



White *Science* **2007**(318), 783.

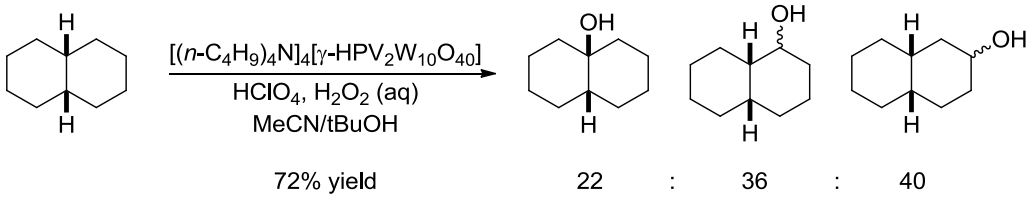


White *Science* **2010**(327), 566.

Further progress in selective C-H oxidation away from tertiary C-H, methine bonds in favor of

secondary, methylene C-H bonds was made with the development of Mizuno's bulky polyoxometalate catalyst (**Figure 7-4**).[10] This system uses hydrogen peroxide (H_2O_2) as the stoichiometric oxidant and is moderately selective for the methylene positions of *cis*-decalin as well as other cyclic alkanes.

Figure 7-4. Sterically Bulky Polyoxotungstate-Mediated C-H Hydroxylation



Mizuno *Nat. Chem.* **2010**, 478.

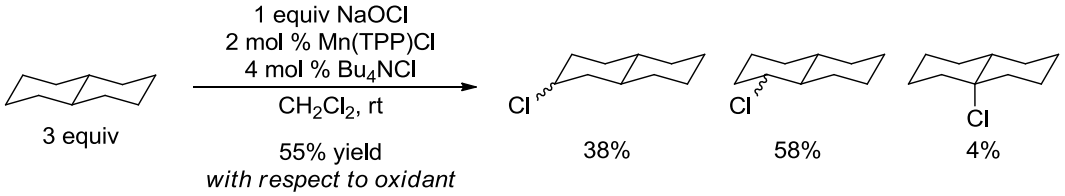
7.2.2 C-H Functionalization – Halogenation

Compared to alkane hydroxylation, a number of fundamental transformations with enormous potential in synthesis, such as alkane halogenation, remain very limited. Unactivated C-H halogenation is a particularly attractive type of C-H functionalization as halogenated organic compounds play a vital role in synthetic chemistry.[11] As of 2004, more than 4500 halogenated natural products have been discovered (98% of which are chlorinated or brominated).[12] Alkyl chlorides and bromides also find widespread use as substrates in synthesis such as in substitution and cross-coupling reactions.[13–15] As a result, more than 95% of agrochemicals, 85% of pharmaceuticals, and 50% of all products marketed by the chemical industry are derivatives of chlorine chemistry.[16]

Nature has a wealth of enzymatic machinery to selectively replace unactivated aliphatic C-H bonds with halogens, especially chlorine and bromine. These halogenases and haloperoxidases use oxidative strategies to convert abundant halide anions into electrophilic or radical species.[17] Achieving selective halogenation of aliphatic C-H bonds in synthesis has proven more difficult. In a rare example of a catalytic aliphatic C-H halogenation system, manganese porphyrins have been shown to catalyze halogenations using sodium hypohalites as the halogen source (**Figure 7-5**).[18] While this work demonstrates a proof of principle, an excess of alkane substrate is required and the

selectivities and efficiencies are not yet at synthetically useful levels.

Figure 7-5. Mn-Porphyrin Catalyzed C-H Halogenations

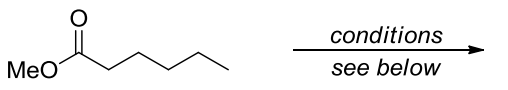


Groves *JACS* **2010**, 12847.

Radical halogenation of alkanes in the absence of transition metals using elemental chlorine or bromine is well documented.[19] However, the control of site-selectivity is a major challenge in these systems. As a result, these prototypical halogenations are largely impractical except in the case of very simple substrates.

A number of intermolecular C-H functionalizations using heteroatom-centered radicals have been reported. Even though these processes involve the use of highly reactive radical intermediates which are typically not considered viable for selective chemistry, they demonstrate impressive levels of steric and electronic selectivities comparable to those of modern aliphatic C-H oxidations. For example, Minisci has developed a remarkably selective aliphatic C-H halogenation reaction using what is ostensibly intermolecular Hofmann-Löffler-Freytag (HLF) chemistry,[20–23] using protonated bromoamines as precursors to cationic aminium radicals (**Figure 7-6**). Although a highly acidic reaction medium is required for efficient and selective reactions, which limit the potential use in synthesis, the electronic selectivities are unparalleled.

Figure 7-6. Electronically Selective Heteroatom-Centered Radical Brominations



$MeO_2C—CH_2—CH_2—CH_2—CH_2—CH_3$

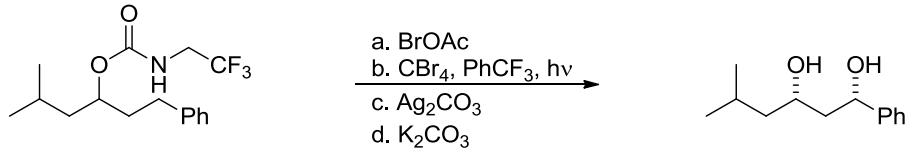
	α	β	γ	ω-1	ω
	% selectivity of bromination				
Me_2NBr, H_2SO_4, AcOH	—	0.4	5.9	87.0	6.8
20 mol % HNO_3, 1 equiv Br_2 20 mol % NHPI, AcOH, 100 °C	6.3	16.0	27.0	50.7	—

Minisci *Tetrahedron Lett.* **1967**, 2207.

Highly electrophilic phthalimido-*N*-oxyl (PINO) radical, derived from *N*-hydroxyphthalimide (NHPI), has also been used in site-selective intermolecular C-H functionalizations (**Figure 7-6**).[24] These protocols also require the use of strong acids (HNO_3), have low conversions (ca. 30-40%), and are limited in substrate scope to simple, linear hydrocarbons.

Conversely, *N*-haloamides have been successfully used in intramolecular HLF reactions under neutral conditions in a variety of synthetic contexts.[25–27] Baran developed an approach to 1,3-diol synthesis from the corresponding alcohol via a controlled, radical-mediated C-H functionalization (**Figure 7-7**).[27] This strategy includes the *N*-bromination of a trifluoroethyl carbamate followed by intramolecular H-atom abstraction, cyclization, and hydrolysis to access diols. Their examples include only functionalization of tertiary and benzylic C-H bonds, and these positions must be accessible by a 1,6-H-atom abstraction.

Figure 7-7. 1,3-Diol Synthesis via Neutral HLF-Type Reactions



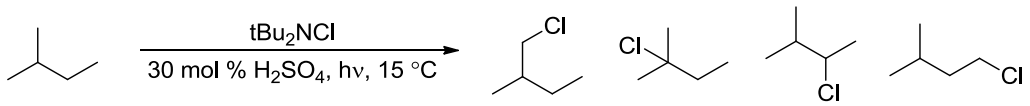
Baran *JACS* **2008**, 7247.

97% yield
5:1 dr

Surprisingly, this promising reactivity of *N*-haloamide derivatives has not been harnessed in intermolecular reactions.

There are also reports of intermolecular heteroatom-centered radical mediated processes that display high levels of steric selectivity. Deno has developed a photochemical C-H halogenation using aminium radicals in strong acid, where primary C-H halogenation is favored over tertiary functionalization as a result of steric effects (**Figure 7-8**).[28] Reactions of bulky *N*-chloroamines under mild photochemical or thermally initiated conditions have also displayed high steric selectivities.[29,30] However, these studies were conducted to assess the physical organic properties of aminium radicals generated from *N*-chloroamines and they did not explore the substrate scope or optimize the reactions for isolated yield of chlorinated products.

Figure 7-8. Sterically Selective Radical Chlorinations



ratios of products : 1.1 1.0 6.0 0.55
(no yields given)

Deno *JACS* **1971**, 2065.

7.3 Reaction Development

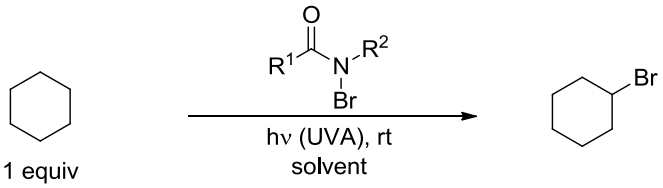
We set out to develop an approach to site-selective C-H halogenation that capitalizes on the highly selective reactivity displayed by electrophilic nitrogen-centered radicals derived from *N*-halo derivatives. Amidyl radicals are successfully produced from homolytic cleavage of the weak N-X bond of *N*-haloamides upon photochemical irradiation or the use of thermal radical initiators. We viewed an amide platform as an excellent way to regulate both the steric and electronic properties of the corresponding amidyl radical, while simultaneously addressing the practical concern of mild reaction conditions.

7.3.1 Simple Substrates

We began our studies investigating the efficiency of C-H halogenation of simple cycloalkanes using a variety of *N*-haloamides and derivatives. Many other alkane functionalization protocols require the use of multiple equivalents of substrate and calculate reaction yields with respect to the amount of oxidant used. This is suboptimal particularly if the protocol is expected to be applied to complex, or precious, substrates. We therefore were interested not only in the efficiency of *N*-haloamide mediated alkane halogenations, but using the alkane substrate as the limiting reagent.

Reaction of *N*-bromoamide **48** with 1 equiv cyclohexane in methylene chloride (CH_2Cl_2), irradiating with UVA light at room temperature resulted in Br-cyclohexane, albeit in low yield (25%, **Table 7-1, entry 1**). A solvent screen revealed that aromatic solvents generally increased the yield of bromination (**entries 2 – 6**). We next assessed the efficiency of this halogenation with respect to the bromoamide reagent used.

Table 7-1. Optimization Studies for the Bromination of Cyclohexane Using *N*-Bromoamides



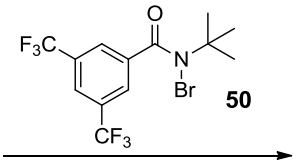
entry	R^1	R^2	bromoamide	solvent	% yield[a]
1	Ph	tBu	**48**	CH_2Cl_2	25
2	Ph	tBu	**48**	$CHCl_3$	29
3	Ph	tBu	**48**	DCE	29
4	Ph	tBu	**48**	$PhCF_3$	50
5	Ph	tBu	**48**	PhCl	61
6	Ph	tBu	**48**	PhH	64
7	p-NO_2 benz-	tBu	**49**	PhH	82
8	3,5-$(CF_3)_2$ benz-	tBu	**50**	PhH	93
9	Ph	CH_2CF_3	**51**	PhH	51
10	3,5-$(CF_3)_2$ benz-	CH_2CF_3	**52**	PhH	65

[a] Yield determined by GC analysis.

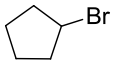
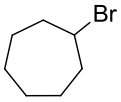
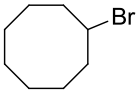
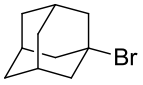
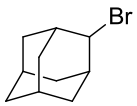
Substituting the phenyl ring of **48** with a *para*-nitro group (**49**) increases the yield of Br-cyclohexane to 82% (**Table 7-1**, **entry 7**) and making the aryl ring even more electron-poor with two trifluoromethyl groups (**entry 8**) further increases the yield to 93%. We also studied the effect of using an electron-poor amino group. Substituting *N*-*tert*-butyl with *N*-trifluoroethyl, (**51**) resulted in decreased efficiency (51% yield, **entry 9**). Combining an electron-poor aryl ring with an electron-poor amino group created the most electron-deficient bromoamide reagent (**52**), resulted in only a moderate yield, 65%, of Br-cyclohexane (**Table 7-1**, **entry 10**).

With optimized conditions in hand, we next examined the reaction yield of bromination of other simple cycloalkane substrates (**Table 7-2**). These reactions proved to be slightly less efficient than with cyclohexane, but cyclopentane, cycloheptane, and adamantane were brominated in preparatively useful yields (**entries 1 – 4**). Notably, bromination of adamantane results almost entirely in tertiary halogenation (above 50%; **entry 4**). See **7.3.3 Steric Selectivity Studies** for further discussion of the bromination selectivity of adamantane.

Table 7-2. Bromination of Simple Cycloalkanes Using *N*-Bromoamide **50**



alkane (1 equiv) → Br-alkane; PhH, hν (UVA), rt

entry	substrate	product	% yield[a]
1			59
2			89
3			99
4			60
			2

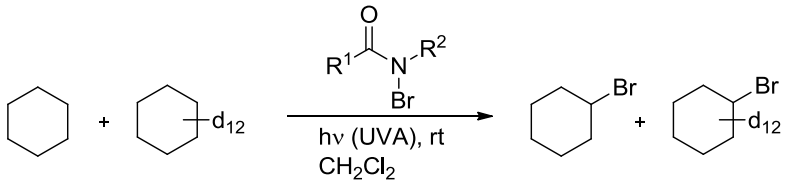
[a] Yield determined by GC analysis.

7.3.2 Identification of the Active H-atom Abstracting Species

In addition to the examination of site-selectivity, much of the early literature precedent of cationic aminium radical halogenation revolved around identifying the active H-atom abstracting species. The common arguments set forth to justify the conclusion of an aminium radical H-atom abstraction include: (1) the halogenation reactions observed are highly selective; that is, they are more selective than free radical chlorination with chlorine radical serving as the abstracting species, (2) there is no significant difference in the site-selectivity between chlorination with *N*-chloroamines and bromination with the analogous *N*-bromoamines, and (3) the Hammett plot value obtained from halogenation of substituted toluenes (ρ = -1.36) is comparable to that for bromination with bromine radical (ρ = -1.46), but is significantly greater than for chlorination using chlorine radical (ρ = -0.66).[31–33] Additionally, the abstracting species was identified by Greene and co-workers by

analyzing the relative rate of abstraction between the secondary and tertiary C-H bonds of adamantane.[29,30] In these reports, Greene demonstrates that while free radical chlorination of adamantane using Cl_2 results in a $k_{tertiary}/k_{secondary}$ value of 1.9, *N*-chloro-*N*-*tert*-butylacetamide and photochemical initiation with a catalytic amount of 2,4,6-trimethylpyridine (TMP) results in a significantly higher k_t/k_s value of 35.0. This strongly suggests that the abstracting species that is sensitive to the steric environment of the C-H bond and that chlorine radical is not responsible for H-atom abstraction under these conditions.

Table 7-3. Kinetic Isotope Studies of Cyclohexane Using *N*-Bromoamides



entry	R^1	R^2	bromoamide	k_H/k_D
1	Ph	tBu	**48**	5.7
2	3,5-$(CF_3)_2$ benz-	CH_2CF_3	**52**	3.3
3	NBS			2.1
4	Ph	CH_2CF_3	**51**	5.8
5	*p*-NO_2 benz-	tBu	**49**	3.8
6	3,5-$(CF_3)_2$ benz-	tBu	**50**	5.6

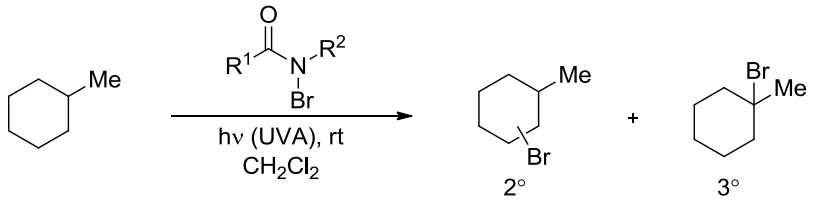
We chose to conduct several kinetic isotope effect studies to help identify the H-atom abstracting species using cyclohexane and d_{12}-cyclohexane (**Table 7-3**). The measured primary KIE for several of our *N*-haloamide reagents was compared to values we obtained using *N*-bromosuccinimde (NBS). The clear difference in KIE values between NBS (k_H/k_D = 2.1, **entry 3**) and our prepared *N*-bromo reagents (k_H/k_D = 3.3 to 5.8, **Table 7-3, entries 1**, **2**, and **4 – 6**) suggests that the bromination of cyclohexane using these reagents does not proceed via the same H-atom abstracting species. And because alkane brominations are thought to proceed via either bromine-radical or succinimidyl-radical chain processes with NBS, this KIE data indicates that halogenations using *N*-bromoamides are not likely proceeding this pathway. While this alone does not confirm that amidyl radicals are responsible for H-atom abstraction, it does support ruling out unselective free-

radical reactivity. Additionally, the bromination of adamantane and methyl cyclohexane using our designed bromoamide reagents is significantly more sterically selective than with Br_2 or NBS. This further supports our hypothesis that H-atom abstraction occurs via amidyl radicals.

7.3.3 Steric Selectivity Studies

A characteristic of any general site-selective, intermolecular C-H functionalization is the presence of multidimensional selectivity, with steric selectivity being a very important component. Steric selectivity in C-H functionalization enables the differentiation of C-H bonds that would otherwise be similar electronically, which is a common occurrence with many organic substrates. The majority of known, site-selective C-H functionalizations prefer to activate tertiary C-H bonds (i.e. methine), which are most sterically blocked, in the presence of other types of bonds (methylene, methyl, etc.). Current electrophilic systems for intermolecular functionalization of aliphatic C-H bonds have demonstrated a potential to favor less hindered sites, however, the selectivity is often modest and/or only observed with certain substrates.[34,35] For example, two methylene or two methine

Table 7-4. Halogenation of Methyl Cyclohexane: steric selectivity studies



entry	R^1	R^2		2° Br	3° Br	k_s/k_t
1	NBS			37.8	62.2	0.06
2	Mn(TPP)Cl/NaOBr			79.8	20.2	0.40
3	Ph	CH_2CF_3	**51**	79.3	20.7	0.38
4	Ph	tBu	**48**	90.2	9.8	0.91
5	*p*-NO_2 benz-	tBu	**49**	97.6	2.4	4.1
6	3,5-$(CF_3)_2$ benz-	tBu	**50**	98.0	2.0	4.9

sites may be differentiated in some cases, but the strong preference for electrophilic systems to functionalize tertiary sites dictates that such groups are not tolerated in substrates without electronic

deactivation or substrate bias. This is a notable obstacle as methine C-H bonds are quite common in organic molecules.

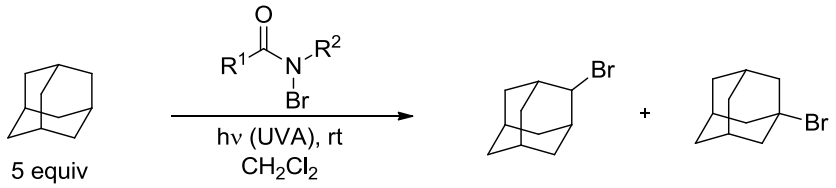
Typically, heteroatom-centered radicals are either highly selective for tertiary C-H bond abstraction as is the case for free-radical bromination, or are generally unselective as with free-radical chlorination. Methyl cyclohexane is an excellent test substrate to assess the methylene verses methine selectivity of an aliphatic C-H functionalization system. The ratio of secondary to tertiary functionalization ($k_{secondary}/k_{tertiary}$ which is corrected for the number of H-atoms at the specified positions) of methyl cyclohexane using chlorine (Cl_2) is 1.0,[36] while bromination using *N*-bromosuccinimide and irradiation results in a k_s/k_t of 0.06 (**Table 7-4, entry 1**), strongly favoring methine halogenation (**Table 7-4**). Even one of the few sterically selective aliphatic C-H halogenations, reported by Groves, using Mn(TPP)Cl/NaOBr, proceeds with rather poor selectivity with a k_s/k_t of 0.40 (**Table 7-4, entry 2**).[18]

Conversely, we have found that the selectivity of halogenation of methyl cyclohexane using *N*-bromoamides is modifiable by altering the steric and electronic nature of the amide reagent (**Table 7-4, entries 3 – 6**). Amide reagent **51** bearing an electron-withdrawing trifluoroethyl amino group brominates methyl cyclohexane with a k_s/k_t of 0.38, making it 2.6 times more selective for functionalization of the methine position compared to any methylene (**entry 3**). By substituting the trifluoroethyl amino group for a comparably more electron rich, but sterically bulkier *tert*-butyl amino group, this selectivity significantly decreases to a k_s/k_t value of 0.91 (**Table 7-4, entry 4**). By introducing electron-withdrawing groups to the aryl ring of the benzamide, the selectivity is greatly altered, to the point that secondary methylene positions are actually favored (k_s/k_t = 4.1 and 4.9, respectively; **entries 5 - 6**). This is quite remarkable as oxidation of methyl cyclohexane using a bulky polyoxometallate, a reagent designed to be highly sterically selective, gives a k_s/k_t of 0.4, which is actually selective for tertiary functionalization.[10] Notably, in all of these cases the amount of methyl halogenation is negligible.

Adamantane is also an excellent substrate to examine the steric selectivity of our reagents

decoupled from electronic effects. This is a result of similar stabilities of 1-adamantyl ($\Delta_f H°$ = 15 kcal/mol) and 2-adamantyl ($\Delta_f H°$ = 12 kcal/mol) radicals, which allows the steric accessibility of the tertiary, which are unhindered, compared to the secondary C-H bonds which are hindered, to be assessed.[37] Therefore, the ratio between functionalization at the tertiary site to the secondary site (k_t/k_s corrected for the number of H-atoms at each specified position) is a possible way to determine steric effects of an H-atom abstracting species. This k_t/k_s ratio has been used in a variety of C-H functionalizations to describe the steric selectivity of a given system.[38] Bromination of adamantane

Table 7-5. Bromination of Adamantane Using *N*-Bromoamides



entry	R^1	R^2		2° Br	3° Br	k_t/k_s
1	NBS			49.9	50.1	3.01
2	Ph	tBu	**48**	7.4	92.6	37.5
3	Ph	CH_2CF_3	**51**	3.0	97.0	95.7
4	p-NO_2 benz-	tBu	**49**	8.0	92.0	34.4
5	3,5-$(CF_3)_2$ benz-	CH_2CF_3	**52**	3.1	96.7	94.5

using NBS gives a low k_t/k_s value of 3.01 (**Table 7-5, entry 1**). However, halogenation using our *N*-bromo-*N*-*tert*-butyl amides **48** and **49** give k_t/k_s values of 37.5 and 34.4, respectively (**entries 2 – 3**). These values are consistent with the sterically selective chlorinations reported by Greene using *N*-chloro-*N*-*tert*-butyl acetamides (k_t/k_s = 38).[30] Conversely, *N*-trifluoroethyl amide reagents **51** and **52** give k_t/k_s values nearly 3 times as high as **48** or **49** (**Table 7-5, entries 4 – 5**). Despite this extremely selective reactivity, it is not consistent with radical functionalization, but rather is likely the result of a reagent-substrate oxidative single-electron transfer unique to adamantane because of its structure.[39,40] In future reagent development, we plan on using adamantane as a quick benchmark to assess the steric selectivity of a given *N*-halo compound, but must keep in mind this possible anomalous single-electron transfer pathway.

7.3.4 Electronic Selectivity Studies

The ability to distinguish between aliphatic C-H bonds of similar reactivity is critical to developing any site-selective C-H functionalization approach, and while steric components are important, examples of organic substrates that possess only steric controlling factors devoid of any electronic influences are rare. Previous heteroatom-centered radical C-H halogenation methods have displayed impressive levels of electronic selectivity. Strong polar effects in these processes are present in both the H-atom abstracting electrophilic cationic aminium radicals and the substrates containing electron-withdrawing groups that are likely protonated in the acidic reaction medium.[41] Electrophilic reagents are most prone to the activation of C-H bonds that are the most electron-rich within a substrate, guiding prediction of which sites of a molecule are most likely to be functionalized.[34,35] Highly strained electrophilic heterocycles like TFDO, are capable of electronically selective aliphatic C-H oxidations, but the sensitivity of TFDO towards both ambient temperature and light and a propensity to oxidize tertiary C-H bonds in preference to either methylene or methyl C-H's, distracts from its applicability in general synthetic contexts.[4] Oxidations using DuBois' benzoxathiazine reagent are similarly electronically selective but are limited to tertiary C-H bonds.[5,6] Halogenation systems developed by Groves using a Mn-porphyrin catalyst have demonstrated promising initial electronic selectivity, but the substrates included in their study are limited and further evaluation would be necessary to determine their viability.[18]

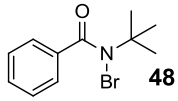
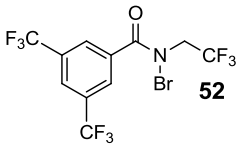
Since the high electronic selectivity displayed by heteroatom-centered radicals is likely a result of the strongly polarized aminium radical as well as the acidic reaction conditions,[41] we hypothesized that a similarly selective C-H halogenation could be achieved using an *N*-haloamide, containing an electron-withdrawing acyl group, under neutral conditions. As a result of the decreased electrophilicity compared to cationic aminium radicals, we proposed that the addition of electron-withdrawing groups to the amide could inductively compensate for the decreased electrophilicity of the neutral amidyl radical.

Our preliminary studies using amidyl radicals have demonstrated promising electronic

selectivity in aliphatic C-H functionalization (**Table 7-6**). We chose to initially investigate halogenation of methyl hexanoate as it has been a substrate of choice in several other C-H functionalization studies and would offer an excellent opportunity for comparison. The most electron-rich C-H bonds of methyl hexanoate are located at the methylene furthest from the ester group, referred to as the ω-1 position. However, the electron-withdrawing effects of the ester functionality drop off exponentially as the distance from ester increases making the electronics of the sites at the end of the alkane chain only subtly different.

Bromination of methyl hexanoate using bromine or *N*-bromosuccinimide irradiated with UVA light, results in similar selectivity profiles, with a majority of functionalization at the most electron-rich ω-1 position, but also a significant amount of α-bromination (**Table 7-6, entries 1** and **2**). This is consistent with this halogenation being influenced by both electronic and enthalpic factors. While the α-position is electronically deactivated (electron-poor), these C-H bonds are the weakest in the substrate by ~3 kcal/mol.[42] Therefore, increasing the electrophilicity of the abstracting amidyl radical is expected to improve selectivity for more electron-rich sites, it simultaneously alters the thermodynamics of the C-H activation step.

Table 7-6. Bromination of Methyl Hexanoate: electronic selectivity studies

	α	β	γ	ω-1	ω
	MeO_2C—CH_2—CH_2—CH_2—CH_2—CH_3				
conditions	% selectivity of bromination				
Br_2, CH_2Cl_2, rt, hν	21.6	8.8	18.8	50.4	1.1
NBS, CH_2Cl_2, rt, hν	17.9	10.7	20.5	47.9	3.1
Mn(TPP)Cl/NaOBr	—	7.7	44.2	45.9	2.3
20 mol % HNO_3, 1 equiv Br_2 20 mol % NHPI, AcOH, 100 °C	6.3	16.0	27.0	50.7	—
 **48** CH_2Cl_2, rt, hν	12.2	9.3	16.9	53.0	8.6
 **52** CH_2Cl_2, rt, hν	4.5	14.4	17.7	58.0	5.4

Conversely, bromination using bromoamide **48** proceeds with ω-1:γ selectivity (3.1:1 of the most electron-rich methylene to the second most electron-rich) comparable to that of both NHPI (1.9:1) and Groves Mn-porphyrin (1.04:1) systems (**entries 3 - 4**). Notably, there is a decrease in the amount of α-bromination observed using **48** compared to Br_2 and NBS, indicating that the abstracting species is more sensitive to the electronics of the C-H being broken as opposed to the reaction enthalpy. However, there is still a significant amount of this undesired α-isomer, as well as the ω-methyl position. Substituting **48** for the more electrophilic bromoamide **52** reduces the amount of both of these undesired isomers, consistent with our hypothesis that site-selectivity can be altered by modifying the electronic nature of the amide reagent (**Table 7-6, entry 6**).

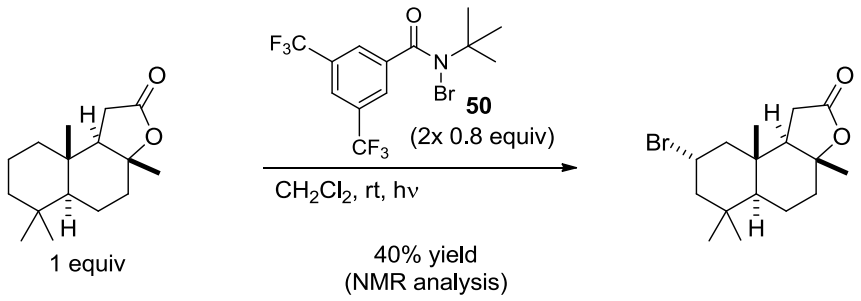
Additional studies are underway to determine the scope of functional groups that enable high electronic differentiation as well as the distance from which an electron withdrawing group can be influential.

7.3.5 Complex Substrate Selectivity Studies

A general synthetic reaction enabling site-selective, intermolecular aliphatic halogenation would be a highly valuable addition to the capabilities of C-H functionalization methods. Applications to complex, functionalized targets are a major challenge for all intermolecular C-H functionalizations owing to the incompatibility of the highly reactive intermediates with common functional groups and the difficulty in differentiating between multiple functionalization sites. We anticipate being able to combine the knowledge gained about the steric and electronic selectivity of our developed *N*-haloamide reagents, to predictably functionalize complex organic substrates. In an initial test of the efficiency of our system, we have studied the bromination of (+)-sclareolide, which is often used as a test substrate for intermolecular C-H functionalization.[9,18] We observed a highly regio- and stereoselective bromination at the C-2 position in 40% yield (NMR analysis) with only 1 equivalent of substrate using **50** (**Figure 7-9**). While this result is unoptimized, we expect that further

studies will lead to an even more efficient halogenation reaction.

Figure 7-9. Bromination of (+)-Sclareolide Using **50**



7.4 Summary

Reactions that achieve site-selective intermolecular functionalization of aliphatic C-H bonds offer exciting possibilities to change the way organic molecules are constructed. We have initiated studies using *N*-haloamides for the sterically and electronically selective halogenation of alkanes under neutral conditions.

7.5 Experimental

7.5.1 General Methods

See **2.5 Experimental** for general methods.

Carbon tetrachloride was purified via successive drying with $CaCl_2$ and $MgSO_4$ followed by distillation and storage under Ar over 4 Å mol sieves. All solvents used in halogenation reactions were degassed through 3 cycles of freeze-pump-thawing and then stored over 4 Å mol sieves in a dry glovebox under an inert atmosphere.

7.5.2 Preparation of Amides

All *N*-trifluoroethyl amides were synthesized by the following general procedure: To a 0 °C solution of 3,5-bistrifluoromethylbenzoic acid (purchased from Oakwood Products Inc) (2.0 g, 7.75 mmol) in CH_2Cl_2 (25 mL plus 10 drops of DMF) was added oxalyl chloride (1.3 mL, 15.5 mmol) dropwise. The reaction mixture was allowed to stir cold for 15 mins before warming to rt and stirring overnight.

The solvent was then removed under reduced pressure and the crude reaction, redissolved in THF (25 mL) and added dropwise to a 0 °C solution of trifluoroethyl amine (730 µL, 9.30 mmol) and triethylamine (781 µL, 7.75 mmol) in THF (25 mL). The reaction was allowed to warm to rt slowly overnight. The mixture was then filtered through Celite and washed with Et_2O (20 mL) and the filtrate concentrated. The crude amide was purified by flash chromatography (17% EtOAc/Hexanes) to isolate *N*-trifluoroethyl 3,5-bistrifluoromethylbenzamide (1.96 g, 5.78 mmol, 75% yield) as a fluffy white solid.

Analytical data for *N*-trifluoroethyl 3,5-bistrifluoromethylbenzamide: **^{1}H NMR** (400 MHz, chloroform-d) δ = 8.27 (s, 2 H), 8.09 (s, 1 H), 6.53 (br. s, 1 H), 4.24 – 4.16 (m, 2 H); **^{13}C NMR** (chloroform-*d*, 126 MHz) 162.67, 135.17, 132.90, 132.68, 132.45, 132.22, 127.49, 125.85, 125.83, 125.81, 125.45, 124.78, 123.64, 122.93, 121.83, 41.70, 41.47, 41.24, 41.01 ppm; **HRMS** (ESI) Calcd. for $[C_{11}H_6F_9NO+H]^+$ = 340.0384, Found = 340.0385.

All *N*-tert-butyl amides were synthesized by the following general procedure: To a 0 °C solution of 4-nitrobenzoic acid (2.5 g, 15.0 mmol) in CH_2Cl_2 (65 mL plus 10 drops of DMF) was added oxalyl chloride (2.5 mL, 29.9 mmol) dropwise. The reaction mixture was allowed to stir cold for 15 mins before warming to rt and stirring overnight. The solvent was then removed under reduced pressure and the crude reaction, redissolved in THF (125 mL) and cooled to 0 °C. *Tert*-butyl amine (3.1 mL, 29.9 mmol) was added dropwise and the mixture stirred cold for 20 mins before warming to rt and stirring overnight. The reaction mixture was then diluted with Et_2O (100 mL), washed successively with 1M HCl (3 x), 2.5M NaOH (3 x), brine, dried over $MgSO_4$ and then concentrated under reduced pressure. This produced analytically pure *N-tert*-butyl 4-nitrobenzamide (1.93 g, 8.68 mmol, 58% yield) as a pale yellow solid. Spectral data was in accordance with literature values.

7.5.3 Preparation of *N*-Bromoamides

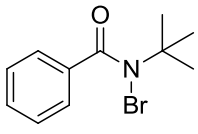
Synthesis of acetyl hypobromite (BrOAc): Bromine (614 µL, 12.0 mmol, 1 equiv) was added dropwise to a 0 °C slurry of silver acetate (2.0 g, 12.0 mmol, 1 equiv) in CCl_4 (54 mL) in a foil

wrapped flask. The reaction mixture was stirred at 0 °C in the dark for 10 mins. In a darkened room, the mixture was filtered quickly through a small amount of Celite and washed with an additional 18 mL CCl_4 into a foil wrapped flask. The concentration of BrOAc was determined by titration against 1 equiv triphenylphosphine in CH_2Cl_2, monitored by TLC (the end point is also marked by a persistent yellow-orange color) immediately prior to use. The solution can be stored at -20 °C for several weeks, with the concentration slightly decreasing over time.

General Synthesis of *N*-Bromo Amides (method according to Beebe and Wolfe)[43] : A foil-wrapped, flame-dried flask was charged with amide (1 equiv) and a solution of freshly titrated acetyl hypobromite in CCl_4 (1.5 equiv) was added at rt with no additional solvent. The mixture was stirred at rt until the amide starting material was completely consumed as was judged by NMR analysis (typically 0.25 – 1 h). The mixture was concentrated under reduced pressure to give *N*-bromoamide that was sufficiently clean to use without subsequent purification.

Modified general prep: Solutions of acetyl hypobromite in CH_2Cl_2 have also been reported in the literature to brominate amides (Baran paper), however these solutions are less stable than in CCl_4. We have also prepared *N*-bromo amides using a CH_2Cl_2 solution, but additional equivalents of BrOAc are required and the reagent must be used immediately.

Acetyl hypobromite (3 equiv) was prepared as above, substituting in CH_2Cl_2 in place of CCl_4. The filtrate was immediately cooled to 0 °C in a foil wrapped flask to exclude light, and amide (1 equiv) substrate directly added. These reactions were monitored by NMR analysis and were typically complete in 5 to 30 mins. The mixture was concentrated under reduced pressure to give *N*-bromoamide that was sufficiently clean to use without subsequent purification.

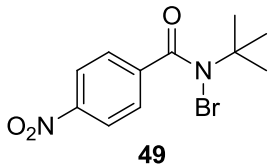


48

48 was synthesized via the general method using *N-tert*-butyl benzamide (500.0 mg, 2.82 mmol, 1

equiv) and BrOAc (24.5 mL of a 0.173M solution in CCl_4, 4.23 mmol, 1.5 equiv). The amide starting material was completely consumed as judged by NMR analysis at 1 h. The reaction mixture was concentrated under reduced pressure to give **48** (540.0 mg, 2.11 mmol, 75% yield) as a yellow solid.

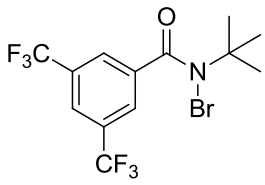
Analytical data for **48**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 7.69 - 7.63 (m, 2 H), 7.47 - 7.37 (m, 3 H), 1.58 (s, 9 H); **^{13}C NMR** (chloroform-*d*, 100 MHz) 177.17, 137.14, 130.90, 128.46, 127.89, 63.50, 28.70 ppm.



49

49 was synthesized via the general method using *N-tert*-butyl 4-nitrobenzamide (750.0 mg, 3.37 mmol, 1 equiv) and BrOAc (28.3 mL of a 0.179M solution in CCl_4, 5.06 mmol, 1.5 equiv). The amide starting material was completely consumed as judged by NMR analysis at 1 h. The reaction mixture was concentrated under reduced pressure to give **49** (796.0 mg, 2.64 mmol, 78% yield) as a yellow solid.

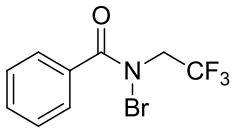
Analytical data for **49**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 8.29 - 8.24 (m, 2 H), 7.79 - 7.74 (m, 2 H), 1.60 (s, 9 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 174.47, 148.77, 143.26, 129.01, 123.22, 64.22, 28.61 ppm.



50

50 was synthesized via the general method using *N-tert*-butyl 3,5-bistrifluorobenzamide (500.0 mg, 1.60 mmol, 1 equiv) and BrOAc (13.8 mL of a 0.173M solution in CCl_4, 2.39 mmol, 1.5 equiv). The amide starting material was completely consumed as judged by NMR analysis at 1 h. The reaction mixture was concentrated under reduced pressure to give **50** (559.0 mg, 1.43 mmol, 89% yield) as a yellow solid.

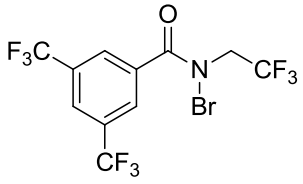
Analytical data for **50**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 8.09 (s, 2 H), 7.95 (s, 1 H), 1.60 (s, 9 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 173.72, 139.28, 131.93, 131.70, 131.48, 131.25, 128.55, 128.53, 125.68, 124.27, 124.25, 124.22, 124.20, 123.87, 122.06, 120.26, 64.41, 28.57 ppm.



51

51 was synthesized via the general method using *N*-trifluoroethyl benzamide (500.0 mg, 2.46 mmol, 1 equiv) and BrOAc (21.3 mL of a 0.173M solution in CCl_4, 3.69 mmol, 1.5 equiv). The amide starting material was completely consumed as judged by NMR analysis at 1 h. The reaction mixture was concentrated under reduced pressure to give **51** (528.0 mg, 1.87 mmol, 76% yield) as a yellow solid.

Analytical data for **51**: **^{1}H NMR** (600 MHz, chloroform-d) δ = 7.58 - 7.50 (m, 3 H), 7.49 - 7.44 (m, 2 H), 4.40 (q, *J* = 8.1 Hz, 2 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 172.46, 132.23, 131.32, 128.52, 127.83, 126.40, 124.54, 122.68, 120.82, 55.62, 55.39, 55.16, 54.93 ppm.



52

52 was synthesized via the general method using *N*-trifluoroethyl 3,5-bistrifluorobenzamide (500.0 mg, 1.47 mmol, 1 equiv) and BrOAc (60 mL of a 0.114M solution in CH_2Cl_2, 6.84 mmol, 4.5 equiv). The amide starting material was completely consumed as judged by NMR analysis at 15 mins. The reaction mixture was concentrated under reduced pressure to give **52** (601.0 mg, 1.44 mmol, 98% yield) as a white solid.

Analytical data for **52**: **^{1}H NMR** (400 MHz, chloroform-d) δ = 8.06 (s, 2 H), 8.04 (d, *J* = 0.7 Hz, 1 H), 4.48 (q, *J* = 8.1 Hz, 2 H) ppm; **^{13}C NMR** (chloroform-*d*, 100 MHz) 170.12, 134.75, 132.62, 132.28, 131.94, 131.62, 128.30, 125.01, 124.97, 124.83, 124.03, 122.05, 121.32, 55.00, 54.64, 54.29, 53.97 ppm.

General Alkane Bromination Procedure: A new 1-dram, flame-dried vial is charged with *N*-bromoamide and magnetic stir bar then taken in to a glove box. Under an atmosphere of N_2, dry, degassed solvent (to make a 0.3M solution with respect to reagent; degassed by three sequential processes of freeze-pump-thaw under hi-vacuum) is added followed by addition of alkane substrate. The reaction mixture is then removed from the glovebox, and allowed to stir in a Luzchem light box equipped with 10, 8 watt UVA light blubs, at room temperature. The crude reaction mixture was then monitored by GC and/or NMR analysis.

7.5.4 ^{1}H and ^{13}C Spectra

Figure 7-10. Spectra of *N*-trifluoroethyl-3-5-bis(trifluoromethyl)benzamide

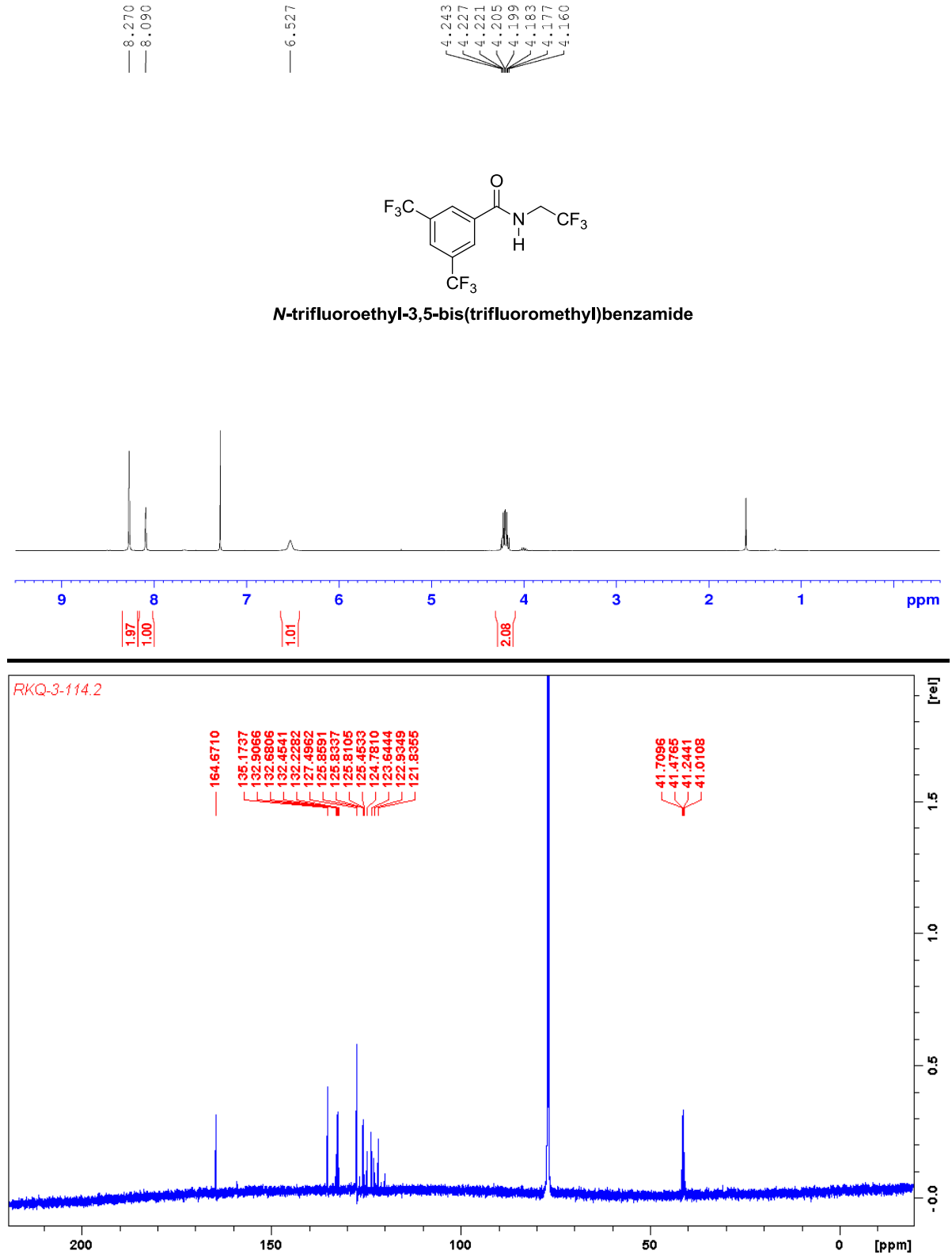


Figure 7-11. Spectra of **48**

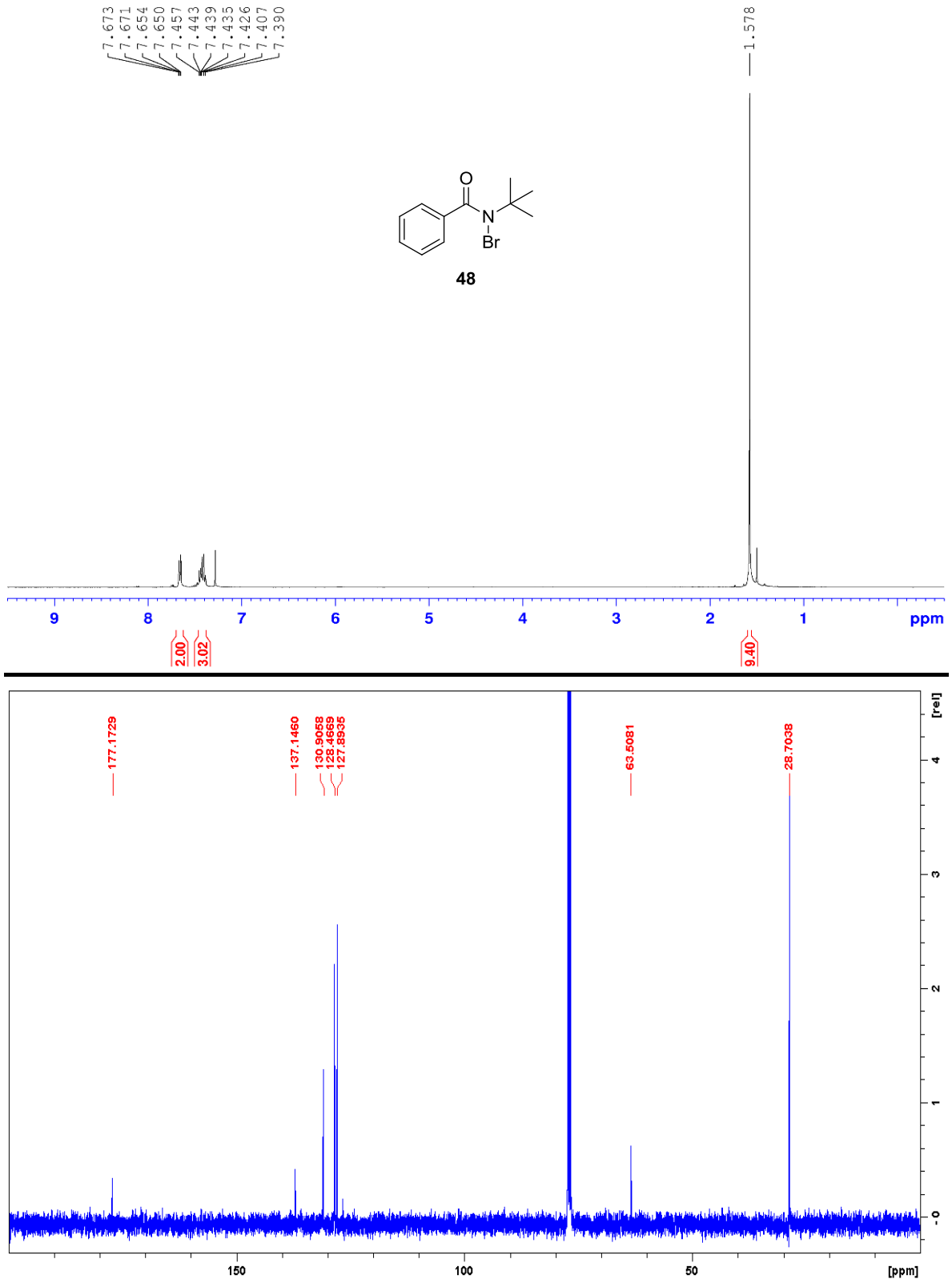


Figure 7-12. Spectra of **49**

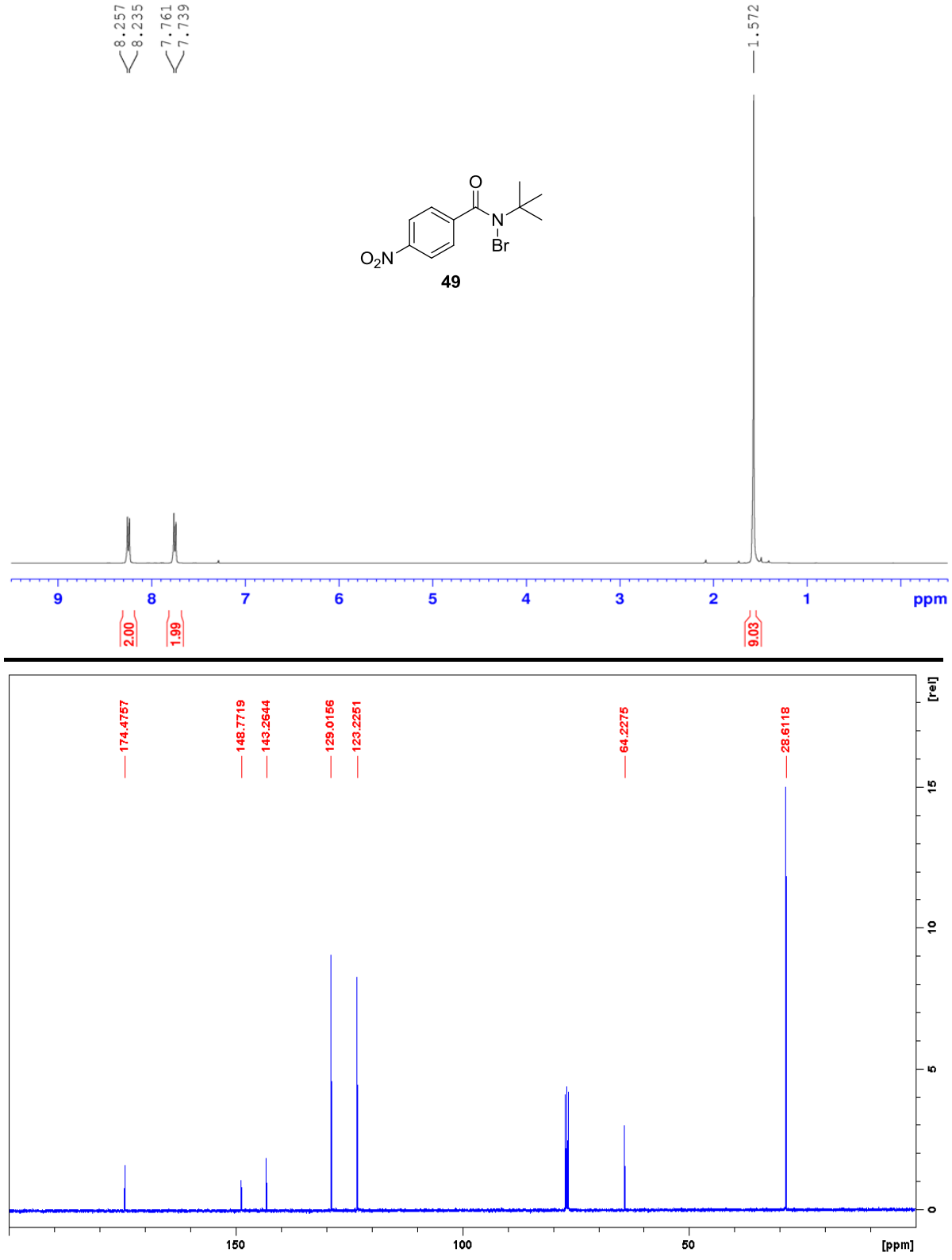


Figure 7-13. Spectra of **50**

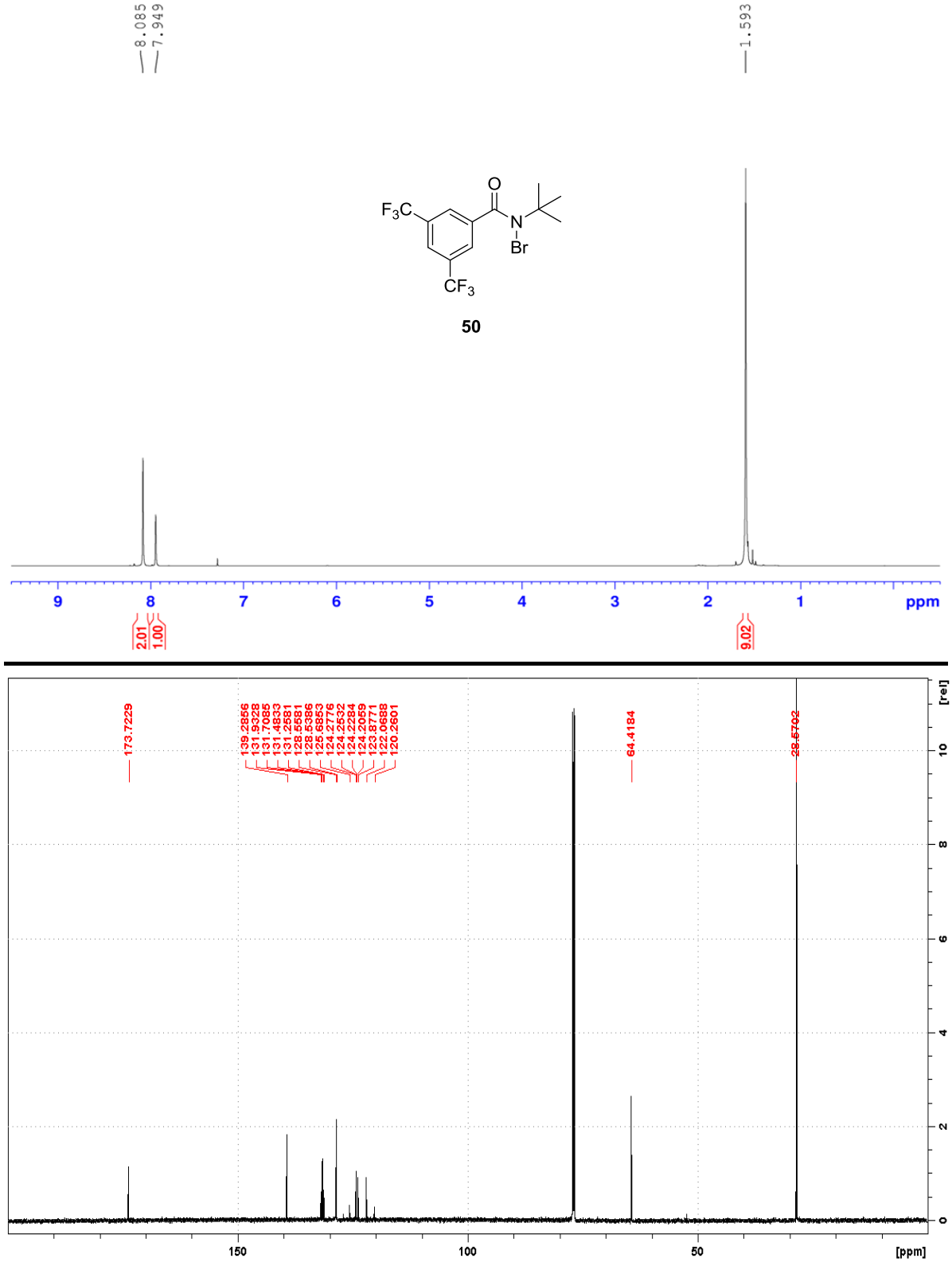


Figure 7-14. Spectra of **51**

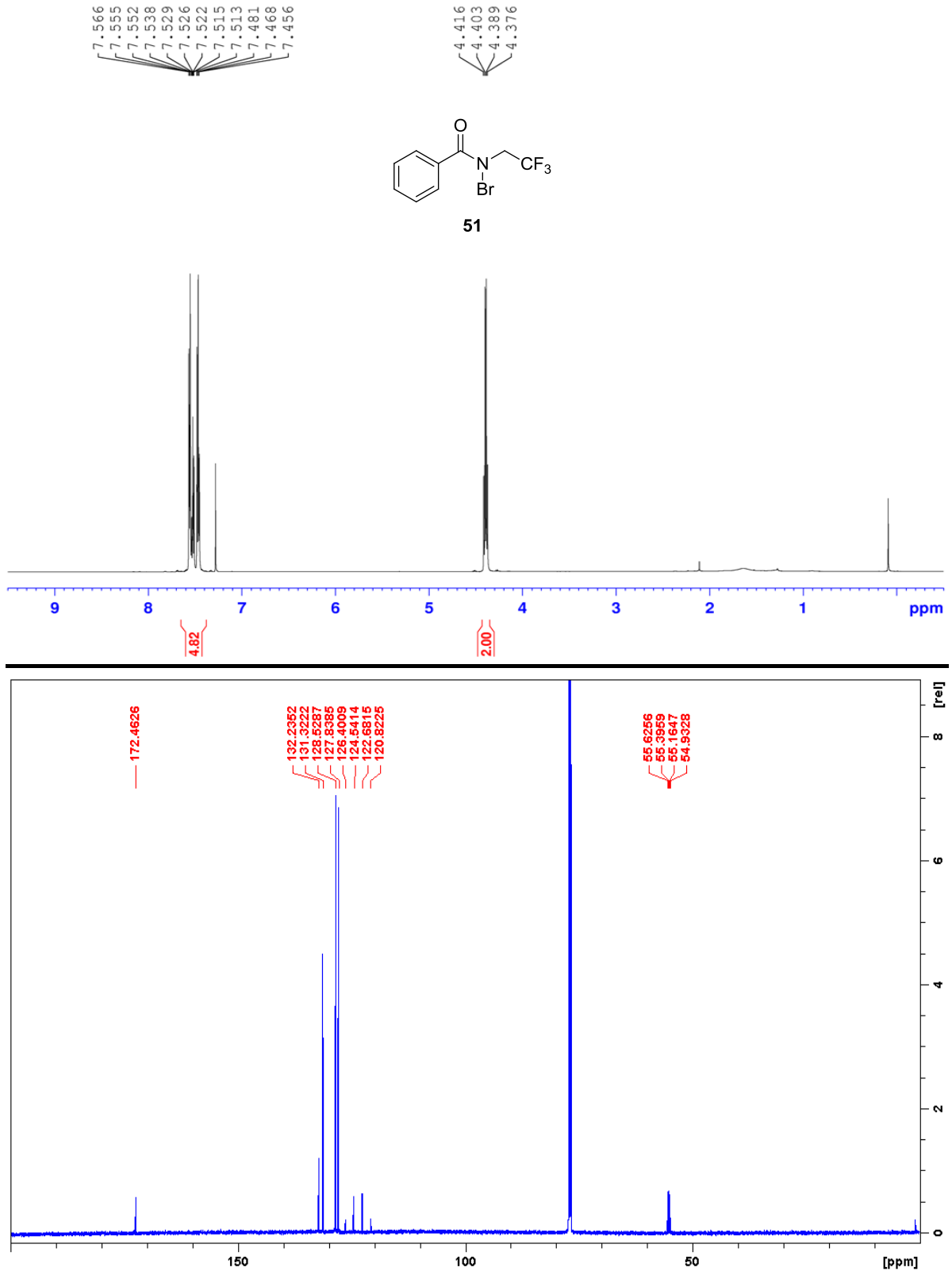
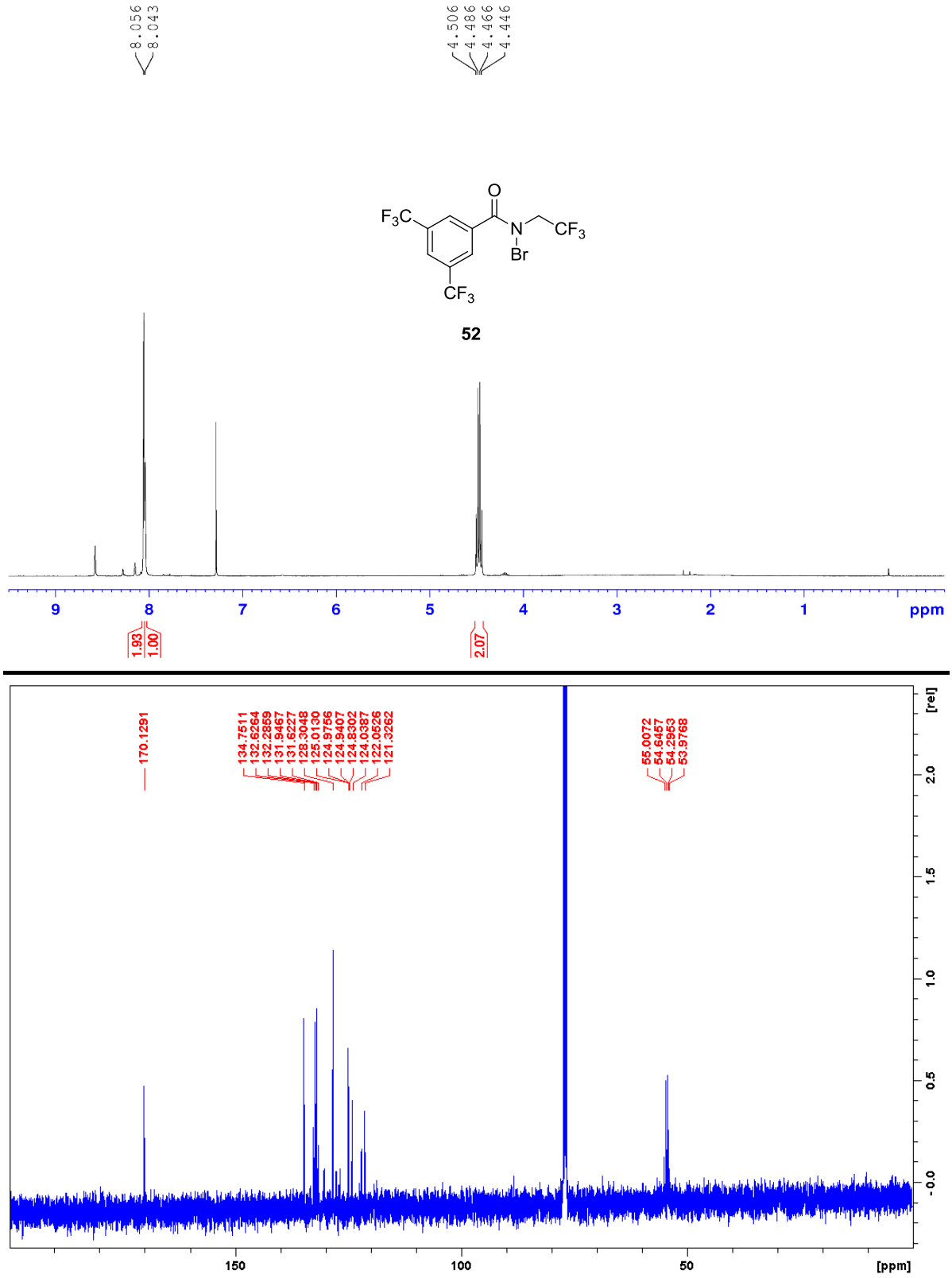


Figure 7-15. Spectra of **52**



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