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Mild Generation and Novel Reactivity of Nitroso Compounds

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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December 2014

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- Palmer, L. I.; **Frazier, C. P.**; Read de Alaniz, J. *"Developments in Nitrosocarbonyl Chemistry: Mild Oxidation of N-Substituted Hydroxylamines Leads to New Discoveries." Synthesis* **2014**, *46*, 269. **DOI:** 10.1055/s-0033-1338569

- **Frazier, C. P.**; Sandoval, D.; Palmer, L. I.; Read de Alaniz, J. *"Electrophilic α-Oxygenation Reaction of β-Ketoesters Using N-Hydroxycarbamates: Control of the Ambident Reactivity of Nitrosoformate Intermediates." Chem. Sci.* **2013**, *4*, 3857. **DOI:** 10.1039/C3SC51658J

- Sandoval, D.; **Frazier, C. P.**; Bugarin, A.; Read de Alaniz, J. *"Electrophilic α-Amination Reaction of β-Ketoesters Using N-Hydroxycarbamates: Merging Aerobic Oxidation and Lewis Acid Catalysis." J. Am. Chem. Soc.* **2012**, *134*, 18948. **DOI:** 10.1021/ja310784f

- **Frazier, C. P.**; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *"Copper-Catalyzed Aerobic Oxidation of N-Substituted Hydroxylamines: Efficient and Practical Access to Nitroso Compounds." Org. Lett.* **2012**, *14*, 3620. **DOI:** 10.1021/ol301414k

- **Frazier, C. P.**; Engelking, J.R.; Read de Alaniz, J. *"Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leads to a Mild Acylnitroso Ene Reaction." J. Am. Chem. Soc.* **2011**, *133*, 10430. **DOI:** 10.1021/ja204603u

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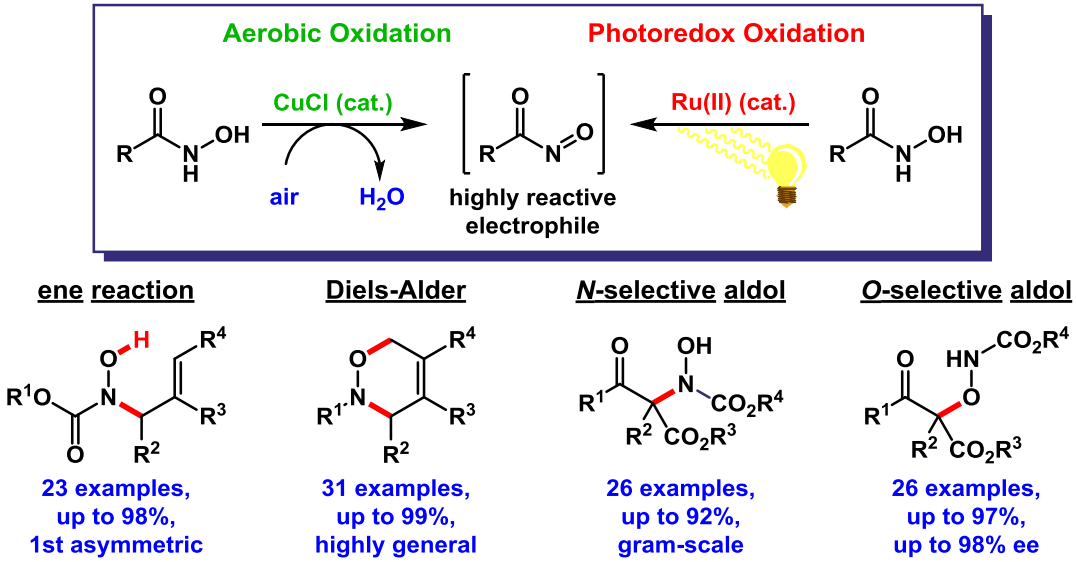
Abstract

Mild Generation and Novel Reactivity of Nitroso Compounds

by

Charles Patrick Frazier



The development of efficient methods for the formation of carbon-nitrogen bonds is of great interest in organic chemistry. While traditional approaches to *C-N* bond formation are well developed and have found widespread use, approaches utilizing an electrophilic source of nitrogen are vastly underdeveloped. Although a number of electrophilic sources of nitrogen have been developed, the efforts of our research have centered on the use of nitrosocarbonyl compounds. Due to their high reactivity, nitrosocarbonyl intermediates can only be generated *in situ* and are classically obtained from the oxidation of hydroxamic acid

derivatives using periodate salts. However, this *in situ* oxidation protocol, which is commonly used in the hetero-Diels-Alder (HDA) reaction, is incompatible with the other reactions because the initially formed adduct is highly susceptible to decomposition. While this has significantly limited the development of chemistry utilizing nitrosocarbonyl compounds, we postulated that if the oxidation conditions were mild enough to circumvent product decomposition, nitrosocarbonyls could be utilized in a wide variety of *C*-*N* bond-forming reactions.

Recently, we reported the first example of the aerobic generation of nitrosoformate intermediates for use in the nitroso ene reaction. The aerobic oxidation method, which relies on the use of catalytic amounts of CuCl (5 mol %) and uses air as the terminal oxidant, proved mild enough to avoid decomposition of the ene adducts, affording the allylic hydroxylamines in up to quantitative yields. Additionally, the oxidation protocol is highly general for a wide variety of *N*-substituted hydroxylamines; the Diels-Alder reaction can be carried out in up to quantitative yields employing an array of nitroso compounds. Moreover, by switching to photoredox conditions using $Ru(bpy)_3Cl_2$, the nitrosocarbonyl intermediates can be efficiently generated with temporal and spatial control.

As proposed, the mild oxidation conditions allowed the expansion of nitrosocarbonyl chemistry into new areas, such as the nitroso aldol reaction. Through the synergistic combination of our aerobic oxidation with known Lewis acid activation of β-ketoesters, the α-amination and α-oxygenation of carbonyl compounds was achieved for the first time using nitrosocarbonyl compounds. All of the reactions are operationally simple to perform, utilize reagent grade solvents and air as the terminal oxidant, and the only byproduct is water.

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List of Abbreviations

2-MeTHF – 2-methyltetrahydrofuran

3Å MS - 3 angstrom molecular sieve

9,10-DMA – 9,10-Dimethylanthracene

AMS – α-methyl styrene

BHT – butylated hydroxytoluene

Bn - benzyl

Boc - *tert*-butyloxycarbonyl

BPO – benzoyl peroxide

Cbz – carbobenzyloxycarbonyl

CV – Cyclic voltammetry

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE – 1,2-dichloroethane

DMB – 2,3-dimethylbutadiene

DMSO - dimethyl sulfoxide

DTBMP – 2,6-di-*tert*-butyl-4-methylpyridine

$Dy(OTf)_3$ - dysprosium(III) trifluoromethanesulfonate

E – Electrophile

EDG - electron donating group

Equiv – equivalent

EtOx – 2-ethyl-2-oxazoline

EWG - electron withdrawing group

Fmoc – Fluorenylmethyloxycarbonyl

HDA – Hetero–Diels–Alder

HEH – Hantzsch Ester

HFIPA – 1,1,1,3,3,3-hexafluoroisopropanol

hrs - hours

hν – light

IR – infrared spectroscopy

LA – Lewis Acid

LDA – lithium diisopropylamide

MeCN – acetonitrile

min - minutes

Moz – *p*-methoxybenzyl carbonyl

MS – mass spectroscopy

MT – Montmorillonite

NMO – *N*-methylmorpholine-*N*-oxide

NMR – nuclear magnetic resonance

NPPOC – 3'-nitrophenylpropyloxycarbonyl

Nu – Nucleophile

OTf - trifluoromethanesulfonate

PFBA – Pentafluorobenzoic acid

PhBox - 2,2′-Isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline]

PIDA – phenyliodoso diacetate

PIFA - [Bis(trifluoroacetoxy)iodo]benzene

PS – Polystyrene

Pyr – pyridine

rt – room temperature

S_EAr – Electrophilic Aromatic Substitution

S_NAr – Nucleophilic Aromatic Substitution

S_OAr – Oxidative Aromatic Substitution

TBS – *tert*-butyldimethylsilyl

TEMPO – 2,2,6,6-tetramethylpiperidine-1-oxy radical

TFA – Trifluoroacetic Acid

TFE – 2,2,2-trifluoroethanol

THF – tetrahydrofuran

TLC – thin layer chromatography

Troc - 2,2,2-Trichlorethoxycarbonyl

TTN – Thallium(III) nitrate

TMS – Trimethylsilyl

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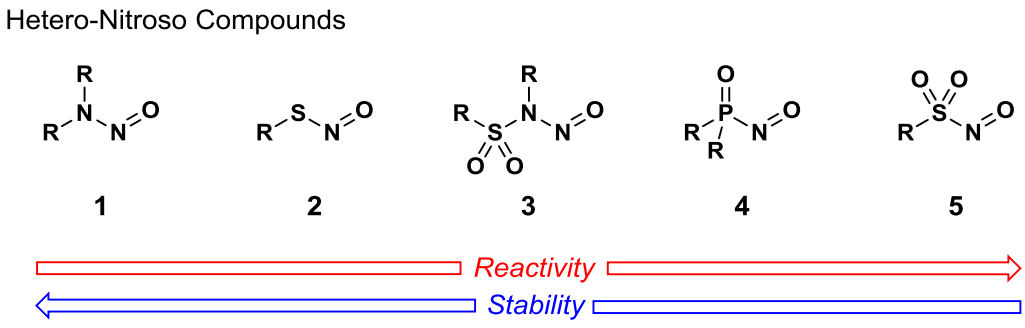
1. Historical Background and Reactivity of Nitroso Compounds

1.1 Stability and Reactivity Patterns of Nitroso Compounds.

1.1.1 Varied Stability of Nitroso Compounds

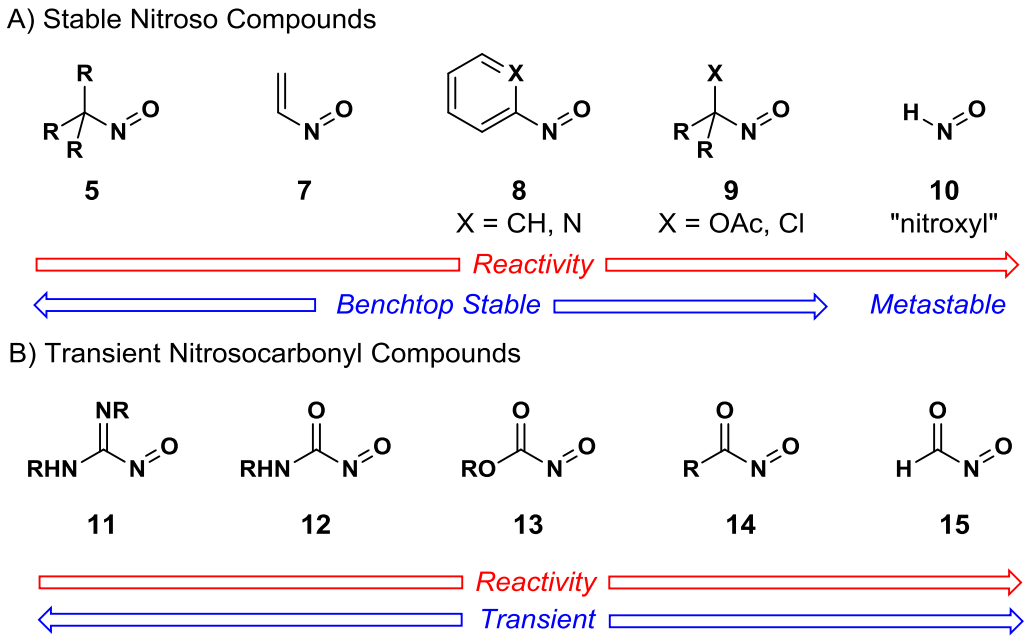
Nitroso compounds are reactive electrophiles use widely in the synthesis of complex molecules.[1] Since the first reported synthesis of nitrosobenzene by Baeyer in 1874,[2] a vast number of nitroso compounds have been synthesized, which vary widely in their reactivity.[3] Although a comparative study of the reactivity of different families of nitroso compounds has not been conducted, nitroso reactivity can generally be characterized by the extent of adjacent electronic effects. For example, in the context of nitroso compounds with adjacent heteroatoms, *N*-nitroso **1** and *S*-nitroso **2** compounds are particularly unreactive toward typical dienes in Diels–Alder reactions. This lack of reactivity can be attributed to the lone pair resonance donation of the attached heteroatom, which can be tempered if the lone pairs are not available for π-electron donation.[1a] For example, while *N*-nitrososulfonamide **3** is still unreactive toward dienes,[4] metastable *P*-nitrosophosphine oxide[5] **4** and *S*-nitrososulfonyl compounds[6] **5** readily engage in Diels–Alder reactions with dienes (Figure 1).

Figure 1. Relative Stabilities and Reactivities of Hetero-Nitroso Compounds



Like hetero-nitroso compounds, the reactivity of *C*-nitroso compounds are innately dependent on the associated electronic environment of the *N*-substitution. For the sake of this dissertation, nitroso compounds will be classified by their stability relative to "nitroxyl" **10**, a metastable nitroso compound widely studied in the context of biological systems. As with hetero-nitroso compounds, the reactivity of these stable nitroso compounds can be modulated by adjusting the electronics of the nitroso. For example, due to the electron withdrawing nature of the substituents, α-chloro-[7] and α-acetoxy[8] nitroso compounds **9** are substantially more reactive toward dienes than other simple aliphatic nitroso compounds **5,** which are unreactive. Similarly, while substitution plays a large role in stability and reactivity, nitrosoarenes[9] and nitrosoheteroarenes[10] **8** are generally more reactive toward dienes than vinylnitroso compounds **7**.[11] Notably, stable nitroso compounds often need additional activation by Lewis acids in order to achieve efficient reactivity.[12] In every case (**5-9**), the nitroso compound can be readily isolated and characterized (Figure 2a).

Figure 2. Relative Stabilities and Reactivities of *C*-Nitroso Compounds



In contrast, nitrosocarbonyls and related compounds are transient, highly reactive intermediates in synthesis.[1] While acylnitroso compounds **14** are the only member of the class whose lifetime has been measured,[13] the transient nature of the other nitrosocarbonyls can be inferred based on lack of reported isolability and similarity of reactivity toward dienes in Diels–Alder reactions. The comparative reactivity of each can be inferred based on the amount of π-donation into the carbonyl, with the nitrosoformimidamide **11** likely the least reactive and nitrosoformaldehyde **15** likely the most reactive (Figure 2b).[1a]

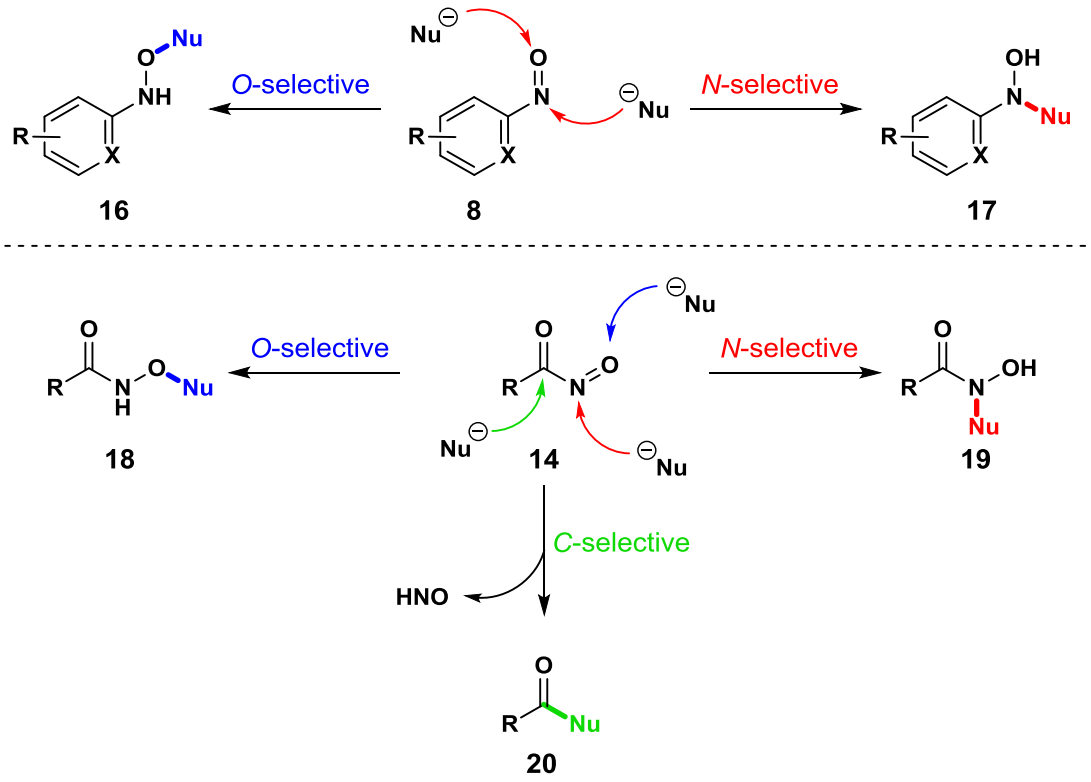
Because nitrosocarbonyl compounds are not bench top stable species, efforts have been made to observe these transient intermediates spectroscopically. Schwarz and co-workers studied both the acylnitroso **14** and nitrosoformaldehyde **15** using neutralization-reionization mass spectrometry. In their study, they found that both compounds could be detected in the gas phase after thermo-retro-cleavage from 9,10-dimethylanthracene HDA adducts.[13b] Toscano and co-workers studied nitrosocarbonyl compounds in solution using time-resolved infrared spectroscopy. In their study, acylnitroso compounds **14** in solution were estimated to have a lifetime of approximately 10 ms at infinite dilution.[13a]

Unlike their stable counterparts, nitrosocarbonyls and related compounds need no additional activation by Lewis and Brønsted acids to achieve efficient reactivity. Unfortunately, this makes asymmetric induction using a chiral catalyst extremely challenging, evidenced by the limited number of reported catalyst-controlled asymmetric reactions with nitrosocarbonyls and related compounds.[14] Therefore, inducing asymmetry in this manner remains the "holy grail" of nitrosocarbonyl chemistry and would likely induce a paradigm shift in the field of electrophilic hetero-functionalization reactions.

1.1.2 Characterization of Ambident Reactivity of Nitroso Compounds

Nitroso compounds are ambident electrophiles with a number of reports of reactivity at the corresponding nitrogen, oxygen, or adjacent carbons of the molecule, dramatically complicating the rational design of new reactions. The ambident reactivity of nitrosoarenes has been well characterized in the context of the aldol reaction,[15] and a number of predictive models have been developed to aid in designing highly selective reactions.[16] In contrast, the ambident reactivity of nitrosocarbonyl compounds has been only minimally explored. The earliest reports postulating the existence of nitrosocarbonyl compounds (see section 1.2.1), exploited reactivity at the carbonyl to form the corresponding carboxylic acid or amides, subsequently releasing nitroxyl as a byproduct.[17] Beginning in the 1970's, pioneering work by Kirby[18] and Keck[19] ushered in a renaissance of *C*-*N* bond forming reactions with nitrosocarbonyl compounds, including reports of ene and Diels–Alder all showing preference for nitrogen reactivity (see section 1.2). In contrast to arylnitroso compounds, reactivity on oxygen has only recently been discovered,[20] and efforts to better understand the principles governing this reactivity pattern have only been minimally explored (Figure 3).[20b]

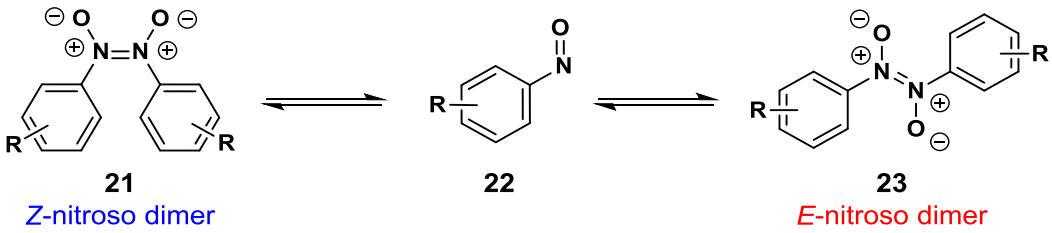
Figure 3. Ambident Reactivity of Arylnitroso and Nitrosocarbonyl Compounds



1.1.3 Common Decomposition Pathways of Nitroso Compounds.

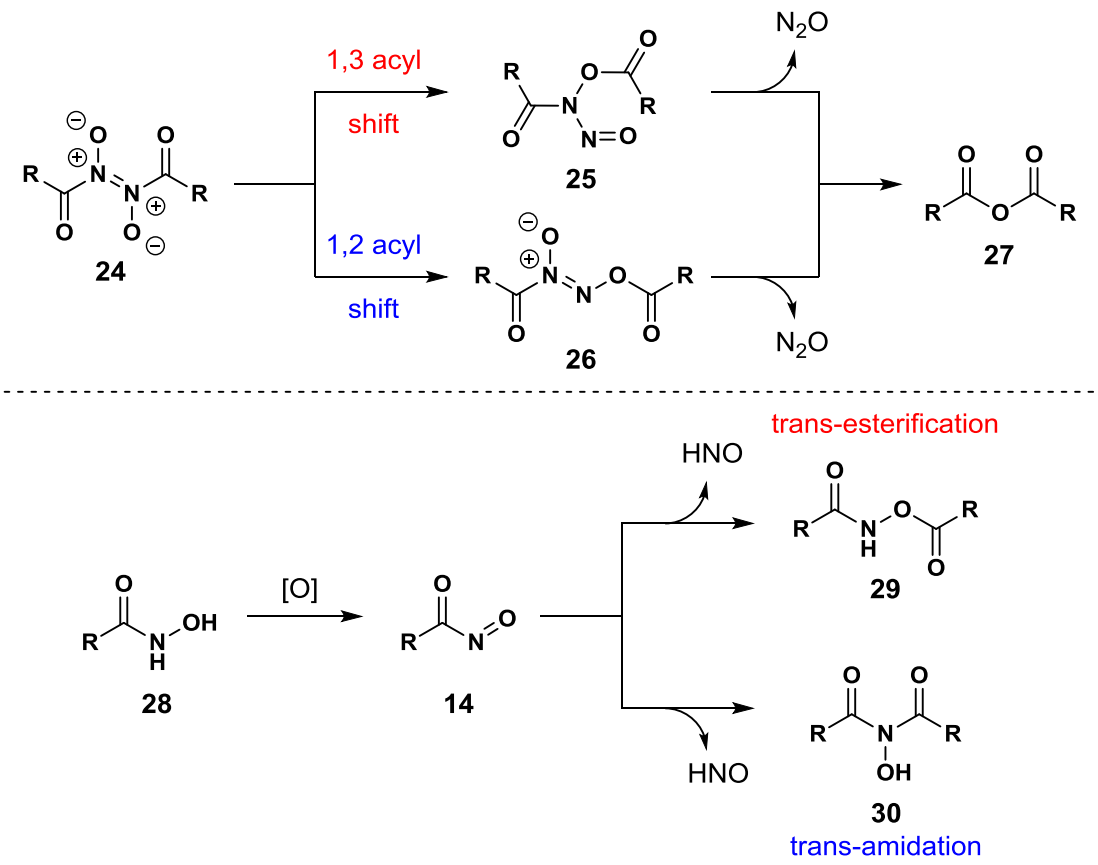
In addition to the complications of reaction development due to the ambident reactivity, nitroso compounds readily undergo decomposition reactions. Nitrosoarenes **22** are known to dimerize in solution to form either the *Z*- or *E*-dimer (**21** and **23**, respectively), depending on the nature of the substitution on the aryl ring.[21] While some nitroso compounds such as *p*-methoxy nitrosobenzene show little to no dimerization in solution, nitrosoarenes bearing electron withdrawing substituents such as *p*-nitro nitrosobenzene rapidly dimerize.[21b] Notably, dimerization is often reversible, which preserves the reactivity of nitrosoarenes (Figure 4).

Figure 4. Dimerization of Nitrosoarene Compounds



In contrast, nitrosocarbonyl compounds exhibit a lack of stability due to dimerization events which lead to decomposition. Acylnitroso compounds dimerize in solution to form a similar azoxy-dimer to nitrosoarenes (**24**), however these intermediates undergo rapid decomposition, irreversibly forming the corresponding anhydride (**27**).[22] Additionally, due to the enhanced reactivity of hydroxylamines due to the α-effect, nitrosocarbonyls generated through the oxidation of *N*-substituted hydroxylamines often undergo trans-esterification reactions to liberate nitroxyl and form the *N*,*O*-disubstituted hydroxylamine (**29**).[17b, 23] Alternatively, the nitrogen of the *N*-substituted hydroxylamine can also add to the carbonyl of the nitroso to form the *N*,*N*-disubstituted hydroxylamine (**30**),[24] with the subsequent liberation of nitroxyl. These pathways are destructive to the nitrosocarbonyl, and therefore, contribute to the overall reduction in reaction efficiency and lead to complicated mixtures of products (Figure 5). However, we felt if we could better understand how to circumvent the decomposition, the reactivity of nitrosocarbonyl compounds could be harnessed for a wide variety of *C*-*N* and *C*-*O* bond-forming reactions.

Figure 5. Decomposition Pathways of Nitrosocarbonyl Compounds



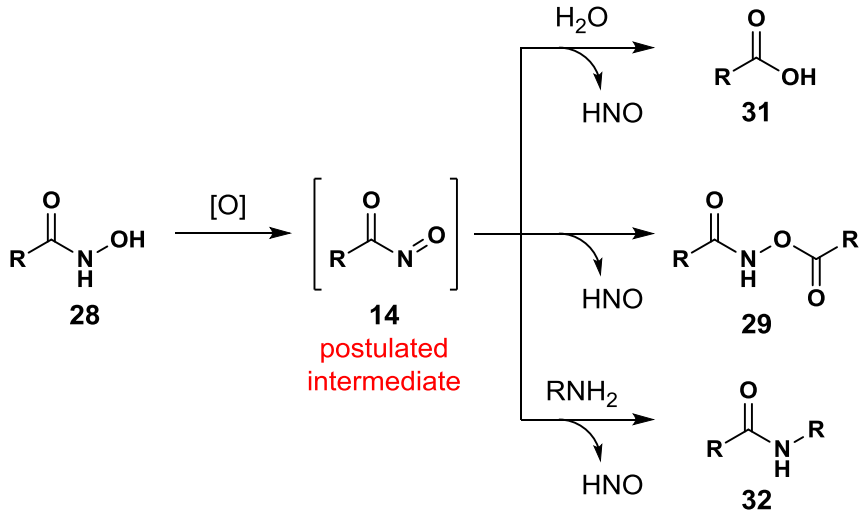
1.2. The Discovery of Nitrosocarbonyl Compounds

1.2.1 Early Postulation of the Existence of Nitrosocarbonyl Compounds

Early efforts in generating nitrosocarbonyl compounds focused on the oxidation of hydroxamic acids with periodate,[17] silver(I) or manganese(IV) oxides,[23] iodine,[23b] or *N*-bromosuccinimide.[17c] Building on the discovery that *N*-alkylhydroxylamines formed the *cis*-nitroso dimer, early researchers were surprised to find that the oxidation of *N*-acylhydroxamic acids did not follow the same trend. Instead, depending on the reaction conditions, the carboxylic acid **31**,[17a] *N,O*-bisacylated hydroxylamine **29**,[17b] or amide[17c] **32** were isolated. Each of these products were formed through the loss of the *N*-*O* moiety under

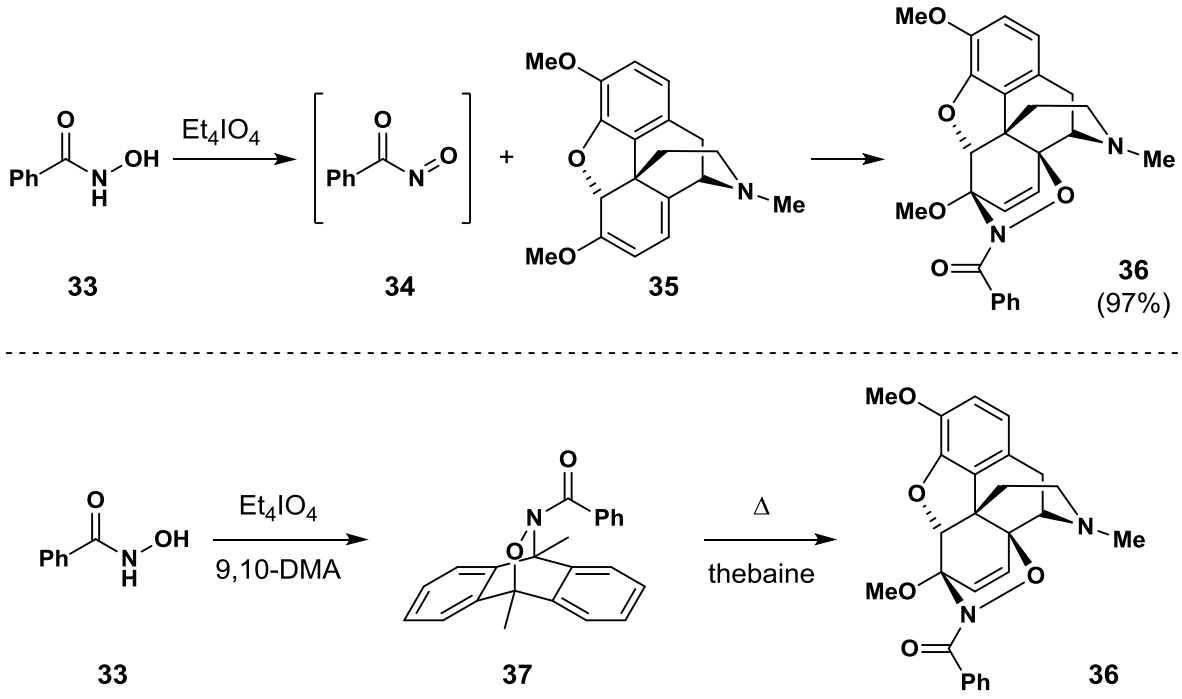
the oxidative conditions. While the nitrosocarbonyl compound **14** was not directly observed, these early experiments reinforced the possible existence of a nitrosocarbonyl intermediate (Figure 6).

Figure 6. First Evidence of the Existence of Nitrosocarbonyl Compounds



The first direct evidence supporting the formation of nitrosocarbonyl compounds from the oxidation of hydroxamic acids was the reported trapping of the nitrosocarbonyl moiety as a Diels–Alder adduct by Kirby in 1973.[18a] In this pioneering report, the nitrosocarbonyl intermediate was trapped with the diene thebaine (**35**) and compared to Diels–Alder adducts previously isolated with stable nitroso compounds. Moreover, it was shown that the nitrosocarbonyl could be regenerated through the thermo-retro-cleavage of 9,10-dimethylanthracene HDA adduct **37** and effectively transferred to another diene, an approach that was expanded on in subsequent communications.[18c, 18e] This was the first example of the retention of the hydroxylamine moiety, providing the direct evidence of the existence of nitrosocarbonyl compounds and laying the foundation for the next 40 years of nitrosocarbonyl research (Figure 7).

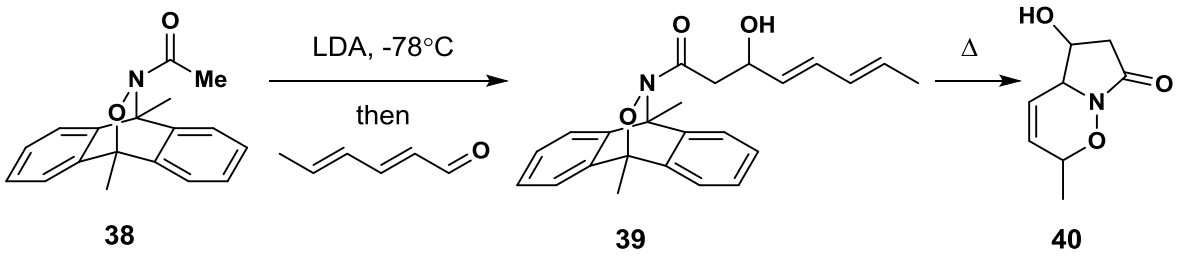
Figure 7. First examples of the Nitrosocarbonyl Hetero-Diels-Alder Reaction



1.2.2 Rendering Nitrosocarbonyl Compounds Useful in Synthesis

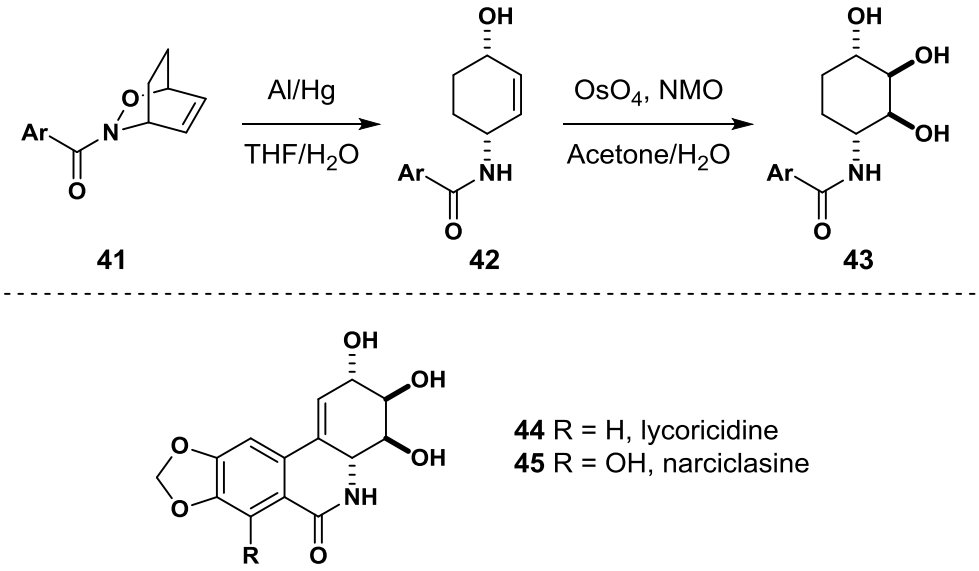
Based on Kirby's pioneering discovery, Keck expanded on the thermo-retro-cleavage approach to generating nitrosocarbonyl compounds by further exploring reactivity of the dienophile-transfer.[19a] While Kirby's work demonstrated that nitrosocarbonyl compounds are formed in the oxidation of hydroxamic acids, Keck was the first to consider the utility of nitrosocarbonyl compounds in synthesis. In particular, Keck reported the intramolecular nitrosocarbonyl Diels–Alder by functionalizing HDA adducts of acetohydroxamic acid with 9,10-dimethylanthracene. Through the thermo-retro-cleavage of the functionalized adducts, Keck generated fused ring systems that could be further elaborated into important lactam building blocks **40** (Equation 1).

Equation 1. Dienophile-Transfer *via* the Thermo-Retro-Cleavage of HDA Adducts



Additionally, Keck exploited the intermolecular nitrosocarbonyl HDA to access a model system for the lycoridine family of alkaloids (**44** and **45**),[19b] showcasing the potential utility of nitrosocarbonyl compounds for the synthesis of complex molecules (Figure 8).

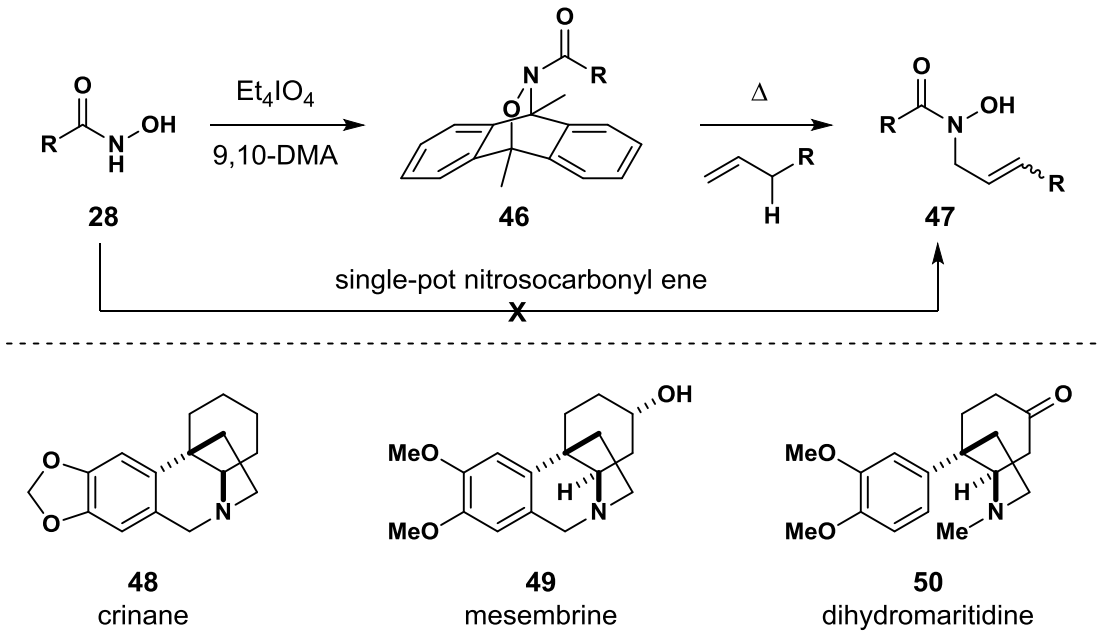
Figure 8. The Intermolecular HDA Reaction: Accessing the Lycoricidine Family



Shortly following his work on the intramolecular HDA reaction, Keck and co-workers reported the first example of a nitrosocarbonyl ene reaction.[19c, 19d, 19f] Generating the nitrosocarbonyl through the thermo-retro-cleavage of HDA adduct **46**, this work displayed the reactivity of nitrosocarbonyl compounds, as the transient intermediates readily undergo ene reactions in the absence of catalyst at moderate reaction temperatures. Moreover, this

reaction provided direct access to a wide range of allylic amines (**47**), which proved useful for the synthesis of complex natural products **48**–**50** (Figure 9).[19e, 19g] Kirby followed Keck's reports with his own example using nitrosoformate intermediates for the inter- and intramolecular ene reaction.[18f, 22a] Notably, in every example, direct oxidation of the *N*-substituted hydroxylamine in the presence of the olefin led to a complex mixture of products, presumably due to over-oxidation of the resultant allylic amine. Therefore, it was necessary to proceed through the two step thermo-retro-cleavage approach, a limitation that was targeted by a number of research groups attempting to improve on Keck and Kirby's methodology.

Figure 9. Two-Step Nitrosocarbonyl Ene Reaction and Natural Product Targets



1.3 Modern Methods of Nitrosocarbonyl Generation

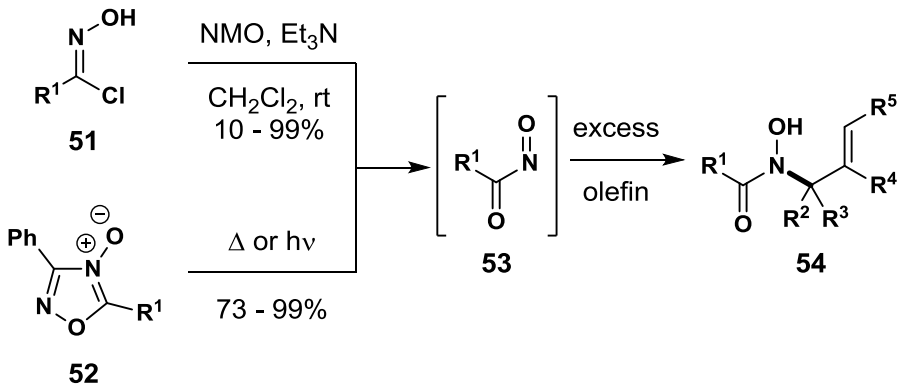
1.3.1.Recent Development for the Generation of Nitrosocarbonyl Intermediates

Since Keck and Kirby's pioneering work, a number of research groups have developed novel methods for the oxidation of *N*-substituted hydroxylamines, including lead(IV) and silver(I) oxides,[25] Dess-Martin periodinane,[26] Swern–Moffat conditions,[27] a variety of transition metal – peroxide complexes,[28] BPO & TEMPO,[29] manganese(II) oxide,[20a, 30] and Rh(II) complexes with Ag_2CO_3,[31] and copper–catalyzed aerobic oxidations,[20b, 32] among others.[33] Additionally, non-oxidative methods have been developed from alternative starting materials, such as *N*-methylmorpholine-*N*-oxide addition to nitrile oxides,[22c, 34] and the photo– or thermal–degradation of 1,2,4-oxadiazole-4-oxides.[22b, 35] While these methods have been used for the Diels–Alder,[25-28, 32a, 32b] ene,[28d, 32c] aldol,[20, 29-30, 32d] and C-H activation reactions,[31] the ene reaction is an effective tool for evaluating the mildness of the conditions, due to the known product decomposition issues. Therefore, methodologies that can be utilized for a single-pot ene reaction we consider the most mild.

1.3.2 Non–Oxidative Methods for Single Pot Generation for Nitrosocarbonyl Ene

The first example of a single-pot nitrosocarbonyl ene reaction was reported by Caramella and co-workers.[34] The non-oxidative protocol, relying on the rearrangement of nitrile oxides with *N*-methylmorpholine-*N*-oxide, yielded the ene adduct **54** in high yield, reinforcing the assessment that there is no inherent instability of nitrosocarbonyl ene adducts under non-oxidative conditions. Caramella and co-workers followed up shortly after with another non-oxidative method which, again produced the nitrosocarbonyl ene adducts in high yield from 1,2,4-oxadiazole-4-oxide **52** (Figure 10).[22b, 35]

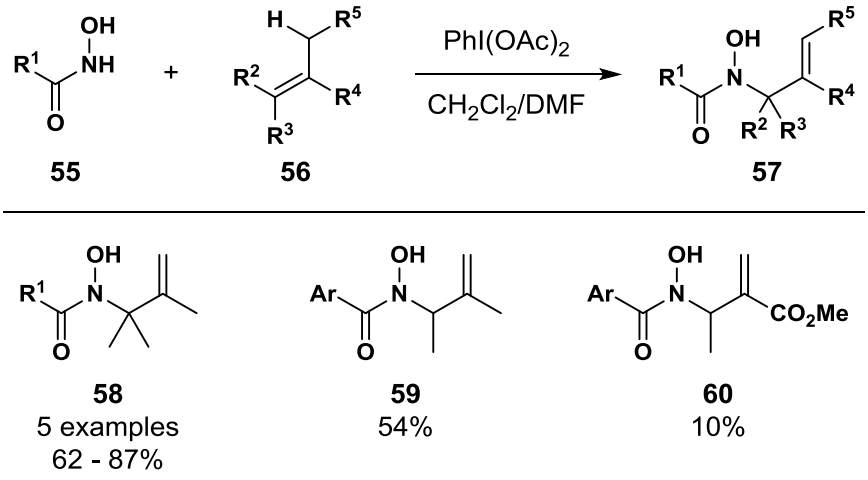
Figure 10. Non-Oxidative Generation of Nitrosocarbonyl Compounds.



1.3.3 Single-Pot Oxidative Nitrosocarbonyl Ene Using Hypervalent Iodine

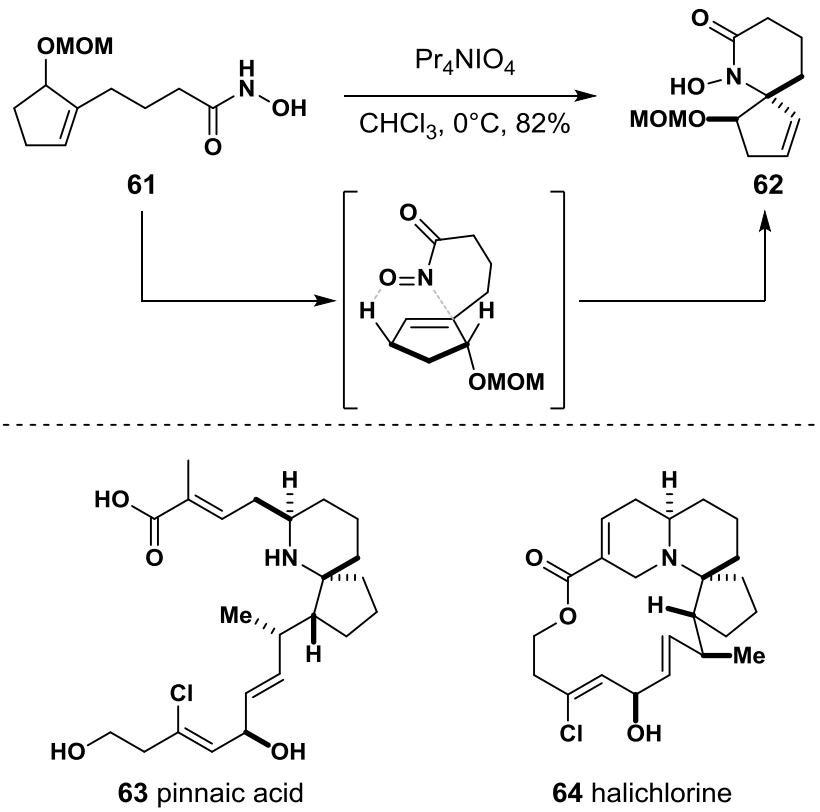
While the work of Kirby[36] and Keck[19f] laid the foundation for the future development of nitrosocarbonyl chemistry, their two-step protocol proved cumbersome and limited the development of the field. Therefore efforts to render the nitrosocarbonyl ene reaction accessible in a single pot were undertaken by a number of research groups. Taking inspiration from Kirby and Keck's use of hypervalent iodine, the first example of a single-pot oxidative generation of nitrosocarbonyl compounds for the ene reaction was reported by Adam and co-workers in 1999 and utilized phenyliodoso diacetate (PIDA) as the stoichiometric oxidant.[37] The method involves the slow addition of the hydroxamic acid to PIDA and 3 equiv of the olefin. The reaction is high yielding for simple dienes with a variety of hydroxamic acids (Table 1, **58** and **59**), however the yield suffered when an olefin bearing a more sensitive functional group was employed (Table 1, **60**).

Table 1. First Single-Pot Nitrosocarbonyl Ene Reaction under Oxidative Conditions



In addition to the work of Adam and co-workers, one example of the single-pot nitrosocarbonyl ene reaction utilizing iodine(V) was carried out by Kibayashi and co-workers in the context of the synthesis of key natural product core **62**.[38] This is the first example of a diastereoselective intramolecular single-pot nitrosocarbonyl ene reaction and was used in the context of a formal total synthesis of both (±) halichlorine **63** and (±) pinnaic acid **64** (Figure 11).[39]

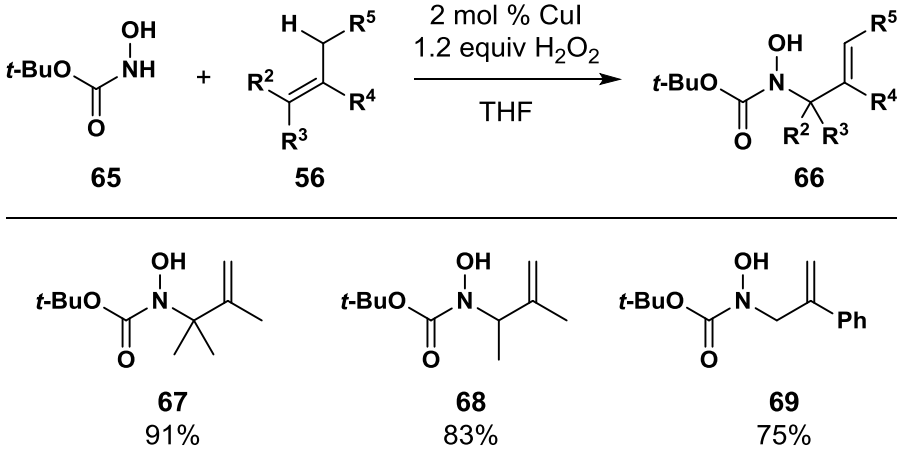
Figure 11. Single-Pot Intramolecular Nitrosocarbonyl Ene Using Hypervalent Iodine



1.3.4 Non-Iodine Based Single-Pot Oxidative Methods

Recently a number of research groups have reported examples of the catalytic oxidation of hydroxamic acids employing transition metals and stoichiometric peroxides for both the Diels–Alder [28a-c] and the ene reaction.[40] The first reported example for the catalytic nitrosocarbonyl ene reaction was reported by Iwasa and co-workers in 2004.[41] While a number of transition metal catalysts were used, the highest yields were achieved using CuI (Table 2, **67–69**). In addition to the work of Iwasa, Malkov recently demonstrated that $FeCl_3$ is an efficient catalyst for the intramolecular nitrosocarbonyl ene reaction.[28d]

Table 2. Transition Metal Catalyzed Nitrosocarbonyl Ene (Iwasa)



In a departure from previously developed methodology, Tan and co-workers reported the use of photoredox catalysis for the oxidation of hydroxamic acids. Under the optimized reaction conditions (3 mol % rose Bengal, 10 mol % pyridine, MeCN, 35 ˚C, 11 W lamp), the nitrosocarbonyl ene adducts were isolated in high yield.[42]

1.3.5 Concluding Remarks

Despite the exceptionally high reactivity, modern methods of generation have enabled the development of nitrosocarbonyl chemistry to where the transient intermediates are effective reagents for *C-N* and *C-O* bond–forming reactions. The duration of this dissertation will detail our contributions to the pantheon of modern generation methods of nitroso compounds and will highlight our subsequent advances based on these discoveries.

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2. Aerobic Oxidation of *N*-Substituted Hydroxylamines: Ene and Diels–Alder Reactions.

2.1 The Nitrosocarbonyl Ene Reaction: Development of an Aerobic Oxidation to Generate Nitrosoformate Intermediates

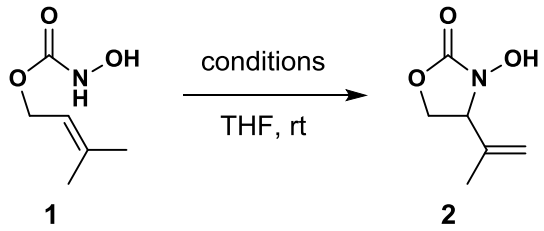
2.1.1 Background and Early Reaction Development with Metal Peroxides

Prior to the genesis of our research, methods that permitted the ene reaction between a nitrosocarbonyl compound and a functionalized alkene partner, and the development of an asymmetric manifold were notably absent from the literature. In addition, excess olefin was frequently utilized in order to obtain high yields of the ene product. A possible reason for the slow advance of nitrosocarbonyl ene reactions was the inability to identify a general and practical oxidant. We sought to rectify these limitations by developing a new catalytic system for the transformation

The recent work of Iwasa,[1] Whiting,[2] and others[3] led us to initially focus on oxidation methods that relied on transition metals and stoichiometric peroxides as the terminal oxidant. A preliminary screen revealed that copper salts in combination with hydrogen peroxide were optimal for the intramolecular ene reaction of *N*-hydroxycarbamate **1** (Table 3, entries 1-5). Treatment of **1** with 5 mol % copper (II) chloride and hydrogen peroxide gave the intramolecular ene product **2** in up to 79**%** yield (Table 3, entry 4). Unfortunately, it was critical to stop the reaction as soon as the starting materials were consumed, because complete ene product decomposition was observed within 30 minutes of the completion of the reaction. Moreover, the rate of decomposition varied depending on the nature of the

substrate, which made obtaining consistent isolated yields problematic. Consequently, an alternative, milder method to oxidize the hydroxamic acids was sought.

Table 3. Screening Metal-Peroxide Reaction Conditions for the Nitrosocarbonyl Ene



1 2

Entry	Catalyst	Additive	Oxidant	Time	% Yield[b]
1	$FeCl_3$	–	HOOH	3 h	25
2	$RuCl_3$	Et_3N	HOOH	6 h	53
3[c]	$NiCl_2$	–	HOOH	6 h	0
4	$CuCl_2$	–	HOOH	20 min	79
5	CuCl	–	HOOH	30 min	78

[a] All reactions were performed with reagent grade THF containing 250 ppm BHT inhibitor. The following amounts of reagents were used according to Table 1: 5 mol % catalyst, 120 mol % peroxide, 1.25 mol % pyridine and 1.25 mol % DTBMP. [b] Isolated yields. [c] Reaction was run at 70˚C.

2.1.2 Motivation for Exploring the Aerobic Oxidation of Hydroxylamines

From both an economical and environmental viewpoint, molecular oxygen represents the ideal oxidant due to its low cost and lack of toxic by-products,[4] and aerobic oxidations have the potential to replace hazardous classical oxidation protocols.[5] However, aerobic oxidation methodologies have largely focused on the oxidation of alcohol-based systems, despite the important role oxidation chemistry plays in other functional group transformations.[6] The analogous aerobic oxidation of hydroxylamines to nitroso compounds has remained underdeveloped, despite its potential synthetic utility and environmental impact.

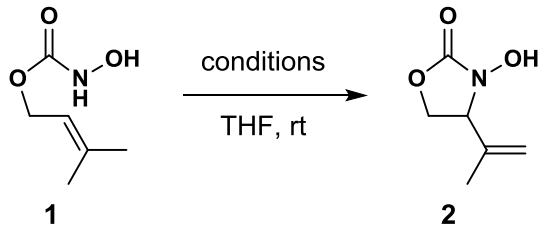
Hydroxylamines not only represent an important structural motif prevalent in natural products and biologically active molecules but they also serve as an attractive precursor to

nitroso compounds. During the last four decades, nitroso compounds have been utilized as synthetically useful intermediates for organic synthesis.[7] In spite of the significant achievements, methods used for preparation of nitroso compounds still rely on the use of stoichiometric oxidants, which leads to issues of functional group incompatibility, limits new reaction development, and require the removal of potentially toxic oxidation by-products.[8] In an effort to circumvent these limitations, we shifted our attention toward an alternative oxidation protocol.

2.1.3 Discovery of Aerobic Oxidation Conditions and Intramolecular Scope

While searching for an alternate oxidant to the problematic metal-peroxide system, preliminary experiments were run utilizing copper(II) chloride and O_2 as the terminal oxidant in refluxing THF (Table 4, entry 1). While the isolated yield was low (8%), the starting material was fully consumed suggesting the viability of an aerobic oxidation for generating the transient nitrosocarbonyl. Fortuitously, by simply lowering the reaction temperature and switching to air as the terminal oxidant, the isolated yield could be dramatically increased using either copper(I) or copper(II) chloride (Table 4, entries 2 and 3). *Importantly, these conditions suppressed the rate of ene product decomposition*. Furthermore, we felt that air was an ideal oxidant because it is readily available, inexpensive and the byproducts are environmentally benign.[6c, 6d] The addition of catalytic pyridine resulted in cleaner and more efficient reactions (Table 4, entry 4), however no rate enhancement was observed when 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was used, which suggests pyridine is not functioning simply as a base (Table 4, entry 5). In addition, no reaction was observed under anaerobic conditions (Table 4, entry 6).

Table 4 Screening Aerobic Reaction Conditions for the Nitrosocarbonyl Ene



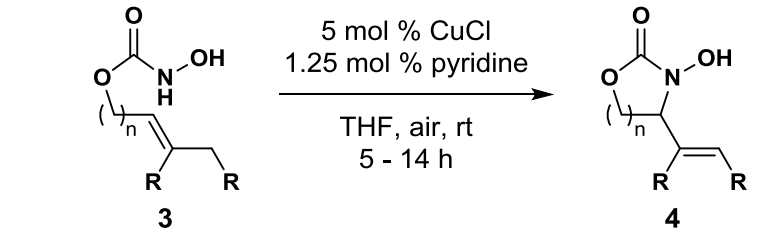
1 2

Entry	Catalyst	Additive	Oxidant	Time	% Yield[b]
1[c]	$CuCl_2$	–	O_2	8 h	8
2	$CuCl_2$	–	air	144 h	68
3	CuCl	–	air	29 h	87
4	CuCl	pyridine	air	6 h	93
5	CuCl	DTBMP	air	29 h	94
6[d]	CuCl	pyridine	–	48 h	0

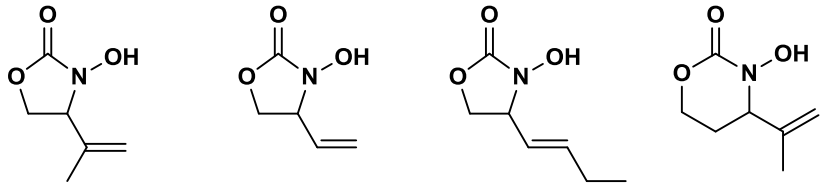
[a] All reactions were performed with reagent grade THF containing 250 ppm BHT inhibitor. The following amounts of reagents were used according to Table 1: 5 mol % catalyst, 120 mol % peroxide, 1.25 mol % pyridine and 1.25 mol % DTBMP. [b] Isolated yields. [c] Reaction was run at 70˚C. [d] Starting material recovered.

With the optimized reaction conditions (5 mol % copper (I) chloride, 1.25 mol % pyridine, reagent grade THF, air, rt), we investigated the scope of the intramolecular nitrosocarbonyl ene reaction (Tale 5). The allylic and homoallylic nitrosoformate esters both cyclize by a Type I mechanism (according to Oppolzer and Snieckus' classification)[9] to construct the 2-oxazolidinone and 1,3-oxazine-2-one scaffold (Table 5, **2, 5–7**). Olefin geometry plays an important role and currently the intramolecular reaction does not accommodate substrates bearing a *Z*-alkene (**8** & **9**), presumably due to the geometric constraints of approaching the alkene with the required *skew* geometry.

Table 5. Substrate Scope Studies for the Intramolecular Nitrosocarbonyl Ene



3 **4**

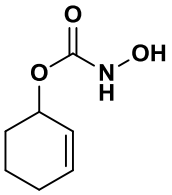


2
93%

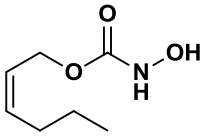
5
71%

6[a]
96%
(5:1 *E*:*Z*)

7
89%



8
0%
(decomp)



9
0%
(decomp)

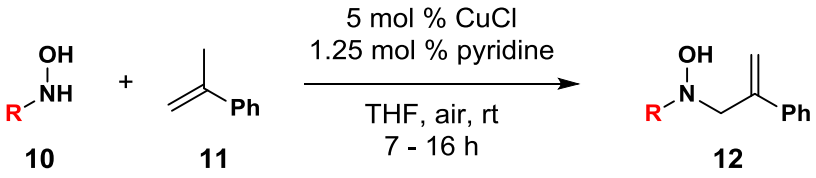
[a] Product **6** resulted from the reaction of trans-2-hexene-yl hydroxycarbamate. The yield is a combined yield of both olefin isomers.

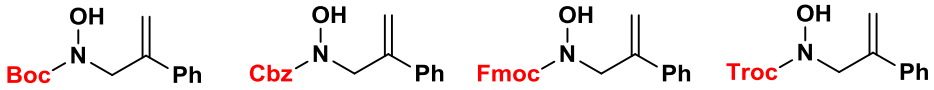
2.1.4 Exploring the Intermolecular Scope of the Nitrosocarbonyl Ene Reaction

Having established a mild, single-pot method for the intramolecular acylnitroso ene reaction, we evaluated the bimolecular reaction which provides a convenient method for effecting allylic amidation. Our investigations focused on *N*-hydroxycarbamates bearing protecting groups that were easy to prepare, commonly used in synthesis and could be orthogonally deprotected. To our gratification, hydroxylamines protected with Boc, Cbz,

Fmoc and Troc groups all participated in the intermolecular ene reaction in greater than 80% yield (Table 6). Significantly, with the exception of *tert*-butyl-*N*-hydroxycarbamate, comparable yields were also obtained with only 1.1 equivalents of α-methyl styrene **11**. Based on reaction trends, *vide infra*, we currently believe the copper-air catalyst system is oxidizing the *N*-hydroxycarbamate and generating a transient acylnitroso intermediate. However, the nature of the copper-oxidant species and the oxidation mechanism require further studies. Under the aerobic oxidation conditions tetrahydrofuran can form peroxides, however, alternative solvents that do not pose a risk of peroxide formation for, such as 2-methyltetrahydrofuran (75%), methanol (68%), ethyl acetate (77%), and toluene (77%) can be utilized to generate compound **14**.

Table 6. Substrate Scope Studies for the Intermolecular Nitrosocarbonyl Ene





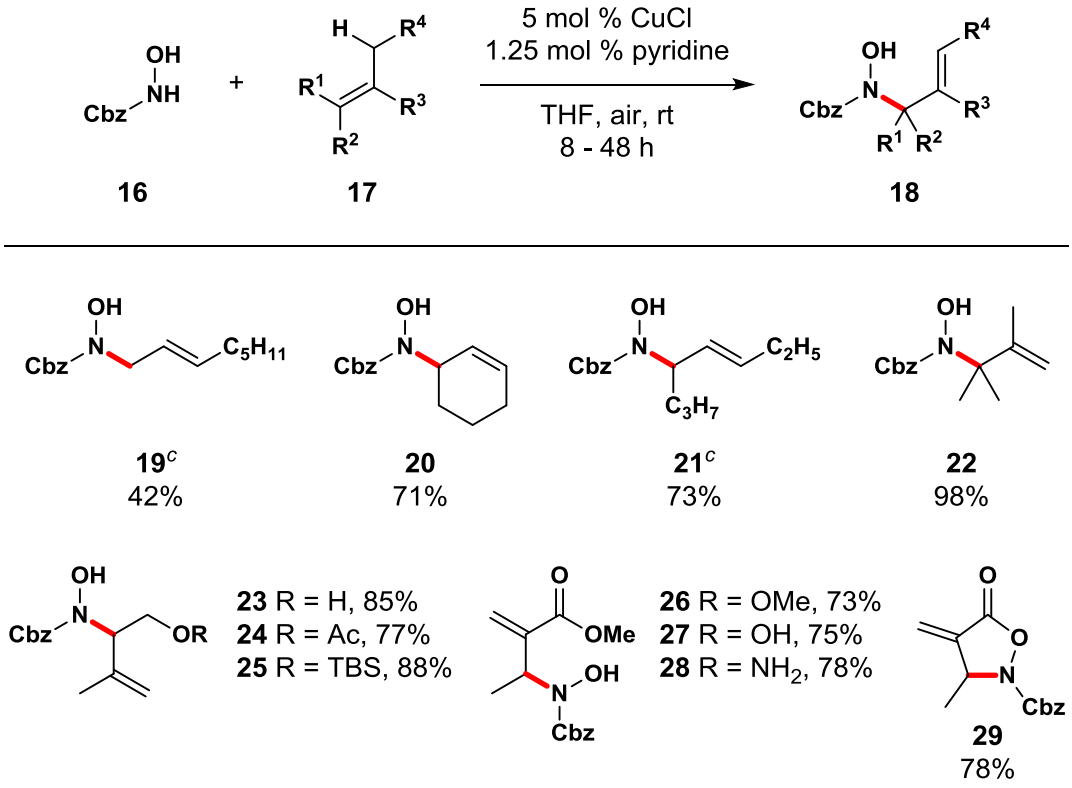
AMS[b]	13	14	15	16
5 equiv ⟹	90%	87%	83%	83%
1.1 equiv ⟹	57%	80%	76%	81%

[a] Reactions were performed with reagent grade THF containing 250 ppm BHT inhibitor. [b] AMS = α-methyl styrene.

We chose to investigate the scope of the intermolecular ene reaction with 1.2 equiv of the alkene partner and the carbobenzyloxy (Cbz) protected hydroxylamine (**16**) (Table 7). The reaction tolerated a series of alkene reaction partners and furnished allylic *N*-

hydroxycarbamate derivates in moderate to excellent yield (Table 7, entries **19**–**22**). The best results were obtained from substrates with electron-rich olefins, which is consistent with other known ene processes. The reaction can also tolerate alkenes that are deactivated by electron withdrawing substituents, as well as an alkene bearing a free hydroxyl group (Table 7, entries **23 – 25**).

Table 7. Olefin Substrate Scope for the Intermolecular Nitrosocarbonyl Ene



[a] Reactions were performed with reagent grade THF containing 250 ppm BHT inhibitor. [b] Isolated yields. [c] The yield is a combined yield of both olefin isomers.

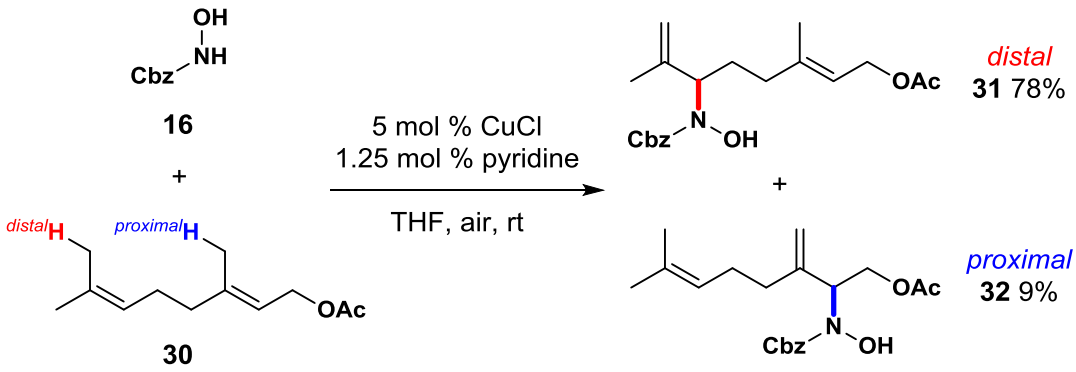
We next turned our attention to bimolecular reactions involving tiglic-acid derivatives because they provide rapid access to α,β-disubstituted amino acids. Direct methods to access this important structural motif are limited.[10] Nitroso ene reactions with electron deficient tiglic-acid derivatives are often low yielding, especially with nitrosocarbonyl enophiles.[8a]

Therefore, we were thrilled when we discovered that use of 1.2 equiv of methyl tiglate resulted in a 73% yield of the desired ene product (Table 7, entry **26**). The unprotected acid and amide derivates also afforded the desired products in 75% and 78%, respectively (Table 7, entry **27** & **28**). The benzamide analogue underwent clean reaction, however it cyclized in situ to form α-methylene isoxazolidinone (Table 7, entry **29**).

2.1.5 Regioselectivity of the Nitrosocarbonyl Ene Reaction

The nitrosocarbonyl ene reaction is heavily influenced by the electronic factors of the olefin. For example, using geranyl acetate to probe the reactivity of electronically differentiated alkenes (Equation 2, **30**), the major product arose from reaction at the distal double bond (Equation 2, **31**), since the allylic acetate electronically deactivates the proximal double bond (Equation 2, **32**).[7a, 7c]

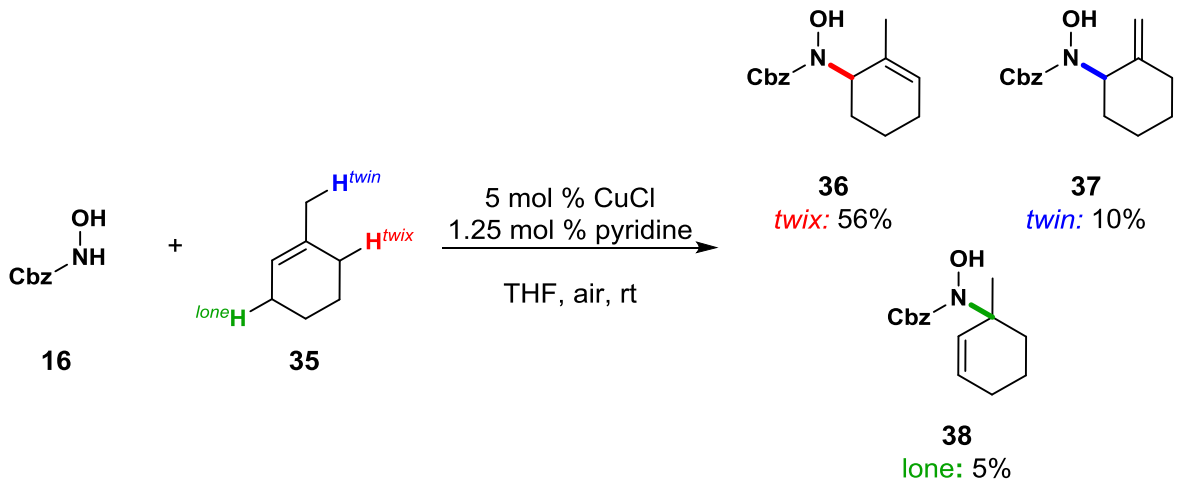
Equation 2. Directing Effects in Geraniol Derivatives in the Nitrosocarbonyl Ene



Similar to nitrosoarene enophiles, nitrosocarbonyl compounds show a strong preference for a *skew* geometry when approaching the olefin.[11] As a consequence, when the starting olefin has a multiple allylic sites of reactivity the nitrosocarbonyl abstracts a hydrogen from the twix position during the ene reaction (as defined on compound **35** in Equation 3). For example, while three products are obtained when using 1-methyl-1-cyclohexene as the olefin

partner, the reaction showed a strong preference for the *twix* product over the *twin* or *lone* (Equation 3, 12:2:1 ratio of **36**:**37**:**38**).[11] This general pattern of reactivity was conserved across all olefin partners screened.[7a, 7c]

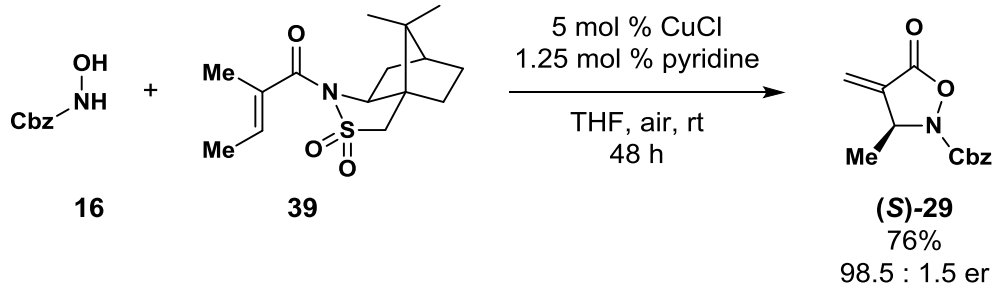
Equation 3. Regioselectivity of Hydrogen Abstraction in the Nitrosocarbonyl Ene



2.1.6 Rendering the Nitrosocarbonyl Ene Reaction Asymmetric

Inspired by Adam's work employing a chiral auxiliary on the tiglic acid derivative,[12] we set out to control the absolute stereochemistry of the nitrosocarbonyl ene reaction. Utilizing tiglic acid with Oppolzer's derived sultam (**39**), the α-methylene isoxazolidinone (**(*S*)-29**) was produced in situ as predominately a single enantiomer (98.5:1.5 er) and Oppolzer's chiral auxiliary could be quantitatively recovered from the reaction. Single-crystal X-ray analysis was used to establish the *S*-configuration of the newly formed stereocenter in ene product **(*S*)-29**. This represents the first example of an asymmetric intermolecular acylnitroso ene reaction (Equation 4).[13]

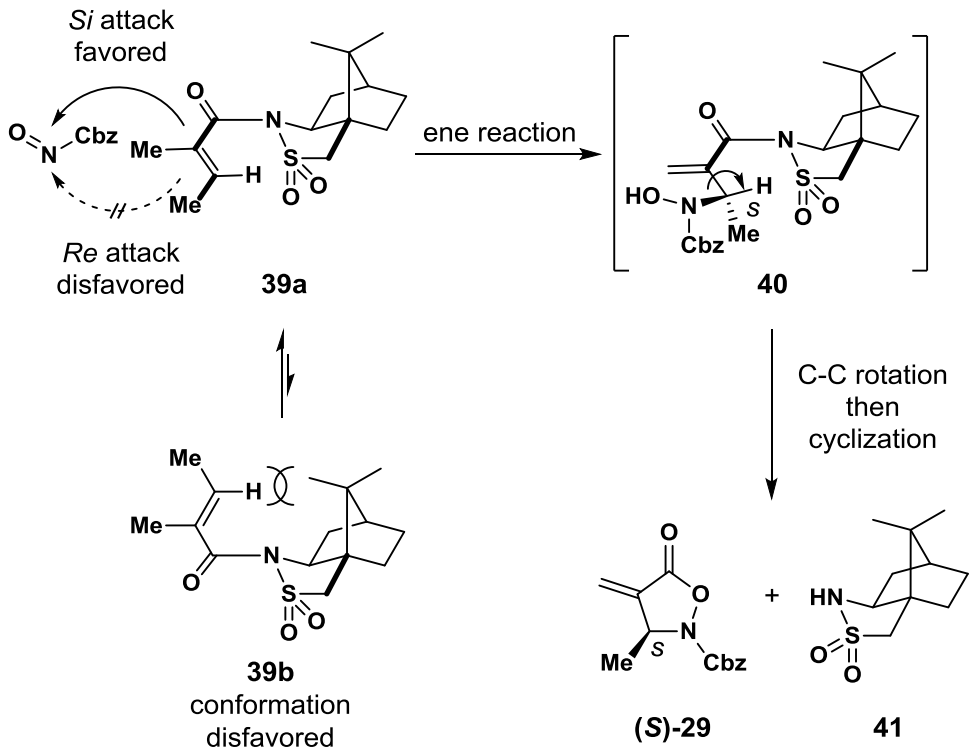
Equation 4. Asymmetric Nitrosocarbonyl Ene using Oppolzer's Sultam



16 **39** **(*S*)-29**
76%
98.5 : 1.5 er

To explain the observed selectivity we postulate a reactive conformation of **39a** based on literature precedent.[12, 14] The favored conformation features an *anti*-orientation between the carbonyl group and the sulfonyl functionality and an *s-trans* conformation of the carbonyl group and the double bond. A *skewed* approach of the enophile from the less hindered *Si*-face is favored because the sulfonyl oxygen atoms shield the *Re*-face. (Figure 12). Since both enantiomers of the camphorsultam chiral auxiliary are commercially available, both stereoisomers of the ene product are available.

Figure 12. Origin of Selectivity for the Asymmetric Nitrosocarbonyl Ene



Preliminary studies demonstrate α-methylene isoxazolidinone compounds have similar biological activity as α-methylidene-γ-lactones and are potent against mouse L-1210 as well as human HL-60 and NALM-6 leukemia cell lines.[15] The precise mechanism of activity is currently unknown but these compounds are believed to react as Michael-type acceptors with bionucleophiles. Despite their potential as possible novel therapeutics, access to α-methylene isoxazolidinone compounds is virtually unknown, especially in an asymmetric sense.[12, 15] Moreover, isoxazolidinones represent well-established building blocks that can serve as synthons for α,β-disubstituted amino acids.[10] While we envisioned extending this methodology to include other enone derivatives, the reaction proved to be limited exclusively to the tiglate derivatives. Other enone partners appended to Oppolzer's sultam

(e.g. 1-cyclohexene-1-carboxylic acid, 1-cyclopentene-1-carboxylic acid, and α-methylcinnamic acid) failed to react under the reaction conditions.

2.1.7 Conclusion an Future Outlook

The mild aerobic oxidation conditions developed for the ene reaction proved to be foundational for our future development of nitrosocarbonyl chemistry. For the first time, nitrosocarbonyl compounds could be accessed at room temperature without significant decomposition of the resulting products. Moreover, the methodology is operationally simple to perform; reactions are performed with reagent grade solvent, are run open to the atmosphere and utilizes a readily available and inexpensive catalyst. Additionally, no hazardous or toxic oxidants are used, and the only byproduct of oxidation is water.[16] Based on this initial discovery, we sought to expand the scope of the aerobic oxidation of hydroxylamines.

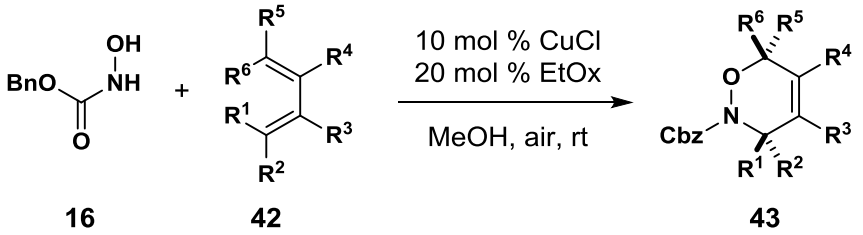
2.2 The Nitroso Hetero Diels–Alder Reaction: Extending the Aerobic Oxidation to Other *N*-Substituted Hydroxylamines

2.2.1 Background and Motivation for Expanding the Aerobic Oxidation

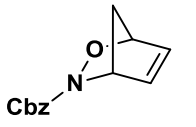
During our study of the nitrosocarbonyl ene reaction, which was based on a copper(I)-catalyzed aerobic oxidation,[16] Shea, Whiting and co-workers simultaneously and independently reported a similar copper(II)-catalyzed aerobic oxidation protocol for the nitrosocarbonyl Diels– Alder reaction.[17] Under their developed methodology, a range of Cbz-protected 1,2-oxazines were accessible, via an intermolecular HDA reaction (Table 8, **44-50**). Additionally, two *N*-substituted hydroxylamines with appended dienes were also trapped as the HDA adducts in an intramolecular fashion (not shown). Importantly, the

reaction showed a significant improvement in yield over the previously developed transition metal systems, and presumably this method will find future widespread applications.

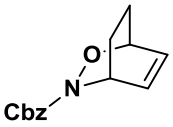
Table 8. Shea and Whiting's Aerobic Oxidation of Cbz-Protected Hydroxylamines



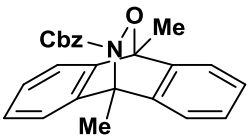
16 **42** **43**



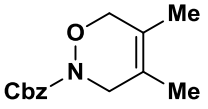
44
97%



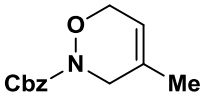
45
92%



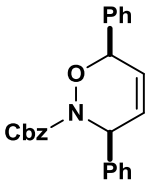
46
88%



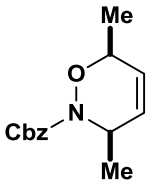
47
85%[a]



48
79%[b]



49
79%



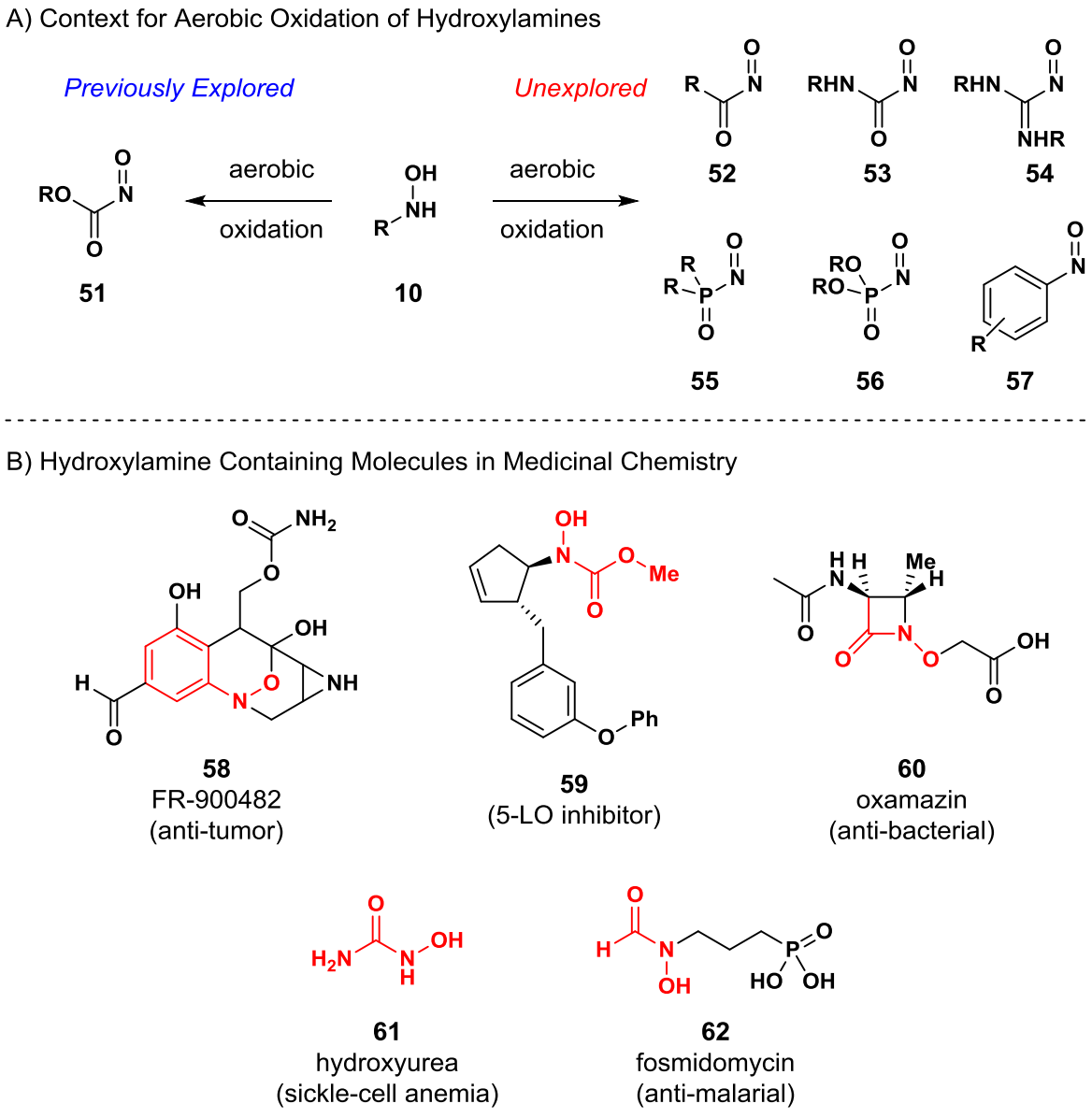
50
97%

[a] 7:1 ratio of Diels–Alder to ene. [b] 2:1 ratio of regioisomers

When we began studying the Diels–Alder reaction with our newly developed methodology, the aerobic oxidation approach was limited to the formation of nitrosoformate derivatives (**51**). Given the importance of nitroso chemistry and the myriad of *N*-substituted nitroso compounds used in synthesis, such as acylnitroso **52**, nitrosoformamide **53**, iminonitroso **54**, *P*-nitroso phosphine oxide **55**, *P*-nitroso phosphate **56**, and arylnitroso **57** derivatives, the development of a general aerobic oxidation of *N*-substituted hydroxylamines is still desired.[7] Moreover, the substituted hydroxylamine motif is present in a number of

pharmaceutically active molecules and natural products (e.g. **58 – 62**), making the development of new methodologies for hydroxylamine functionalization imperative. This section details our development of a general aerobic oxidation for these classes of substituted hydroxylamines, which provides a general, catalytic and sustainable alternative to stoichiometric oxidation methods to access a range of nitroso compounds (Figure 13).

Figure 13. Motivation for Expanding the Scope of Aerobic Oxidation

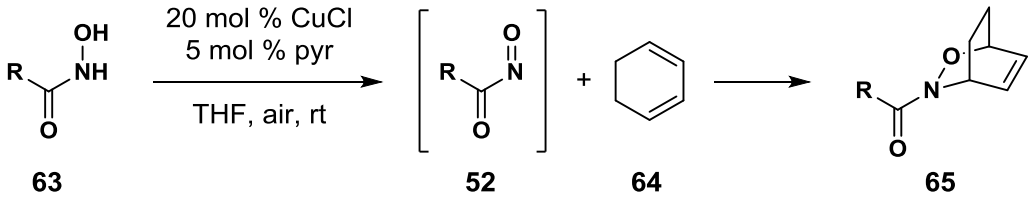


2.2.2 Development of Aerobic Oxidation for *N*-Substituted Hydroxylamines

Due to the instability and transient nature of nitroso compounds **51-56**, we elected to use the nitroso HDA reaction as a means to investigate the generality of our catalytic aerobic oxidation protocol. It is well known that nitroso compounds that are directly connected to an electron-withdrawing group (**51-54**) undergo rapid [4+2] cycloaddition reactions with conjugated dienes. Furthermore, the HDA reaction is a valuable transformation that plays a central role in the synthesis of natural products and biologically active molecules. These advantageous properties were key factors in our selection of the nitroso HDA reaction as a platform on which to test our new oxidation methodology.

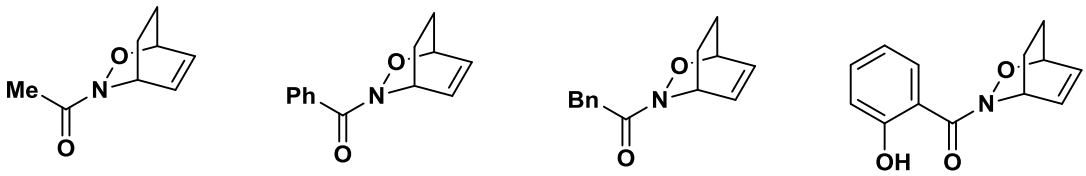
Our investigations began with our previously developed oxidation conditions (5 mol % CuCl, 1.25 mol % pyridine, reagent grade THF and 1 atm air). Under these conditions, reactions with acyl-substituted hydroxylamines required long reaction times and proved impractical. However, it was found that the aerobic oxidation protocol was more efficient and tolerant of a variety of *N*-substituted hydroxylamines when the catalyst loading was increased to 20 mol % and 5 mol % pyridine (Table 9). Generally, compounds containing a more electron-withdrawing group on the nitrogen substituent reacted slower. Within the acyl-substituted series, *N*-hydroxyacetamide **66** and *N*,2-dihydroxybenzamide **69** afforded the lowest yields (Table 9, 58% and 73% respectively) and required heating to 50 ºC to help facilitate the reaction. Under these conditions decomposition of the acylnitroso species became competitive with the HDA reaction, which resulted in the lower yields.

Table 9. Nitroso HDA reaction of Nitroso Compounds Bearing Carbonyls



63 **52** **64** **65**

Acylnitroso Substrates



66 58%

67 80%

68 93%

69 73%

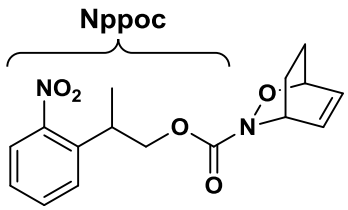
Nitrosoformate Ester Substrates

45 96%

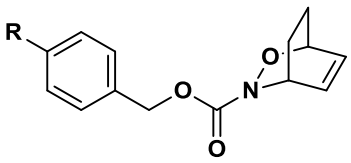
70 96%

71 87%

72 99%

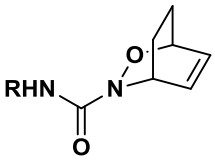


73 96%

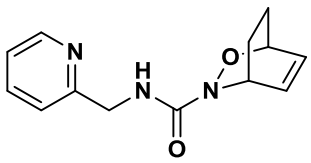


74 R = OMe, 97%
75 R = OTBS, 85%
76 R = CF_3, 97%
77 R = vinyl, 94%

Nitrosoformamide Substrates



78 R = H, 89%
79 R = Ph, 94%
80 R = Bn, 99%



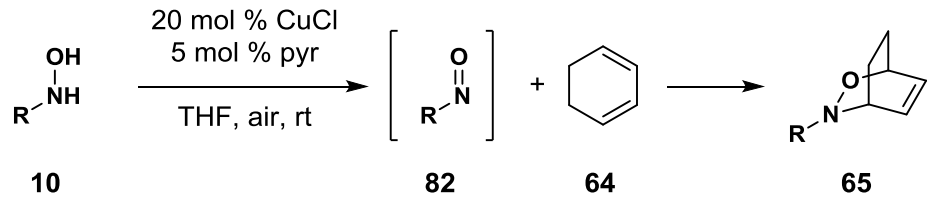
81 77%

Hydroxylamines bearing formate-based protecting groups, such as Cbz, Boc, Troc, Fmoc, and Nppoc, all participated in the acylnitroso HDA reaction in greater than 87% yield

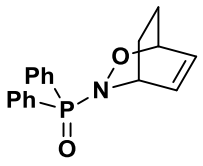
(Table 9, **45**, **70**–**73**). Other Cbz-derived *N*-hydroxycarbamates bearing *p*-substituted functional groups proceeded under the reaction conditions with no complications (Table 9, **74**–**77**). Nitrosoformamide compounds **78**–**81** reacted analogously and universally afforded products in high yield. Importantly, this includes hydroxyurea **78** that previously suffered from low isolated yield when stoichiometric periodate oxidation was used.[18] Hydroxyurea **61** is used clinically for the treatment of sickle-cell anemia[19] and evidence suggests that its biological activity can be attributed to N–O oxidation by hemoglobin.[20] Finally, the mild oxidation protocol can be performed successfully in a number of reagent grade solvents, such as 2-MeTHF, MeOH, EtOH, *i*-PrOH, EtOAc, and toluene.

We next explored the capacity of these conditions to catalyze the aerobic oxidation of other known classes of *N*-substituted hydroxylamines (Table 10). Although less studied, HDA reaction with *P*-nitrosophosphine oxide and nitrosoamidine allows for the direct installation of phosphinamide and guanidine functional groups, which are prevalent in asymmetric catalysts and biologically active molecules.[21] In addition, King and co-workers have shown that *N*-phosphinoylnitroso compounds hydrolyze to liberate nitroxyl (HNO), the biologically important reduced form of nitric oxide.[22] Therefore, we were happy to observe that *N*-hydroxyphosphinamide **83** and *N*-hydroxyphosphoramidate **84** could be oxidized and readily trapped with 1,3-cyclohexadiene in moderate to excellent yield. Phosphorous-migration is a known problem with *N*-hydroxyphosphoramidates and may contribute to the reduced yield of **84**.[22c] The oxidation protocol also worked with *N,N'*-bis-Boc-*N''*-hydroxylguanidine (Table 10, **85**).[21c]

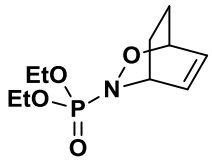
Table 10. Nitroso HDA reaction of Nitroso Compounds Bearing Other Functionalities



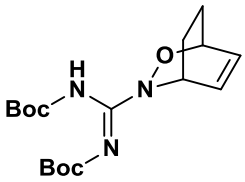
10 **82** **64** **65**



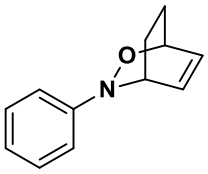
83
99%



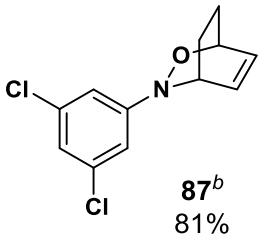
84[a]
49%



85
66%



86[b]
84%



87[b]
81%

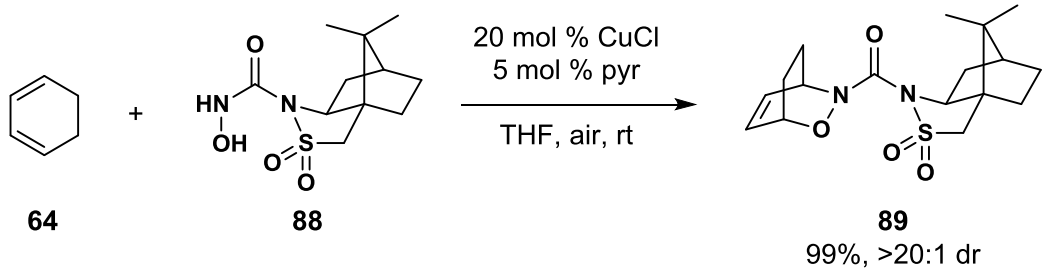
[a] Synthesis of **84** commenced from diethyl (trimethylsilyl)oxy-phosphoramidate, see supporting information. [b] The arylhydroxylamines were added over 2 h via syringe pump.

Arylnitroso compounds are bench-top stable and consequently much less reactive in the hetero Diels–Alder reaction relative to acylnitroso compounds.[7b] In general, a considerable drop in yield is observed for these reactions. In addition, *in-situ* oxidation of the arylhydroxylamine is usually avoided because it is difficult to prevent over-oxidation and formation of coupling by-products, such as azoxybenzene.[23] Initially, subjection of phenylhydroxylamine to the optimized reaction conditions resulted in the exclusive formation of azoxybenzene. To circumvent this undesired side reaction, we added the arylhydroxylamine via syringe pump over the course of 2 h. Utilizing this protocol, the azoxybenzene formation could be minimized and the nitroso HDA adducts were isolated in

high yield (Table 10, **86** & **87**). Notably, this approach provided arylnitroso Diels–Alder adducts in high yield and represents a viable solution to the notoriously less efficient arylnitroso Diels–Alder cycloaddition.

Finally, we wanted to investigate a diastereoselective nitroso HDA reaction. While there are a number of elegant methods for performing asymmetric nitroso HDA reactions, the most common method for inducing chirality utilizes a chiral auxiliary on the acylnitroso dienophile. We chose to investigate the asymmetric HDA reaction using Oppolzer's camphorsultam derivative **88**. As shown in Equation 5, exposure of **88** to the optimized reaction conditions produced **89** as a single diastereomer in 99% yield.

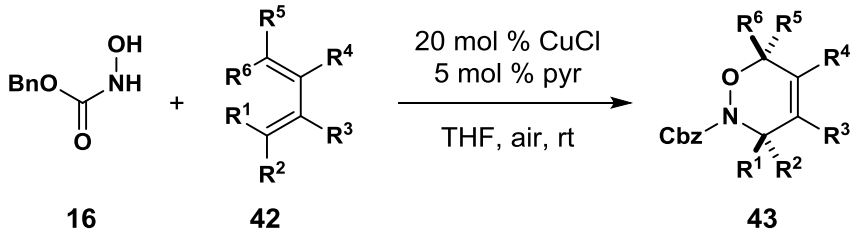
Equation 5. Asymmetric Nitroso HDA reaction using Oppolzer's Sultam



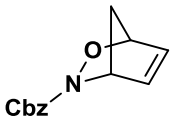
2.2.3 Exploring the Scope of Dienes for the Nitroso HDA Reaction

HDA trapping of transient nitroso-species is not limited to the use of 1,3-cyclohexadiene; other more elaborate and less reactive dienes can also be used (Table 11, **44**, **46**, & **49**). Good functional group compatibility was observed; for example, nitroso Diels–Alder adducts of both ergosterol **90** and ergosteryl acetate **91** were isolated in good yield and with excellent regioselectivity (16:1 and 35:1 respectively).[24] Derivatives of these and other diene-containing natural products have been studied for their biological activity.[25]

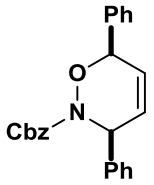
Table 11. Diene Scope for the Nitroso HDA Reaction



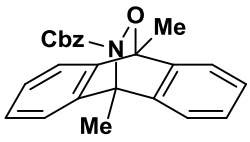
16 **42** **43**



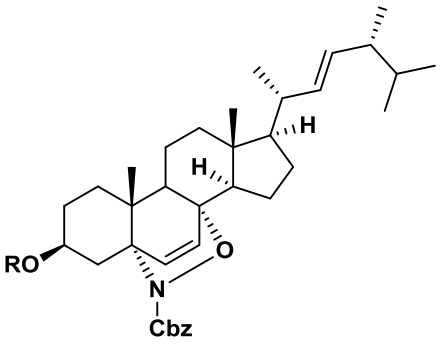
44
94%



49
80%



46
96%



90 R = H, 99%[a]
91 R = Ac, 86%[b]

[a] Isolated as an inseparable mixture of regioisomers (16:1) [b] Isolated as an inseparable mixture of regioisomers (35:1)

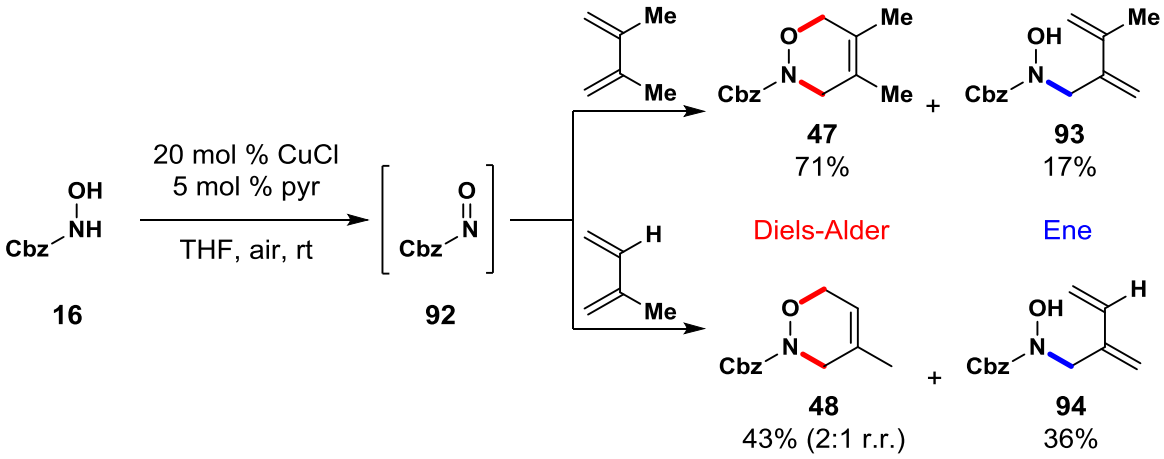
2.2.4. Determining the Relative Preference for Diels–Alder over Ene

It is generally believed that the HDA reaction is more rapid if the free nitroso compound is present. Therefore, many research groups have hypothesized that the preference for ene over Diels–Alder is a reflection of whether or not the nitroso is bound to a metal, and a number of studies have invoked this argument when the ene adduct is observed as a major product in the presence of a Diels–Alder trapping agent.[26] However, these control experiments are typically conducted with 2,3-dimethylbutadiene (DMB) as the Diels–Alder

trapping agent despite the fact that it is well known that DMB exists as a mixture of *s*-trans and *s*-cis conformers.[27] We sought to study this further based on the fact that we did not observe formation of the ene adduct with the ergosterol derivatives, despite the presence of an olefin on the substrate.

Shea and Whiting showed that using their mild oxidation protocol they could accurately determine the product distribution for dienes that are capable of undergoing both Diels–Alder cycloaddition and ene reactions.[17] As expected, we observed similar results with 2,3-dimethylbuta-1,3-diene (DMB) **47** and 2-methyl-buta-1,3-diene **48** (Figure 14). The combined yields were high and the Diels–Alder adducts could be isolated in 71% and 43% yield, respectively. Based on these results we hypothesized that the formation of the ene product could be a reflection of the diene conformation/reactivity

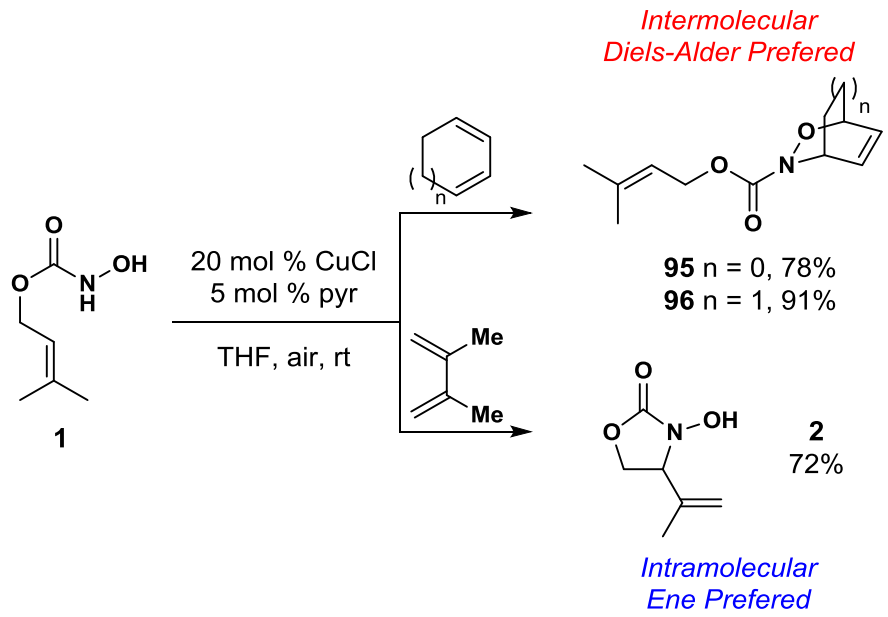
Figure 14. Analyzing the Reactivity of Dienes for Diels–Alder versus Ene



In order to further evaluate the rate difference between ene and HDA, a competition experiment between an intermolecular HDA cycloaddition and intramolecular ene reaction was designed at room temperature using prenyl alcohol-derived *N*-hydroxycarbamate **1**. Cyclic dienes locked in the required and reactive *s*-cis conformation were found to out-

compete the intramolecular ene reaction and no product derived from the intramolecular ene reaction was observed (Figure 15, **95**–**96**). In contrast, in the presence of DMB the predominant product resulted from an intramolecular ene reaction (72%). The overall ratio of products for this transformation was 14:3:1 (Figure 15, intramolecular ene **2** (72%, shown): nitroso HDA cycloaddition (16%, not shown): intermolecular ene (6%, not shown)). These results provide clear evidence that the use of unreactive dienes are required if the ene reaction is to proceed in preference to the Diels–Alder cycloaddition. While this result does not directly rule out the possibility of a metal-bound nitroso complex, special care must be taken to ensure that the diene selected is sufficiently reactive so as to not unfairly bias the results.

Figure 15. Examining Intramolecular Ene vs. Intermolecular HDA for Various Dienes



2.2.5 Concluding remarks

The developed aerobic oxidation proved to be a general solution for accessing nitroso compounds from the corresponding *N*-substituted hydroxylamines.[28] Additionally, the

aerobic oxidation is operationally simple to perform, uses readily available catalyst systems and produces only water as an oxidation byproduct. Based on this, we feel that the aerobic oxidation will be a widely used methodology for the future of nitroso chemistry. With the insight gained from our study into the aerobic oxidation, we felt confident exploring new areas of nitrosocarbonyl chemistry.

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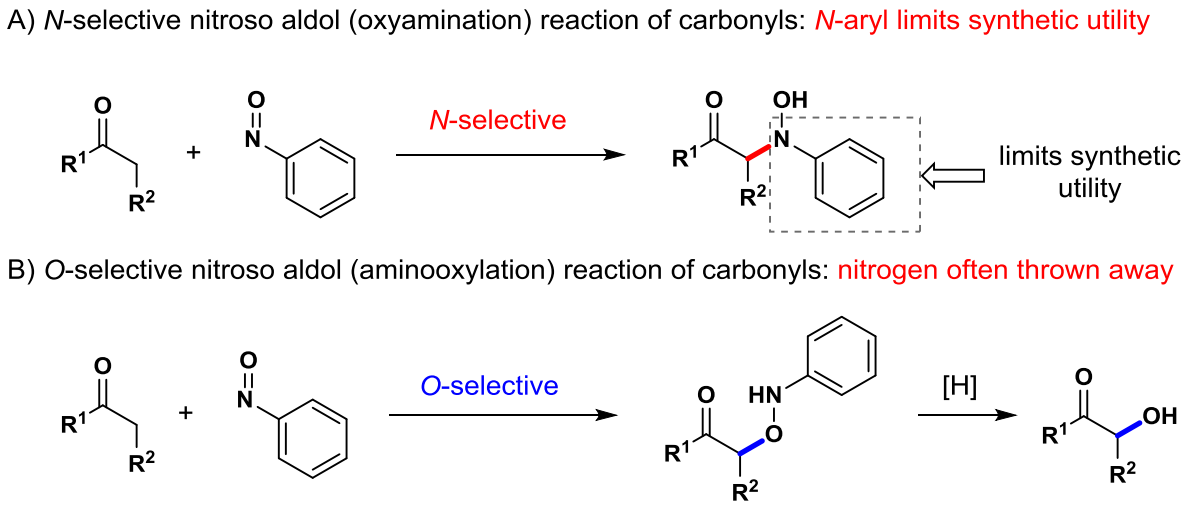
3. Expanding the Scope of Nitrosocarbonyl Transformations: The Nitroso Aldol Reaction

3.1 Historical Background on Nitroso Aldol Reaction

The efficient and direct α-functionalization of carbonyl compounds with heteroatoms utilizing an electrophilic reagent is a significant challenge in organic synthesis.[1] Although a number of methods have been developed for the direct α-heterofunctionalization of carbonyl compounds, nitrosobenzene and its analogues have been recognized as an attractive electrophile for such transformations due to the ease of handling.[2]

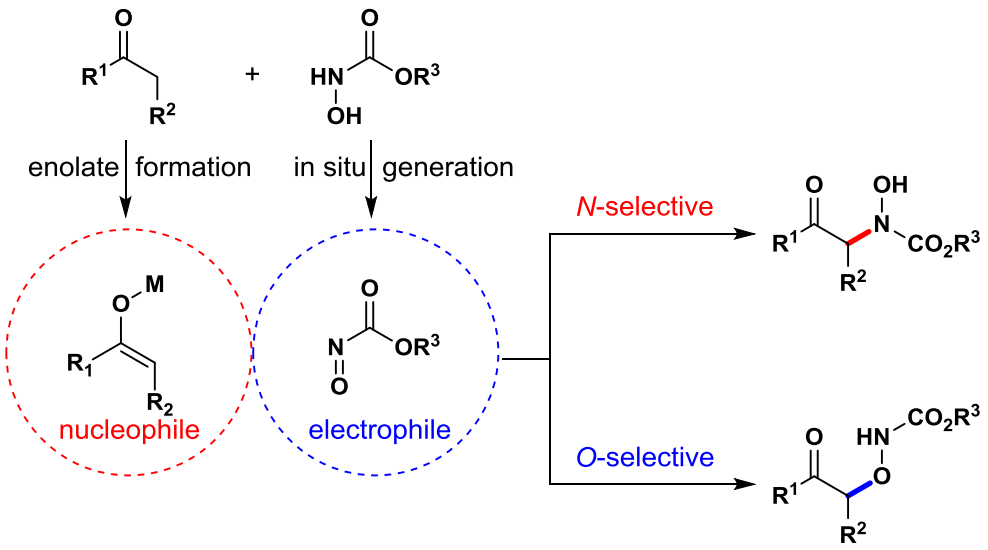
Nitrosoarenes can serve as both an electrophilic source of nitrogen or oxygen and determining the factors that influence the ambident reactivity has been the major goal of a number of research programs.[3] Although examples of the regioselective nitroso aldol reaction have existed since 1924,[4] the pioneering work of Yamamoto and co-workers has ushered a renaissance in the field, culminating in the report of numerous methodologies using arylnitroso compounds to install either an oxygen[5] or nitrogen heteroatom.[6] While the *N*-selective nitroso aldol reaction has made considerable progress, the products of the oxyamination reaction are synthetically limited because it is prohibitively difficult to cleave the *N*-aryl bond to allow for subsequent nitrogen-bond forming transformations.[6i, 7] Comparatively, the aminooxylation reaction (i.e. *O*-selective aldol) to afford α-oxygenated carbonyl compounds has been extensively developed and now represents a versatile method to gain access to the α-oxycarbonyl synthon.[5] However, the synthetic drawbacks of the *N*-aryl bond often render the nitrogen as disposable waste, limiting the *O*-selective aldol with nitrosobenzene primarily to α-hydroxylation reactions (Figure 16).[8]

Figure 16. The Nitroso Aldol Reaction using Nitrosobenzene



The significant limitations of nitrosobenzene has inspired the search for alternative nitroso compounds that bear *N*-substituents that are easier to manipulate but have similar versatility. In principle, nitrosocarbonyl compounds can function in this role.[9] However, due to their high reactivity, nitrosocarbonyls must be generated in situ[10] and identifying conditions compatible with enolate formation has been a significant synthetic challenge. Inspired by the dearth of reports utilizing the transient electrophile, we elected to pursue the transformation (Figure 17).

Figure 17. The Nitrosocarbonyl Aldol Reaction

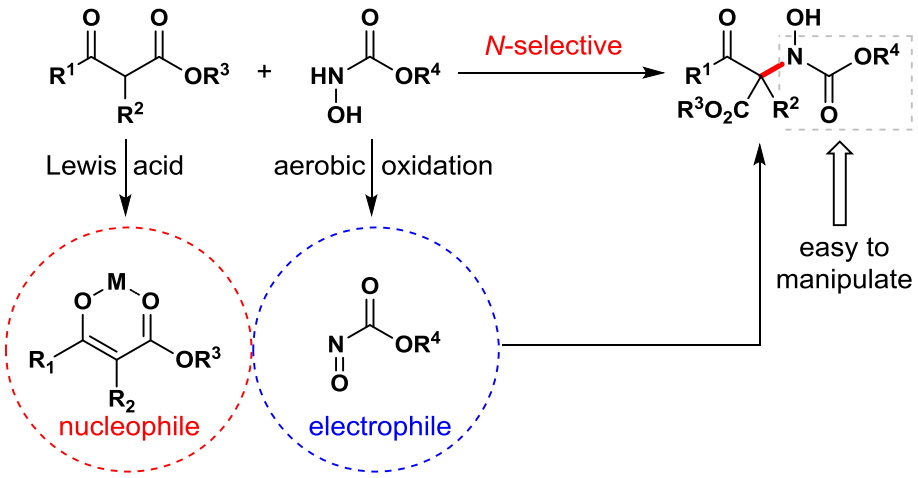


3.2 Electrophilic α-Amination of Carbonyl Compounds: The *N*-Selective Nitrosocarbonyl Aldol Reaction

3.2.1 Reaction Development Through Synergistic Catalysis

Based on our previous success generating nitrosocarbonyl compounds under aerobic conditions,[11] we set out to merge aerobic oxidation with Lewis acid catalysis. The use of synergistic catalysis is a powerful approach to reaction design and has emerged as a highly attractive strategy for developing new and valuable transformations.[12] As shown in Figure 18, we envisioned that the concurrent activation of latent nucleophilic (β-ketoester) and electrophilic (nitrosoformate) partners could be achieved. The union of these catalytic processes would result in a direct α-amination reaction of β-ketoesters.

Figure 18. Proposed Method of Accessing the *N*-Selective Nitrosocarbonyl Aldol

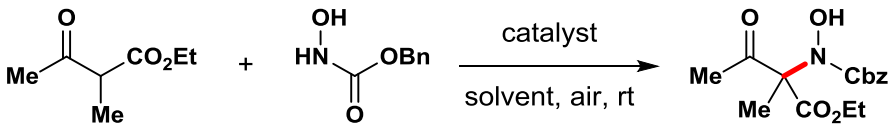


The central challenge was to identify conditions that would allow for the compatible formation of the electrophile and nucleophile in situ, would facilitate subsequent C–N bond formation and would avoid decomposition of the highly reactive nitrosoformate ester intermediate. In addition to our studies on Cu(I)-catalyzed nitroso formation, Shea and Whiting have developed a Cu(II)-catalyzed aerobic oxidation of *N*-hydroxycarbamates to nitrosoformates.[13] Moreover, copper(II) complexes have proven effective as a means of enolate generation in metal-catalyzed functionalization of β-ketoesters.[14] In this regard, we felt copper complexes held tremendous promise and would be an excellent choice to initiate our investigations.

The reaction of ethyl β-ketoester **1** with carbobenzyloxy (Cbz)-protected hydroxylamine **2** was chosen as a test reaction. Initial screening of Lewis acids revealed that the proposed α-amination with nitrosoformates could be accomplished by the addition of copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) to our original optimized conditions for the ene reaction (Table 12, entry 1), albeit in a modest 3:1 *N/O*-selectivity. To our gratification, promising levels of *N/O*-selectivity were obtained by changing the solvent from THF to

MeOH (Table 12, entry 2). A further increase in *N*-selectivity (11:1 to 14:1) resulted when pyridine was removed from the reaction (Table 12, entry 3). We found that other polar protic solvents, such as ethanol and isopropanol, negatively affected the *N*-selectivity (Table 12, entries 4 and 5). In the absence of either $Cu(OTf)_2$ or CuCl we observe a slight decrease in efficiency and *N/O*-selectivity (Table 12, entries 6 and 7). The conditions that provided the optimal balance between efficiency and selectivity was 5 mol % CuCl and 5 mol % $Cu(OTf)_2$ (Table 12, entry 8). It is conceivable that two separate catalysts simultaneously activate the nucleophile and electrophile, however other possibilities cannot be ruled out at this time. Importantly, the optimized protocol is practical and operationally simple. It involves simultaneous addition and mixing of all reagents, at room temperature, open to air, with reagent grade solvent and inexpensive and readily available materials.

Table 12. Optimization of *N*-Selective Nitrosocarbonyl Aldol Reaction



1 **2** **3**

Entry	CuCl/Cu(OTf)$_2$	Additive	Solvent	Time (h)	Yield (%)[a]	N/O[b]
1	10 / 10 mol %	pyr [c]	THF	56	86	3:1
2	10 / 10 mol %	pyr [c]	MeOH	9	91	11:1
3	10 / 10 mol %	—	MeOH	12	94	14:1
4	10 / 10 mol %	—	EtOH	24	90	4:1
5	10 / 10 mol %	—	*i*PrOH	53	80	2:1
6	10 / 0 mol %	—	MeOH	48	91	9:1
7[d]	0 / 10 mol %	—	MeOH	192	74	14:1
8	**5 / 5 mol %**	**—**	**MeOH**	**24**	**97**	**14:1**

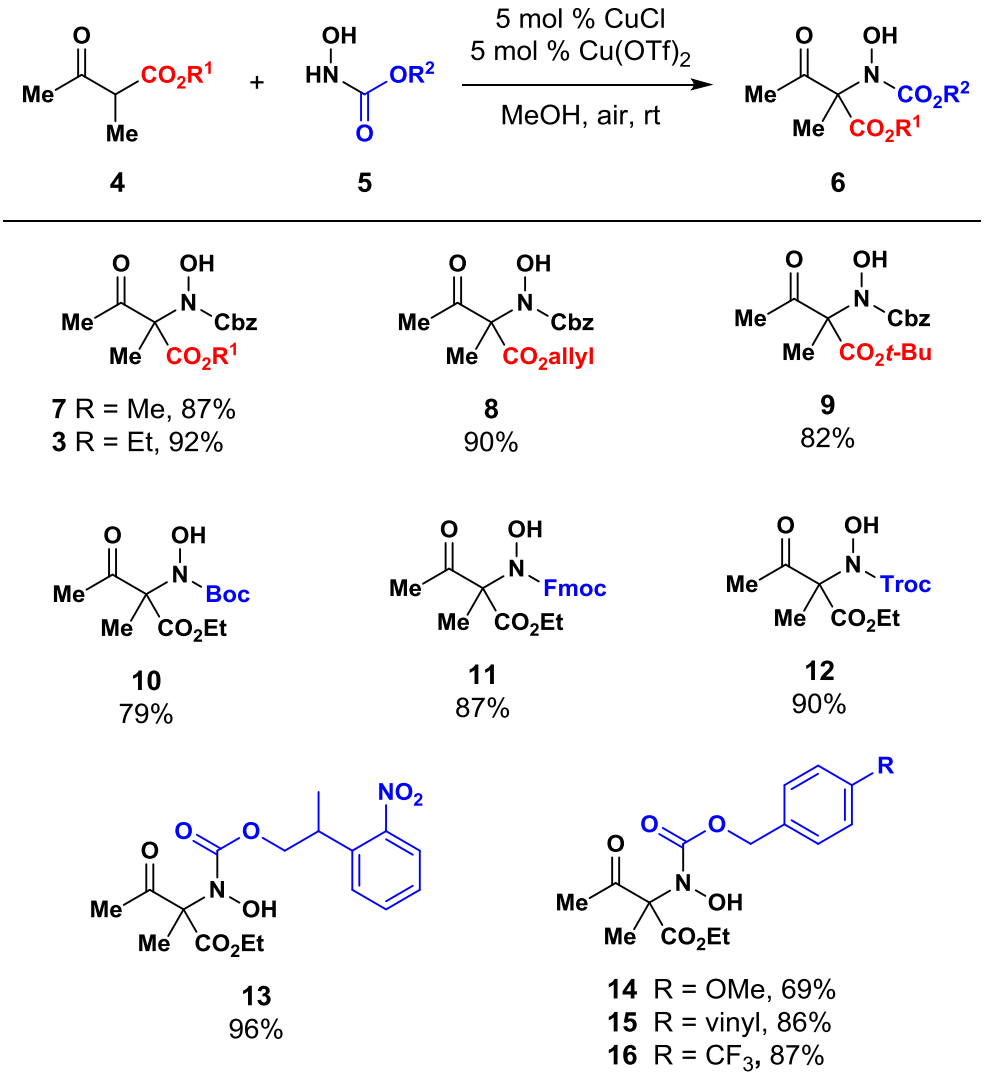
[a] Isolated yield of the N- and O-product mixture. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Reaction conducted with 1.25 mol % of pyridine. [d] The reaction with 5 mol % catalyst was prohibitively long.

3.2.2 Exploring the Scope of the *N*-Selective Nitrosocarbonyl Aldol Reaction

With optimized reaction conditions in hand (5 mol % CuCl and Cu(OTf)$_2$, MeOH, air, rt), we investigated the scope of the α-amination reaction by initially varying the ester group (R^1) on the β-ketoesters and the *N*-substituent on the hydroxylamine (R^2) (Table 13). There appears to be no substantial steric restrictions of the ester moiety; methyl, ethyl, allyl and *t*-butyl derivatives all proceed in high yield, with comparable reaction rates (Table 13, **3** and **7–9**). X-ray crystal structure analysis of **9** was used to establish that the reaction had taken place on nitrogen. In addition, steric and electronic modifications to the *N*-substituent on the hydroxylamine were also well tolerated. *N*-Hydroxycarbamates bearing protecting groups that could be orthogonally deprotected, Cbz, Boc, Fmoc, Troc, and Nppoc, all participated in

greater than 79% yield (Table 13, **10–13**). In all cases the *O*-selective adduct was observed in minor amounts and could be separated by column chromatography

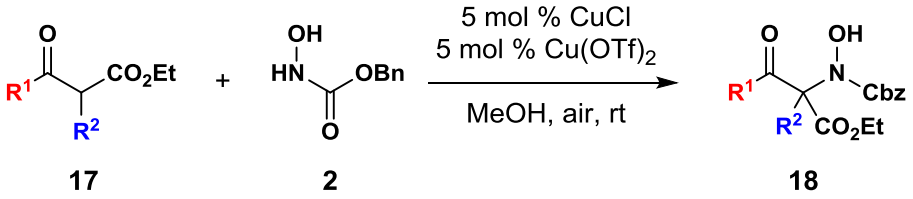
Table 13. Ester and Carbamate Scope Studies for the *N*-Selective Nitrosocarbonyl Aldol



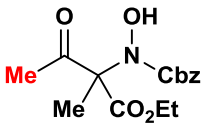
Encouraged by these results, we further explored the scope of the transformation with a series of substituted β-ketoesters (Table 14). β-Ketoesters with alkyl, benzyl, or aryl substituents at R^1 all afforded excellent yields of the desired hydroxyamination product (Table 14, **3**, **19**–**22**). Notably, a more sterically bulky α-branched substrate underwent smooth conversion to give **21** in 91% yield. Next, the electronic nature of aryl substituents

at R^1 was investigated and found to have minimal effect on the reaction outcome. Both electron rich and electron deficient aryl groups were found to be compatible (Table 14, **23–26**). Importantly, initial studies suggest that there is some leeway in the steric bulk of the α-substituent (R^2) (Table 14, **27–29**). For example, α-substitution (R^2) with methyl, ethyl and benzyl groups all proceeded in excellent yield. The methodology can also be used for cyclic β-ketoesters (Table 14, **30** and **31**) but the *O*-regioisomer became more competitive in such cases, affording *O*-selective products in 30% and 58%, respectively. In general the rate of the reaction slowed and higher ratios of the *O*-selective adduct were observed as the steric bulk of the α-substitution increased and with cyclic substrates. Unsubstituted carbonyl compounds can be activated toward electrophilic substitution as well. Interestingly, in this case we observed N−O bond heterolysis and presumably the formation of an α-imino β-ketoester that is trapped by methanol to afford compound **32**.[4, 15]

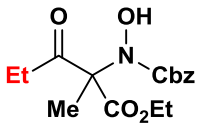
Table 14. Scope of Substitution on β-Ketoester for *N*-Selective Nitrosocarbonyl Aldol



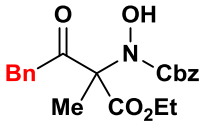
17 2 18



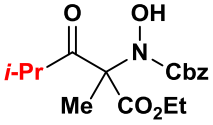
3
92%



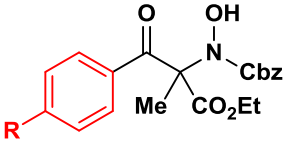
19
86%



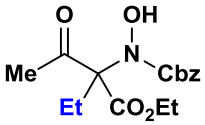
20
90%



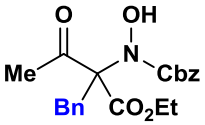
21
91%



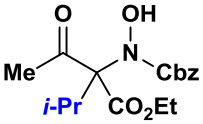
22 R = H, 87%
23 R = OMe, 90%
24 R = *t*-Bu, 87%
25 R = Br, 79%
26 R = NO_2, 63%



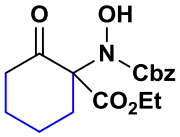
27
84%



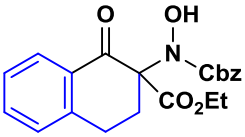
28
72%



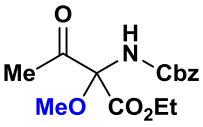
29
42%



30
43%



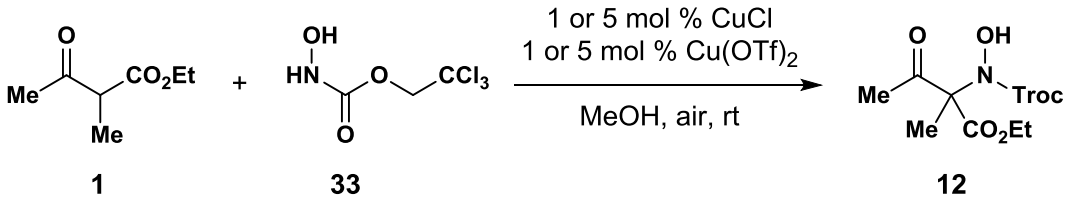
31
70%



32
61%

To demonstrate the synthetic utility of this method, the reaction was performed on gram-scale (Equation 6). The catalyst loading could be lowered to 1 mol % with no significant loss in overall yield, although the reaction required ten days for completion.

Equation 6. Gram Scale *N*-Selective Nitrosocarbonyl Aldol Reaction

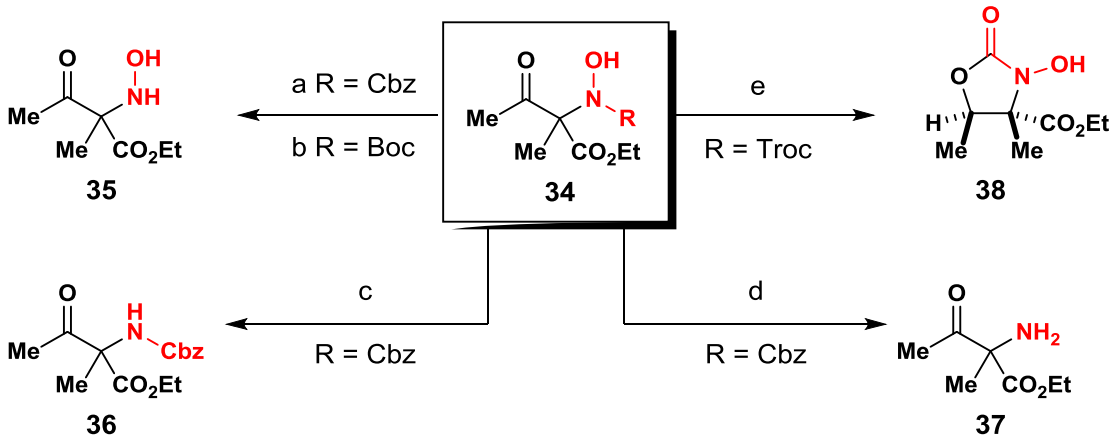


3.2.3 Synthetic Manipulations on the *N*-Selective Nitrosocarbonyl Aldol Products

While we envisioned a number of synthetic transformations for the α-amination products, we focused on a series of functional group manipulations that highlight the utility of using a nitrosoformate intermediate as the electrophilic source of nitrogen. For example, hydrogenation of the Cbz-group with 5 mol % Pd/C or an acid catalyzed deprotection of Boc-group leads to α-hydroxylamine product (Figure 19, **35**). It is worth noting that the expected N–O bond cleavage under the reducing conditions was not observed. In addition, this compound was surprisingly stable to column chromatography; presumably these effects are due to steric hindrance. Alternatively, the N–O bond can be cleaved using Zn and 2N HCl to afford **36** in excellent yield. Most notably, the free amine can be obtained by a hydrogenation of **36**.[16] Given the difficulty in isolating **37** and its tendency to undergo self-condensation, we were unable to go directly from the α-amination product (Table 13, **3** or **12**) to the free amine because more forcing conditions were required to break the N–O bond. Lastly, *N*-oxazolidinone **38** can be obtained directly by a reduction of the β-keto functionality with sodium borohydride. The reduction was highly diastereoselective and the relative stereochemistry was established by X-ray crystal structure analysis of a corresponding *O*-acylated derivative. As illustrated in Figure 19, the hydroxylamine (**35**), the

carbamate (**36**), the free amine (**37**) and the *N*-oxazolidinone (**38**) were all obtained in a straightforward manner using conditions that should be amenable to a more complex setting and would be difficult to access using current methodology.

Figure 19. Facile Derivitization of *N*-Selective Nitrosocarbonyl Aldol Products



[a] Pd/C (5 mol %), MeOH, H_2 (73%). [b] TFA, CH_2Cl_2 (95%), [c] Zn, 2N HCl, reflux, (79% yield) [d] 1. Zn, 2N HCl, reflux (79%), 2. Pd/C (5 mol %), H_2 (90%)
[e] i. $NaBH_4$, MeOH, ii. SiO_2 (71%).

3.2.4 Conclusion and Future Outlook

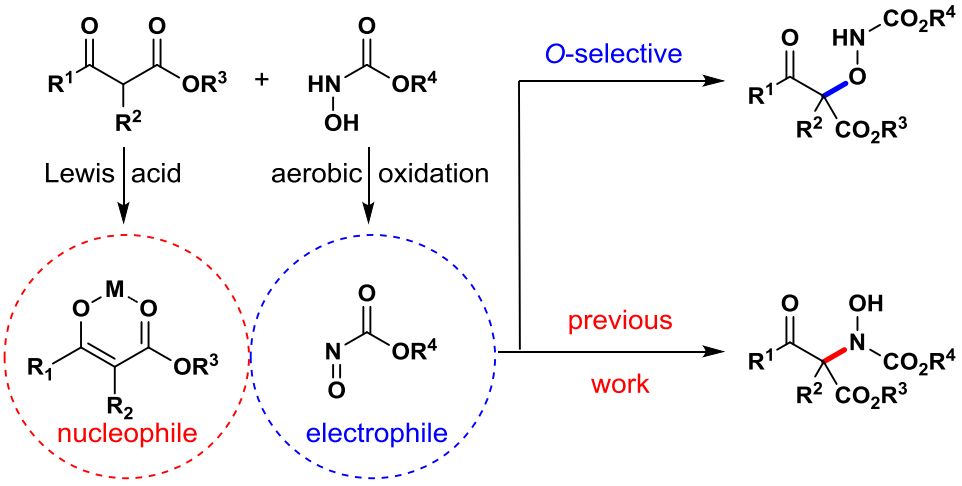
The first example of the *N*-selective nitrosocarbonyl aldol facilitated the expansion of nitrosocarbonyl chemistry beyond the ene and Diels – Alder reactions.[17] Since our report, a number of research groups have reported variations on the *N*-selective aldol through both Lewis acid activation,[18] and organocatalysis.[19] While these examples show the significant progress has been made on rendering the transformation asymmetric through activation of pro-chiral nucleophiles, utilizing the electrophile as the asymmetry inducing element is still unprecedented. We anticipate that accomplishing this goal will dramatically impact the future of nitrosocarbonyl chemistry.

3.3 Electrophilic α-Oxygenation of Carbonyl Compounds: the *O*-Selective Nitrosocarbonyl Aldol Reaction

3.3.1 Background and Optimization Studies for the *O*-Selective Aldol Reaction

Although conditions are known to reverse the regioselectivity (*O*- vs *N*-selectivity) for the nitroso aldol reaction using stable arylnitroso compounds,[5-6] the ability to tune the reaction conditions to regioselectively control whether nucleophiles react on nitrogen or oxygen with highly reactive and transient nitrosocarbonyls remained unexplored prior to our work.[20] Despite this, we envisaged that if our *N*-nitrosocarbonyl aldol reaction conditions could be tuned without disturbing the aerobic oxidation process,[11, 17] the regioselectivity of the nitroso aldol reaction could be reversed (Figure 20).

Figure 20. Proposed Development of an *O*-Selective Nitrosocarbonyl Aldol



Inspired by some initial results from the *N*-selective transformation, we found that, of the *N*-protected hydroxylamines screened, *N*-Boc-hydroxylamine (**42**) with β-ketoester **1** provided the aldol product with an increased amount of the *O*-regioisomer; However, the reaction was still predominantly *N*-selective (Table 15, entry 1-4). By switching from MeOH

as the solvent to a more sterically encumbered alcohol, such as EtOH and *i*-PrOH, the process could be rendered more *O*-selective (Table 15, entries 5 & 6). Switching from copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) to copper(II) chloride to copper(II) acetate monohydrate ($Cu(OAc)_2 \cdot H_2O$) further increased O-selectivity while maintaining a high yield (Table 15, entries 7 & 8). To our gratification, the *O*-selectivity and the rate could be increased significantly by the addition of 5 mol % of 2-ethyl-2-oxazoline (EtOx),[13] with $Cu(OAc)_2 \cdot H_2O$ being the optimal Cu(II) source (Table 15, entries 9–11). Pyridine, among other ligands, was also screened but led to reduced *O*-selectivity (Table 15, entry 12). Removal of the Cu(I) source led to a dramatic decrease in rate (Table 15,entry 13), while removal of the Cu(II) source adversely affected both the selectivity and yield of the reaction (Table15, entry 14). As with the *N*-selective system, the formation of a single discrete catalyst from the mixed metal system cannot be ruled out, but we believe the observed trends in reactivity (Table 15) are suggestive of a dual catalytic process.

Table 15. Optimization of the *O*-Selective Nitrosocarbonyl Reaction

1 **39** **40**

Entry	Cu^{II} Source	CO_2R	Ligand[a]	Solvent	Time (h)	Yield (%)[b]	O/N ratio[c]
1	$Cu(OTf)_2$	Boc	–	MeOH	24	96	1:4
2	$Cu(OTf)_2$	Troc	–	MeOH	24	99	1:9
3	$Cu(OTf)_2$	Fmoc	–	MeOH	24	95	1:10
4	$Cu(OTf)_2$	Cbz	–	MeOH	24	97	1:13
5	$Cu(OTf)_2$	Boc	–	EtOH	24	82	1:1
6	$Cu(OTf)_2$	Boc	–	*i*-PrOH	48	83	2:1
7	$CuCl_2$	Boc	–	*i*-PrOH	120	90	3:1
8	$Cu(OAc)_2$[d]	Boc	–	*i*-PrOH	196	97	3:1
9	$Cu(OTf)_2$	Boc	EtOx	*i*-PrOH	24	93	3:2
10	$CuCl_2$	Boc	EtOx	*i*-PrOH	20	75	6:1
11	**$Cu(OAc)_2$**[d]	**Boc**	**EtOx**	***i*-PrOH**	**18**	**94**	**10:1**
12	$Cu(OAc)_2$[d]	Boc	Pyr	*i*-PrOH	24	97	7:1
13[e]	$Cu(OAc)_2$[d]	Boc	EtOx	*i*-PrOH	52	90	20:1
14	–	Boc	EtOx	*i*-PrOH	8	53	5:1

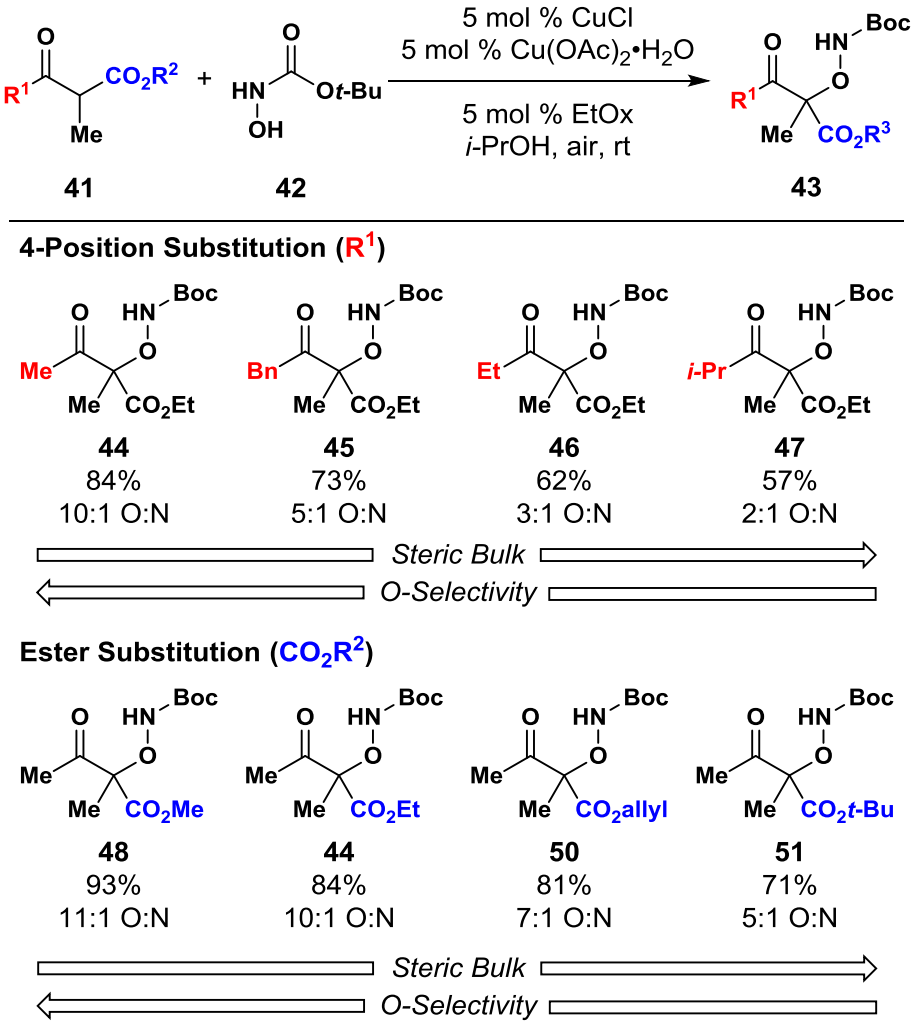
[a] EtOx=2-ethyl-2-oxazoline. [b] Isolated yield of the O- and N-product mixture. [c] Determined by 1H NMR spectroscopy of the mixture of crude material. [d] The hydrate of $Cu(OAc)_2$ was used. [e] No CuCl was added to the reaction.

3.3.2 Exploring the Scope of the *O*-Selective Nitrosocarbonyl Aldol Reaction

With optimized reaction conditions in hand (5 mol % CuCl, 5 mol % $Cu(OAc)_2$•H_2O, 5 mol % 2-ethyl-2-oxazoline, *i*-PrOH, air, rt), we investigated the scope of our aminooxylation reaction by varying the β-ketoester component (Table 16). In contrast to our previously developed *N*-nitrosocarbonyl aldol reaction,[17] the regioselectivity was noticeably influenced by the substitution of the β-ketoester. As a general trend, with more steric bulk at the 4-position (R^1) of the β-ketoester, the regioselectivity of the transformation was reduced; methyl (Table 16, **44**, 10:1 O:N) proved to be much more regioselective than benzyl (able

16, **45**, 7:1 O:N), ethyl (Table 16, **46**, 3:1 O:N), and isopropyl (Table 16, **47**, 2:1 O:N). Varying the steric component at the ester position (R^2) also had an effect on regiochemistry. The methyl ester (Table 16, **48**, 11:1 O:N) proved to be more *O*-selective than the ethyl ester (Table 16, **49**, 10:1 O:N), whereas the allyl (Table 16, **50**, 7:1 O:N) and the *t*-Bu (Table 16, **51**, 5:1 O:N) esters showed a reduction in regioselectivity.

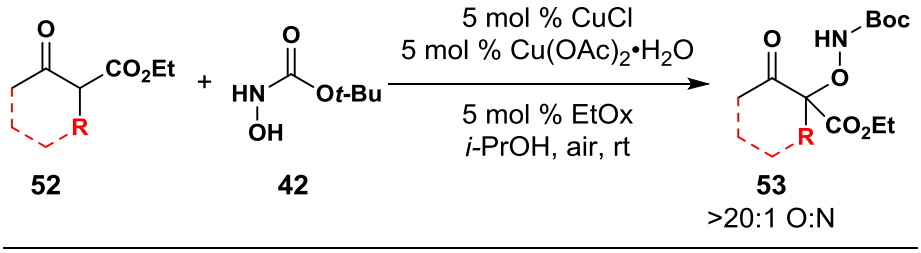
Table 16. Scope of 4-Position and Ester for the *O*-Selective Nitrosocarbonyl Aldol



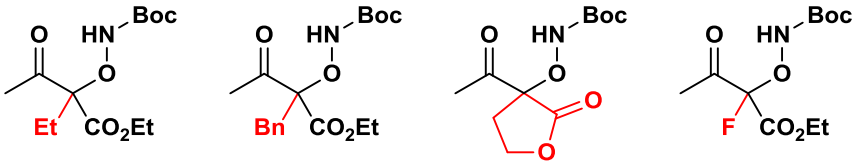
With regards to substitution at the 2-position of the β-ketoester, the converse was true: increasing the steric bulk rendered the transformation completely O-selective (Table

17, entries **54**–**56**). However, to obtain excellent yields of **54** and **55**, 3 equivalents of the corresponding β-ketoester was required in order to outcompete the condensation between the in situ formed nitrosocarbonyl species and the *N*-Boc-hydroxylamine. The scope of the β-ketoester could also be extended to include non-alkyl substituents, such as fluorine, with no reduction in efficiency or regioselectivity (Table 17, entry **57**). Additionally the scope of the transformation could be extended to include cyclic β-ketoesters; the reaction was tolerant of both 5- and 6-membered rings (Table 17, entries **58** & **59**) as well as substitution on the cyclic backbone (Table 17, entry **60**), with all cases being completely *O*-selective.

Table 17. Scope of 2-Position and Cyclic Substrates for the *O*-Selective Aldol



2-Position Substitution (R^2)



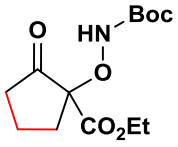
54 90%

55 96%

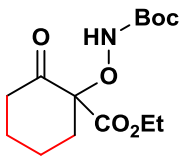
56 93%

57 96%

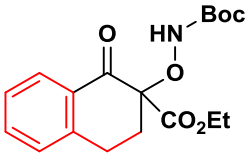
Cyclic Substitution



58 89%



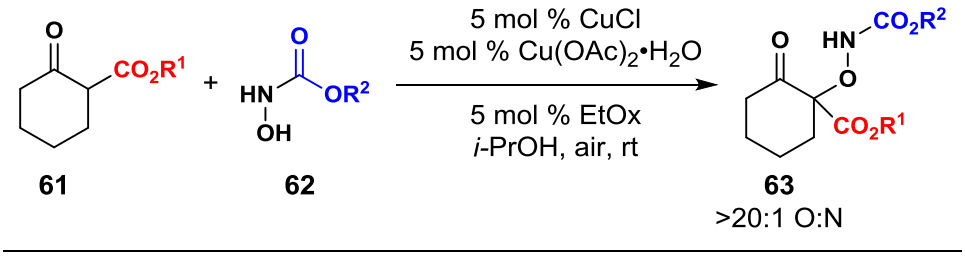
59 94%

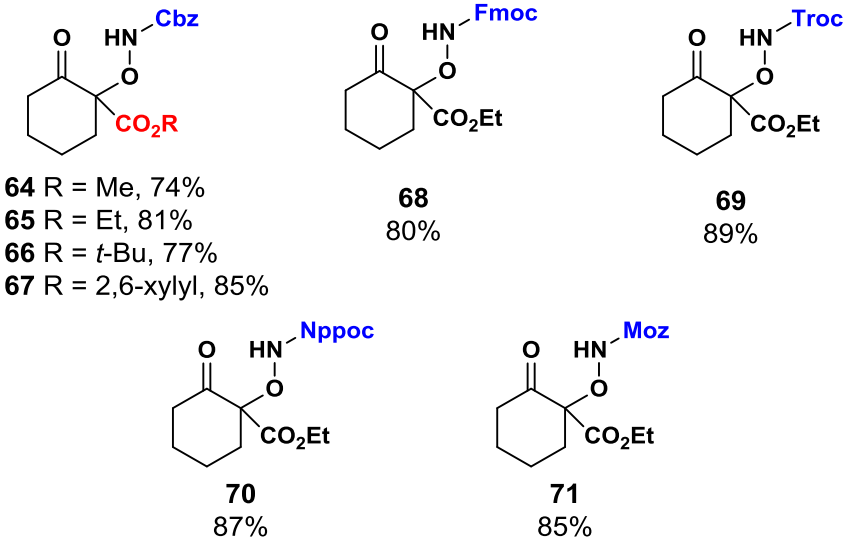


60 97%

In addition to *N*-Boc hydroxylamine, a wide variety of carbamate-derived protecting groups can be used: Cbz, Fmoc, Troc, Nppoc and Moz all gave the O-aldol product in good yield (Table 18, entries **65**, **68**–**71**). In contrast to the acyclic substrates, changes to the ester component (Table 18, entries **64**–**66**) were well tolerated as methyl, ethyl, and *tert*-butyl all proceeded in good yield and with perfect regiocontrol. The notable exception was the reaction derived from the ester bearing a 2,6-dimethyl phenol (Table 18, **67**). In this case, we observed a 3% yield of the N-regioisomer. Further investigations are underway to help elucidate the difference in reactivity between the acyclic and cyclic substrates.

Table 18. Scope of Ester and Carbamate for Cyclic Compounds

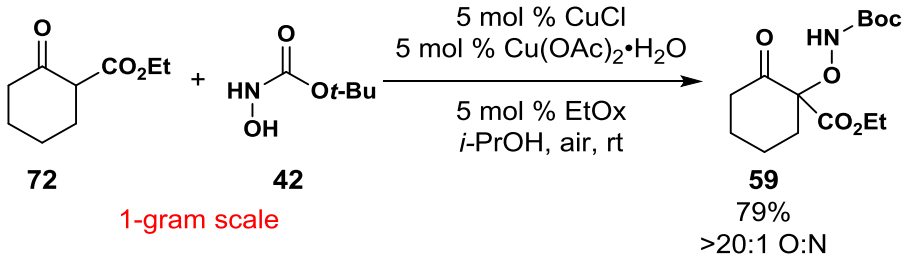




In all cases, the combined yield of both regioisomers was high (>90%) and the *O*-selective product could easily be isolated in moderate to excellent yield after column

chromatography. It is particularly noteworthy that simultaneous mixing of all reagents at room temperature can be used, even in the most challenging cases. Presumably, the slow rate of oxidation relative to enolization is the key to avoiding deleterious side reactions; the transient nitrosocarbonyl is immediately trapped by the nucleophilic β-ketoester upon formation. Moreover, the reaction could be conducted at gram scale, with only slight reduction in reaction efficiency (Equation 7)

Equation 7. Gram Scale Reaction for the *O*-Selective Nitrosocarbonyl Aldol Reaction

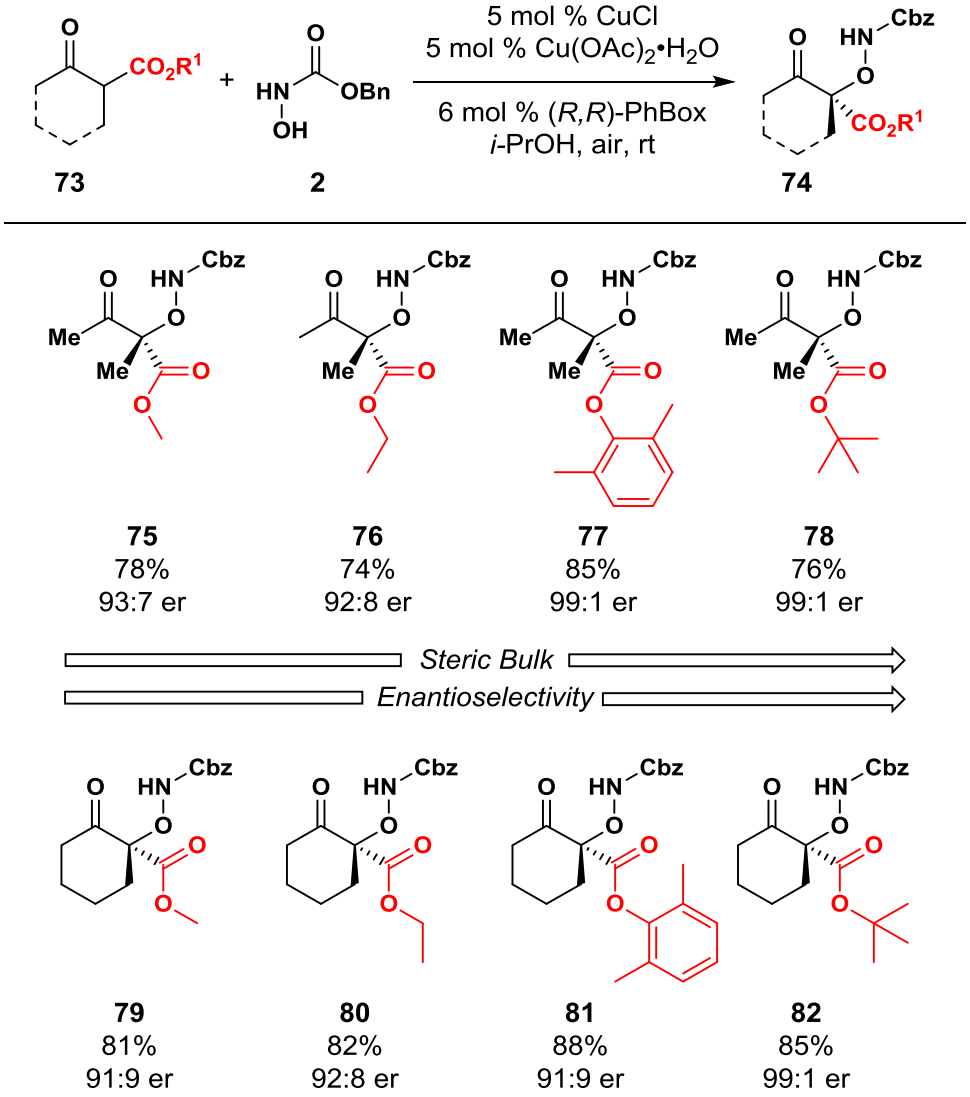


3.3.3 Asymmetric Studies for the *O*-Selective Nitrosocarbonyl Aldol Reaction

Due to the Lewis Acid-ligand combination used, the reaction can be rendered asymmetric by simply substituting the 2-ethyl-2-oxazoline ligand with 6 mol % (*R,R*)-PhBox ligand (Table 19).[20] Interestingly, the steric bulk of the β-ketoester played a role in achieving higher levels of enantioinduction. Initially, we were pleased to observe that the reaction with commercially available β-ketoester **1** afforded good levels of enantioselectivity in the formation of product **76** (Table 19, 92:8 er). Replacement of the ethyl ester moiety with the more sterically demanding *tert*-butyl ester significantly improved the enantioselectivity from 92:8 er to 99:1 er, respectively (Table 19, **78)**. The product derived from an ester bearing a 2,6-dimethyl phenol (Table 19, **77**) also resulted in excellent enantioselectivity (99:1 er) and was slightly more efficient (85% yield). To our delight the same asymmetric reaction

conditions could be extended to the cyclic substrates (Table 19, entries **79**–**82**). Once again, the *tert*-butyl ester moiety provided the highest levels of enantioselectivity (**82**, 99:1 er). While not a perfect correlation, the general trend of the transformation suggests that the greater the steric demand of the ester group, the higher the level of enantioinduction. Single crystal X-ray analysis of a derivative of **82** was used to determine the absolute stereochemistry.

Table 19. Ester Dependence of Enantioselective *O*-Selective Nitrosocarbonyl Aldol

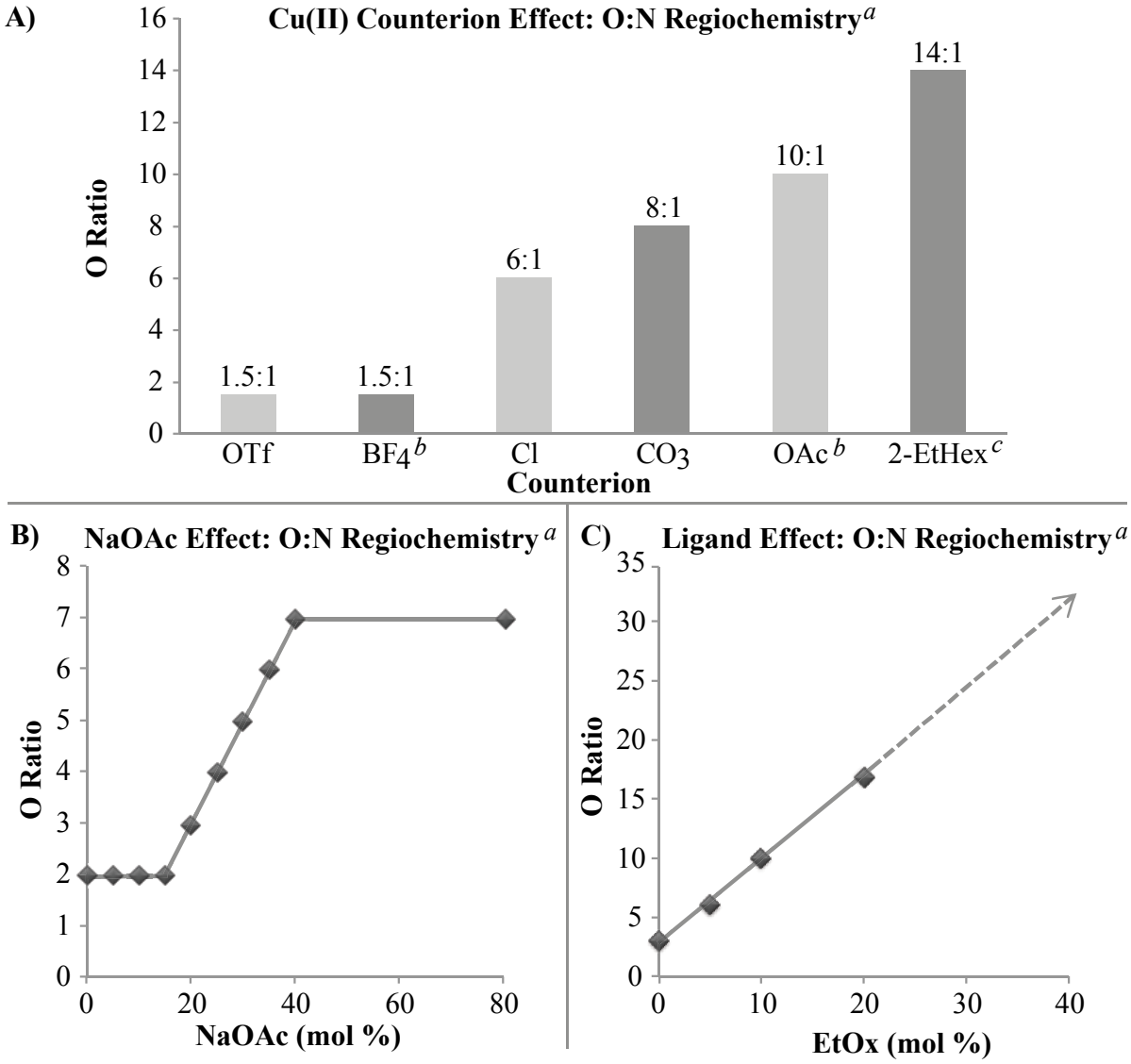


3.3.4 Elucidating Factors Influencing the Regiochemistry of the Aldol Reaction

While models have been developed to rationalize the ambident reactivity of arylnitroso compounds for the aldol reaction,[3] similar guiding principles for nitrosocarbonyl species are non-existent. Therefore, we sought to better understand the source of the regiochemical switch by studying the steric and electronic environment about the Lewis acid. From our optimization studies (Table 15, entries 9 and 11) a dramatic difference was observed in regiochemistry when the Lewis acid was switched from $Cu(OTf)_2$ to $Cu(OAc)_2•H_2O$ when EtOx ligand was present. Based on that observation, we screened a number of Cu(II) Lewis acids using our optimized reaction conditions to determine what role the counterion played in selectivity. Weakly coordinating counterions, such as -OTf and $-BF_4$ favor an unselective aldol reaction, whereas strongly associating carboxylate counterions favor reaction on oxygen (1.5:1 vs 10:1 O:N, see Figure 21A). Additionally, with two electronically similar carboxylate counterions, the increased steric bulk of the 2-ethylhexanoate counterion further enhances the O-selectivity from 10:1 to 14:1.

In order to better understand the influence of the acetate–metal complex on the regiochemistry, a varying amount of NaOAc was added to an unselective reaction (20 mol % CuCl, 20 mol % $Cu(OTf)_2$, 20 mol % EtOx, *i*-PrOH, air, rt.). At low concentrations of NaOAc (0–15 mol%), the reaction showed no increase in *O*-selectivity (2:1, O:N; see Figure 21B). However, above 15 mol% the regiochemistry linearly increased up to 40 mol % (7:1, O:N), which equaled the molar concentration of the copper catalysts. Employing greater than 40 mol% of NaOAc showed no additional influence on the regiochemistry (Figure 21B). Without the addition of NaOAc the reaction gave a 9 : 1 selectivity (O : N) and with 40 mol % NaOAc the reaction was completely O-selective (not depicted).

Figure 21. Effect of Reaction Conditions on *O*-Selectivity



A) Role of counterion derived from the Cu(II) Lewis acid on the *O*- and *N*-selectivity. B) Addition of NaOAc to an unselective reaction (20 mol % CuCl, 20 mol % $Cu(OTf)_2$, 20 mol % EtOx, *i*-PrOH, air, rt.) leads to an increase in *O*-selectivity. C) Addition of EtOx ligand results in an increase in *O*-selectivity. [a] Regioselectivity was determined by ^1H NMR analysis of the crude reaction mixture. [b] the hydrate of the Cu(II) source was used. [c] 2-EtHex = 2-ethylhexanoate.

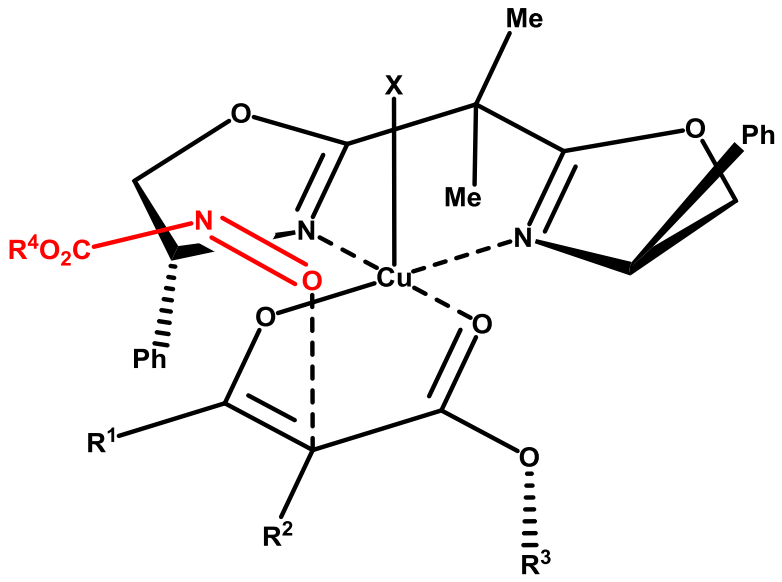
Based on the experiments with NaOAc, we decided to re-examine the effects of EtOx ligand on the regiochemistry (Figure 21C). Previously we only evaluated the reaction

without EtOx and with 5 mol % EtOx (Table 15). The same trend was also observed when the amount of EtOx ligand was varied from 0 to 40 mol %. However, to our gratification, the reaction was completely *O*-selective in the presence of 40 mol % EtOx (Figure 21C, depicted by dotted arrow) and the same effect was observed when using (*R,R*)-PhBOX as the ligand instead of EtOx (not shown). Combined, these studies elucidate that weakly Lewis acidic metal complexes bearing strongly coordinating counterions and ligands are important for the *O*-selective process.[21]

On the basis of the absolute configuration of the products and the combined results obtained during our investigations, we tentatively propose a reaction mechanism that involves the approach of the nitrosocarbonyl to the catalyst-coordinated β-ketoester, as shown in Figure 22. We speculate that the decreased Lewis acidity and the increased steric environment associated with the catalyst-β-ketoester complex during the bond-forming event largely govern the reversal in selectivity. Assuming the reaction proceeds through a square-pyramidal or octahedral geometry (not depicted),[21a-d] it is conceivable that the counterion occupies the axial position, which would prevent coordination of the nitroso species to the Lewis acid and force the nitroso electrophile to approach over the β-ketoester. Using large and more associating counterions, excess ethyl oxazoline or sterically bulky PhBox ligand further enhances this effect. Presumably, the reaction predominately occurs on oxygen because this helps avoid unfavorable steric interactions between the protecting-group of the nitroso species and the β-ketoester-metal complex. This hypothesis is consistent with the observation that the use of *N*-Boc-protected hydroxylamine gave the best results for the O-selective process (Table 15, entries 1-4) and helps rationalize why the sterics of the β-ketoester can have a significant effect on the regiochemical outcome, specifically at the R^1

and R^3 position of the β-ketoester (see Table 16). Further investigations are underway to help elucidate the complexities of the regiochemical outcome of the nitrosocarbonyl aldol reaction and explore other possible models.

Figure 22. Proposed Stereochemical Model for the *O*-Selective Nitrosocarbonyl Aldol

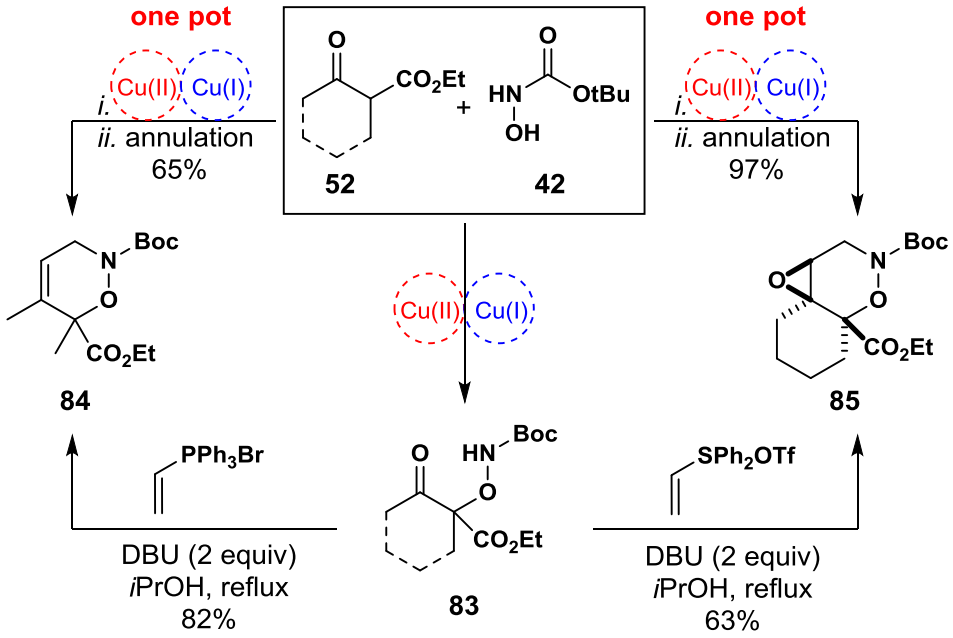


3.3.5 Synthetic Manipulations on the *O*-Selective Nitrosocarbonyl Aldol Products

Finally, we wanted to display the synthetic utility offered by using nitrosocarbonyl compounds. Typically, the utility of the *O*-selective nitroso aldol reaction has been highlighted by the transformation of the α-aminooxy-carbonyl to the corresponding α-hydroxy-carbonyl.[5b, 5c, 5f, 5j, 6e, 20] This approach provides efficient access to a highly valued synthetic target, α-hydroxy-carbonyl.[8] However, it also treats the substituted nitrogen group as a waste byproduct, which diminishes the atom economy and can restrict the synthetic utility of the overall transformation. This phenomenon is most likely a consequence of using nitrosobenzene as the electrophile and the difficulties associated with cleaving the *N*-aryl bond for subsequent transformations. Thus, we chose to take advantage of the appended

nitrogen group by utilizing it in a series of annulation reactions (Figure 23).[22] Treatment of the O-aldol product with DBU and vinyltriphenylphosphonium bromide efficiently affords the highly substituted 1,2-oxazine **84** via cascade Michael and Wittig reactions. This transformation provides an attractive and synthetically useful approach to access to 1,2-oxazine bearing a quaternary center and a nitrogen substituent that can be easily deprotected.[17] This structural motif can be challenging to construct using the nitrosocarbonyl hetero-Diels–Alder reaction because moderate regioselectivity is often observed in these cases.[9b] Alternatively, the O-aldol product can be treated with vinyldiphenylsulfonium triflate to access the highly substituted epoxyoxazine **85** as a single diastereomer, determined by X-ray. We were thrilled to discover that both annulation reactions could be carried out conveniently in a one-pot process by simply adding the reagents for the annulation reaction directly to the reaction mixture after the O-nitrosocarbonyl aldol reaction was complete. These one-pot annulation reactions are feasible because the aerobic oxidation conditions are mild and the oxidation byproducts produced do not interfere with the subsequent reaction.

Figure 23. Combining *O*-Selective Nitrosocarbonyl Aldol with Annulation Chemistry



3.3.6 Conclusion and Future Outlook

The *O*-selective methodology complements our previously disclosed N-selective nitroso aldol reaction and the two, as a set, showcase the ambident reactivity of nitrosocarbonyl compounds. While the *O*-selective variant has garnered much less attention than the *N*-selective counterpart,[18-19] we envision that the next frontier of *O*-selective aldol chemistry is the expansion of the scope to include unactivated carbonyls (e.g. ketones and aldehydes). Moreover, a better mechanistic understanding of the factors contributing to the regiochemical outcome would be foundational in the development in new nitrosocarbonyl chemistry.

3.4 References

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4. Accessing Nitrosocarbonyl Compounds with Temporal and Spatial Control *via* the Photoredox Oxidation of *N*-substituted Hydroxylamines

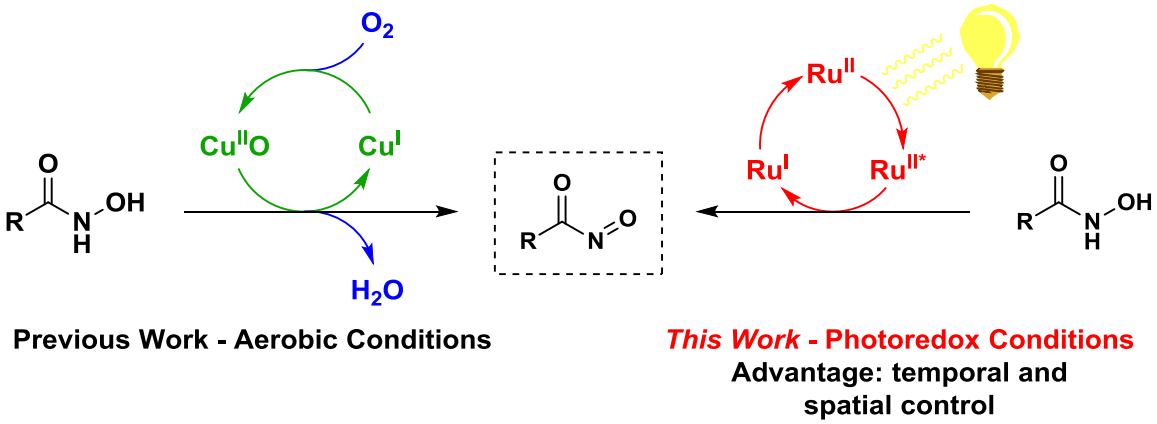
4.1 Background and Significance

Nitrosocarbonyl compounds are exceptionally reactive intermediates that have found widespread use in a number of classic C-N or C-O bond–forming reactions, such as the ene,[1] Diels–Alder,[2] and aldol reactions.[3] In recent years, a number of research groups have explored new methodologies to generate nitrosocarbonyl intermediates, such as oxidation under aerobic conditions,[1-3] utilizing transition metals with stoichiometric peroxide,[4] manganese dioxide oxidations, [5] and oxidations employing TEMPO and BPO,[6] among others.[7] While many of these new oxidation methodologies have facilitated the expansion of nitrosocarbonyl chemistry, none have explored the potential of generating nitrosocarbonyl intermediates with temporal and spatial control. This unique property, often neglected in the context of small molecule organic synthesis, is an important facet to consider when expanding nitrosocarbonyl chemistry into biological and materials science applications.

Photoredox catalysis is an emerging tool for the synthesis of complex molecules that has been shown to be effective in contexts requiring temporal and spatial control. While the genesis of photoredox catalysis can be traced back to Kellog in the 1970's, the field has undergone a renaissance in recent years, based on the pioneering work of a number of research groups.[8] In particular, the recent work by the groups of Yoon,[9] and Stephenson,[10] highlight the advantageous usage of photoredox catalysis in the oxidative generation of reactive intermediates. Recently, Hawker and co-workers have translated photoredox catalysis into material science,[11] which provides excellent spatial arrangement of functional

groups at surfaces.[12] The key to this methodology was visible-light mediated Ir-catalyzed ATRA chemistry developed by Stephenson and co-workers.[13] Because nitrosocarbonyl compounds participate in a variety of organic reactions, the *in-situ* formation of this highly reactive functional group using photoredox conditions would furnish a general procedure for patterning surfaces bearing a range of properties. Moreover, because nitrosocarbonyl compounds serve as HNO donors,[14] it could also provide a means to generate HNO in using visible-light to control its release. To evaluate this potential, we began by investigating the *in-situ* generation of nitrosocarbonyl compounds using photoredox conditions**.** A recent report by Tan inspired us to disclose our results in this area (Figure 24).[15]

Figure 24. Exploring Photoredox Conditions for the Generation of Nitrosocarbonyls



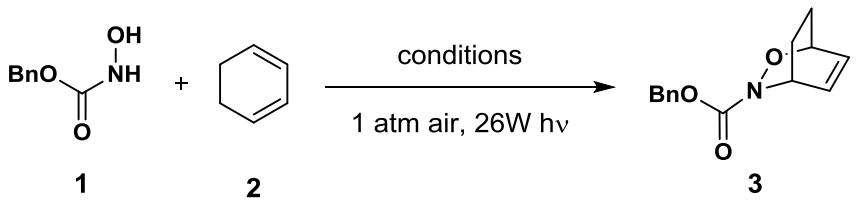
4.2 Development of Photoredox Methodology to Generate Nitrosocarbonyls.

4.2.1 Optimization of the Photoredox Reaction

Due to the transient nature of nitroso compounds and their associated inherent instability,[16] we selected the nitroso HDA reaction to test the feasibility of a photoredox catalyst system. Nitroso compounds directly attached to an electron withdrawing group undergo rapid [4+2] cycloaddition reactions with conjugated dienes, a reaction platform that

has been explored extensively by our research group[2a] and others.[17] Cbz-protected hydroxylamine **1** and 1,3-dicyclohexadiene **2** were elected as candidates for standardizing reaction conditions (Table 20) and investigations began with commercially available and widely employed $Ru(bpy)_3Cl_2•6H_2O$. At 1 mol % loading and in DCE at room temperature, we were pleased to see a 35% yield of the desired oxazine product (Table 20, entry 1). Analysis of the reaction mixture revealed a large amount of an undesired HDA product resulting from reaction of the diene with diatomic oxygen in a [4+2] cycloaddition and subsequent ring-opening reaction,[18] suggesting the potential interference of singlet oxygen on our desired reaction pathway.[19] Pleasingly, the addition of pyridine (2.0 equiv) completely inhibited this unproductive pathway (Table 20, entry 2) and allowed us to achieve an improved yield of 80%. Screening other Ru photocatalysts, (Table 20 entries 3–6) showed no improvement in yield or reaction duration over $Ru(bpy)_3Cl_2•6H_2O$. In considering which photoredox catalysts to employ, $Ru(bpy)_3^{2+*}$ is both a good oxidant and reductant.[8] Switching to a photocatalyst like $Ir(ppy)_3$, which is more reducing in its excited state, had a negative impact on the yield (Table 20, entries 7 & 8). Using Eu-based catalyst (Table 20, entry 9) satisfactorily augmented the yield but has the added disadvantage of requiring UV light for activation. Based on this, we elected to further optimize the reaction with $Ru(bpy)_3Cl_2•6H_2O$.

Table 20. Optimization of Photoredox Conditions for Generation Nitrosocarbonyls



1 2 3

Entry	Catalyst (1 mol %)	Solvent	Additive (equiv)	Yield (%)[a]
1	$Ru(bpy)_3Cl_2•6H_2O$	DCE	-	35
2	$Ru(bpy)_3Cl_2•6H_2O$	DCE	pyridine (2.0)	80
3	$Ru(bpz)_3Cl_2$	-	-	49
4	$Ru(bpz)_3Cl_2$	DCE	pyridine (2.0)	73
5	$Ru(bpm)_3BArF_2$	DCE	pyridine (2.0)	30
6	$Ru(phen)_3Cl_2$	DCE	pyridine (2.0)	24
7	Ir-*fac*$(ppy)_3$	DCE	pyridine (2.0)	34
8	$Ir(BTP)_3$	DCE	pyridine (2.0)	63
9	$Eu(dbm)_3(phen)$[b]	DCE	pyridine (2.0)	95
10	**$Ru(bpy)_3Cl_2•6H_2O$**	**DCE**	**2,6-lutidine (2.0)**	**87**
11	$Ru(bpy)_3Cl_2•6H_2O$	DCE	2,6-lutidine (0.5)	74
12	$Ru(bpy)_3Cl_2•6H_2O$	DCE	2,6-lutidine (0.05)	60
13	$Ru(bpy)_3Cl_2•6H_2O$	$MeNO_2$	2,6-lutidine (2.0)	63
14	$Ru(bpy)_3Cl_2•6H_2O$	MeCN	2,6-lutidine (2.0)	55
15	$Ru(bpy)_3Cl_2•6H_2O$	DCE	2,6-lutidine (2.0)	<5%[c]
16	-	DCE	2,6-lutidine (2.0)	<5%[c]

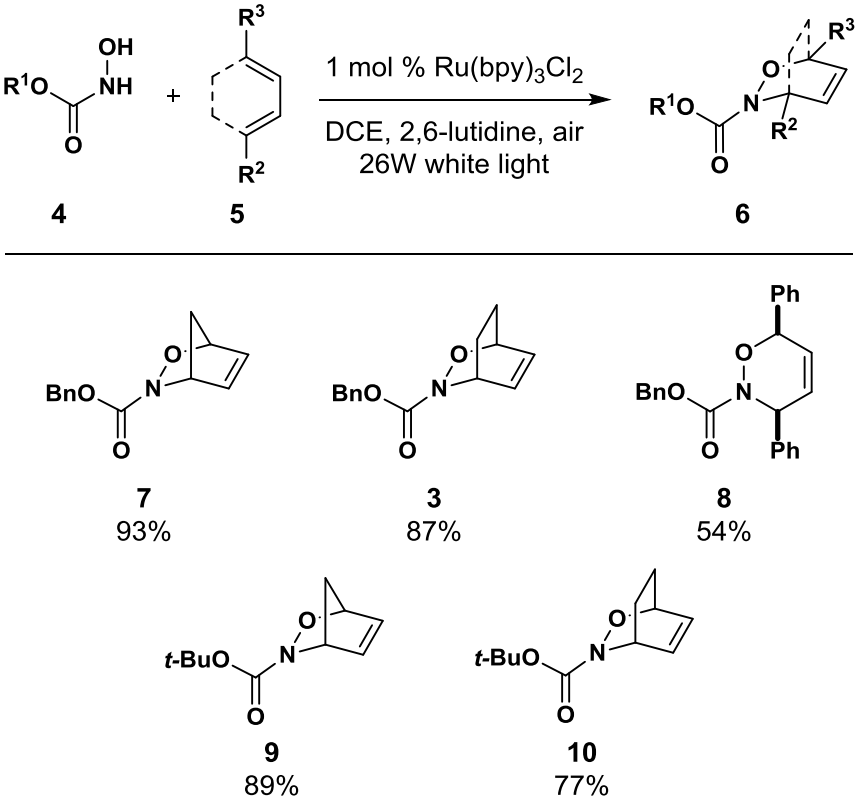
[a] Isolated yields. [b] 280 nm light was used. [c] Starting material was recovered

Next we looked at the dependence of the reaction on the chosen additive; screening various bases (NEt_3, iPr_2NEt, etc.) led us to determine that 2,6-lutidine was the additive of choice for our reaction set up. Variations in the additive loading (Table 20, entries 10 – 12) indicated 2.0 equiv of 2,6-lutidine was optimal, and a brief solvent screen (Table 20, entries 13 & 14) indicated DCE to indeed be our preferred solvent. Finally, the reaction does not proceed in the dark under the same conditions and duration (Table 20 entry 15), nor is any conversion observed in the absence of catalyst (Table 20, entry 16). Based on these results we elected to explore the reaction with 1 mol % $Ru(bpy)_3Cl_2•6H_2O$ and 2 equiv 2,6-lutidine in DCE (Table 20, entry 10).

4.2.2 Exploration of the Scope with Nitrosocarbonyl Diels–Alder and Ene Reactions

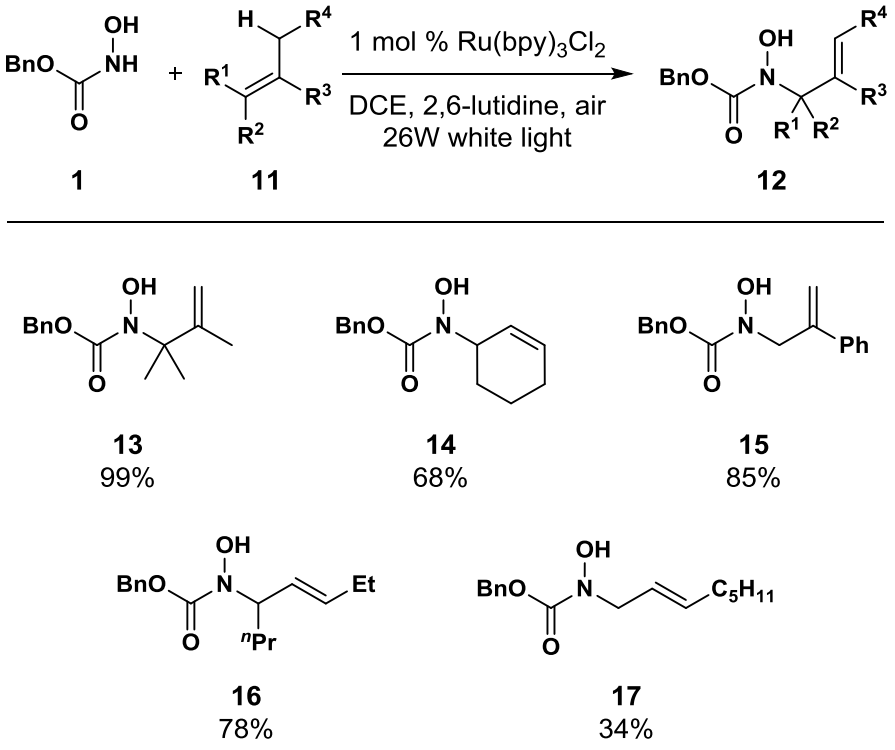
With optimized reaction conditions in hand, we elected to briefly explore the scope of the Diels–Alder reaction to ensure generality of reaction conditions. Fortunately both the 5– and 6– membered ring dienes readily underwent the Diels–Alder reaction with no competing production of the endoperoxide or hydroxyenone (Table 21, **7** & **3**). Additionally, 1,4-diphenylbutadiene also underwent clean conversion to the desired oxazine product (Table 21, **8**). The reaction was not limited to Cbz-protected hydroxylamines, as Boc-protected hydroxylamines were readily converted to the corresponding oxazine products (Table 21, entries **9** & **10**).

Table 21. Scope of the Nitrosocarbonyl HDA under Photoredox Conditions.



While the Diels–Alder reaction with nitrosoformate intermediates is known to be a highly efficient reaction,[17] the corresponding ene reaction of nitrosoformate intermediates often suffers from poor yields due to the over-oxidation of the allylic hydroxylamine products.[20] Recent efforts have been undertaken by a number of research groups to circumvent this known decomposition reaction,[21] and thus the ene reaction has proven to be an effective tool for evaluating the mildness of oxidation reaction conditions.[7] In this context, we elected to test our newly developed oxidation conditions with a subset of olefin partners. We were delighted to find that the ene adducts were readily formed under our optimized conditions with no observable product decomposition. As with other studies, the efficiency of the ene reaction is directly correlated to the substitution of the olefin; fully substituted olefins, such as 2,3-dimethylbutene, form the corresponding allylic hydroxylamine in quantitative yield (Table 22, **13**). In contrast, mono-substituted olefins such as 1-octene react with nitrosocarbonyl compounds with reduced yields (Table 22, **17**). In each case, the photoredox conditions compared favorably with previous oxidative nitrosocarbonyl ene methodologies (Table 22, **13**–**17**).[1] Based on these results, we envision that these conditions can be utilized for a wide variety of reaction platforms and will facilitate the expansion of nitrosocarbonyl chemistry into previously unexplored areas of organic synthesis.

Table 22. Scope of Nitrosocarbonyl Ene Reaction Under Photoredox Conditions



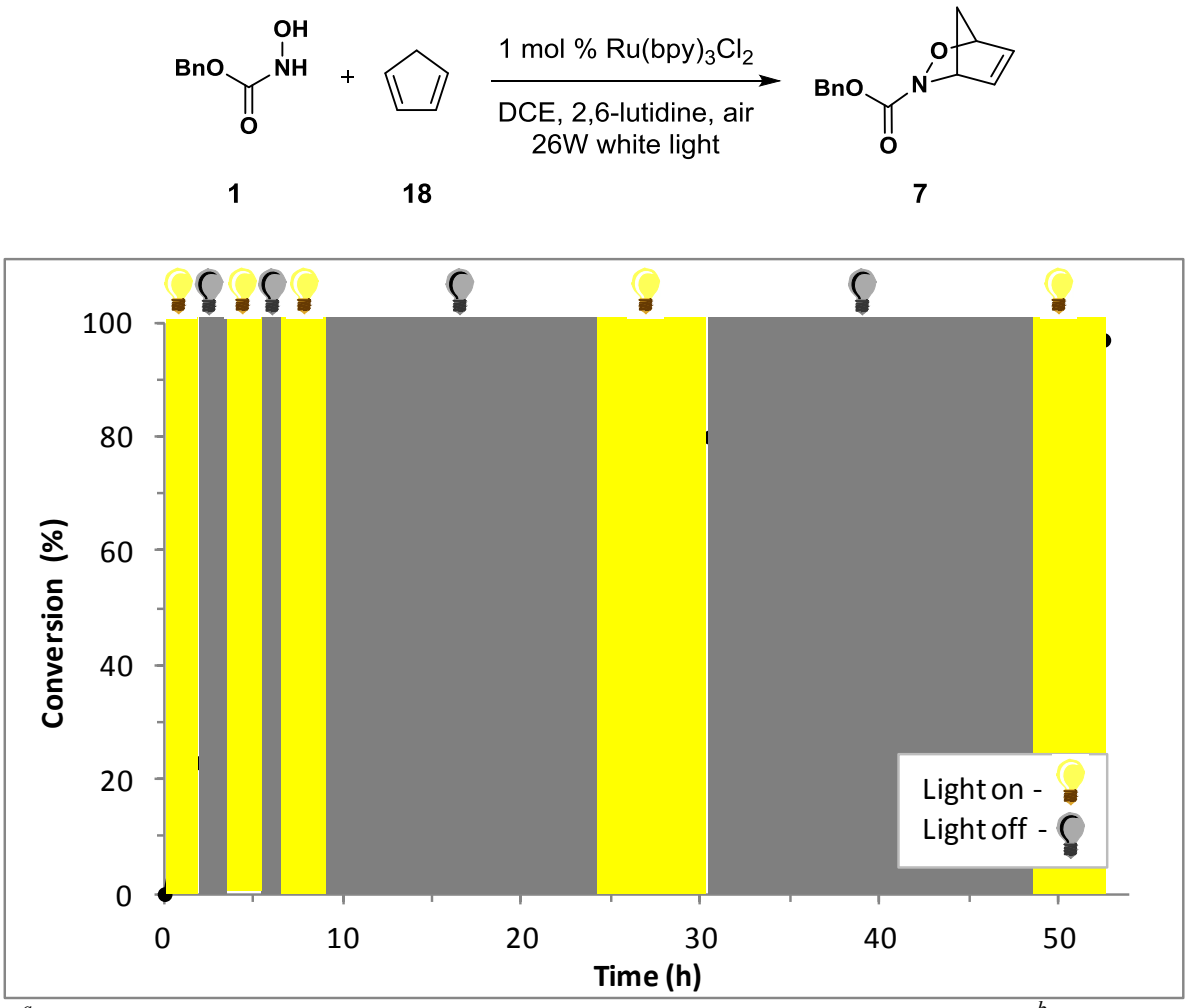
4.3. Mechanistic Investigation of the Photoredox Generation of Nitrosocarbonyls

4.3.1 Probing the Temporal and Spatial Control of the Photoredox Oxidation

Encouraged by the mildness of our reaction conditions, we next elected to explore the efficiency of temporal control for our optimized conditions. While on-off studies are not normally performed for photoredox reactions in small molecule chemistry, this type of experiment is regularly conducted with photoredox polymerizations,[11, 22] and is a prerequisite for transitioning a methodology into a number of materials science applications such as the patterning of functionalized surfaces.[12] Therefore, we were delighted to find that the reaction could be effectively turned on and off based on the presence or absence of light. The reaction showed no reduction in efficiency even after iteratively turning the light on and

off. Moreover, the reaction could even be shut off for extended periods of time (e.g. 18 hours) and started again once the light was reintroduced, highlighting a unique element of control never exploited for the generation of nitrosocarbonyl intermediates (Figure 25).

Figure 25. On-Off Studies for the Newly Developed Photoredox Oxidation



[a] Reactions conducted using dimethyl terephthalate as the internal standard. [b] Aliquots were removed at the indicated times and conversion was determined by ^{1}HNMR analysis

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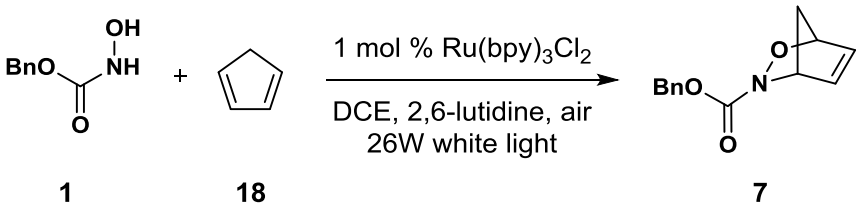
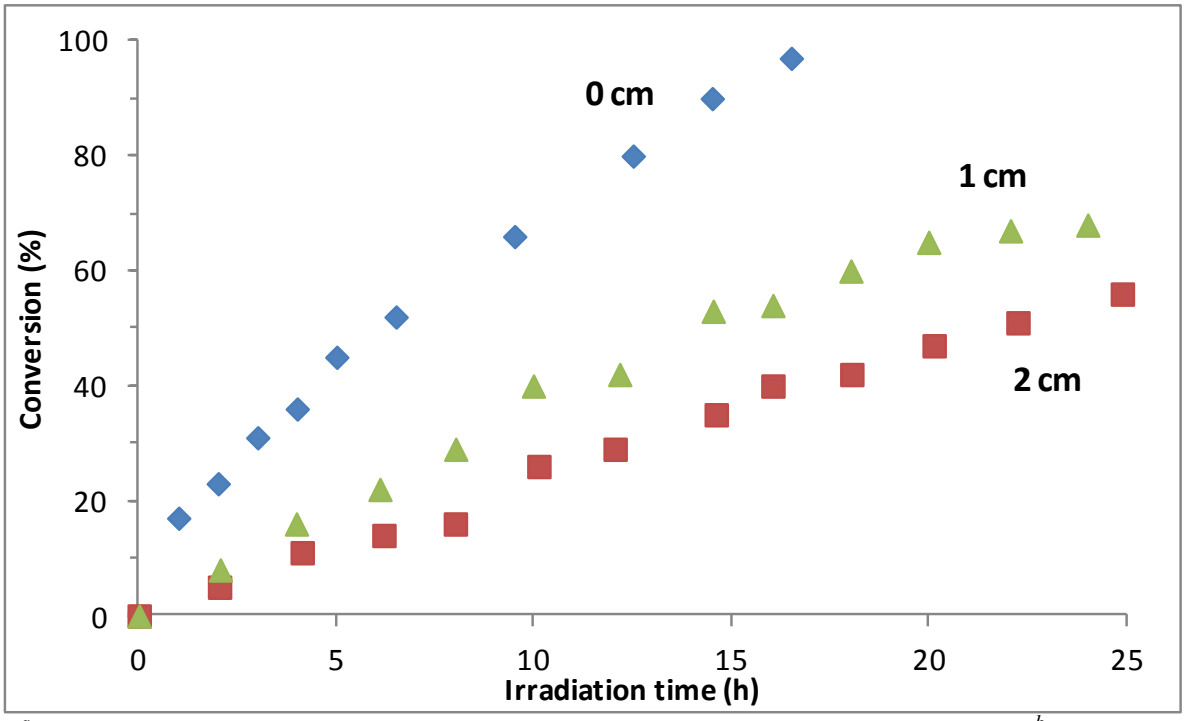
We next explored the distance dependence of our newly developed reaction conditions. For the design of this experiment, the lights were placed at a variable distance away from the sidewall of the reaction flask and the reaction was monitored periodically for conversion. As

expected, when the lights were touching the sidewall of the flask, the reaction proceeded the fastest, with a rate paralleling our on-off study. As the lights were moved further from the flask, the reaction rate dropped precipitously. Based on these results, there is a clear spatial dependence of the reaction rate: the intensity of the light has a direct effect on the reaction (Figure 26). Based on the distance dependence and the on-off studies, we believe that this reaction has the potential to find widespread use in applications where temporal and spatial control are desired, and our studies in this area will be reported in due time.

Figure 26. Distance Dependence of Newly Developed Photoredox Oxidation





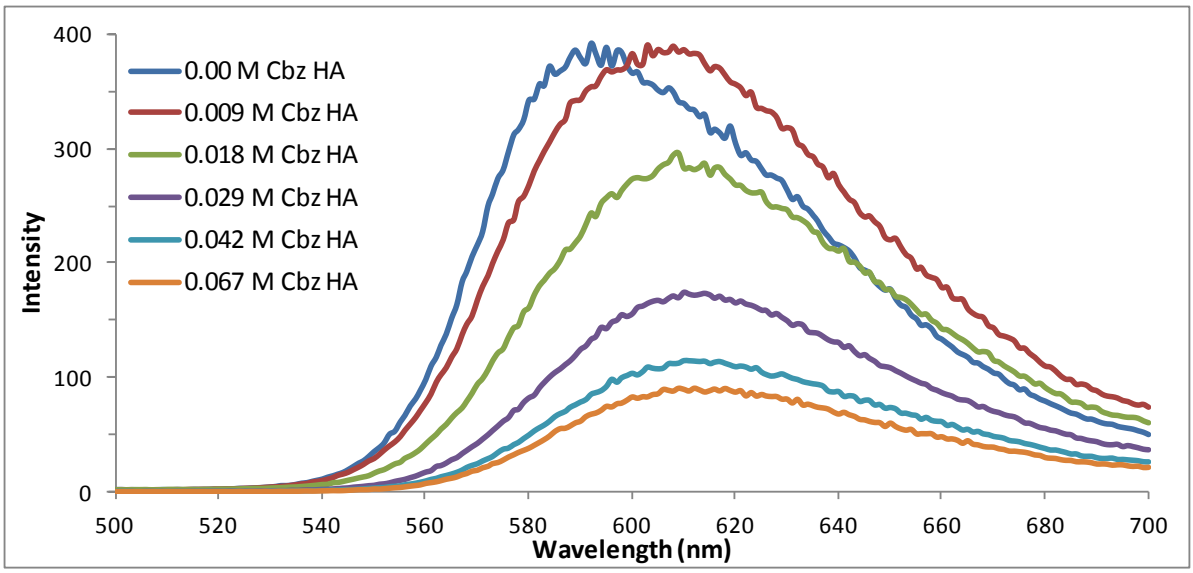
[a] Reactions conducted using dimethyl terephthalate as the internal standard. [b] Aliquots were removed at the indicated times and conversion was determined by ^{1}HNMR analysis. [c] The 26W lights were placed at the indicated distances relative to the sidewall of the reaction vessel.

4.3.2 Exploring Possible Mechanistic Pathways

Based on the trends we observed during the reaction development, we were interested in further exploring the mechanism. In particular, we wanted to distinguish between a photoredox mechanism and a mechanism involving singlet oxygen. In order to probe this, we turned to Stern-Volmer studies to confirm the direct interaction between the catalyst and

the Cbz-protected hydroxylamine.[23] As expected, the magnitude of fluorescence of the catalyst had a linear dependence on the concentration of the Cbz-protected hydroxylamine,[24] indicating an interaction between the excited state of the catalyst and the Cbz-protected hydroxylamine (Figure 27). In contrast, no fluorescence quenching was observed in the presence of varying concentrations of the diene (See SI for more information). Based on these results, we propose that the excited state of the catalyst ($Ru(bpy)_3Cl_2^*$) is directly oxidizing the Cbz-protected hydroxylamine to the corresponding radical cation, consistent with the known redox potentials of the catalyst excited state ($E_{1/2}$ = 1.08V vs $Ag/AgNO_3$)[8] and the Cbz-protected hydroxylamine ($E_{p/2}$ = 0.95V vs $Ag/AgNO_3$, see supporting information). The subsequent reduction of molecular oxygen forms the corresponding superoxide radical, which facilitates the conversion of the Cbz-hydroxylamine radical cation to the nitrosocarbonyl species (Figure 28, mechanism A).

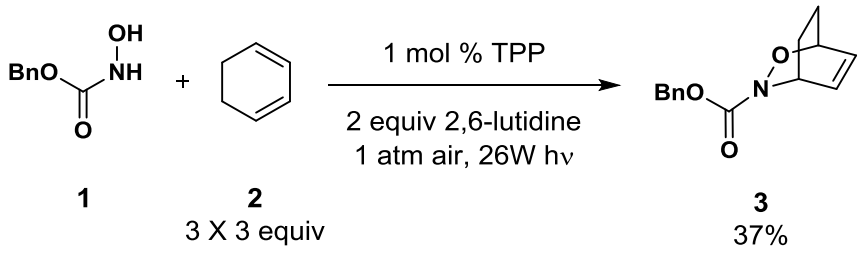
Figure 27. Fluorescence Quenching Experiments with Cbz-Protected Hydroxylamine



[a] Fluorescence quenching studies were performed in a sealed cuvette under an atmosphere of argon using 1 mg/mL of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ in 1,2-dichloroethane.

To explore the mechanism further, we tested the reaction efficiency in the presence of a known singlet oxygen sensitizer, tetraphenylporphyrin (TPP).[25] To our surprise, upon irradiation of the reaction, a small amount of hetero–Diels–Alder adduct was observed, although additional aliquots of cyclohexadiene were added periodically (3 equivalents every 2 hours), due to competing consumption of the diene by singlet oxygen.[19] Under these conditions, a significant amount of both the endoperoxide and ring–opened 4-hydroxy-2-cyclohexenone were isolated,[18] along with the desired nitrosocarbonyl HDA adduct (Equation 8). Under the optimized reaction conditions, direct energy transfer from $Ru(bpy)_3Cl_2^*$ to molecular oxygen will produce singlet oxygen, which can potentially oxidize the Cbz-protected hydroxylamine directly and form the corresponding nitrosocarbonyl compound (Figure 28, mechanism B).

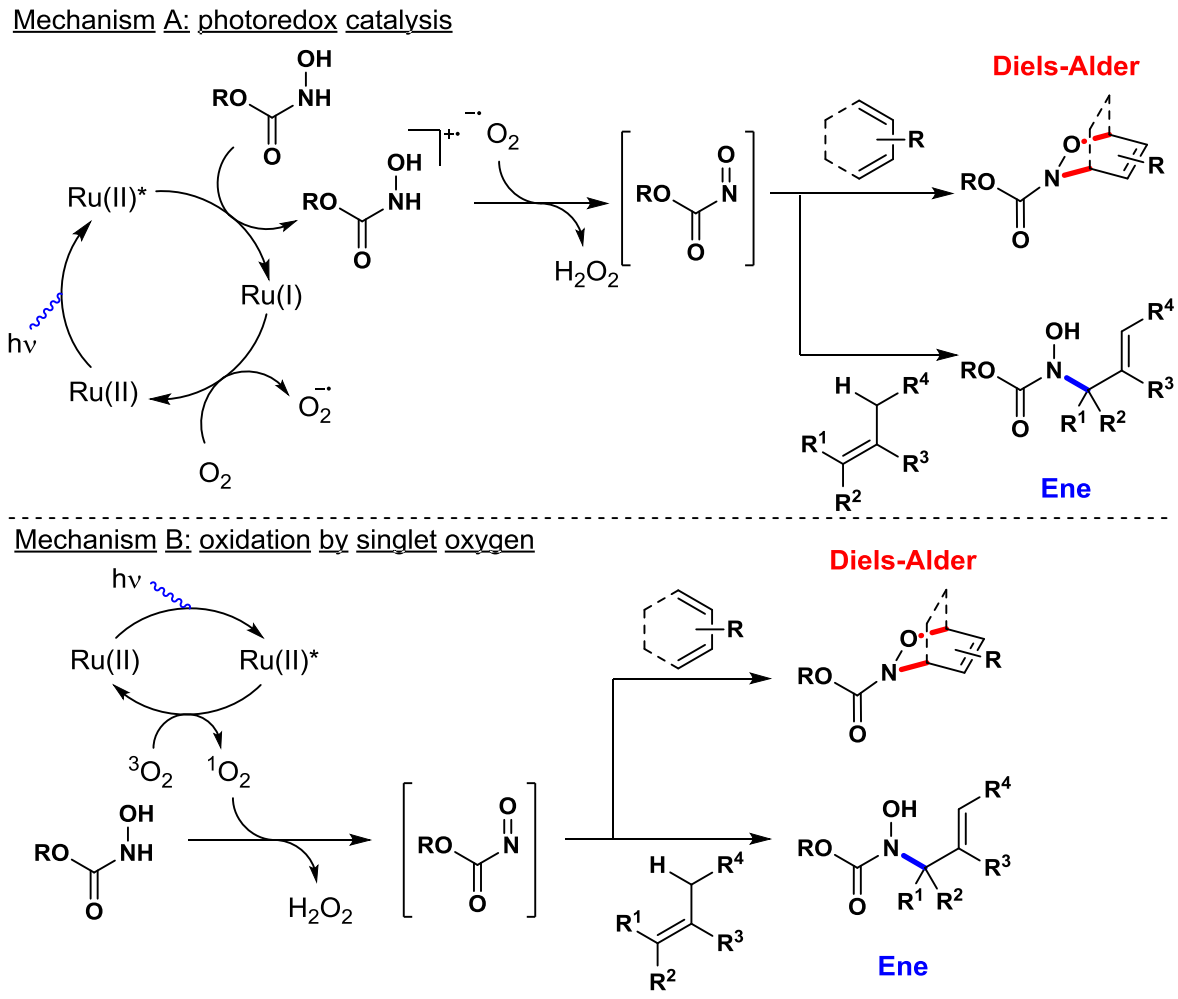
Equation 8. Singlet Oxygen Mediated Oxidation using 5,10,15,20-Tetraphenylporphyrin



1 **2** 3 X 3 equiv **3** 37%

Despite the results using TPP, we believe that the reaction proceeds predominantly through a photoredox mechanism (Figure 28, mechanism A), based on the compatibility of redox potentials between the hydroxylamine and $Ru(bpy)_3Cl_2^*$, the Stern-Volmer studies, and on the lack of formation of products derived from singlet oxygen under the optimized conditions. However, at this time a singlet oxygen–mediated mechanism cannot be ruled out (Figure 28, mechanism B).

Figure 28. Proposed Mechanisms for the Photoredox Generation of Nitrosocarbonyls



4.4 Concluding Remarks

In conclusion, the developed photoredox conditions provide a unique pathway to generate transient nitrosocarbonyl intermediates with both temporal and spatial control, demonstrated by the capacity to turn the reaction on and off and the distance dependence. Additionally, the reaction conditions are sufficiently mild so as to not decompose the ene products, suggesting the oxidation methodology can be used to explore new frontiers of nitrosocarbonyl chemistry. The reaction is operationally simple to perform, using lights

purchased from a local hardware store, reagent grade solvents, air as the terminal oxidant and a readily available photoredox catalyst. We envision, based on the results, that this newly developed methodology has significant potential utility both in the context of small molecule chemistry and in the applied context of biology or materials science.

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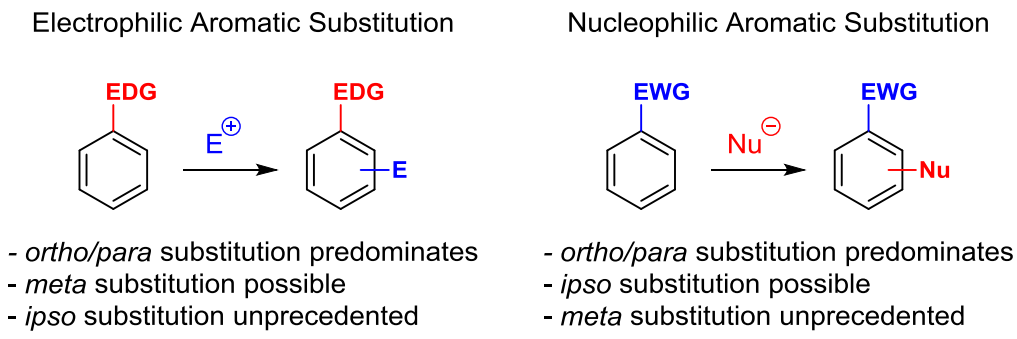
5. Iodine(III)–Mediated Oxidative Aromatic Substitution (S_OAr) of Phenols and Aniline Derivatives

5.1 The Synthetic Strategy of Oxidative Aromatic Substitution

The direct functionalization of substituted aromatic compound with regiochemical control is a great challenge in organic synthesis. Prior to the advent of transition metal catalyzed aromatic functionalization reactions, the predominant strategy for aromatic functionalization was electrophilic or nucleophilic aromatic substitution (S_EAr and S_NAr, respectively). These strategies rely on matching of intrinsic electronic environments between the two coupling partners in order to achieve efficient reactivity. As a consequence, the incorporation of specific functionalities to modulate electronics prior to substitution is required. Moreover, the electronic matching of coupling partners leads to specific regiochemical outcomes, which significantly limits substitution at electronically mismatched positions.

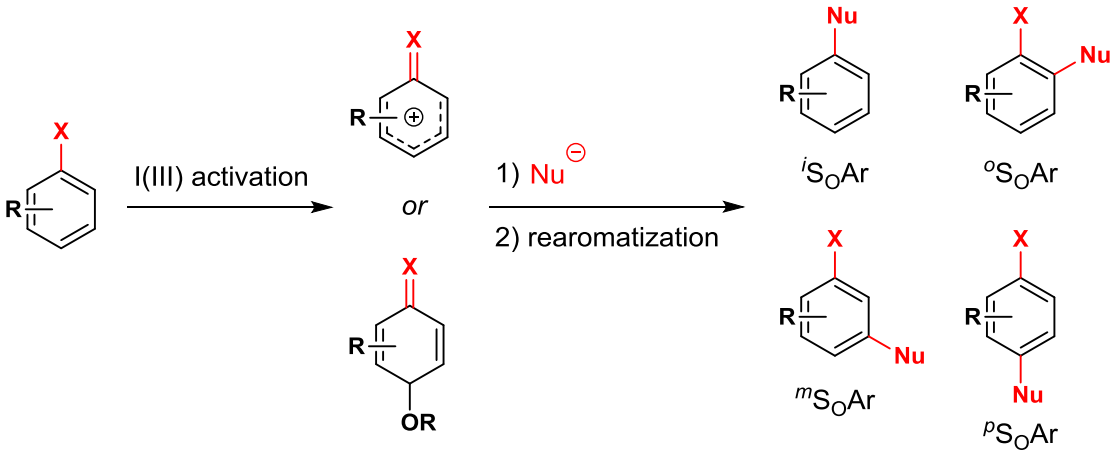
Figure 29. Direct Aromatic Substitution Strategies



Recently, an alternative to the classic S_EAr and S_NAr strategies has emerged that allows direct aromatic substitutions without the requisite matching of electronic environments. Termed "oxidative aromatic substitution," or S_OAr, nucleophilic functionalization of all four

sites of an aromatic ring can be accomplished through the oxidation of electron rich phenols and aniline derivatives. While aromatic oxidations are commonly used as a dearomatizing strategy, rearomatization under a variety of reaction conditions after nucleophilic addition is also possible, providing a complementary aromatic substitution pathway to S_EAr and S_NAr.

Figure 30. Synthetic Strategy of Oxidative Aromatic Substitution (S_OAr)



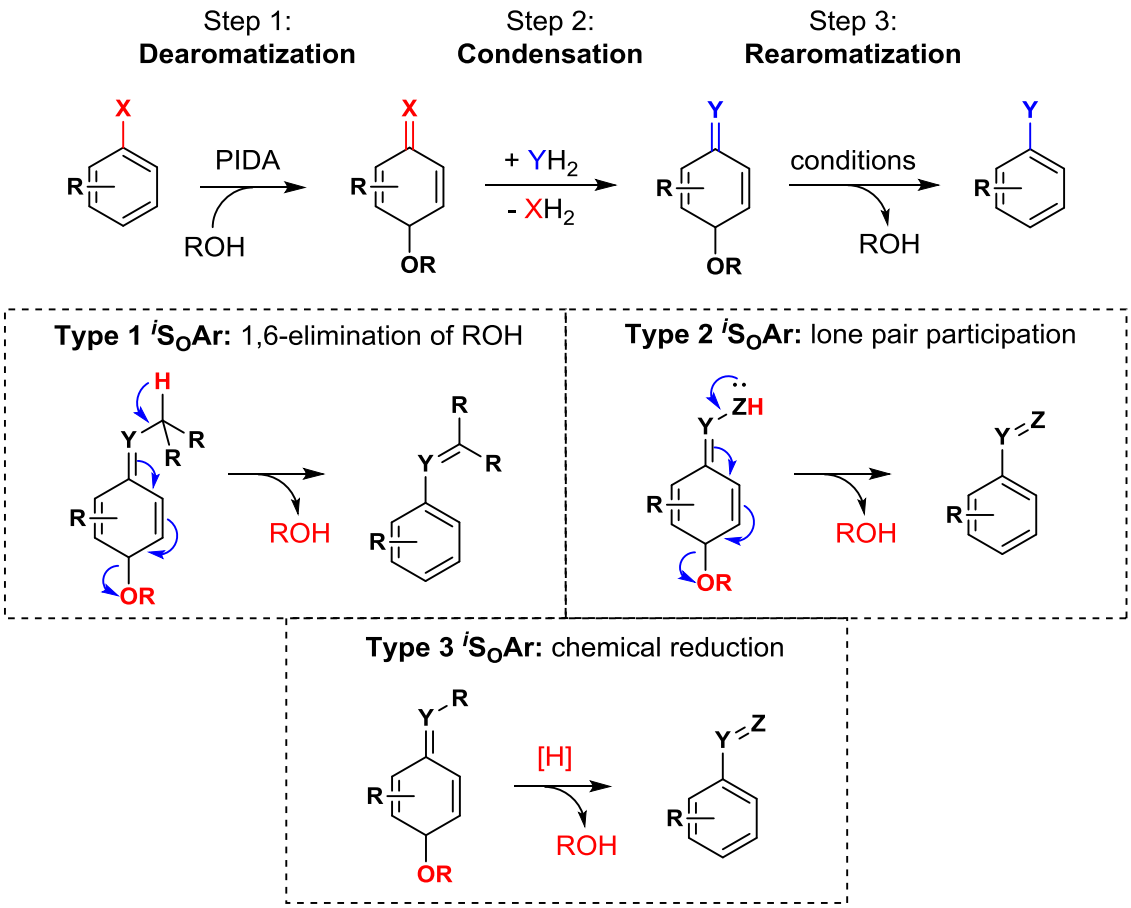
Although other oxidants can be utilized in the dearomatization step,[1] the recent widespread use iodine(III) reagents has facilitated the expansion of the S_OAr synthetic strategy.[2] In light of recent developments in the field, this review will focus specifically on the iodine(III)–mediated oxidative aromatic substitution synthetic strategy as applied to the functionalization of phenols and aniline derivatives.

5.2 *ipso*–Selective Oxidative Aromatic Substitution (^iS_OAr)

The *ipso*–selective variant of the S_OAr synthetic strategy is, by far, the most underutilized of the set. While examples of ^iS_OAr date back to the work of Taylor and co-workers in the 1970's who utilized toxic thallium(III) nitrate (TTN) as the oxidizing agent,[3] to date only a small subset of potential synthetic transformations have been explored, all of which exploit the hetero-functionalization of the corresponding quinine intermediate. To

date, three specific mechanisms have been exploited in $^{i}S_{O}Ar$ reactions. In all examples, the $^{i}S_{O}Ar$ reaction necessarily proceeds through the quinone intermediate (step 1: dearomatization) with concomitant condensation of a nucleophile onto the ketone (step 2: condensation). The major differentiating factor of the developed approaches is the mechanism of rearomatization (step 3). The first (Type 1 $^{i}S_{O}Ar$) invokes the 1,6 elimination of ROH through the deprotonation of an adjacent carbon. Often this step is followed by hydrolysis of the rearomatized product to generate the primary heteroatom. In contrast, if a nucleophile with an adjacent heteroatom is utilized (e.g. hydroxylamines and hydrazines), the lone pair participated in the rearomatization process by helping facilitate the elimination of MeOH (Type 2 $^{i}S_{O}Ar$). If a nucleophile with no adjacent acidic protons or heteroatoms is utilized, the rearomatization can be accomplished by the chemical reduction of the quinone intermediate (Type 3 $^{i}S_{O}Ar$, Figure 31). Examples of each of these mechanisms will be discussed in the following sections.

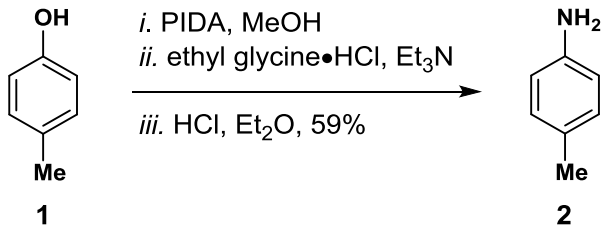
Figure 31. Divergent Pathways for the $^{i}S_{O}Ar$ Reaction



5.2.2 Examples of Type 1 $^{i}S_{O}Ar$

To date, only one example of Type 1 $^{i}S_{O}Ar$ has been reported that specifically utilizes an iodine(III) reagent. This example, reported by our research group, allows the direct conversion of phenol derivatives into the corresponding aniline. We found that *p*-cresol **1** could be directly converted to aniline derivative **2** using ethyl glycine, an inexpensive source of nitrogen, as the nucleophile (Equation 10). After rearomatization *via* the Type 1 pathway, hydrolysis of the imine intermediate afforded the aniline.

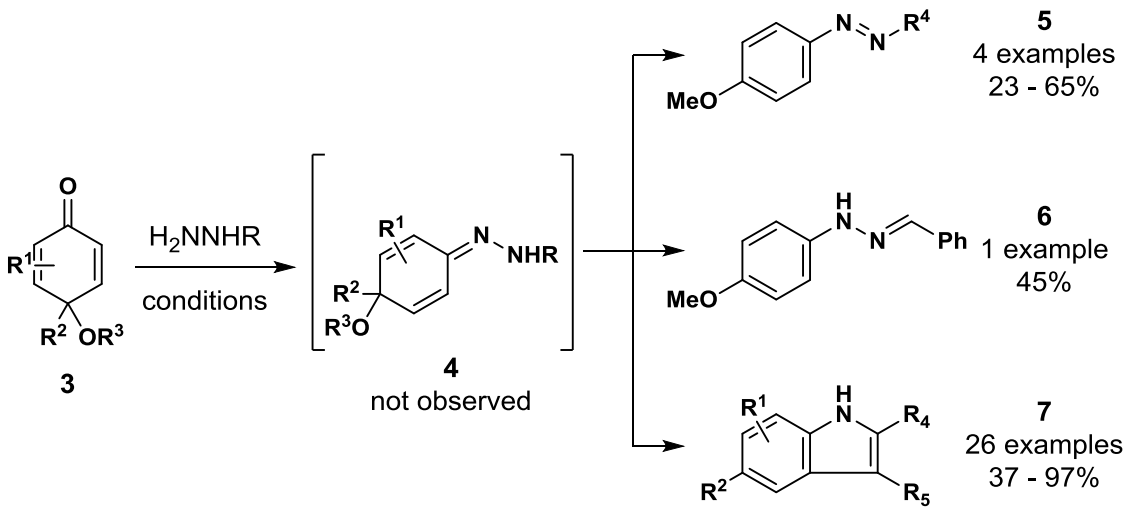
Equation 9. Direct Conversion of *p*-Cresol to *p*-Toluidine *via* Type 1 $^{i}S_{O}Ar$



5.2.3 Examples of Type 2 $^{i}S_{O}Ar$

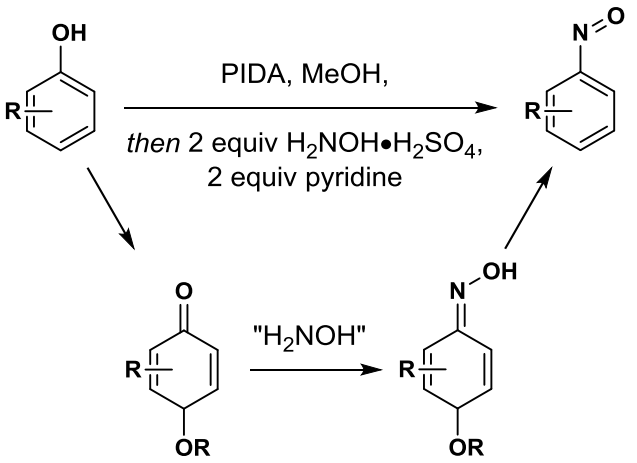
To date, two examples of Type 2 $^{i}S_{O}Ar$ have been reported, both of which converted phenols into nitrogenous aromatic compounds. The first reported example by Zheng and coworkers utilized substituted hydrazines to gain access to aromatic azo compounds **5**, aryl hydrazones **6**, and indoles **7** from the corresponding phenols, depending on the substitution pattern of the starting material (Figure 32). When hydrazines lacking adjacent acidic protons are employed, the reaction proceeds directly to the azo compound **5**, which could be isolated in moderate yield. In contrast, when hydrazines with tautomeric protons are utilized, hydrazone intermediate **4** will funnel directly to the indole, through a Fischer indolization pathway in good yield (Figure 32).[4]

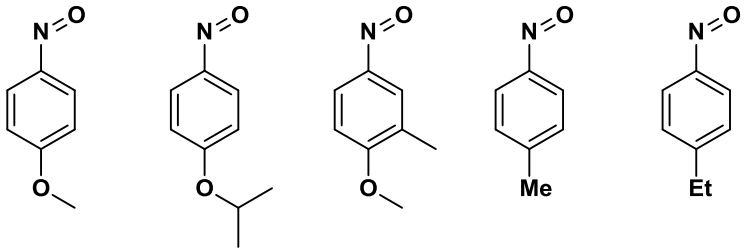
Figure 32. Divergent Reaction Pathways When Utilizing Hydrazines in Type 2 $^{i}S_{O}Ar$



Inspired by the work of Zheng and co-workers, we elected to explore the Type 2 $^{i}S_{O}Ar$ synthetic strategy for accessing substituted nitrosoarene compounds. Based on our longstanding interest in utilizing nitroso compounds in synthesis, we were delighted to discover that *p*-methoxynitroso benzene could be accessed in high yield from *p*-methoxy phenol in one pot. Whereas Zheng and co-workers observed bis-1,4 addition to form the [1,2,2] bridged structure when substituted hydroxylamines were utilized, under the optimized reaction conditions, we observed exclusive 1,2 addition of the unsubstituted hydroxylamine with the concomitant elimination of methanol to form the nitrosoarene directly. When *p*-alkoxy phenols were utilized, the nitrone intermediate was not observed during the course of the reaction. In contrast, with *p*-cresol, the nitrone was the only observable product, and aqueous hydroxylamine and an additional Lewis acid (10 mol % $Dy(OTf)_3$) had to be utilized in order to fully convert the nitrone to the nitrosoarene (Table 23).

Table 23. Accessing Nitrosoarenes from Phenols *via* a Type 2 $^{i}S_{O}Ar$ Pathway



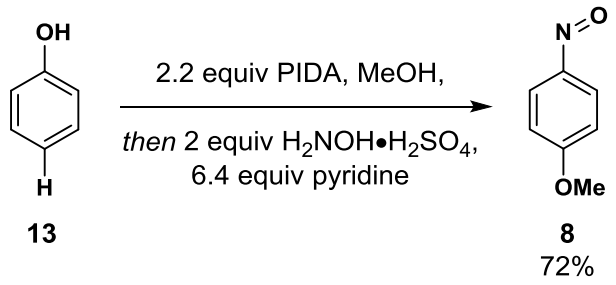


8	**9**[a]	**10**	**11**[b]	**12**[b]
79%	56%	58%	60%	40%

[a] Isolated as an inseparable 5:1 mixture of *p*-O*i*-Pr:*p*-OMe nitrosobenzene. [b] 2 equiv $H_2NOH_{(aq)}$ and 5 mol % $Dy(OTf)_3$ were used instead

Additionally, the reaction was not limited solely to *p*-substituted phenol starting materials. A double oxidation procedure can also be used to gain access to *p*-methoxynitroso benzene directly from phenol. Under the reaction conditions, the *p*-methoxy group is incorporated from the first oxidation of the aromatic ring, and constitutes a tandem $^{p}S_{O}Ar$ and $^{i}S_{O}Ar$ reaction (Equation 11).

Equation 10. Tandem S_OAr reactions to Access Nitrosoarenes Directly from Phenol

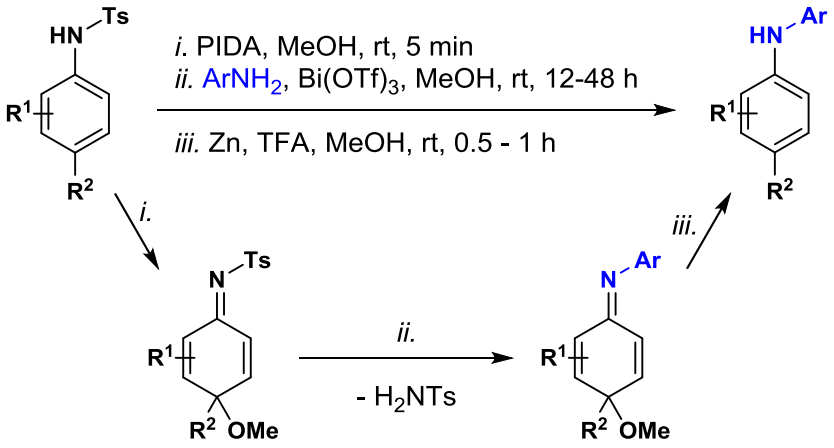


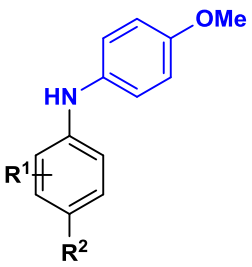
13 **8** 72%

5.2.4 Examples of Type 3 $^{i}S_OAr$

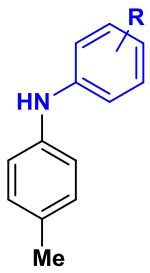
When the condensing nucleophile used does not have adjacent functionalities that can participate in the rearomatization process, an additional reducing agent is required to complete the $^{i}S_OAr$ pathway. To date, Fan and co-workers are the only research group to utilize this particular strategy, gaining access to a wide variety of diarylamines from *N*-tosyl aniline derivatives. While a number of Lewis acids were screened for the condensation step of the reaction, $Bi(OTf)_3$ was the most optimal, efficiently converting the *N*-tosyl iminoquinone to the corresponding, *N*-aryl iminoquinone. Elemental zinc and trifluoroacetic acid was determined to be the most efficient conditions for the rearomatization process, and fortuitously, all three reaction steps could be carried out consecutively in a single pot. Under the optimized reaction conditions, a wide variety of differentially functionalized diarylamines were accessible (Table 24).[5]

Table 24. Scope of Diaraylamine Formation from Type 3 $^{i}S_{O}Ar$





14 R^1 = H, R^2 = Me, 83%
15 R^1 = H, R^2 = *n*Bu, 75%
16 R^1 = H, R^2 = Et, 88%
17 R^1 = H, R^2 = *i*Pr, 70%
18 R^1 = H, R^2 = OMe, 45%
19 R^1 = H, R^2 = Ph, 63%
20 R^1 = 2-Me, R^2 = Me, 35%
21 R^1 = 3-Me, R^2 = Me, 73%



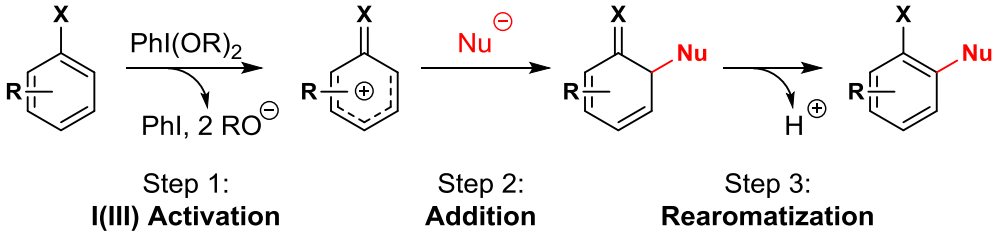
22 R = H, 76%
23 R = 4-Me, 80%
24 R = 4-*i*Pr, 80%
25 R = 2-Me, 98%
26 R = 2,6-$(Me)_2$, 73%
27 R = 2,4,6-$(Me)_3$, 80%
28 R = 4-OH, 91%
29 R = 2-OH, 83%
30 R = 2-I, 48%
31 R = 4-F, 85%
32 R = 1-naphtyl, 85%

5.3. *Ortho*–Selective Oxidative Aromatic Substitution ($^{o}S_{O}Ar$)

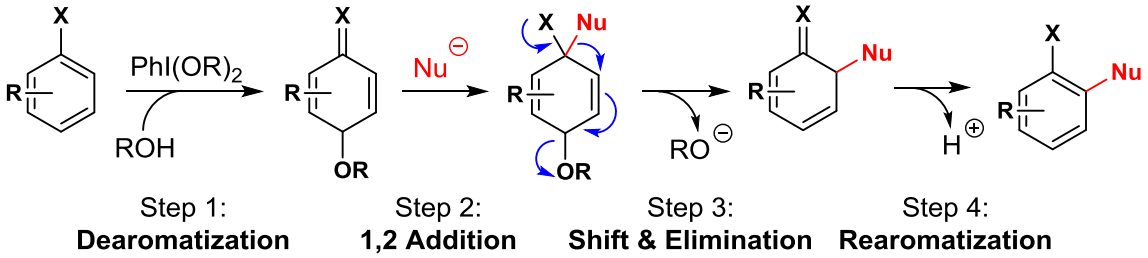
The *ortho*-selective variant of oxidative aromatic substitution is a widely explored transformation that proceeds through a variety of mechanistic pathways. Nucleophilic addition to the *ortho* position of the phenol or aniline can proceed directly from the iodonium intermediate with concomitant elimination of iodobenzene and 2 equivalents of the acetate derivative (Type 1 $^{o}S_{O}Ar$). This pathway typically occurs in non–alcoholic solvents when soft nucleophiles are used. Alternatively, addition can occur to the *ipso* position of the starting phenol or aniline derivative after oxidation to the quinone intermediate. After addition, a pinacol–type rearrangement can occur to induce rearomatization (Type 2 $^{o}S_{O}Ar$). This reaction pathway often occurs when hard nucleophiles

are used under strongly basic conditions, although rearomatization can be accomplished under strongly basic or acidic conditions. Finally, another mechanism can be invoked under strongly acidic conditions after oxidation to the quinone. In this mechanism, elimination of methanol from the quinone intermediate affords the stabilized cation which, after addition and rearomatization, affords the *ortho* functionalized phenol or aniline derivative (Type 3 $^{o}S_{O}Ar$). Specific examples of each reaction type are provided in the following section.

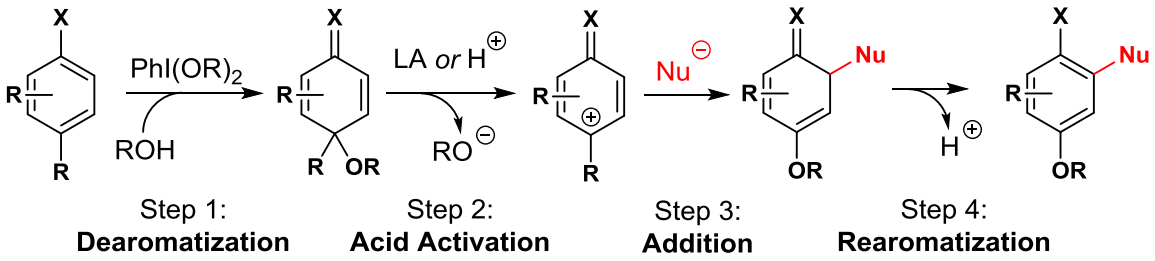
Type 1 $^{o}S_{O}Ar$ - non-alcoholic solvents with soft nucleophiles



Type 2 $^{o}S_{O}Ar$ - hard nucleophiles and basic conditions



Type 3 $^{o}S_{O}Ar$ - various nucleophiles and acidic conditions

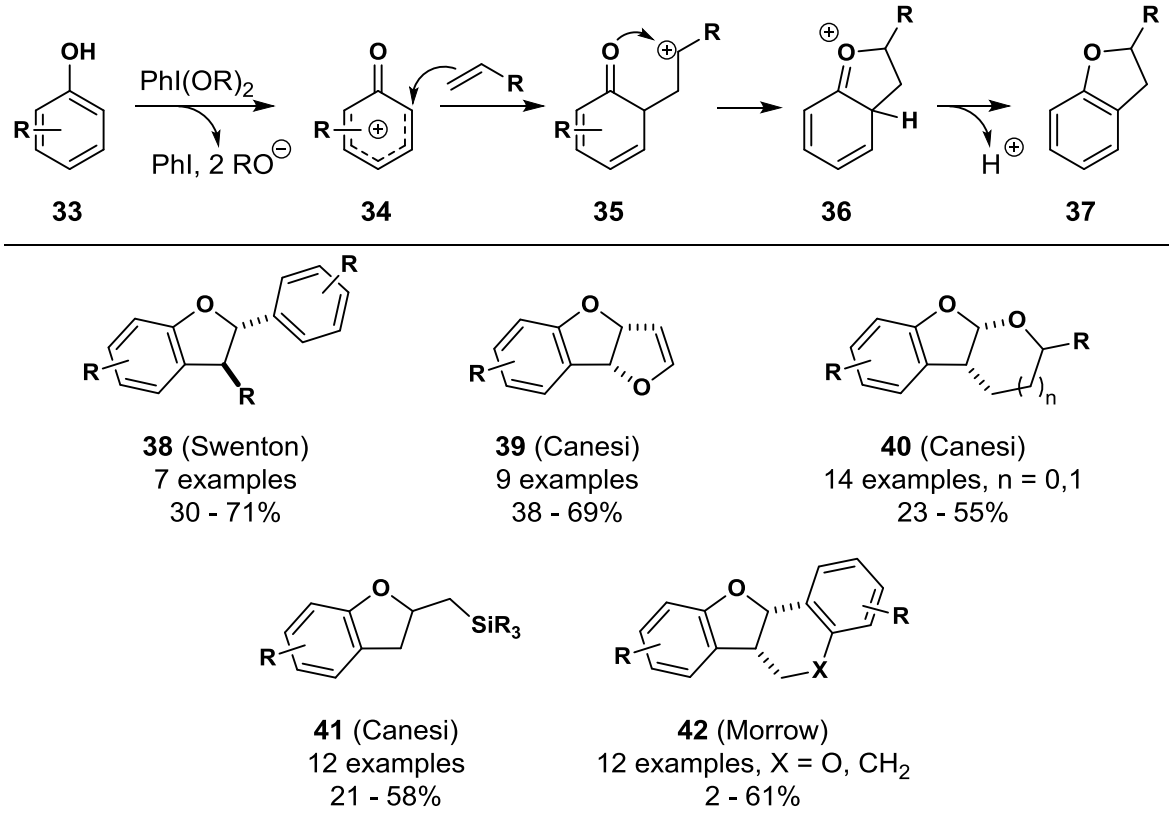


5.3.1 Examples of Type 1 $^{o}S_{O}Ar$

The most widely used nucleophile in Type 1 $^{o}S_{O}Ar$ are substituted olefins. In particular, a number of research groups have utilized phenols to form a variety benzofuran derivatives

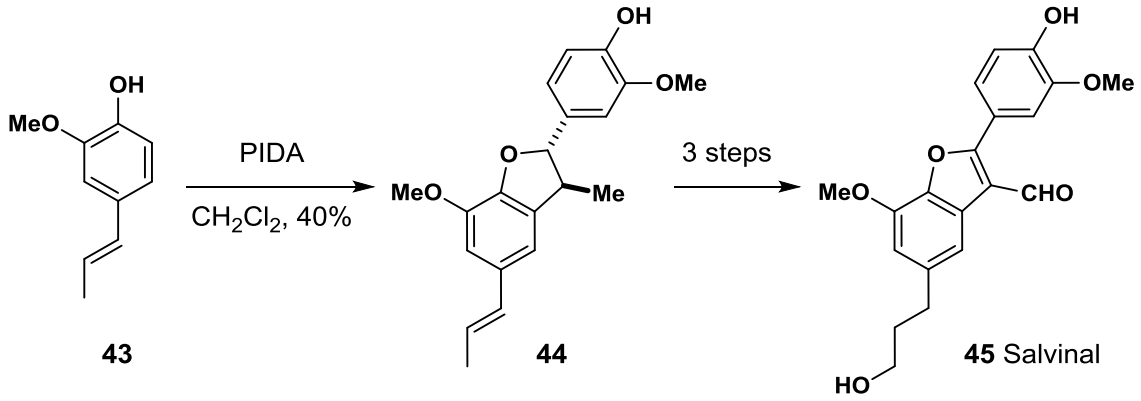
through the addition of an electron rich olefin to the oxidized phenol intermediate. Olefin addition to **34** affords cationic ketone intermediate **35**, which cyclizes to form the corresponding oxonium **36**. Upon deprotonation, the desired dihydrobenzofuran derivative **37** is formed. To date a number of nucleophilic olefins have been employed, including styrenes,[6] furans,[7] vinyl ethers,[8] allyl silanes[9] and naphthalene derivatives.[10]

Figure 33. Olefin Addition to Oxidized Phenols to Form Benzofuran Derivatives



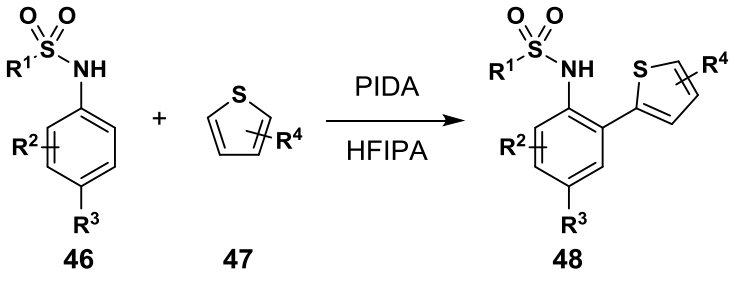
This reaction pathway has also been utilized in natural product synthesis. Taking inspiration from the work of Swenton and co-workers who explored the addition of styrene derivatives to oxidized phenol intermediates,[6] Kuo and co-workers exploited the dimerization of isoeugenol to form the desired benzofuran, which was used to form the natural product salvinal in three additional steps (Equation 13).[11]

Equation 11. Synthesis of Salvinal Through a Type 1 $^{o}S_{O}Ar$ Synthetic Strategy

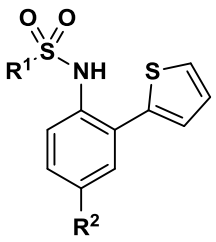


Substituted anilines have also been utilized as coupling partners in Type 1 $^{o}S_{O}Ar$ reactions. Like the phenol derivatives, it is not necessary to fully oxidize the aniline to the iminoquinone intermediate, since the addition of iodine(III) reagents effectively activate the aniline for nucleophilic addition. For example, Canesi and co-workers observed the direct addition of thiophene derivatives to the *ortho* position of sulfonate protected anilines after oxidation with PIDA.[12] Mechanistically, cyclization onto the thiophenium intermediate after addition was not observed, unlike reactions with the furan derivatives. The reaction was tolerant of a variety of substitution patterns on both the aniline and the thiophene component. Additionally, while a number of *N*-tosyl anilines were utilized, the reaction also tolerated a variety of substitution patterns on the sulfone, such as the ethyl, vinyl, and 4-NO_2Ph sulfonamides (Table 25).[12]

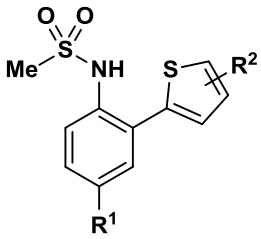
Table 25. Addition of Thiophene Derivatives to Aryl Sulfonamides *via* Type 1 $^{o}S_{O}Ar$



46 **47** **48**



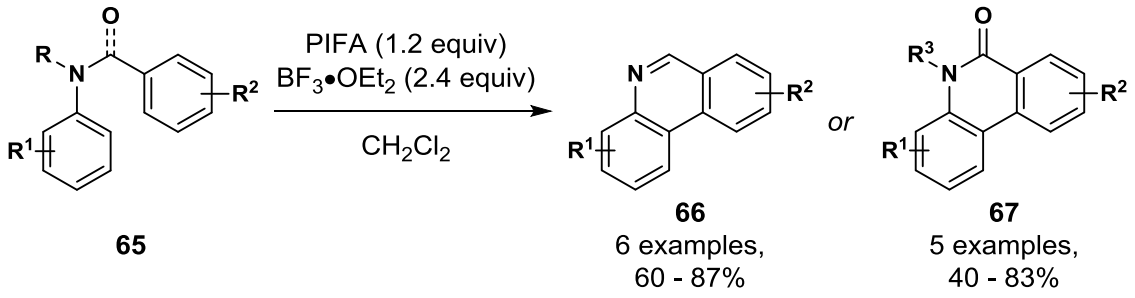
49 R^1 = Me, R^2 = Me, 76%
50 R^1 = Et R^2 = Me, 76%
51 R^1 = CH=CH_2, R^2 = Me, 76%
52 R^1 = 4-NO_2Ph, R^2 = Me, 76%
53 R^1 = Me, R^2 = *n*-Pr, 84%
54 R^1 = Me, R^2 = *i*-Pr, 74%
55 R^1 = Me, R^2 = $(CH_2)_2OH$, 75%
56 R^1 = Me, R^2 = Cl, 72%



57 R^1 = Me, R^2 = 3-Br, 67%
58 R^1= *n*-Pr, R^2 = 3-Br, 63%
59 R^1 = *i*-Pr, R^2 = 3-Br, 62%
60 R^1 = $(CH_2)_2OH$, R^2 = 3-Br, 64%
61 R^1 = Cl, R^2 = 3-Br, 64%
62 R^1 = Me, R^2 = 2-Me, 58%
63 R^1= *n*-Pr, R^2 = 2-Me, 63%
64 R^1 = *i*-Pr, R^2 = 2-Me, 64%

Nucleophilic addition to the ortho position of aniline derivatives can also be accomplished in an intramolecular fashion. For example, electron rich benzyl and benzoate substituted anilines readily cyclize to form the phenanthridine and phenanthridinone species (Equation 13). Notably, electron rich benzyl and benzoate substitution leads directly to the desired compound (Equation 13, **66** and **67**), whereas use of less nucleophilic substituents on nitrogen lead to exclusive dimer formation (not shown).[13] Mechanistically, this particular transformation may proceed through the radical cation, a mechanism commonly seen in the work of Kita and co-workers utilizing phenyl ethers.[14]

Equation 12. Intramolecular Cyclization to Phenanthridine And Phenanthridinones



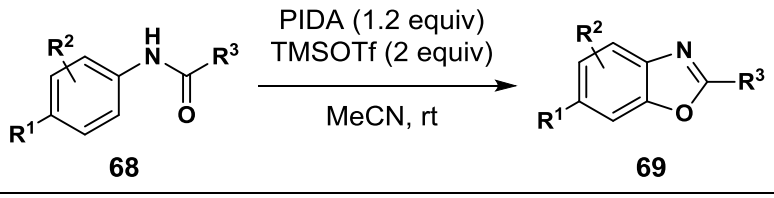
65

66
6 examples,
60 - 87%

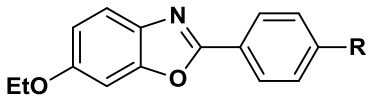
67
5 examples,
40 - 83%

An alternative reaction is observed when PIDA is used instead of PIFA. Rather than addition through the aromatic ring of the benzoate, Yu and co-workers observed the addition of the oxygen component of the benzamide to form the benzoxazole in high yield when PIDA and TMSOTf were used. Unlike Dominguez and co-workers, no dimerization was observed. Notably, both the *p*–anisidine and *p*–phenylenediamine both participated in the reaction with no reduction in yield (Table 26).[15]

Table 26. Formation of Benzoxazoles Through an Intramolecular Type 1 $^{o}S_{O}Ar$

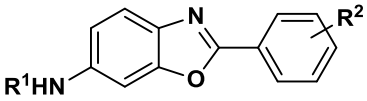


68 **69**



70 R = H, 96%
71 R = Me, 97%
72 R = OMe, 98%
73 R = Br, 93%
74 R = OTBS, 90%
75 R = NO_2, nr

76 R^1 = H, R^2 = 2-IPh, 72%
77 R^1 = H, R^2 = 3-MePh, 96%
78 R^1 = 4-Me, R^2 = Ph, 99%
79 R^1 = 5-I, R^2 = Ph, 88%
80 R^1 = H, R^2 = 2-furyl, 74%
81 R^1 = H, R^2 = CH=CHPh, 76%



82 R^1 = Ac, R^2 = Ph, 86%
83 R^1 = Ac, R^2 = 4-OMe 96%
84 R^1 = Ac, R^2 = 4-OTBS 55%
85 R^1 = Ac, R^2 = 3-Me 90%
86 R^1 = Ac, R^2 = 2-Cl 75%
87 R^1 = Ac, R^2 = 2,3-$(Me)_2$ 82%
88 R^1 = Boc, R^2 = H 37%
89 R^1 = Boc, R^2 = 4-Br 27%

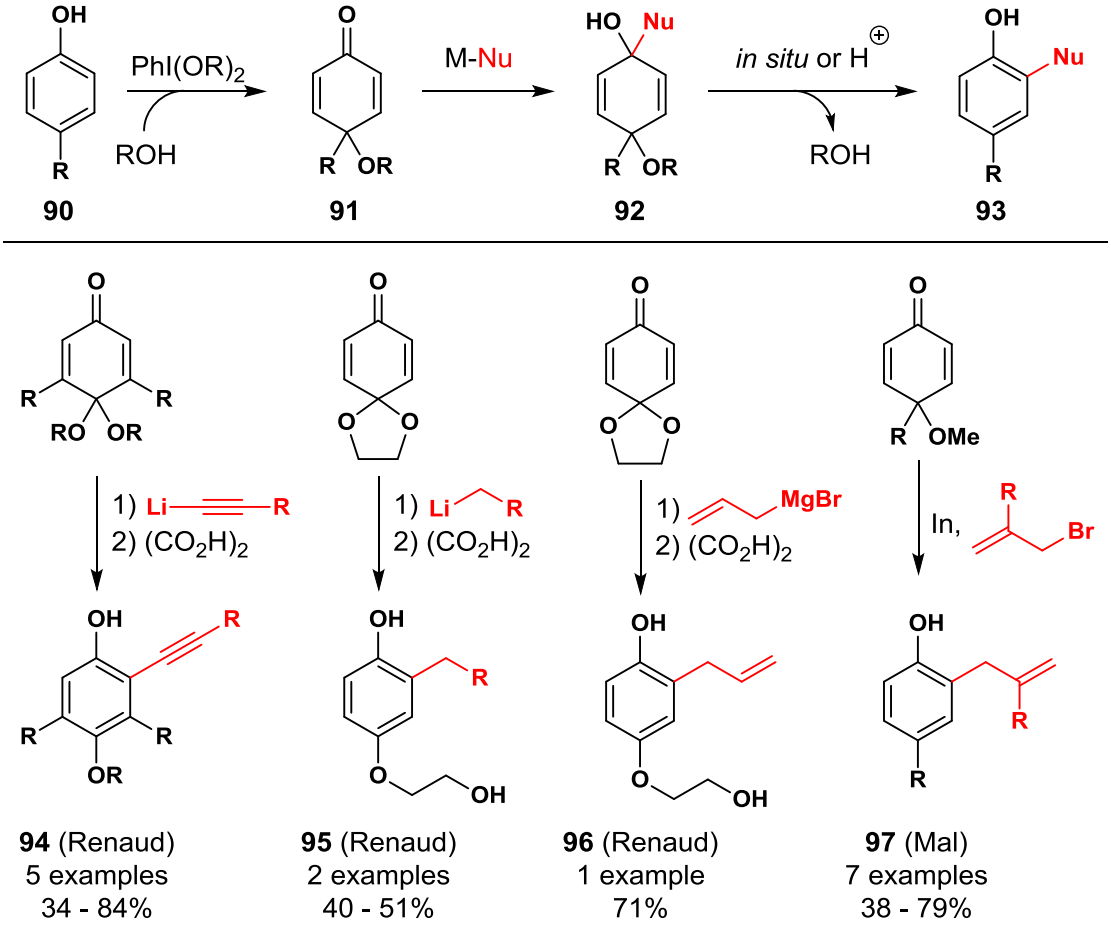
It is worth noting that Kita and co-workers have extensively explored this pathway for the functionalization of phenyl ethers.[14] While it is beyond the scope of this review, many research groups exploring Type 1 $^{o}S_{O}Ar$ with phenols and anilines have been directly influenced by Kita's work.

5.3.2 Examples of Type 2 $^{o}S_{O}Ar$

As an alternative to direct addition to oxidized phenol intermediates, the $^{o}S_{O}Ar$ synthetic strategy can proceed through the quinone intermediate instead. Using hard nucleophiles such is alkyl and alkynyl lithium species or Grignard reagents, 1,2 addition is the predominant pathway. However, under the strongly basic conditions, intermediate **92** will undergo a

pinacol–type rearrangement with elimination of the corresponding alkoxide to form the *ortho*-functionalized phenol (Figure 34). Renaud and co-workers explored this pathway extensively with the quinone monoacetal species.[16] Alternatively, allylindium bromides can react in the same manner, although acidic conditions are required to induce the desired pinacol–type rearomatization pathway.[17]

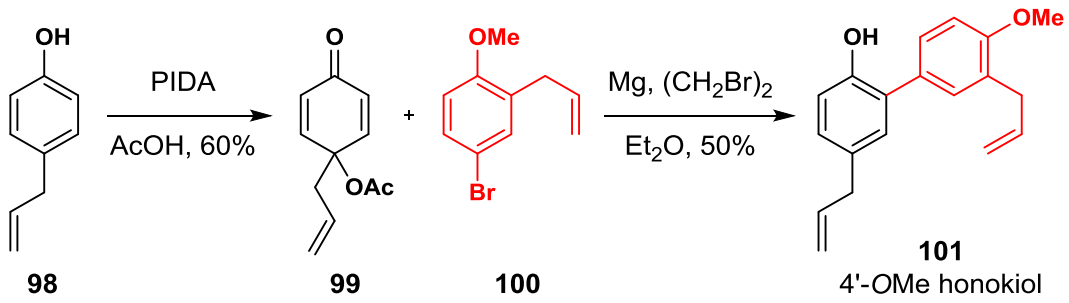
Figure 34. *Ortho* Functionalization of Phenols *via* a Type 2 $^{o}S_{O}Ar$ Pathway



The Type 2 $^{o}S_{O}Ar$ synthetic strategy was utilized in the synthesis of biaryl natural product derivative 4'-OMe honokiol by Denton and co-workers. Denton, who extensively explored $S_{O}Ar$ reactions under electrochemical oxidation conditions, used the addition or aryl Grignard reagent **100** to dienone **99** to form the desired compound in moderate yield.

Notably, as observed in the work of Renaud, elimination of the acetate anion occurred *in situ* to form the rearomatized product (Equation 14).[18]

Equation 13. Synthesis of 4'-OMe Honokiol *via* a Type 2 $^{o}S_{O}Ar$ Synthetic Strategy

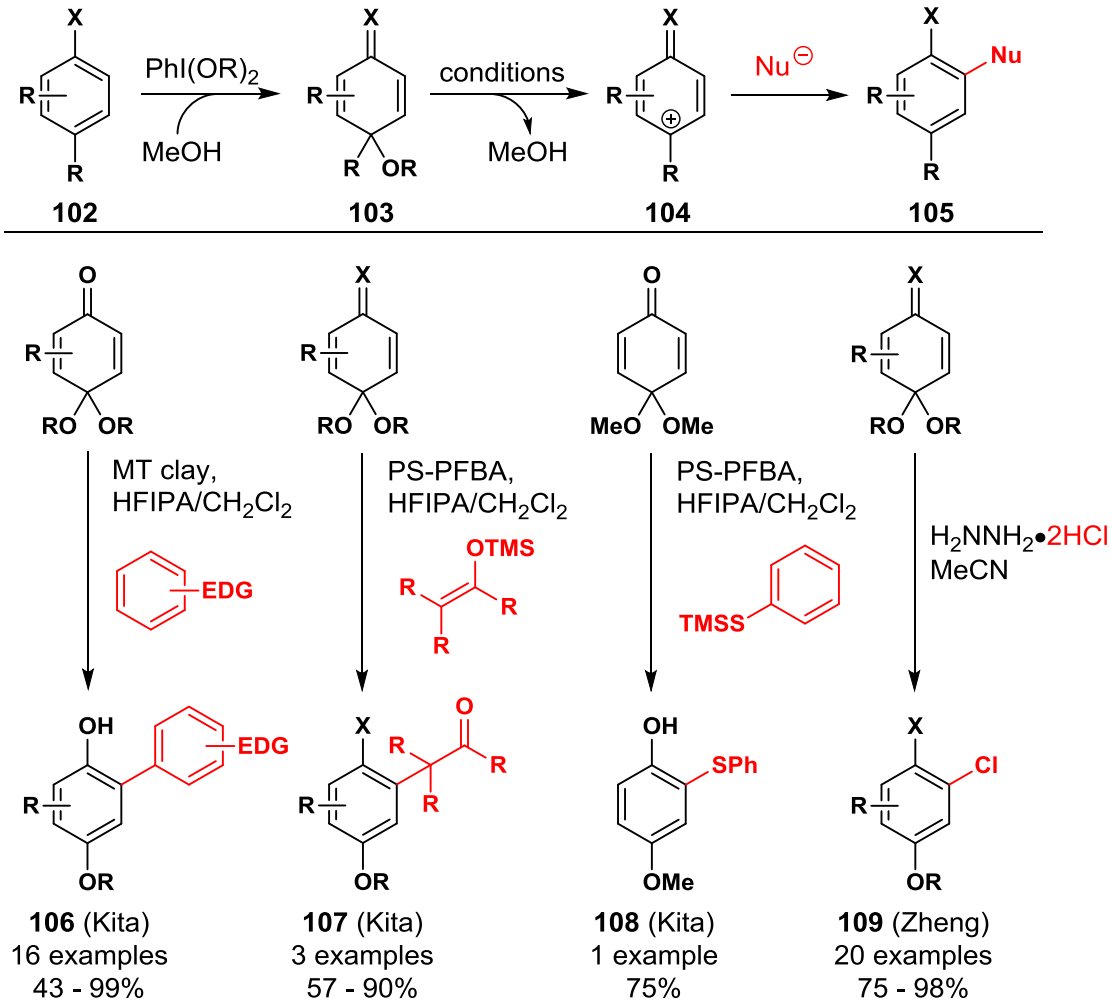


5.3.2 Examples of Type 3 $^{o}S_{O}Ar$

As an alternative to the strongly basic conditions of Type 2 $^{o}S_{O}Ar$, acidic conditions can also be utilized to accomplish the *ortho* functionalization of phenols and aniline derivatives. After iodine(III) oxidation to the quinone intermediate, activation by a Brønsted acid will afford quinonium intermediate **104**, which allows the selective formation of the *ortho*–substituted phenol or aniline derivative. This pathway has been most extensively explored by Kita and co-workers for the addition of electron rich arenes using montmorillonite (MT) clay as the Brønsted acid (**106**, Figure 35),[19] and for the addition of silyl enol ethers using a polystyrene–anchored perfluorobenzoic acid (**107**, Figure 35).[20] Notably, Kita also explored the synthesis of oxygenated terphyl compounds through the sequential addition of multiple electron rich arenes (not shown).[21] The reaction is not limited *C-C* bond forming reactions, as MT clay could be used to induce TMS-thiophenol addition (**108**, Figure 35).[20] Additionally, serendipitous halogen addition to the *ortho* position of phenol and aniline derivatives was observed by Zeng and co-workers when the quinone derivatives were treated

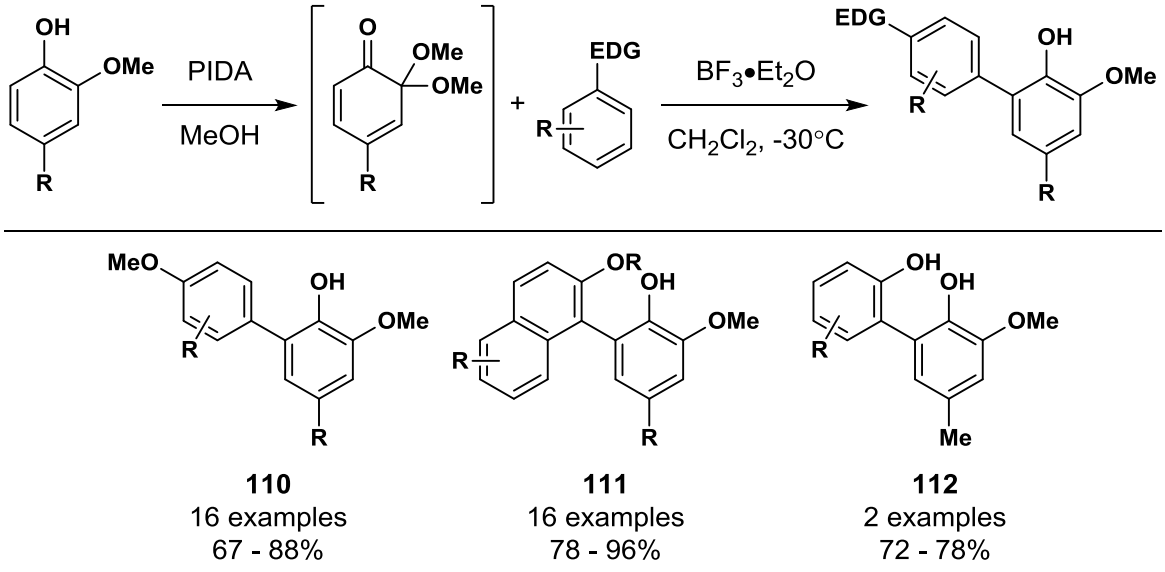
with hydrazine hydrochloride (**109**, Figure 35).[22] Finally, Novak and co-workers explored the kinetics of type 3 $^{o}S_{O}Ar$ reaction using azides and other nucleophiles (not shown).[23]

Figure 35. Type 3 $^{o}S_{O}Ar$ Reactions using Brønsted Acids.



Similarly, nucleophilic addition can occur at the *ortho* position of *ortho*-quinone monoacetals. Peddinti and co-workers found that treatment of *ortho*-methoxyphenols led to exclusive *ortho*-quinone acetal formation, however Lewis acid (BF_3•Et_2O) activation of the quinone intermediate still lead to a Type 3 $^{o}S_{O}Ar$ pathway. Under the optimized conditions a breadth of biaryl compounds were accessible (Table 27).[24]

Table 27. Synthesis of Biaryl Compounds Through the *Ortho*-Quinone



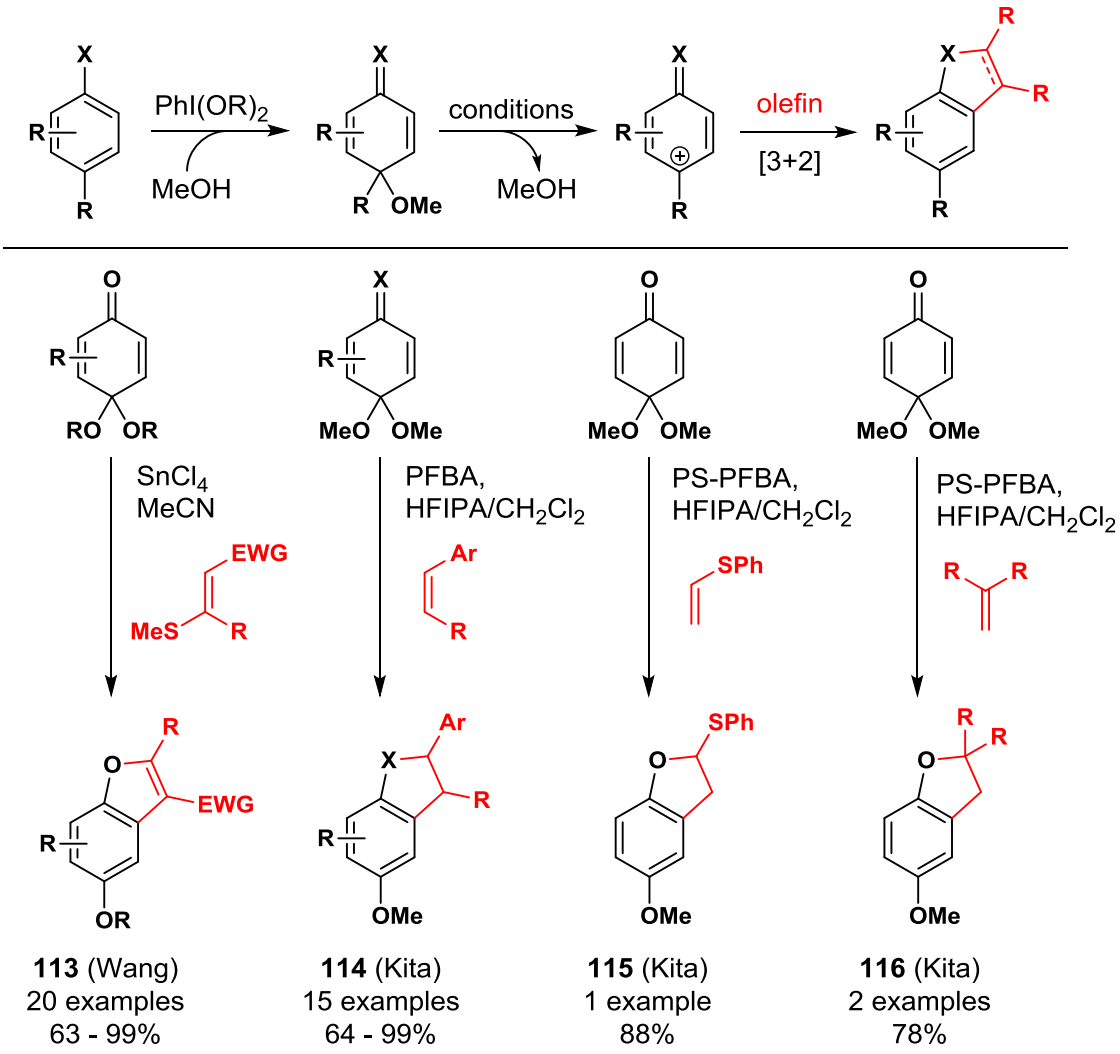
110
16 examples
67 - 88%

111
16 examples
78 - 96%

112
2 examples
72 - 78%

Substituted olefins can also react with quinone intermediates to form similar dihydrobenzofuran products from the Type 1 $^{o}S_{O}Ar$. Unlike their Type 1 $^{o}S_{O}Ar$ counterparts, the quinone intermediate was first generated in each case, and the Lewis or Brønsted acids activate the quinone for nucleophilic addition through the loss of MeOH. Wang and co-workers utilized $SnCl_4$ as a Lewis acid to activate quinone monoacetals for *ortho* addition.[25] After elimination of methyl sulfide, the benzofuran could be isolated in good yield. Kita also made significant contributions to this reaction pathway. Using pentafluorobenzoic acid (PFBA), or the polystyrene–immobilized PFBA as a Brønsted acid, Kita and co-workers explored the addition of styrene derivatives, vinyl thioethers and simple olefins all in good yield.[26] In each case, rearomatization occurred after cyclization, as the benzofuran derivatives were isolated exclusively (Figure 36).

Figure 36. Addition of Olefins to Acid Activated Quinone Monoacetals

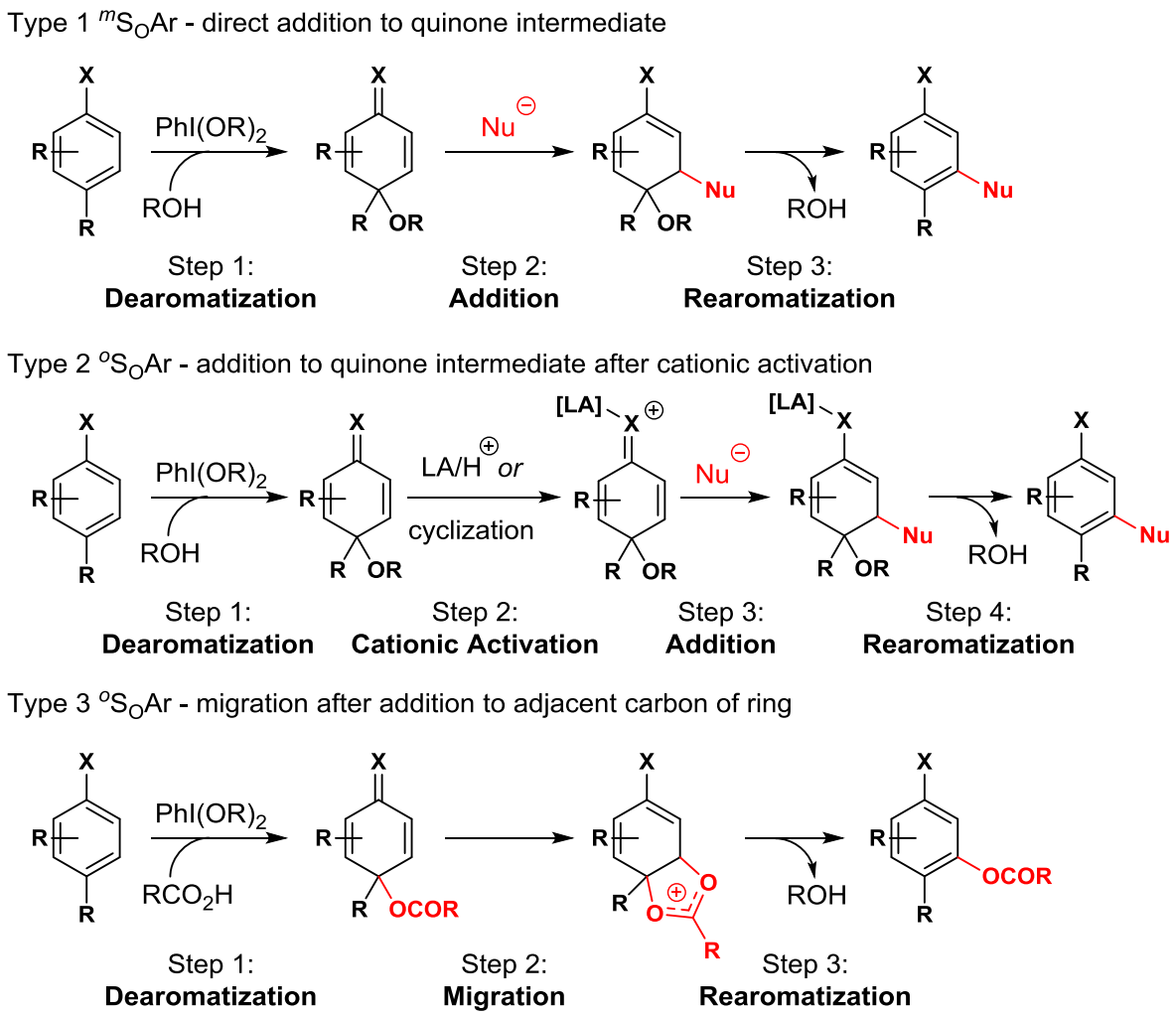


5.4 *meta*–Selective Oxidative Aromatic Substitution

As an aromatic functionalization methodology, the *meta*-selective variant of oxidative aromatic substitution complements S_EAr nicely. Whereas phenols and anilines typically react at the *ortho* or *para* positions of the aromatic ring in S_EAr reactions, functionalization of the same starting materials at the *meta* position can be accomplished with S_OAr. As with addition to other positions of the ring, $^{m}S_OAr$ can occur through a variety of mechanism, but the formation of the quinone intermediate is a necessity. Type 1 $^{m}S_OAr$ occurs through direct

1,4–addition of a nucleophile with concomitant elimination of the alcohol to facilitate rearomatization. Type 2 $^{m}S_{O}Ar$ reactions invoke the cationic activation of quinone intermediate through either a Lewis or Brønsted acid, or through cyclization onto a tethered functional group. Elimination of the alcohol again facilitates rearomatization, Finally, Type 3 $^{m}S_{O}Ar$ can occur through the quinone intermediate when acetate derivatives are used during the dearomatization. Under the reaction conditions, the acetate can migrate from the *para* to the *meta* position, activating the ring for rearomatization. Examples of each are given in the following section (Figure 37).

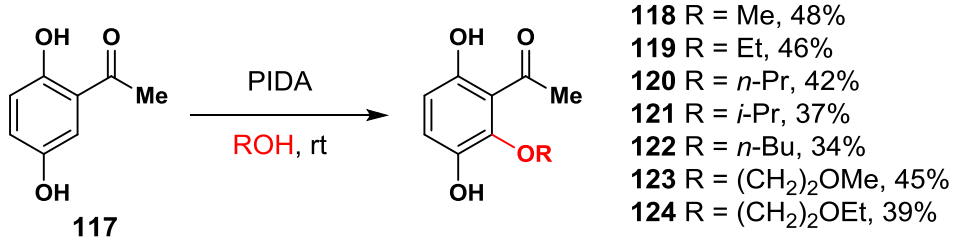
Figure 37. Mechanistic pathways for *meta*–Selective Oxidative Aromatic Substitution



5.4.1 Examples of Type 1 $^{m}S_{O}Ar$

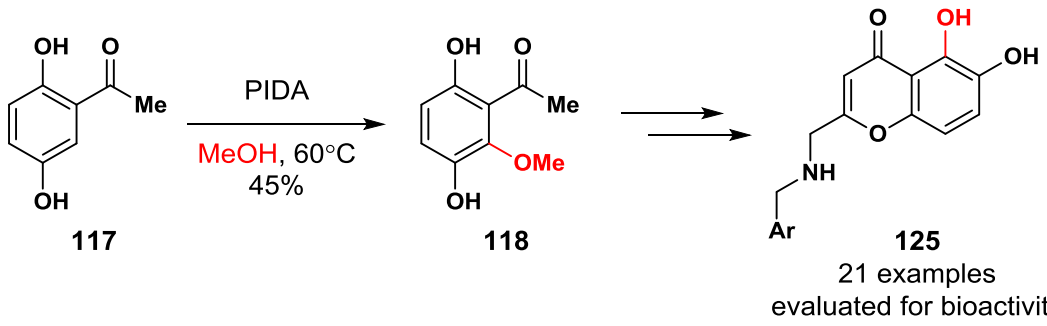
The direct addition of alcohols to the *meta* position of an aromatic ring can be accomplished provided that the starting phenol can form the quinone intermediate. Therefore, hydroquinones are the required starting material, and additional electron withdrawing groups are necessary to further activate the quinone intermediate. By subjecting hydroquinone **117** to PIDA in a variety of protic solvents, Prakash and co-workers found that the desired phenyl ethers can be isolated in moderate yield (Equation 15).[27]

Equation 14. Addition of Alcohols to Hydroquinones *via* Type 1 $^{m}S_{O}Ar$



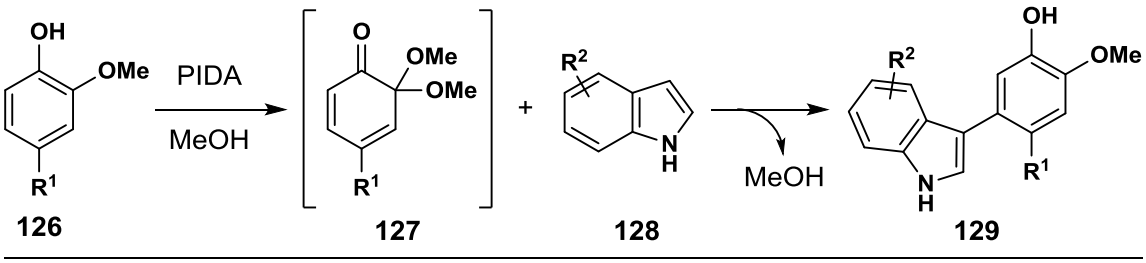
Utilizing Prakash's methodology, Chong and coworkers synthesized a wide variety of dihydroxychromone derivatives that were evaluated for bioactivity, highlighting the unique potential of $^{m}S_{O}Ar$ reactions in the synthesis of natural product derivatives and pharmaceutically active compounds (Equation 16).[28]

Equation 15. Synthesis of Dihydroxychromone

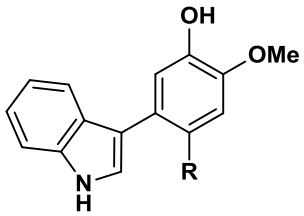


As with other S_OAr reactions, it is not necessary to proceed through the *para*-quinone intermediate; the *ortho*-quinone acetal can also be employed. In particular, Liao and co-workers found that the nucleophilic addition of indoles to the *meta*-position of *ortho*-quinones provided the 3-arylindoles in good yield (Table 28). Notably, no Diels–Alder was observed between the indole and the *ortho*-quinone if the reactions were run in refluxing methanol.[29]

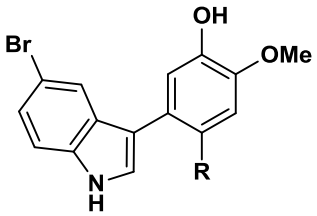
Table 28. Direct Addition of Indoles to *ortho*-Quinone Intermediates



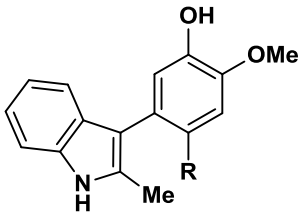
126 **127** **128** **129**



130 R = CO_2Me, 96%
131 R = COMe, 91%
132 R = CN, 53%



133 R = CO_2Me, 92%
134 R = COMe, 90%
135 R = CN, 67%

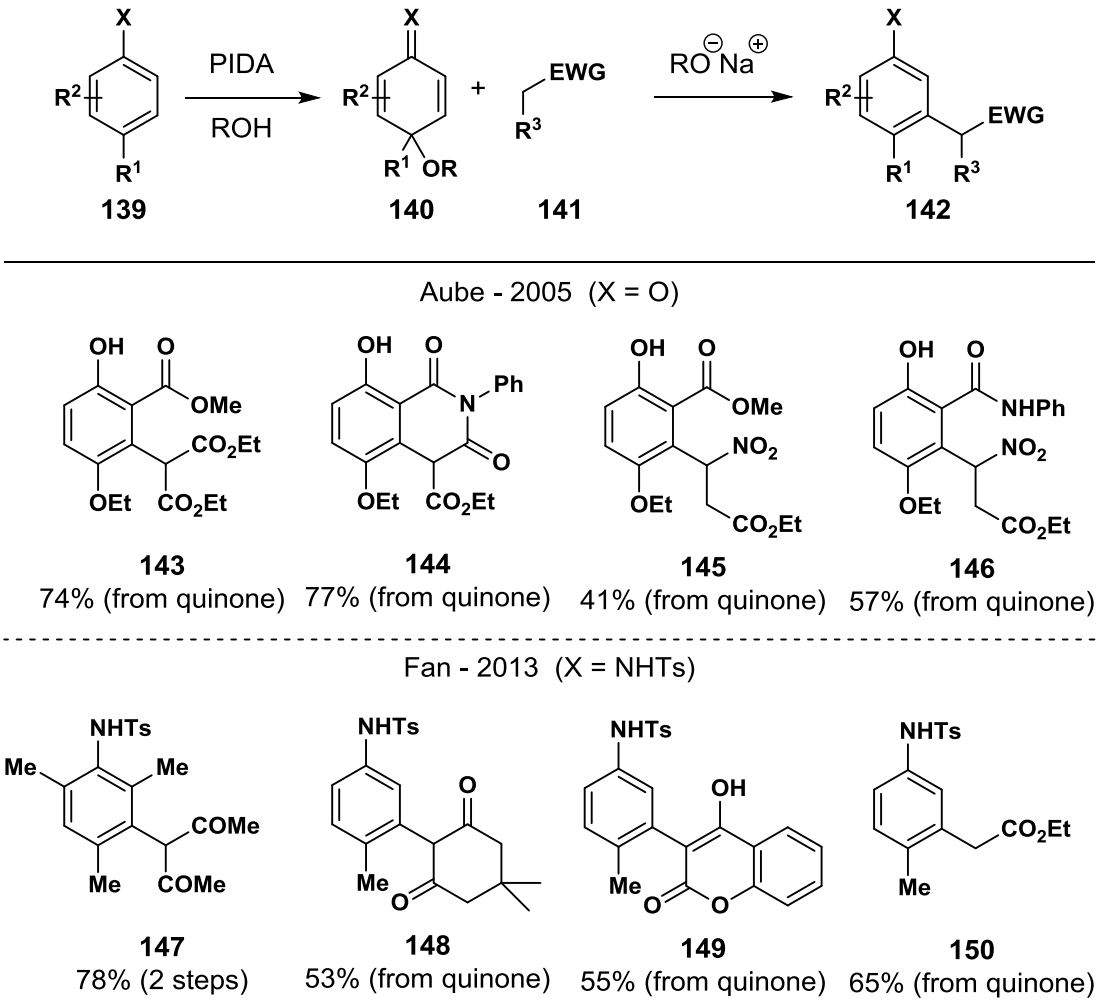


136 R = CO_2Me, 86%
137 R = COMe, 96%
138 R = CN, 75%

Enolates and enolate derivatives are commonly used nucleophiles in Type 1 $^{m}S_OAr$ reactions. Aube and co-workers were the first to make significant contributions to this reaction type, using phenols bearing *ortho* electron withdrawing groups and a variety of enolate derived nucleophiles. Although Michael addition without rearomatization, and double Michael addition products were observed, the Type 1 $^{m}S_OAr$ products could also be isolated in good yield from the quinone intermediate (Table 29, **143** – **146**).[30] Fan and co-workers also found that enolate derivatives could be added to iminoquinones to form the

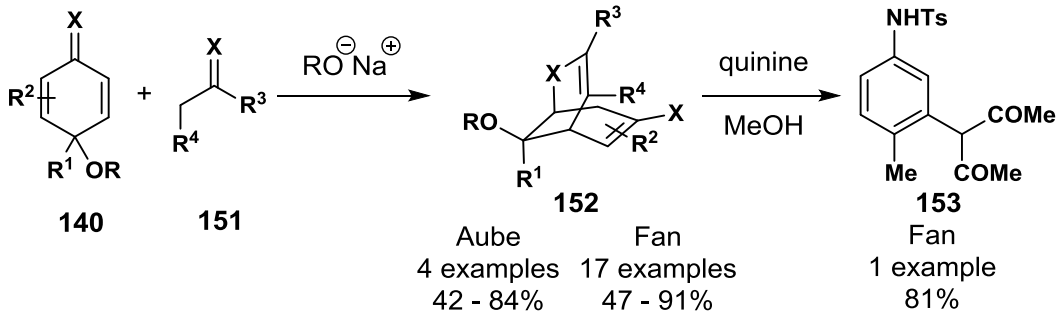
rearomatized *meta*-functionalized aromatic compound (Table 29, **148** – **150**). Additionally, this transformation could be carried out in one pot directly from the tosyl–protected aniline in high yield (Table 29, **147**).[31]

Table 29. Addition of Enolate Derivatives to Quinones *via* Type 1 $^{m}S_{O}Ar$



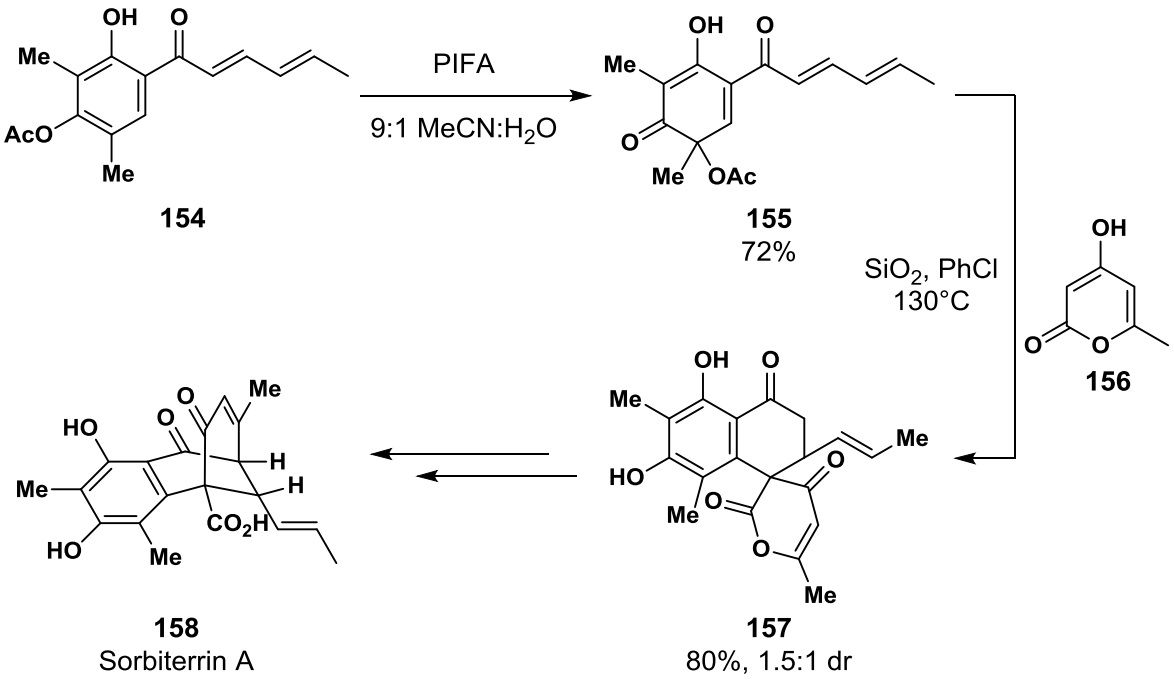
In addition to the single Michael addition products, Both Aube and Fan observed double Michael addition adducts resulting from the addition of the heteroatom of the nucleophile, forming the [3,3,1] bridged species.[30-31] While **152** was the primary product isolated in a number of transformations, Fan and co-workers observed that the addition of quinine induced the retro-Michael elimination and formation of the $^{m}S_{O}Ar$ product in high yield.[31]

Equation 16. Double Michael Addition and Elimination to Form the $^{m}S_{O}Ar$ Product



The $^{m}S_{O}Ar$ synthetic strategy has also found use in the total synthesis of sorbiterrin A by Porco and co-workers. After formation of *ortho*-quinone **155** through the treatment of **154** with PIFA, the addition of enol **156** and silica gel induced the Type 1 $^{m}S_{O}Ar$ reaction and subsequent cyclization onto the appended dienone. This product was then carried onto sorbiterrin A **158** in three additional steps (Equation 18).[32]

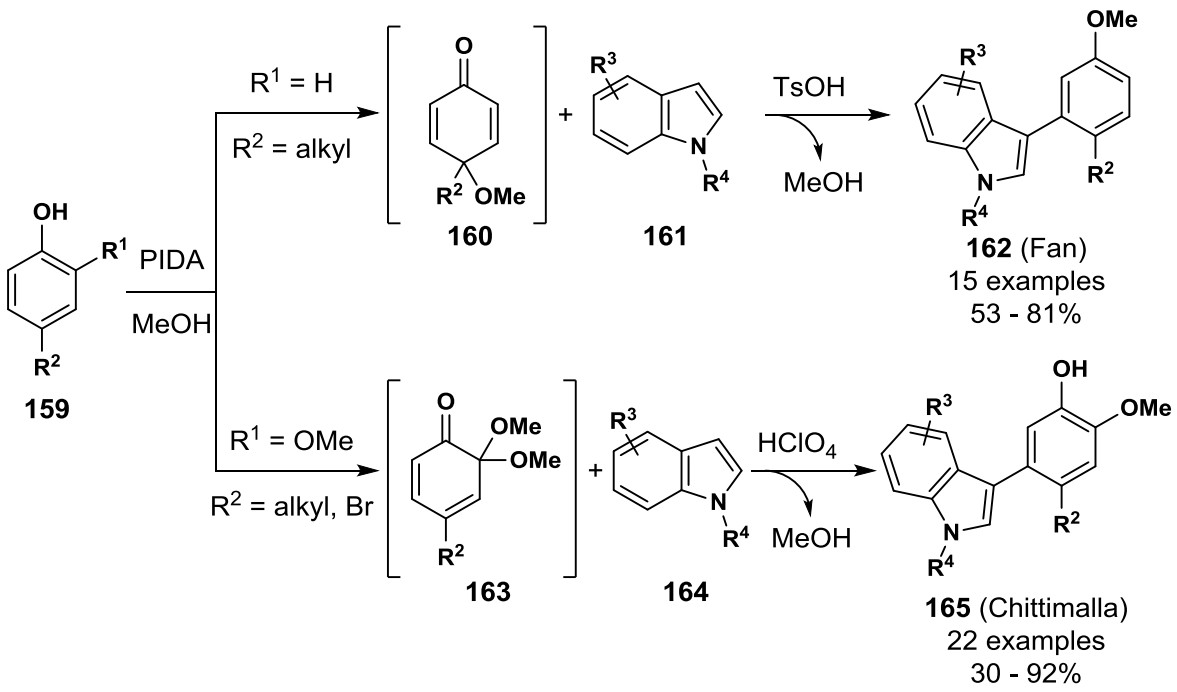
Equation 17. Synthesis of Sorbiterrin A *via* a Type 1 $^{m}S_{O}Ar$ Synthetic Strategy



5.4.2 Examples of Type 2 $^{m}S_{O}Ar$

Cationic activation of the quinone intermediate is a common pathway for promoting *meta* substitution. As with Type 1 $^{m}S_{O}Ar$, electron rich aromatics are common nucleophiles used. In particular, Fan and co-workers found that treatment phenol with PIDA followed by the addition of *p*-toluenesulfonic acid and the desired indole led directly to the $^{m}S_{O}Ar$ product **162** in good yield. Notably, under the acidic conditions, the phenol was converted to the methylphenyl ether.[33] Similarly, Chittimalla found that indoles could be added to phenols after *ortho* oxidation, providing the desired products in moderate to high yield. In both reactions, the addition of a Brønsted acid activates the quinone intermediates for 1,4 addition, and helps facilitate rearomatization (Figure 38).[34]

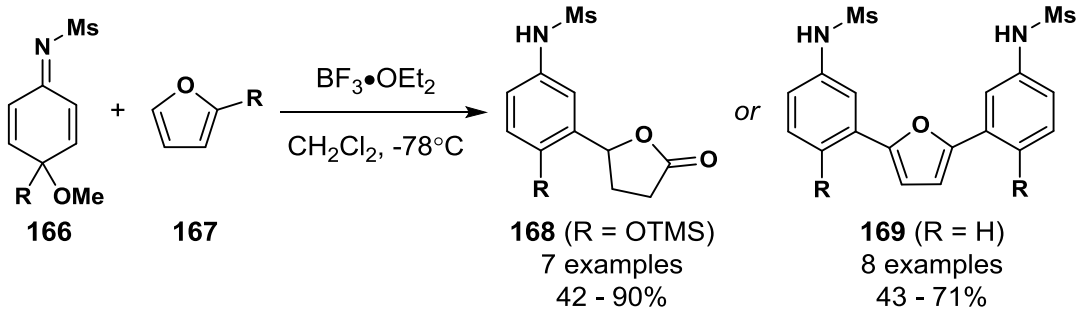
Figure 38. Addition of Indoles to Phenols *via* a Type 2 $^{m}S_{O}Ar$ Reaction



Alternatively, electron rich furans can undergo Michael addition to iminoquinone intermediate. Treatment of iminoquinone **166** with a Lewis acid promotes addition of furan

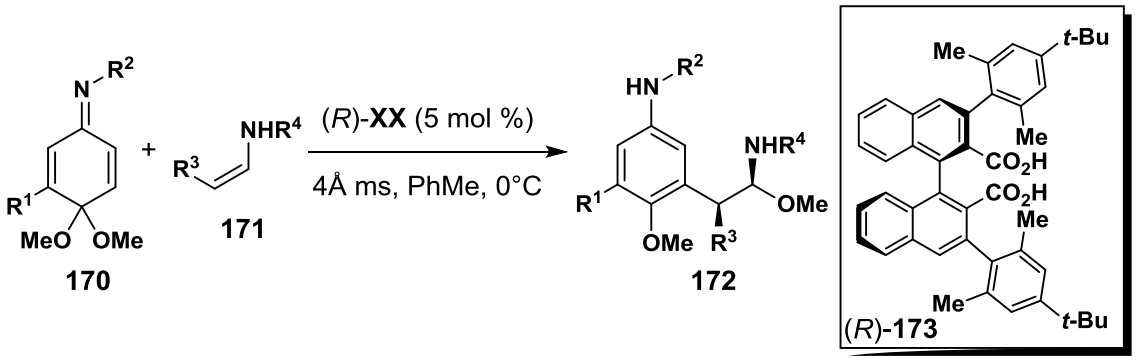
to the *meta* position. When the 2-OTMS furan is used, lactone product **168** is isolated, whereas the use of unsubstituted furan gives triaryl compound **169** (Equation 19).[35]

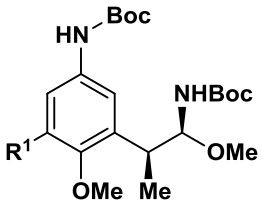
Equation 18. Addition of Furan to Iminoquinone Acetals *via* Type 2 $^{m}S_{O}Ar$



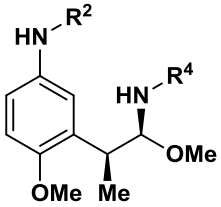
The Type 2 $^{m}S_{O}Ar$ synthetic strategy is not limited to the addition of electron rich aromatics; Maruoka and co-workers found that enamines were also viable nucleophiles for *meta* addition. Using a binaphthyl-derived Brønsted acid (R)-**173**, Maruoka found that the absolute stereochemistry of the homobenzylic aminal products could be set with high enantio– and diastereoselectivities. In particular, the reaction was tolerant of amine substitution on both the starting iminoquinone acetal and enamine, as well as *meta* substitution on the iminoquinone acetal (Table 30).[36]

Table 30. Addition of Enamines to Iminoquinone Acetals *via* Type 2 $^{m}S_{O}Ar$

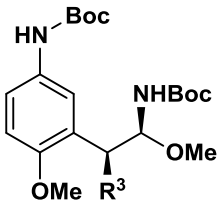




174 R^1 = H, 83%, 14:1 dr, 97% ee
175 R^1 = Me, 81%, >20:1 dr, 98% ee
176 R^1 = Cl, 81%, >20:1 dr, 97% ee
177 R^1 = Ph, 75%, 16:1 dr, 97% ee
178 R^1 = OMe, 74%, 12:1 dr, 95% ee
179 R^1 = vinyl, 81%, >20:1 dr, 99% ee



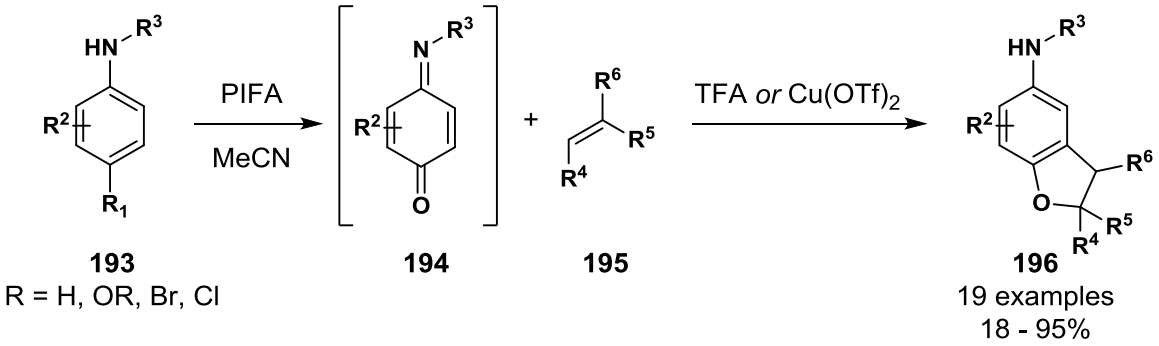
180 R^2 = Bz, R^4 = Boc, 81%, 3:1 dr, 96% ee
181 R^2 = Ac, R^4 = Boc, 74%, 12:1 dr, 78% ee
182 R^2 = Cbz, R^4 = Boc, 80%, 12:1 dr, 98% ee
183 R^2 = Boc, R^4 = Cbz, 53%, >20:1 dr, 82% ee
184 R^2 = Boc, R^4 =Bz, 78%, >20:1 dr, 78% ee



185 R^3 = Et, 86%, >20:1 dr, 96% ee
186 R^3 = *i*-Pr, 89%, 6.7:1 dr, 94% ee
187 R^3 = Bn, 83%, 12:1 dr, 95% ee
188 R^3 = allyl, 77%, >20:1 dr, 99% ee
189 R^3 = $(CH_2)_2OTBDPS$, 71%, 19:1 dr, 97% ee
190 R^3 = $(CH_2)_2CO_2Me$, 82%, 9.5:1 dr, 98% ee
191 R^3 = CH_2NHCbz, 71%, >20:1 dr, >99% ee
192 R^3 = OBn, 86%, 7.2:1 dr, 98% ee

Electron rich olefin can also participate in type 2 $^{m}S_{O}Ar$ reactions directly from the substituted aniline by proceeding through iminoquinone **194**. Addition of PIFA to aniline derivatives bearing a *para* proton, halogen of alkoxide facilitates the formation of the iminoquinone *in situ*. After oxidation, the addition of a Lewis or Brønsted acid along with an olefin produces dihydrobenzofuran **196** in low to excellent yield (Equation 20).[37]

Equation 19. Formation of Dihydrobenzofurans from Anilines *via* Type 2 $^{m}S_{O}Ar$



193 R = H, OR, Br, Cl

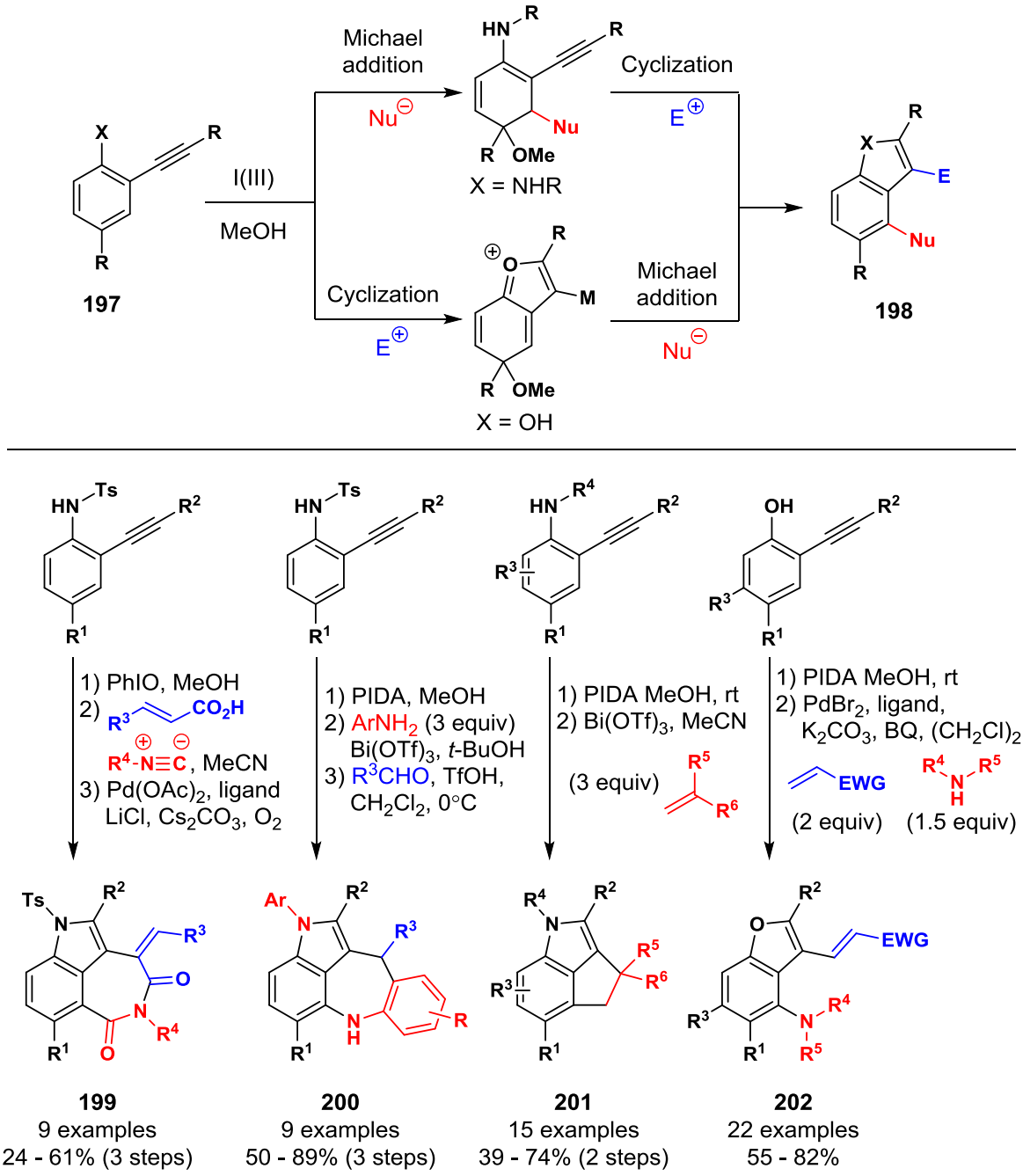
194

195

196 19 examples 18 - 95%

As an alternative to cationic activation by the addition of a Lewis or Brønsted acid, Fan has extensively explored the use of *ortho*-alkynyl phenols and anilines which readily cyclize to form cationic benzofuran or indole intermediates. Mechanistically, the anilines and phenols proceed through different pathways; After oxidation, anilines first undergo Michael addition followed by cyclization onto the alkyne, whereas phenols are activated for Michael addition by the cyclization onto the alkyne. In both cases, cyclization forms an organometallic intermediate which readily traps electrophiles. To date, this cascade approach to functionalized indoles and benzofurans has been utilized to form azepinoindoles from isocyanides and α,β-unsaturated acids (Figure 39, **199**)[38] and from substituted anilines and aldehydes (Figure 39, **200**),[39] to form the dihydrocyclopentadiene indole from reactions with substituted olefins (Figure 39, **201**),[40] and to form the difunctionalized benzofurans from anilines and α,β-unsaturated acids (Figure 39, **202**).[41] Notably, all the transformations can be conducted in one reaction vessel from the aniline or phenol, and without purification at intermediate steps through the sequential addition of reagents.

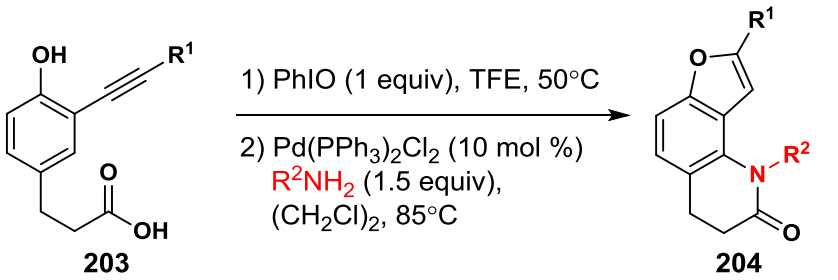
Figure 39. Cationic Activation of Phenols and Anilines Through Cyclization



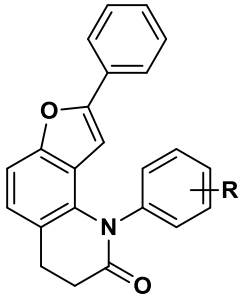
Fan and co-workers also observed that it is not necessary to use an exogenous electrophile to functionalize the C-3 position of the benzofuran or indole; proto-demetallation of the organometallic intetrmediate afford the C-3 unsubstituted product. For

example, after oxidation with PhIO in TFE, the addition of Pd(II) induces cyclization of the phenol onto the alkyne, and the cationic intermediate could be trapped with substituted anilines to afford the furoquinoline derivatives directly in good yield (Table 31).[42]

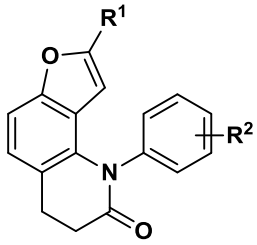
Table 31. Formation of Furoquinoline Derivatives Through a Type 2 $^{m}S_{O}Ar$ Reaction



203 **204**



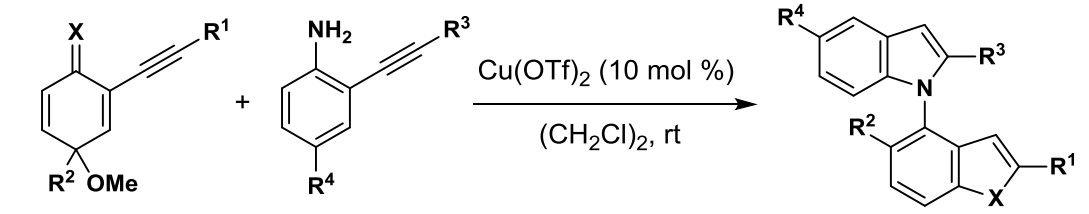
205 R = 4-CH_3, 62%
206 R = H, 63%
207 R = 4-OCH_3, 62%
208 R = 4-Br, 61%
209 R = 4-Cl, 67%
210 R = 4-F, 64%
211 R = 4-CF_3, 38%
212 R = 2,4,6-$(CH_3)_3$, 53%
213 R = 3,5-$(CH_3)_2$, 63%



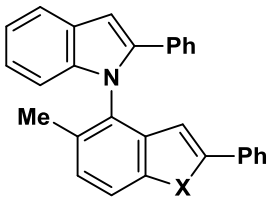
214 R^1 = 4-$CH_3C_6H_4$, R^2 = 4-CH_3, 62%
215 R^1 = 4-ClC_6H_4, R^2 = 4-CH_3, 36%
216 R^1 = *n*-Bu, R^2 = 4-CH_3, 82%
217 R^1 = *t*-Bu, R^2 = 4-CH_3, 91%
218 R^1 = *t*-Bu, R^2 = 4-OCH_3, 85%
219 R^1 = *t*-Bu, R^2 = 4-Cl, 90%
220 R^1 = cyclopropyl, R^2 = 4-CH_3, 63%

Fan also explored a double cyclization reaction to form the *N*-heteroarylated indole and benzofuran products. By treatment of the combination of *ortho*-alkynyl quinones and *ortho*-alkynyl anilines with $Cu(OTf)_2$, the *meta* addition-double cyclization product could be isolated in good yield. This methodology was used to access a wide variety of indole and benzofuran products and showcases the unique potential of $S_{O}Ar$ methodologies for use in cascade reactions (Table 32).[43]

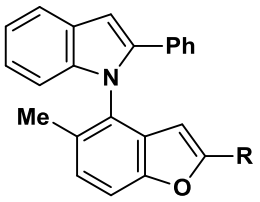
Table 32. Use of Type 3 $^{m}S_{O}Ar$ in a *Meta* Addition-Double Cyclization Cascade



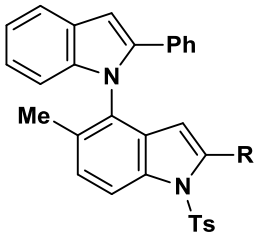
221 X = NR, O **222** **223** X = NR, O



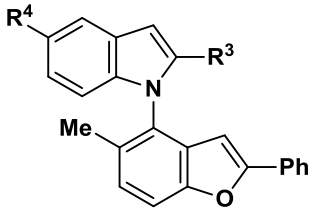
224 X = NTs, 95%
225 X = NNs, 72%
226 X = NMs, 88%
227 X = O, 92%



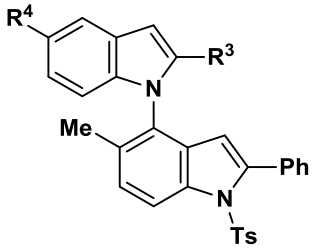
228 R = 4-$CH_3C_6H_4$, 95%
229 R = cyclopropyl, 95%
230 R = *n*-Bu, 95%
231 R = *t*-Bu, 95%



232 R = 4-ClC_6H_4, 90%
233 R = 4-$CH_3C_6H_4$, 63%
234 R = 4-$OCH_3C_6H_4$, 93%
235 R = cyclopropyl, 99%
236 R = *n*-Bu, 98%
237 R = *t*-Bu, 40%



238 R^3 = 4-$CH_3C_6H_4$, R^4 = H, 74%
239 R^3 = 4-ClC_6H_4, R^4 = H, 61%
240 R^3 = cyclopropyl, R^4 = H, 85%
241 R^3 = *n*-Bu, R^4 = H, 85%
242 R^3 = *t*-Bu, R^4 = H, 30%
243 R^3 = C_6H_5, R^4 = Me, 97%
244 R^3 = C_6H_5, R^4 = *i*-Pr, 86%
245 R^3 = C_6H_5, R^4 = F, 63%
246 R^3 = C_6H_5, R^4 = Cl, 93%



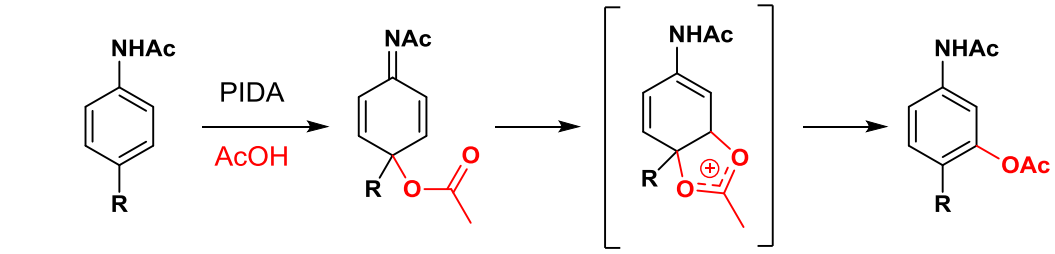
247 R^3 = 4-ClC_6H_4, R^4 = H, 90%
248 R^3 = cyclopropyl, R^4 = H, 90%
249 R^3 = H, R^4 = H, 31%
250 R^3 = C_6H_5, R^4 = Me, 95%
251 R^3 = C_6H_5, R^4 = *i*-Pr, 79%
252 R^3 = C_6H_5, R^4 = F, 72%

5.4.1 Examples of Type 3 $^{m}S_{O}Ar$

Type 3 $^{m}S_{O}Ar$ reactions are the least explored of the reaction types for *meta* functionalization. The migratory approach to *meta* addition was first explored by Barlin and Riggs in 1954. While the addition of PIDA in MeOH to *p*-substituted acetanilide yielded the

quinone product, conducting the reaction in AcOH yielded the *m*-acetoxy acetanilide.[44] This dichotomy in reactivity was studied further by Nair and co-workers, who determined that the acetate's ability to bridge to the *meta*-position (intermediate **255**) facilitated the isolation of the *m*-acetoxy acetanilide primarily.[45] While other functionalities could presumably participate in this reactivity platform, to date, the acetate and propionate are the only nucleophiles that have been utilized. This approach has also been utilized in the synthesis of rolipram from paracetamol by Schmidt and co-workers (not shown).[46]

Equation 20. *Meta*-Acetoxylation of *p*-Substituted Acetanilides by Type 3 $^{m}S_{O}Ar$

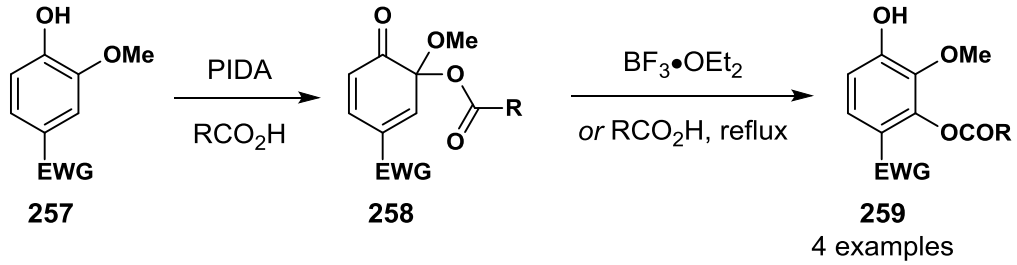


253 **254** **255** **256**

R = Me, OMe, OEt

Migration can also occur from *ortho*-quinone acetals by the same mechanism. Treatment of phenols bearing *ortho*-methoxy groups with PIDA in acetic or propionic acid yielded the *ortho*-quinone acetal, which could be converted to the *m*-substituted phenol by exposure to a Lewis or Brønsted acid. This particular synthetic strategy was used by Stevens and co-workers to derivatize tyrphostatin protein kinase inhibitors (Equation 22).[47]

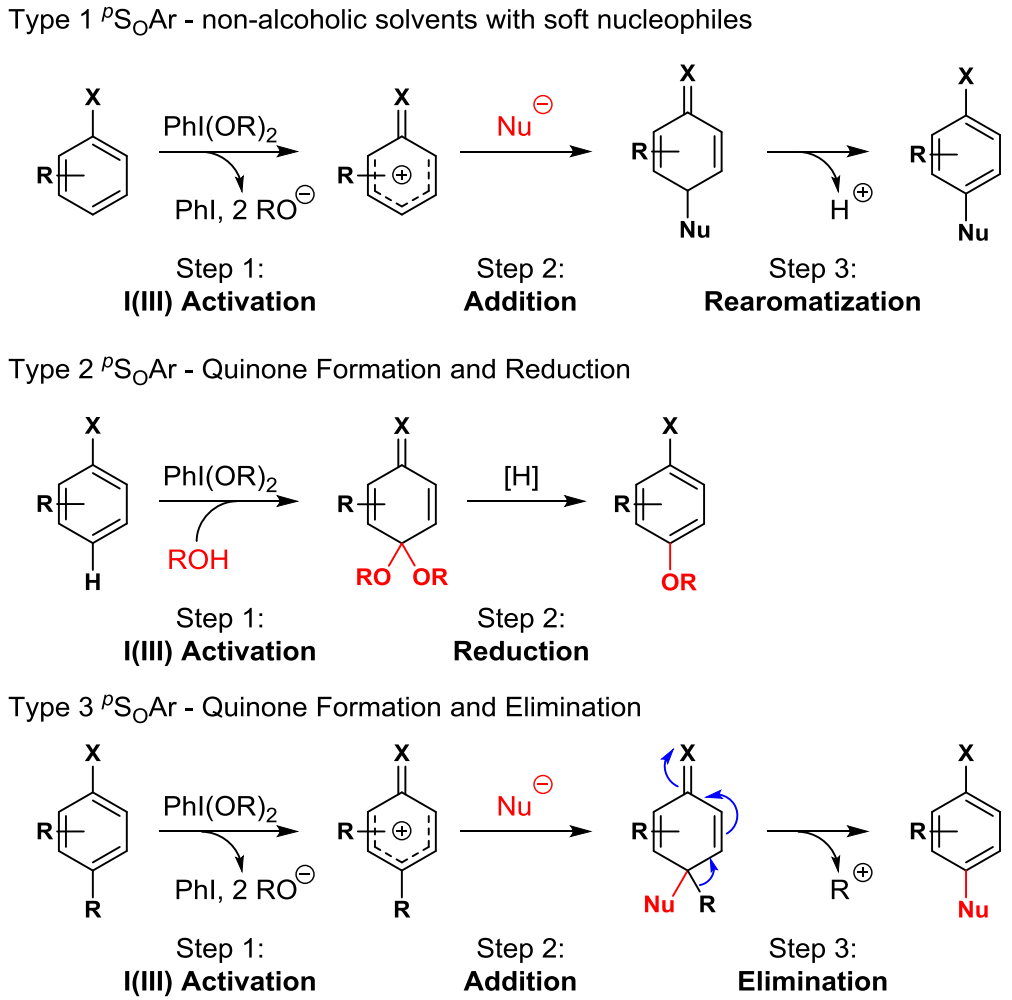
Equation 21. Synthesis of Tyrphostatin Protein Kinase Inhibitors by Type 3 $^{p}S_{O}Ar$



5.5 *para*–Selective Oxidative Aromatic Substitution

The addition of nucleophiles to the *para* position in oxidative aromatic substitution is the most commonly observed reaction type for *p*-unsubstituted anilines and phenols. As with all other oxidative aromatic substitution reactions, $^{p}S_{O}Ar$ reactions proceed through a variety of mechanisms. Type 1 $^{p}S_{O}Ar$ is mechanistically similar to Type 1 $^{o}S_{O}Ar$ in the nucleophilic addition occurs after activation by iodine(III). Although *ortho* addition (Type 1 $^{o}S_{O}Ar$) is a competing pathway, *para*-addition is the favored reaction in most cases. Care must be taken to ensure that over-oxidation to the quinone acetal does not occur. Type 2 $^{p}S_{O}Ar$ proceeds specifically through the quinone acetal and requires the addition of a reducing agent after oxidation. Finally, Type 3 $^{p}S_{O}Ar$ is an underexplored methodology that, to date, has only been utilized to form 4-fluorophenols through the elimination of a *tert*-butyl group. Examples of each reaction type are given in the following section.

Figure 40. Mechanistic Pathways for *para*–Selective Oxidative Aromatic Substitution

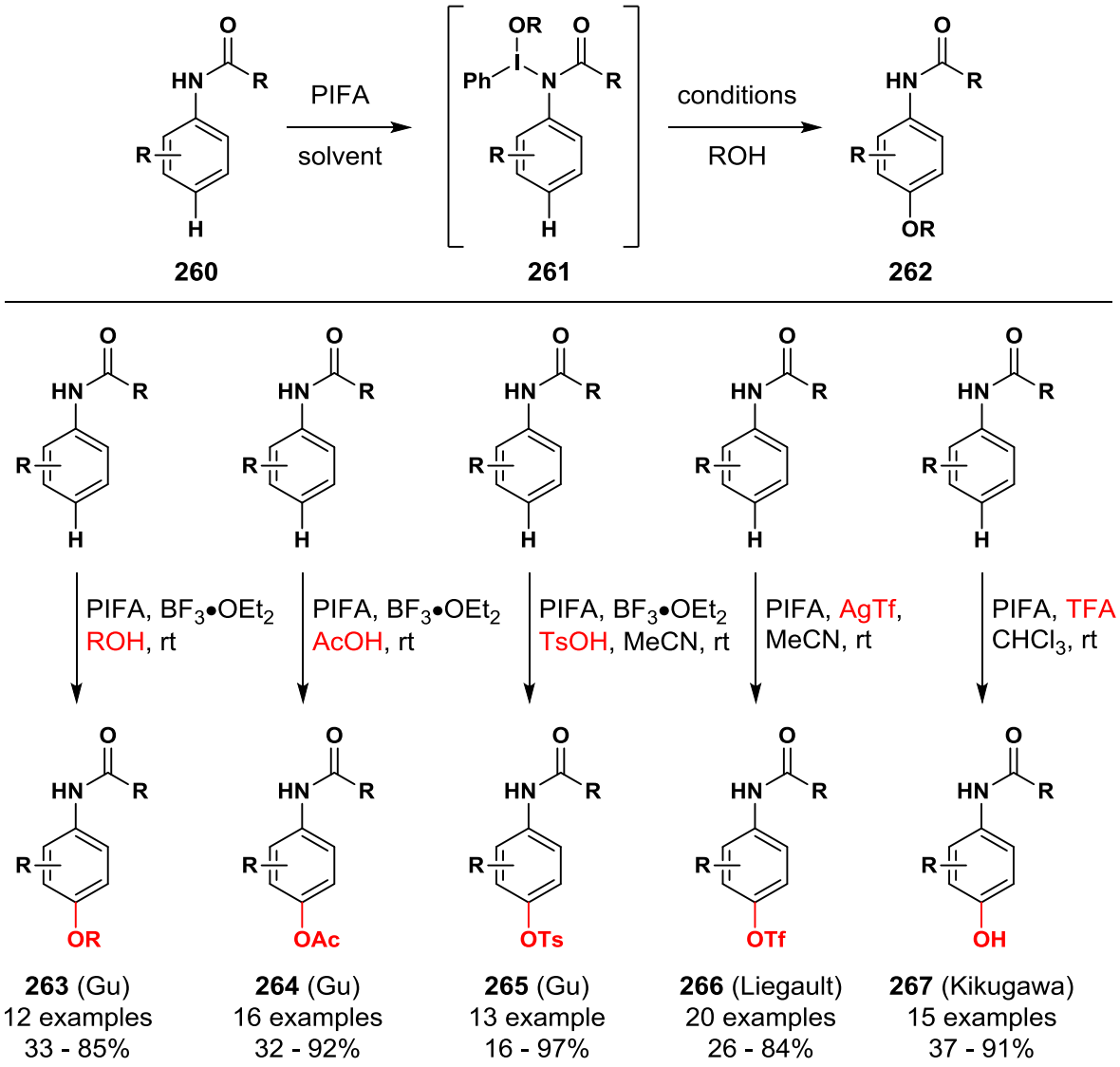


5.4.1 Examples of Type 1 $^{p}S_{O}Ar$

Alcohols and other oxygen-based nucleophiles are the most widely used reagents for Type 1 $^{p}S_{O}Ar$, although often a second oxidation occurs to form the quinone acetal. Despite this, a number of research groups have explored controlled additions to the *para* position using *N*-protected anilines. For example, Gu and co-workers investigated the addition of various alcohols, acetate and tosylate mediated by the addition of BF_3•OEt_2 (Figure 41, **263**–**265**).[48] Alternatively, Liegault developed the *para*-triflation of substituted anilines using

AgTf as the triflate-source,[49] and Kikugawa used the *in situ* hydrolysis of *p*-trifluoroacetate-substituted anilines to access the *p*-aminophenol products (Figure 41, **266**–**267**).[50]

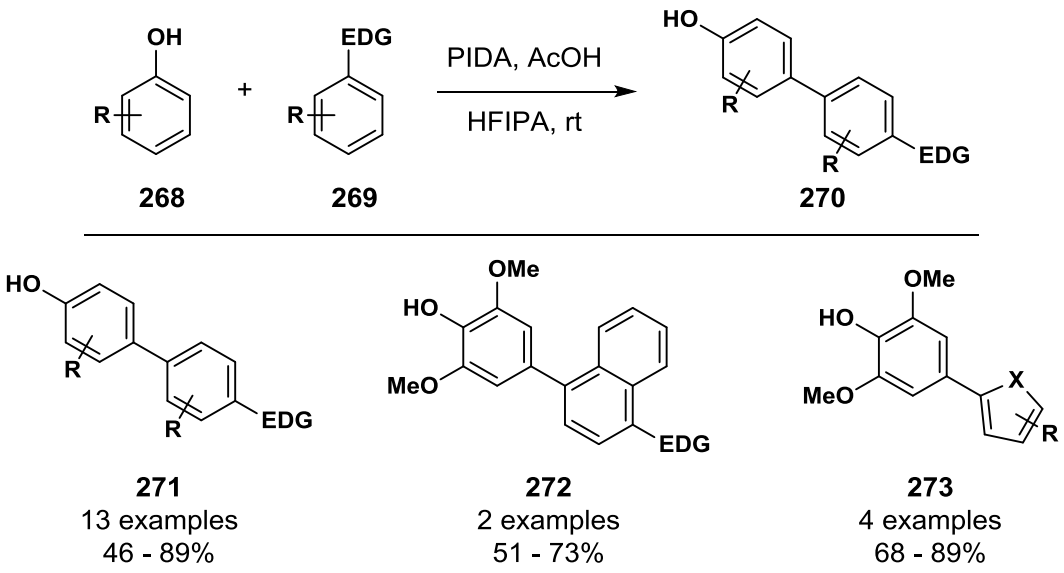
Figure 41. *Para*-Addition of Oxygen Nucleophiles *via* Type 1 $^{p}S_{O}Ar$



To date, only one example off a C-C bond forming reaction by a type 1 $^{p}S_{O}Ar$ mechanism has been explored. Specifically, Kita and co-workers extended their type 1 $^{o}S_{O}Ar$ method for the addition of electron rich aromatics. Specifically Kita found that electron rich benzenes (**271**), napthyls (**272**) and heteroaromatics (**273**) all formed the biaryl compounds

in moderate to high yield (Table 32). Additionally this approach can be combined in a sequential process with the previously developed Type 1 $^{o}S_{O}Ar$ to afford the poly-arylated product (not shown).[51]

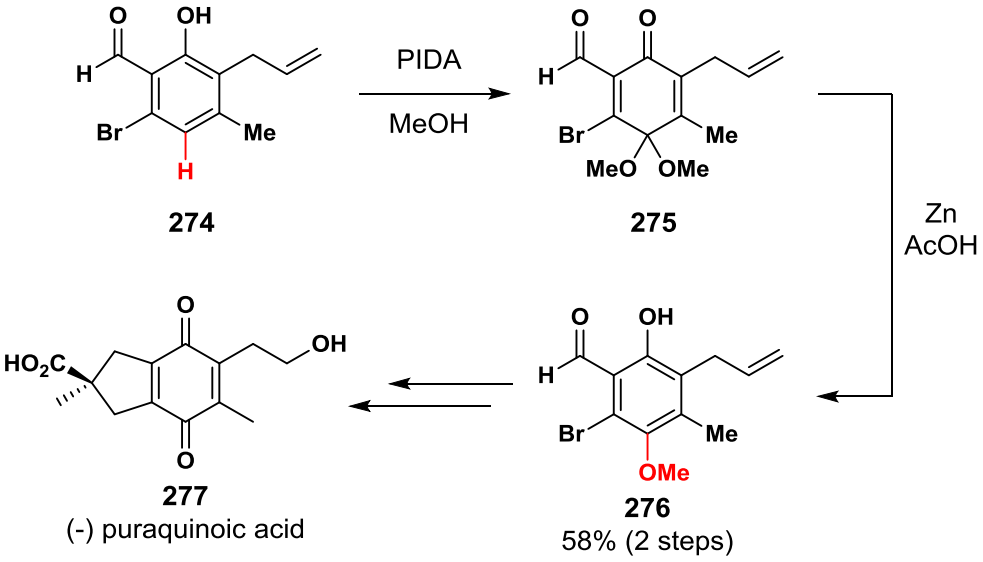
Table 33. Addition of Electron Rich Aromatics *via* a Type 1 $^{p}S_{O}Ar$



5.4.1 Examples of Type 2 $^{p}S_{O}Ar$

In contrast to Type 1 $^{p}S_{O}Ar$, the Type 2 synthetic strategy is vastly underexplored. To date, the only reported example is in the context of (–) puraquinoic acid by Clive and co-workers. Oxidation of phenol **274** using PIDA in MeOH afforded quinone acetal intermediate **275**, and reduction with Zn in acetic acid yielded the desired hydroquinone **276** in 58% over the two steps. This product was further elaborated into (–) puraquinoic acid **277**, highlighting the potential utility of Type 2 $^{p}S_{O}Ar$ in the synthesis of complex molecules.[52]

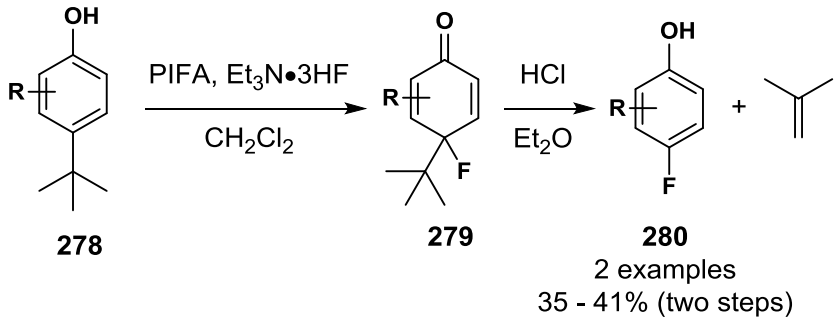
Equation 22. Synthesis of (–) Puraquinoic Acid *via* Type 2 $^{p}S_{O}Ar$



5.4.1 Examples of Type 3 $^{p}S_{O}Ar$

In its current state of development, Type 3 $^{p}S_{O}Ar$ is the most limited of the approaches to *para*-functionalizations. To date, fluorine is the only nucleophile that has been employed in Type 3 $^{p}S_{O}Ar$ reactions and the scope is currently limited to *p-tert*-butyl phenols (Equation 24).[53] However, despite the limited scope, this methodology has been used to incorporate ^{18}F into phenols for potential use in positron emission tomography (not shown).[54] If the scope of nucleophiles can be expanded, this synthetic strategy has the potential for more widespread use.

Equation 23. Addition of Fluoride to Phenols *via* Type 3 $^{p}S_{O}Ar$



5.6 Conclusions and Future Outlook

Iodine(III) –mediated oxidative aromatic substitution is a highly efficient synthetic strategy to functionalize phenol and aniline derivatives. By carefully tuning the reaction conditions, each position of the ring can selectively functionalized under mild reaction conditions. Despite sizeable contributions from a number of research groups, there is still substantial room to make significant advancements in this underdeveloped field.

5.7 References

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6. Supporting Information

6.1 Chapter 2 Supporting Information

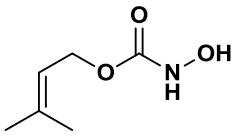
6.1.1 Supporting Information for the Nitrosocarbonyl Ene Reaction

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ˚C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). ^{1}H NMR spectra were recorded on Varian Spectrometers (at 400, 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Jasco FT/IR 4100 and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra and X-Ray analyses were obtained from the UC Santa Barbara Mass Spectrometry and X-Ray Facilities. Enantiomers were separated using a Shimadzu HPLC fitted with a Chiralpak IB column (4.6mm x 250mm). All HPLC analyses used to determine enantiopurity were calibrated with samples of the racemate. Optical rotation was recorded on a Rudolph Research Analytical Autopol III.

Hydroxycarbamates **1**, **S-1**, **S-2**, **S-3**, and **S-4**, were prepared according to literature precedent.[1] Hydroxycarbamate **16**, **S-5**, **S-6**, **S-7** and all olefins were used as received. Imide **S-17** and sultam **39** were prepared according literature precedent.[2] The crystal structure data for isoxazolidinone **(*S*)-29** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 824260

Starting Materials

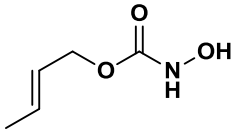
(1) 3-Methylbut-2-en-1-yl hydroxycarbamate



1

Spectral data matched literature precedent. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (bs, 2H), 5.33 – 5.26 (m, 1H), 4.59 (d, *J* = 7.3 Hz, 2H), 1.71 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 159.8, 140.2, 118.3, 63.2, 25.9, 18.2 ppm.

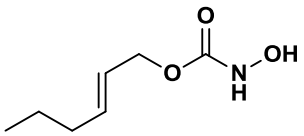
(S-1) (*E*)-But-2-en-1-yl hydroxycarbamate



S-1

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (bs, 1H), 6.47 (bs, 1H), 5.87 – 5.78 (m, 1H), 5.60 (dt, *J* = 13.6, 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 2H), 1.73 (d, *J* = 6.5, 3H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 159.3, 132.6, 124.9, 67.2, 18.0 ppm; IR (thin film) 3399, 1715, 1455, 1271, 1115 cm^{-1}, HRMS (ESI) *m/z* 154.0511 (154.0475 calcd for $C_5H_9NNaO_3^+$ $[MNa]^+$).

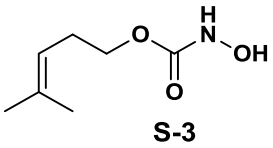
(S-2) *E*)-Hex-2-en-1-yl hydroxycarbamate



S-2

Spectral data matched literature precedent. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 7.53 (s, 1H), 5.77 (dt, *J* = 14.7, 6.7 Hz, 1H), 5.54 (dt, *J* = 14.1, 6.6 Hz, 1H), 4.56 (d, *J* = 6.5 Hz, 2H), 2.01 (q, *J* = 7.2 Hz, 2H), 1.43 – 1.34 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 137.3, 123.7, 67.2, 34.4, 22.2, 13.8 ppm.

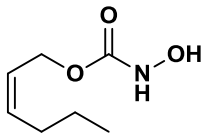
(S-3) 4-Methylpent-3-en-1-yl hydroxycarbamate



S-3

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (bs, 1H), 7.49 (s, 1H), 5.07 (t, *J* = 7.1 Hz, 1H), 4.09 (t, *J* = 7.1 Hz, 2H), 2.32 (q, *J* = 7.1 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 135.2, 119.0, 66.1, 28.0, 25.9, 17.9 ppm. IR (thin film) 3272, 2963, 1697, 1434, 1251, 1102 cm^{-1}; MS (ESI) *m/z* 182.08 (182.08 calcd for $C_7H_{13}NNaO_3^+$ $[MNa]^+$).

(S-4) (*Z*)-Hex-2-en-1-yl hydroxycarbamate

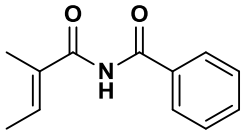


S-4

Spectral data matched literature precedent. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (bs, 2H), 5.69 – 5.61 (m, 1H), 5.56 – 5.49 (m, 1H), 4.69 (d, *J* = 6.9 Hz, 2H), 2.07 (q, *J* = 7.3 Hz, 2H),

1.43 – 1.34 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 136.0, 123.2, 62.2, 29.7, 22.7, 13.8 ppm.

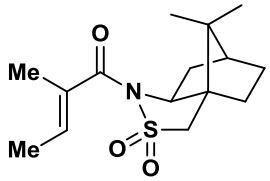
(S-17) (*E*)-*N*-(2-Methylbut-2-enoyl)benzamide



S-17

Spectral data matched literature precedent.[3] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (bs, 1H), 7.79 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 6.57 (q, J = 6.5 Hz, 1H), 1.91 (s, 3H), 1.84 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 166.7, 134.9, 133.8, 133.0, 132.9, 128.9, 128.0, 14.4, 12.6 ppm.

(39) (*E*)-1-((6S,7aS)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6 methanobenzo[c]isothiazol-1- yl)-2-methylbut-2-en-1-one



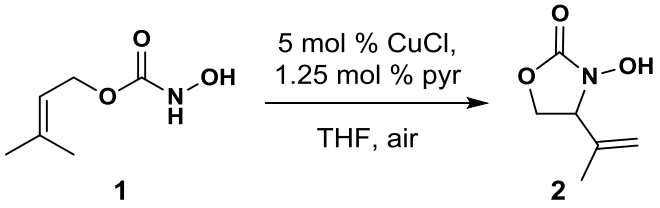
39

Spectral data matched literature precedent. **[**α]$_D^{25}$ 7.50° (c 1.00, $CHCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.37 (dddd, J = 6.9, 6.9, 6.9, 1.3 Hz, 1H), 4.04 (dd, J = 7.7, 4.6 Hz, 1H), 3.48 (d, J = 13.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 2.02 (dd, J = 13.6, 7.8 Hz, 1H), 1.98 – 1.84 (m, 7H), 1.82 (d, J = 6.9, 3H), 1.45 – 1.33 (m, 2H), 1.23 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 137.7, 131.7, 65.6, 53.8, 48.1, 47.9, 45.5, 38.5, 33.5, 26.8, 21.5, 20.1, 14.3, 12.9 ppm.

Substrate Scope for Nitrosocarbonyl Ene Reaction

General Procedure for the Ene Reaction: To a stirred solution of benzyl hydroxycarbamate **16** and olefin **17** in THF was added 5 mol % CuCl and 1.25 mol % pyridine. The reaction was stirred at 23 ˚C open to the air until complete by TLC. Upon completion, the reaction was quenched with EDTA (0.5 M, pH 7.0), diluted with ethyl acetate and stirred until color no longer persisted in organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **18**.

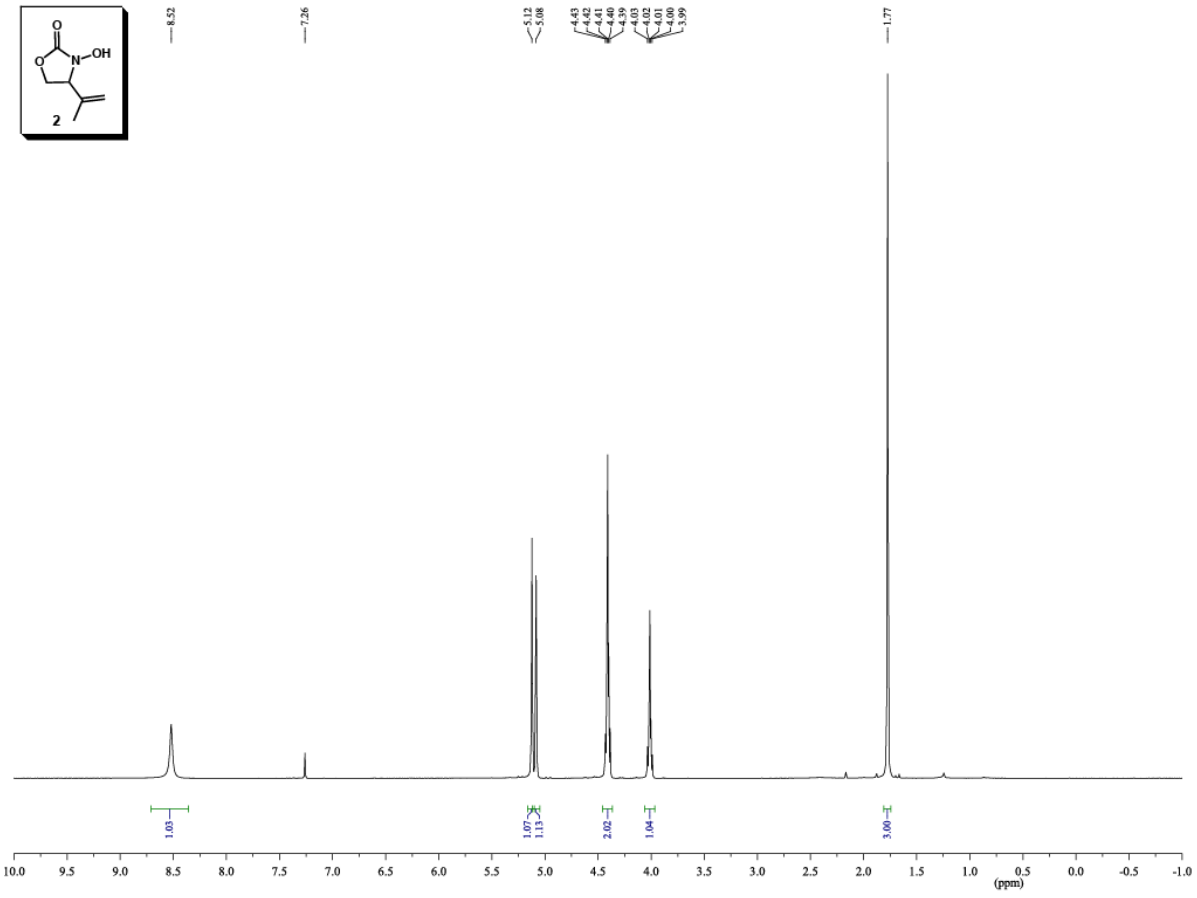
(2) 3-Hydroxy-4-(prop-1-en-2-yl)oxazolidin-2-one

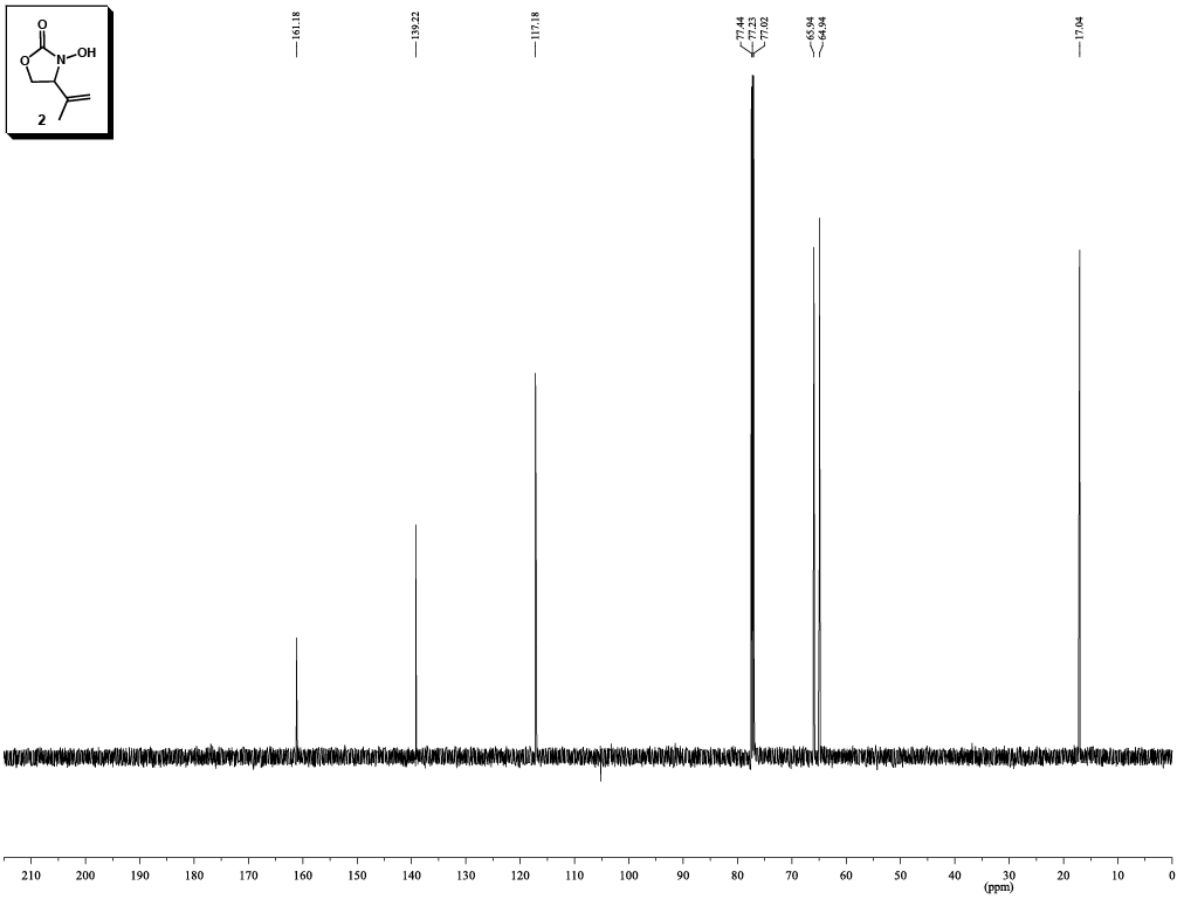


1 **2**

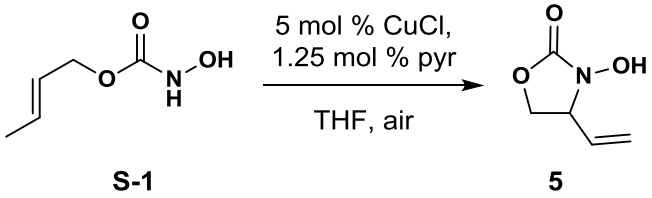
According to the general procedure, CuCl (3.4 mg, 0.034 mmol, 0.05 equiv) and pyridine (0.67 μL, 0.0086 mmol, 0.0125 equiv) were added to 3-methylbut-2-en-1-yl hydroxycarbamate **1** (100 mg, 0.69 mmol, 1.0 equiv) in 20 mL THF. The resulting mixture was stirred for 6 h at 23 ˚C. The reaction was quenched with 20 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazolidinone **2** (92 mg, 93%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (bs, 1H), 5.12 (s, 1H), 5.08 (s, 1H), 4.46 – 4.37 (m, 2H), 4.06 – 3.97 (m, 1H), 1.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 139.2, 117.2, 65.9, 64.9,

17.0 ppm; IR (thin film) 3270, 2976, 1762, 1475, 1213, 1092 cm^{-1}; MS (ESI) *m/z* 166.06 (166.05 calcd for $C_6H_9NNaO_3^+$ $[MNa]^+$).





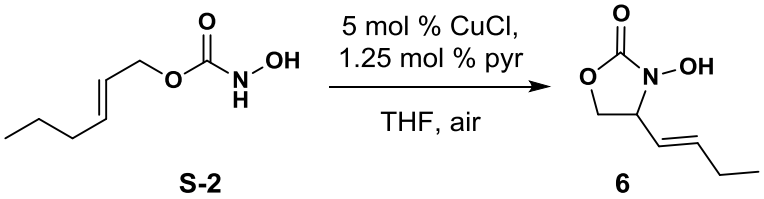
(5) 3-Hydroxy-4-vinyloxazolidin-2-one



According to the general procedure, CuCl (3.8 mg, 0.038 mmol, 0.05 equiv) and pyridine (0.74 μL, 0.0095 mmol, 0.0125 equiv) were added to (*E*)-but-2-en-1-yl hydroxycarbamate **S-1** (100mg, 0.763 mmol, 1.0 equiv) in 22 mL THF. The resulting mixture was stirred for 14 h at 23 ˚C. The reaction was quenched with 22 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 22 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford

oxazolidinone **5** (70 mg, 71%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (bs, 1H), 5.75 (ddd, *J* = 17.6, 10.1, 7.8 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.34 (d, *J* = 10.2 Hz, 1H), 4.37 (t, *J* = 8.3 Hz, 1H), 4.30 (dd, *J* = 16.5, 8.2 Hz, 1H), 3.92 (t, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 160.8, 132.5, 122.2, 66.6, 62.8 ppm; IR (thin film) 3270, 2913, 1764, 1428, 1216, 1092 cm^{-1}; HRMS (ESI) *m/z* 152.0316 (152.0318 calcd for $C_5H_7NNaO_3^+$ $[MNa]^+$).

(6) -Hydroxy-4-(but-1-en-1-yl)oxazolidin-2-one

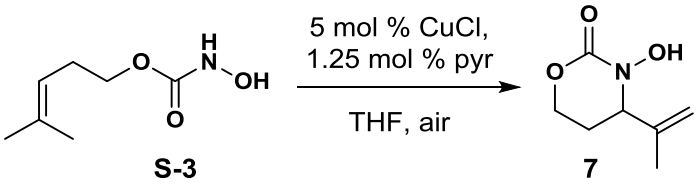


S-2 **6**

According to the general procedure, CuCl (1.5 mg, 0.016 mmol, 0.05 equiv) and pyridine (0.31 μL, 0.0039 mmol, 0.0125 equiv) were added to (*E*)-hex-2-en-1-yl hydroxycarbamate **S-2** (50 mg, 0.31 mmol, 1.0 equiv) in 10 mL THF. The resulting mixture was stirred for 8 h at 23 ˚C. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazolidinone **6** (48 mg, 96%) as an inseparable 3:1 *E*:*Z* mixture as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (bs, 1H), 5.93 (dt, *J* = 15.3, 6.3 Hz, 1H), δ 5.83 (dt, *J* = 10.7, 7.6 Hz, 1H), 5.42 – 5.32 (m, 1H), 4.72 (q, *J* = 8.6 Hz, 1H), 4.38 (t, *J* = 8.3 Hz, 4H), 4.30 (q, *J* = 8.4 Hz, 3H), 3.95 (t, *J* = 8.9 Hz, 1H), 3.92 (t, *J* = 9.2 Hz, 1H), 2.23 – 2.03 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.9, 160.8, 141.1, 140.7, 123.3, 123.2, 67.0, 66.8, 62.7, 57.1, 25.5, 21.3, 14.4, 13.2 ppm;

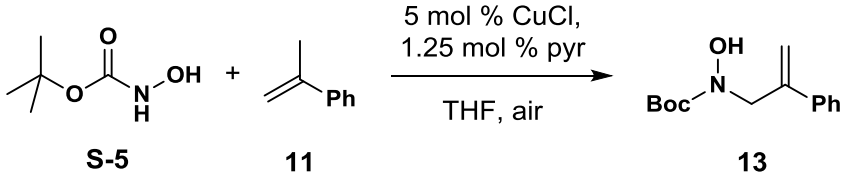
IR (thin film) 3290, 2965, 1767, 1462, 1211, 1086 cm^{-1}; MS (ESI) *m/z* 180.07 (180.06 calcd for $C_7H_{11}NNaO_3^+$ $[MNa]^+$).

(7) 3-Hydroxy-4-(prop-1-en-2-yl)-1,3-oxazinan-2-one

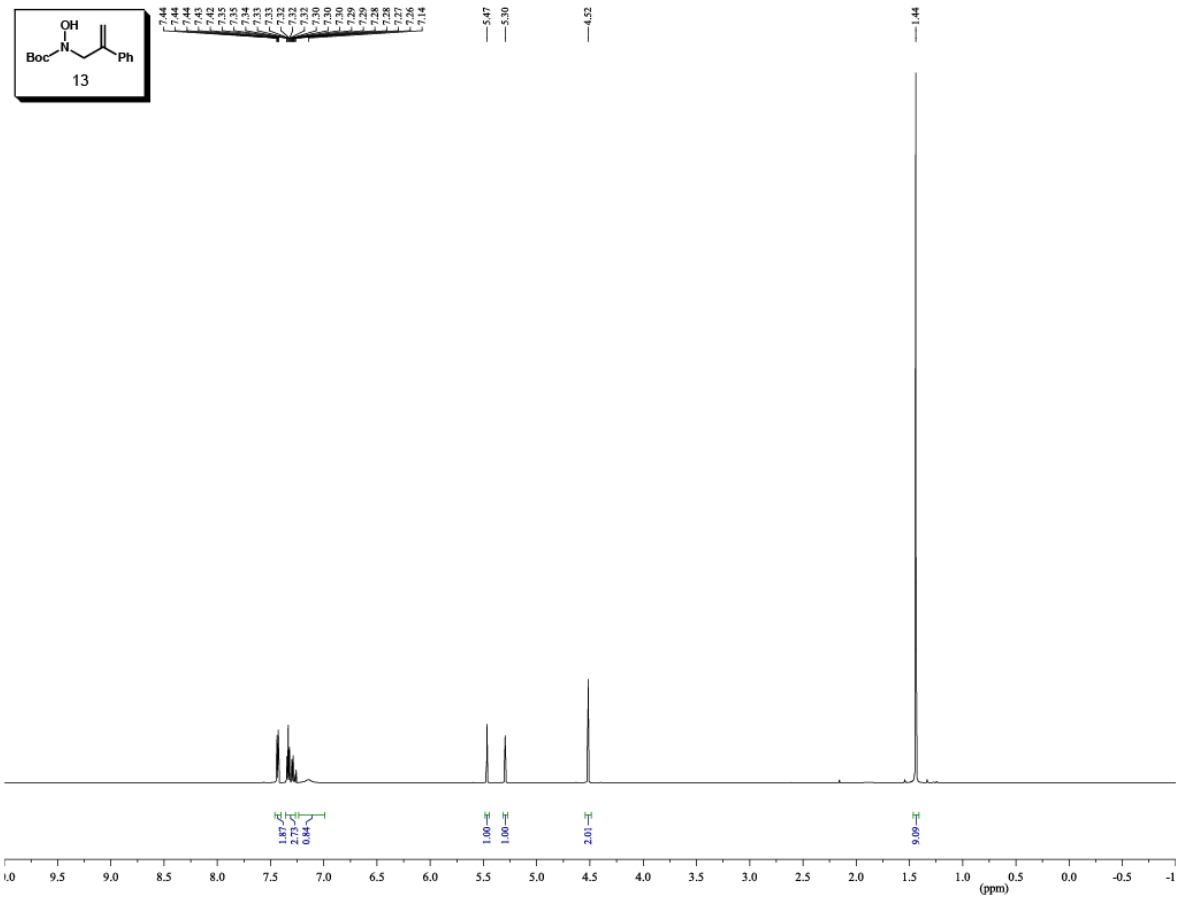


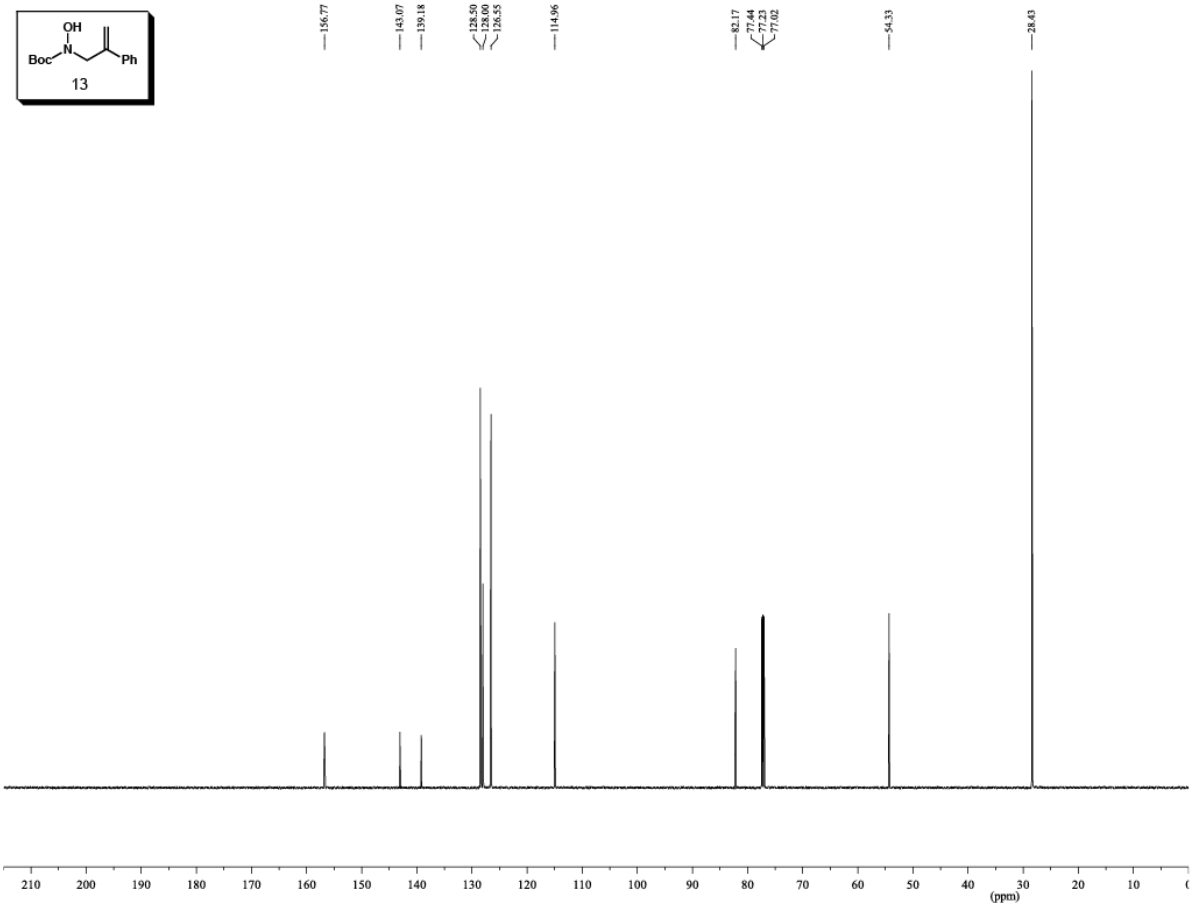
According to the general procedure, CuCl (1.5 mg, 0.016 mmol, 0.05 equiv) and pyridine (0.31 μL, 0.0039 mmol, 0.0125 equiv) were added to 4-methylpent-3-en-1-yl hydroxycarbamate **S-3** (50 mg, 0.314 mmol, 1.0 equiv) in 10 mL THF. The resulting mixture was stirred for 13 h at 23 °C. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazinone **7** (43 mg, 88%) as a colorless solid. ^1H NMR (600 MHz, $CDCl_3$) δ 8.95 (bs, 1H), 5.07 (s, 1H), 5.06 (s, 1H), 4.27 – 4.13 (m, 3H), 2.21 (dddd, *J* = 14.2, 9.2, 6.7, 3.9 Hz, 1H), 2.02 – 1.96 (m, 1H), 1.75 (s, 3H) ppm; 13C NMR (150 MHz, $CDCl_3$) δ 155.6, 141.3, 114.2, 63.9, 63.8, 27.1, 18.5 ppm; IR (thin film) 3422, 2918, 1690, 1435, 1284, 1125 cm^{-1}; HRMS (ESI) *m/z* 180.0586 (180.0631 calcd for $C_7H_{11}NNaO_3^+$ $[MNa]^+$).

(13) *tert*-butyl hydroxy(2-phenylallyl)carbamate

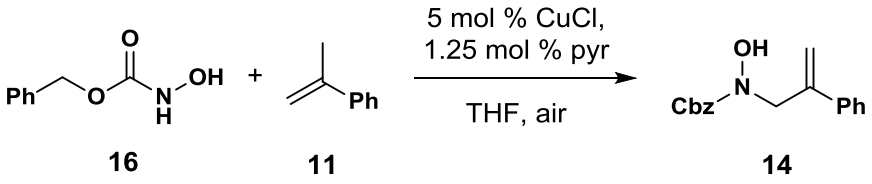


According to the general procedure CuCl (1.9 mg, 0.019 mmol, 0.05 equiv) and pyridine (0.38 μL, 0.0048 mmol, 0.0125 equiv) were added to *tert*-butyl hydroxycarbamate **S-5** (50 mg, 0.38 mmol, 1.0 equiv) and α-methylstyrene **11** (49 mg, 0.42 mmol, 1.1 equiv) in 5 mL THF. The resulting reaction mixture was stirred for 14 h at 23 ˚C. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **13** (55 mg, 57%) as a colorless solid. Spectral data matched literature precedent. ^{1}H NMR (600 MHz, $CDCl^3$) δ 7.46 – 7.41 (m, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.14 (bs, 1H), 5.47 (s, 1H), 5.30 (s, 1H), 4.52 (s, 2H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.8, 143.1, 139.2, 128.5, 128.0, 126.6, 115.0, 82.2, 54.3, 28.4 ppm.





(14) Benzyl hydroxy(2-phenylallyl)carbamate

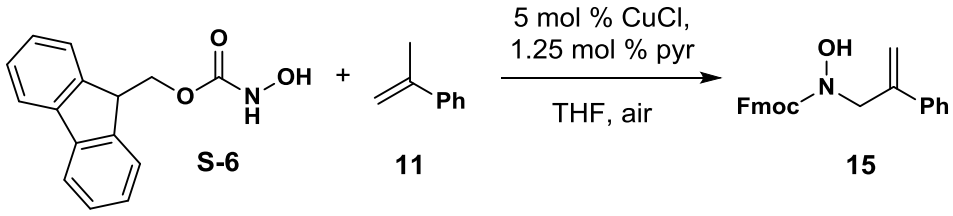


16 **11** **14**

According to the general procedure, CuCl (4.4 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (150 mg, 0.90 mmol, 1.0 equiv) and α-methylstyrene **11** (127 mg, 1.1 mmol, 1.1 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 16 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue

was purified by column chromatography to afford hydroxycarbamate **14** (204 mg, 80%) as a colorless solid. ^{1}H NMR (600 MHz, CDCl3) δ 7.34 – 7.15 (m, 10H), 6.98 (bs, 1H), 5.39 (s, 1H), 5.18 (s, 1H), 5.02 (s, 2H), 4.48 (s, 2H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 157.4, 142.5, 138.8, 136.0, 128.7, 128.6, 128.5, 128.3, 128.1, 126.5, 115.4, 68.3, 54.5 ppm; IR (thin film) 3271, 2930, 1700, 1454, 1234, 1099 cm^{-1}; HRMS (ESI) *m/z* 306.1392 (306.1108 calcd for $C_{17}H_{17}NNaO_3^+$ $[MNa]^+$).

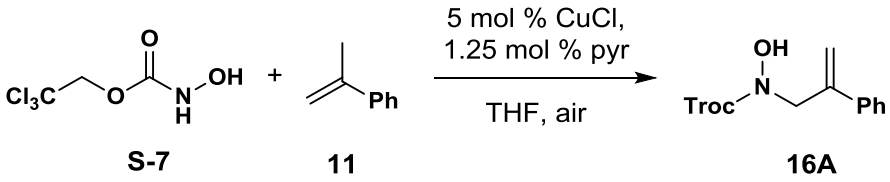
(15) (9H-Fluoren-9-yl)methyl hydroxy(2-phenylallyl)carbamate



According to the general procedure, CuCl (1.0 mg, 0.011 mmol, 0.05 equiv) and pyridine (0.21 μL, 0.0028 mmol, 0.0125 equiv) were added to (9H-fluoren-9-yl)methyl hydroxycarbamate **S-6** (55 mg, 0.21 mmol, 1.0 equiv) and α-methylstyrene **11** (28 mg, 0.23 mmol, 1.1 equiv) in 2 mL THF. The resulting reaction mixture was stirred for 7 h at 23 °C. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **15** (62 mg, 78%) as a yellow solid. 1H NMR (600 MHz, CDCl3) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.36 (m, 4H), 7.33 – 7.26 (m, 5H), 5.48 (s, 1H), 5.26 (s, 1H), 4.53 (s, 2H), 4.43 (d, *J* = 6.9 Hz, 2H), 4.21 (t, *J* = 6.8Hz, 1H) ppm; 13C NMR (150 MHz, CDCl3) δ 157.5, 143.7, 142.4, 141.5, 138.7, 128.6, 128.1, 127.9, 127.3, 126.4, 125.2, 120.2, 115.1, 68.4, 54.5, 47.2 ppm; IR (thin film) 3270, 3060, 2953, 1701,

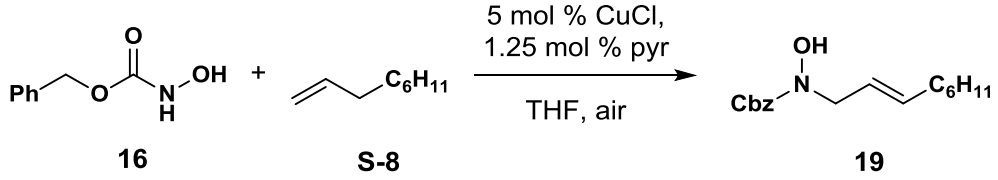
1449, 1248, 1117 cm-1; HRMS (ESI) *m/z* 394.1417 (394.1421 calcd for C24H21NNaO3+ [MNa]+).

(16A) 2,2,2-Trichloroethyl hydroxy(2-phenylallyl)carbamate



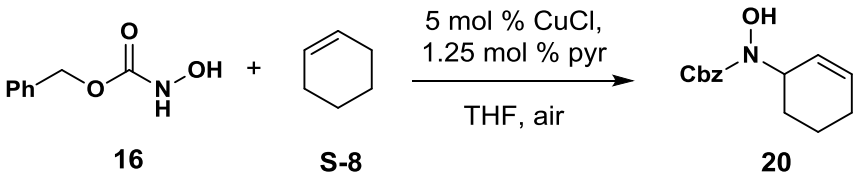
According to the general procedure, CuCl (1.2 mg, 0.012 mmol, 0.05 equiv) and pyridine (0.24 μL, 0.0030 mmol, 0.0125 equiv) were added to 2,2,2-trichloroethyl hydroxycarbamate **S-7** (50 mg, 0.24 mmol, 1.0 equiv) and α-methylstyrene **11** (31 mg, 0.26 mmol, 1.1 equiv) in 2 mL THF. The resulting reaction mixture was stirred for 11 h at 23 ˚C. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **16A** (63 mg, 81%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 2H), 7.35 – 7.29 (m, 3H), 5.53 (s, 1H), 5.33 (s, 1H), 4.70 (s, 2H), 4.65 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 142.1, 138.4, 128.7, 128.3, 126.6, 116.2, 95.2, 75.6, 54.7 ppm; IR (thin film) 3255, 2954, 1720, 1444, 1230, 1125 cm^{-1}; HRMS (ESI) *m/z* 346.0074 (345.9783 calcd for $C_{12}H_{12}Cl_3NNaO_3^+$ $[MNa]^+$).

(19) Benzyl hydroxy(oct-2-en-1-yl)carbamate



According to the general procedure, CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (151 mg, 0.90 mmol, 1.0 equiv) and 1-octene **S-8** (121 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 32 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **19** (106 mg, 42%) as an inseparable 3:1 *E*:*Z* mixture as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 6.98 (bs, 1H), 5.67 (dt, *J* = 15.0, 6.7 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.51 – 5.45 (m, 1H), 5.18 (s, 2H), 4.20 (d, *J* = 5.0 Hz, 1H), 4.18 (d, *J* = 6.9 Hz, 2H), 4.07 (d, *J* = 6.3 Hz, 2H), 2.06 (q, *J* = 7.1 Hz, 2H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.38 – 1.22 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.7, 157.6, 136.1, 136.0, 128.7, 128.7, 128.5, 128.5, 128.3, 128.3, 123.2, 123.0, 68.3, 68.2, 52.9, 47.7, 32.4, 31.6, 31.6, 29.3, 28.9, 27.5, 22.7, 14.2 ppm; IR (thin film) 3270, 2926, 1702, 1455, 1354, 1237, 1097 cm^{-1}; HRMS (ESI) *m/z* 300.1522 (300.1578 calcd for $C_{16}H_{23}NNaO_3^+$ $[MNa]^+$).

(20) Benzyl cyclohex-2-en-1-yl(hydroxy)carbamate

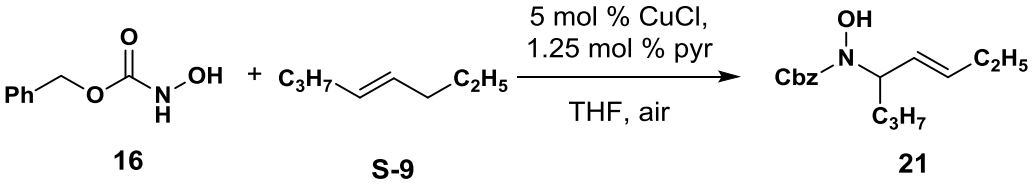


16 **S-8** **20**

According to the general procedure, CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (150 mg, 0.9 mmol, 1.0 equiv) and cyclohexene **S-8** (89 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 34 h at 23 ˚C. The reaction was quenched with 18

mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **20** (156 mg, 71%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 6.48 (bs, 1H), 5.96 – 5.90 (m, 1H), 5.56 (dd, J = 10.2, 1.4 Hz, 1H), 5.20 (s, 2H), 4.70 – 4.64 (m, 1H), 2.09 – 2.02 (m, 1H), 2.00 – 1.80 (m, 4H), 1.66 – 1.56 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.5, 136.2, 132.2, 128.8, 128.5, 128.3, 126.6, 68.2, 55.8, 25.9, 24.6, 21.3 ppm; IR (thin film) 3177, 2929, 1685, 1414, 1294, 1102 cm^{-1}; MS (ESI) *m/z* 270.14 (270.11 calcd for $C_{14}H_{17}NNaO_3^+$ $[MNa]^+$).

(21) (*E*)-Benzyl hydroxy(oct-5-en-4-yl)carbamate

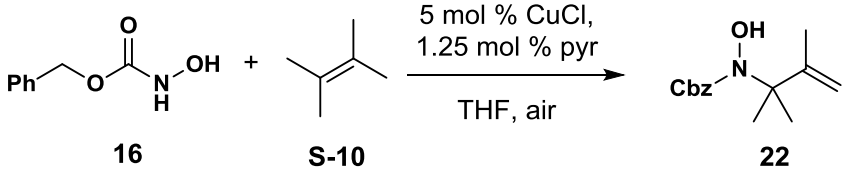


16 **S-9** **21**

According to the general procedure, CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (150 mg, 0.90 mmol, 1.0 equiv) and (*E*)-4-octene **S-9** (121 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 45 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **21** (181 mg, 73%) as an inseparable 3:1 *E*:*Z* mixture as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 7.15 (bs, 1H), 5.65 (dt, J = 15.5 Hz, 1H), 5.54 – 5.45 (m, 1H), 5.20 (d, J = 12.3 Hz, 1H), 5.16 (d, J = 12.4 Hz, 1H), 4.79 (apt. q, J = 8.4 Hz, 1H), 4.45 (apt. q, J = 7.2 Hz, 1H), 2.06 –

1.99 (m, 2H), 1.80 – 1.75 (m, 1H), 1.54 – 1.48 (m, 1H), 1.47 – 1.43 (m, 1H), 1.31 – 1.18 (m, 3H), 0.90 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 157.5, 136.3, 136.2, 135.1, 134.4, 128.7, 128.4, 128.4, 128.2, 128.2, 126.6, 126.5, 68.0, 68.0, 61.0, 55.9, 34.5, 33.9, 25.5, 21.3, 19.5, 19.4, 14.3, 14.0, 14.0, 13.6 ppm; IR (thin film) 3255, 2961, 1698, 1456, 1320, 1094 cm^{-1}; HRMS (ESI) *m/z* 300.1592 (300.1578 calcd for $C_{16}H_{23}NNaO_3^+$ $[MNa]^+$).

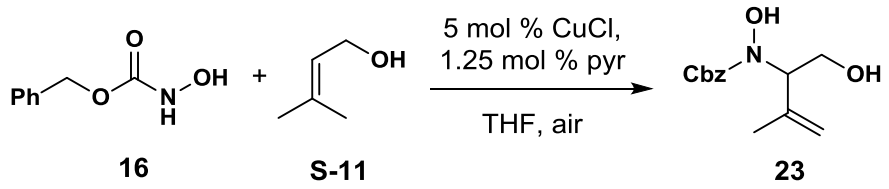
(22) Benzyl (2,3-dimethylbut-3-en-2-yl)(hydroxy)carbamate



16 **S-10** **22**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and pyridine (0.30 μL, 0.0038 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (49 mg, 0.30 mmol, 1.0 equiv) and 2,3- dimethylbut-2-ene **S-10** (30 mg, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting reaction mixture was stirred for 8 h at 23 ˚C. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **22** (72 mg, 98%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 6.77 (bs, 1H), 5.16 (s, 2H), 4.84 (s, 1H), 4.76 (s, 1H), 1.74 (s, 3H), 1.48 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 149.8, 136.0, 128.6, 128.4, 128.3, 109.5, 68.1, 66.1, 25.7, 19.3 ppm; IR (thin film) 3324, 2987, 1685, 1454, 1329, 1104 cm^{-1}; MS (ESI) *m/z* 272.16 (272.13 calcd for $C_{14}H_{19}NNaO_3^+$ $[MNa]^+$).

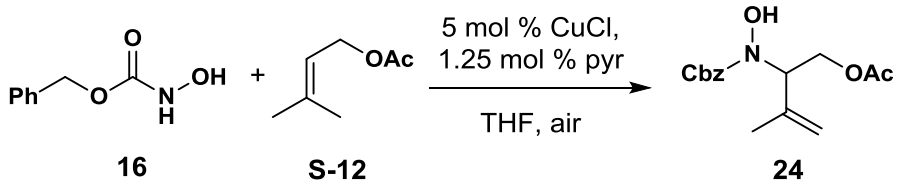
(23) Benzyl hydroxy(1-hydroxy-3-methylbut-3-en-2-yl)carbamate



16 S-11 23

According to the general procedure, CuCl (4.4 mg, 0.044 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (150 mg, 0.9 mmol, 1.0 equiv) and 3- methylbut-2-en-1-ol **S-11** (93 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 17 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **S 23** (193 mg, 85%) as a colorless solid. ^{1}H NMR (600 MHz, CD3OD) δ 7.41 – 7.37 (m, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.32 – 7.28 (m, 1H), 5.17 (apt. q, *J* = 12.4 Hz, 2H), 4.94 (s, 1H), 4.89 (s, 1H), 4.59 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.90 (dd, *J* = 11.1, 9.4 Hz, 1H), 3.75 (dd, *J* = 11.3, 5.0 Hz, 1H), 1.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, CD3OD) δ 159.6, 142.7, 137.9, 129.5, 129.1, 128.9, 113.9, 68.6, 66.0, 60.7, 21.3 ppm; IR (thin film) 3232, 2942, 1697, 1402, 1315, 1248, 1103 cm^{-1}; HRMS (ESI) *m/z* 274.0956 (274.1058 calcd for $C_{13}H_{17}NNaO_4^+$ $[MNa]^+$).

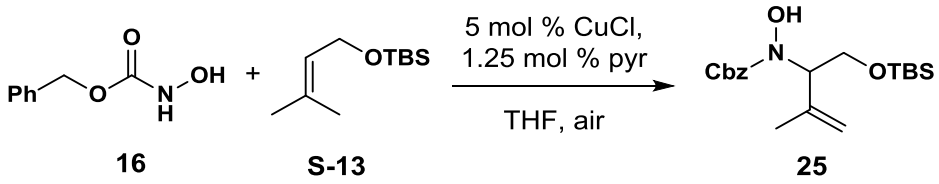
(24) 2-(((Benzyloxy)carbonyl)(hydroxy)amino)-3-methylbut-3-en-1-yl acetate



16 S-12 24

According to the general procedure, CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (151 mg, 0.9 mmol, 1.0 equiv) and 3-methylbut-2-en-1-yl acetate **S-12** (139 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 32 h at 23 ˚C. The reaction was then quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **24** (203 mg, 77%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.65 – 6.55 (m, 1H), 5.20 (apt. q, J = 12.3 Hz, 1H), 4.99 (s, 1H), 4.92 (s, 1H), 4.81 – 4.75 (m,1H), 4.71 (t, J = 10.9 Hz, 1H), 4.20 (dt, J = 11.3, 3.5 Hz, 1H), 1.89 (s, 3H), 1.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 157.6, 139.9, 136.1, 128.6, 128.4, 128.2, 114.3, 68.0, 61.5, 61.4, 21.2, 20.8 ppm; IR (thin film) 3306, 2959, 1702, 1454, 1240, 1113 cm^{-1}; HRMS (ESI) *m/z* 316.1123 (316.1163 calcd for $C_{15}H_{19}NNaO_5^+$ $[MNa]^+$).

(25) Benzyl (1-((*tert*-butyldimethylsilyl)oxy)-3-methylbut-3-en-2-yl)(hydroxy)carbamate

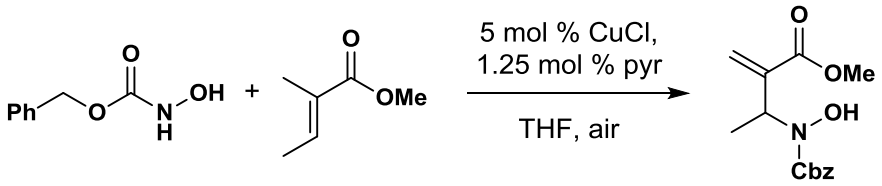


16 S-13 25

According to the general procedure CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (151 mg, 0.9 mmol, 1.0 equiv) and *tert*-butyldimethyl((3-methylbut-2-en-1-yl)oxy)silane **S-13** (218 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 23 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with

ethyl acetate (3 × 18 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **25** (290 mg, 88%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 6.37 (s, 1H), 5.19 (apt. q, *J* = 12.3 Hz, 2H), 4.96 (s, 1H), 4.93 (s, 1H), 4.63 (dd, *J* = 8.6, 5.0 Hz, 1H), 4.02 (t, *J* = 9.7 Hz, 1H), 3.82 (dd, *J* = 10.3, 5.0 Hz, 1H), 1.78 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.1, 141.0, 136.2, 128.7, 128.4, 128.2, 113.6, 68.1, 64.6, 61.2, 26.0, 25.8, 21.3, 18.3, -3.4, -5.3, -5.3 ppm; IR (thin film) 3244, 2953, 2855, 1699, 1406, 1322, 1253, 1109 cm^{-1}; HRMS (ESI) *m/z* 388.1902 (388.1922 calcd for $C_{19}H_{31}NNaO_4Si^+$ $[MNa]^+$).

(26) Methyl 3-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methylenebutanoate

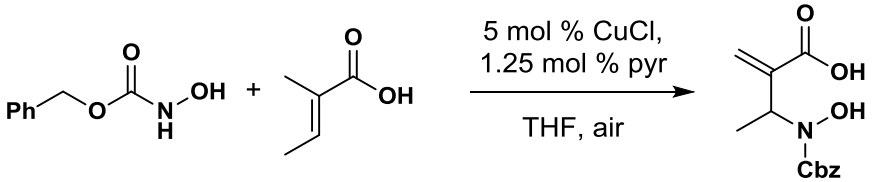


16 **S-14** **26**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and pyridine (0.30 μL, 0.0037 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and (*E*)-methyl 2-methylbut-2-enoate **S-14** (48 mg, 0.36 mmol, 1.2 equiv) in 10 mL THF. The resulting mixture was stirred for 24 h at 23 ˚C. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **26** (61 mg, 73%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.29 (s, 1H), 5.88 (s, 1H), 5.17 (s, 2H), 5.14 (q, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H)

ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 156.8, 139.7, 136.2, 128.7, 128.3, 128.2, 127.3, 68.0, 54.9, 52.3, 16.3 ppm; IR (thin film) 3312, 2951, 1717, 1439, 1299, 1080 cm-1; MS (ESI) *m/z* 302.0917 (302.0999 calcd for $C_{14}H_{17}NNaO_5^+$ $[MNa]^+$).

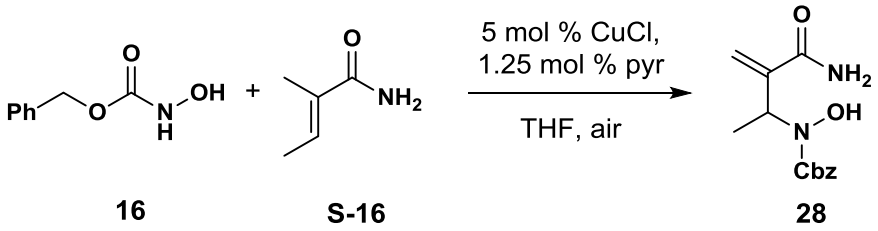
(27) 3-(((Benzyloxy)carbonyl)(hydroxy)amino)-2-methylenebutanoic acid



16 **S-15** **27**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and pyridine (0.30 μL, 0.0037 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and (*E*)-2-methylbut-2-enoic acid **S-15** (35 mg, 0.36 mmol, 1.2 equiv) in 10 mL THF. The resulting mixture was stirred for 36 h at 23 ˚C. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **26** (60 mg, 75%) as a colorless solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.40 – 7.27 (m, 5H), 6.28 (s, 1H), 5.87 (s, 1H), 5.20 (q, *J* = 7.0 Hz, 1H), 5.16 (s, 2H), 1.37 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 169.4, 158.7, 142.4, 137.9, 129.5, 129.1, 128.9, 126.2, 68.6, 55.1, 16.5 ppm; IR (thin film) 3397, 2950, 1646, 1456, 1273, 1019 cm^{-1}; HRMS (ESI) *m/z* 288.0763 (288.0842 calcd for $C_{13}H_{15}NNaO_5^+$ $[MNa]^+$).

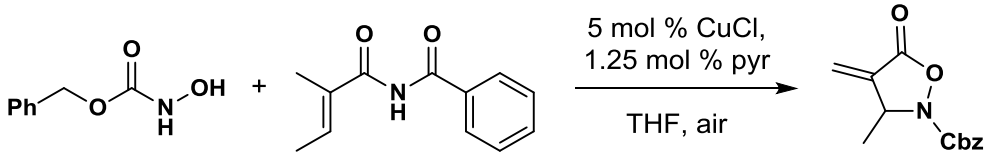
(28) Benzyl (3-carbamoylbut-3-en-2-yl)(hydroxy)carbamate



16 **S-16** **28**

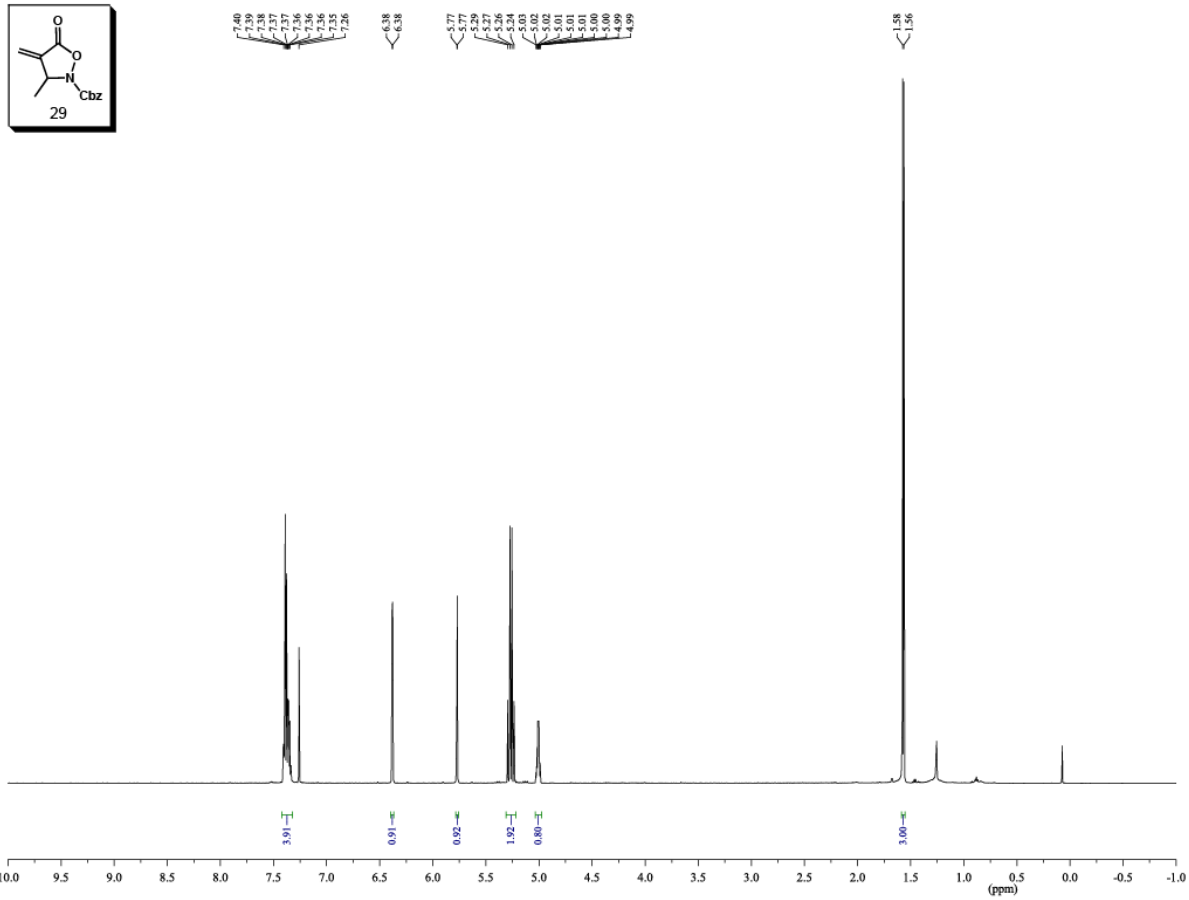
According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and pyridine (0.30 μL, 0.0037 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and (*E*)-2- methylbut-2-enamide **S-16** (35 mg, 0.36 mmol, 1.2 equiv) in 10 mL THF. The resulting mixture was stirred for 12 h at 23 ˚C. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **27** (58 mg, 72%) as a colorless solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.40 – 7.26 (m, 5H), 5.83 (s, 1H), 5.60 (d, J = 1.4 Hz, 1H), 5.20 (q, J = 7.2 Hz, 1H), 5.16 (apt. d, J = 1.6, 2H), 1.37 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 172.9, 158.7, 145.4, 137.8, 133.1, 129.5, 129.1, 128.9, 120.4, 68.6, 55.6, 16.0, 14.0, 12.4 ppm; IR (thin film) 3408, 3231, 2943, 1635, 1429, 1310, 1118 cm^{-1}; HRMS (ESI) *m/z* 287.1060 (287.1002 calcd for $C_{13}H_{16}N_2NaO_4^+$ $[MNa]^+$).

(29) Benzyl 3-methyl-4-methylene-5-oxoisoxazolidine-2-carboxylate



16 **S-17** **29**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and pyridine (0.30 μL, 0.0037 mg, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and (*E*)-N-(2-methylbut-2-enoyl)benzamide **S-17** (73 mg, 0.36 mmol, 1.2 equiv) in 10 mL THF. The resulting mixture was stirred for 44 h at 23 ˚C. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford 5-oxoisoxazolidine **29** (58 mg, 78%) as a colorless solid. The enantiomers were separated by chiral HPLC (Chiralpak IB column, 4.6mm x 250mm, 95:5 hexanes/*i*-PrOH, 1 mL/min, (*R*) Rt = 13.9 min, (*S*) Rt = 18.8 min). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 5H), 6.38 (d, *J* = 2.8 Hz, 1H), 5.77 (d, *J* = 2.4 Hz, 1H), 5.28 (d, *J* = 12.2 Hz, 1H), 5.25 (d, *J* = 12.2 Hz, 1H), 5.03 – 4.98 (m, 1H), 1.57 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 156.4, 136.4, 135.1, 128.9, 128.9, 128.6, 124.1, 69.0, 59.6, 22.0; IR (thin film) 2922, 1783, 1455, 1246, 1130 cm^{-1}; HRMS (ESI) *m/z* 270.0790 (270.0737 calcd for $C_{13}H_{13}NNaO_4^+$ $[MNa]^+$).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O
N
Cbz
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6.38
6.38
5.77
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5.26
5.24
5.03
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1.56
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0.80
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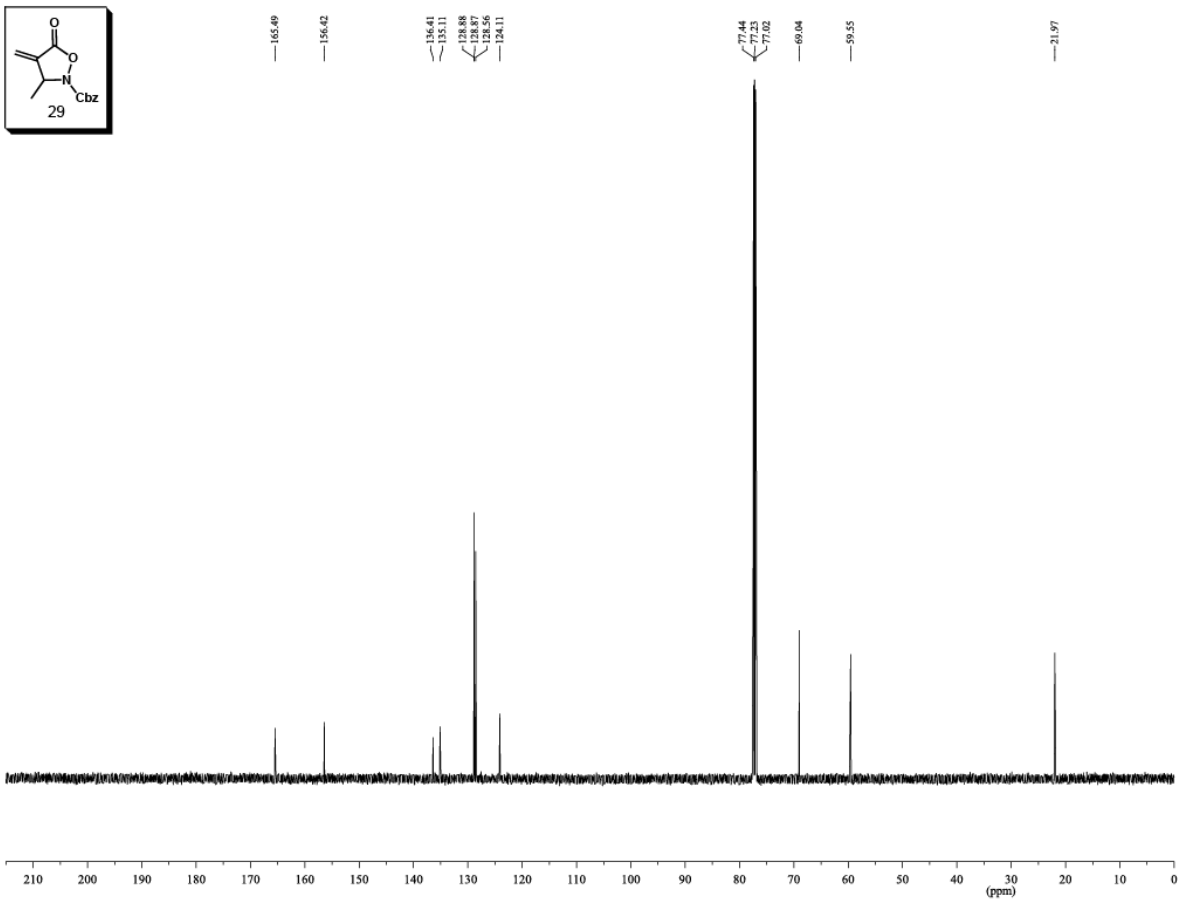
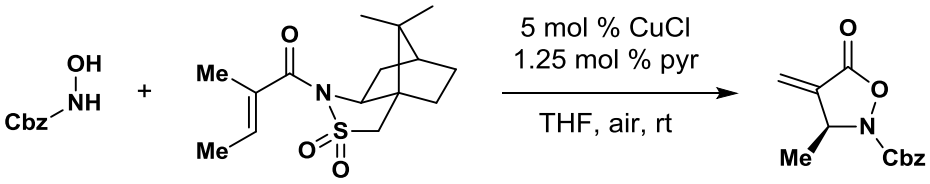
-1.0
(ppm)



((*S*)-29) (*S*) Benzyl 3-methyl-4-methylene-5-oxoisoxazolidine-2-carboxylate

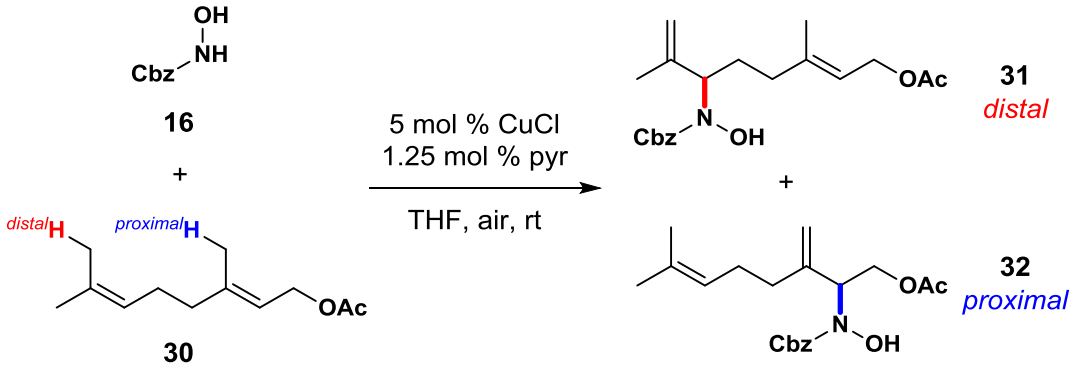


16 **39** **(*S*)-29**

According to the general procedure, CuCl (1.0 mg, 0.0090 mmol, 0.05 equiv) and pyridine (0.18 μL, 0.0023 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (30 mg, 0.18 mmol, 1.0 equiv) and (*E*)-1-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1- yl)-2-methylbut-2-en-1-one **39** (64 mg, 0.22 mmol, 1.2 equiv) in 5 mL THF. The resulting mixture was stirred for 48 h at 23 ˚C. The reaction was

quenched with 5 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford 5-oxoisoxazolidine **(*S*)-29** (34 mg, 76%) as a solid. The enantiomeric excess was determined by chiral HPLC (Chiralpak IB column, 4.6mm x 250mm, 95:5 hexanes/*i*- PrOH, 1 mL/min, (*R*) Rt = 13.9, (*S*) Rt = 18.7 min). $[\alpha]_D^{25}$ +131.3° (c 1.00, $CHCl_3$); Spectral data consistent with **29.**

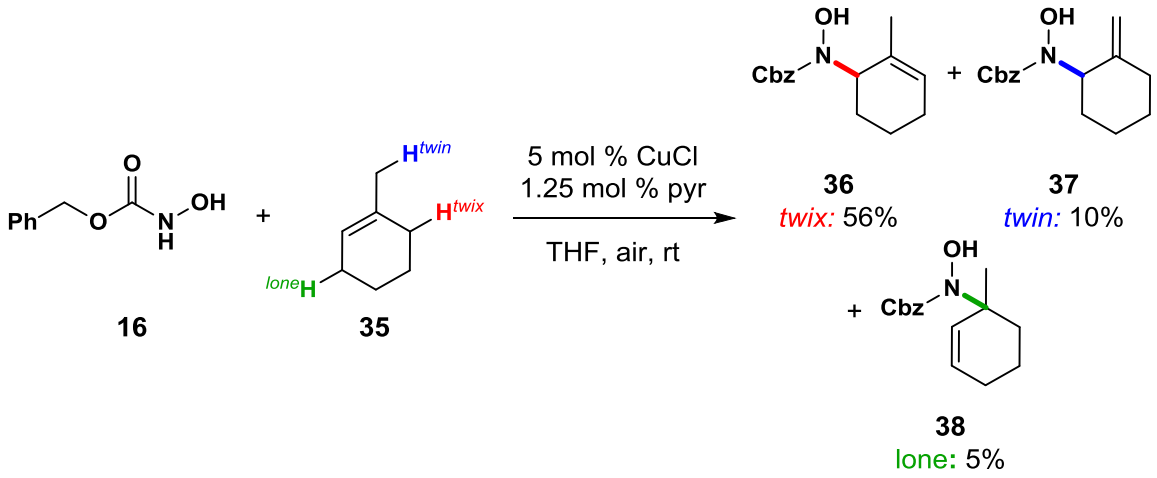
(31) (*E*)-6-(((Benzyloxy)carbonyl)(hydroxy)amino)-3,7-dimethylocta-2,7-dien-1-yl acetate



According to the general procedure, CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 µL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (151 mg, 0.90 mmol, 1.0 equiv) and geranyl acetate **30** (213 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 26 h at 23 ˚C. The reaction was quenched with 18 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 × 18 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **31** and **32** (284 mg, 87%) in a 9:1 mixture as a colorless oil. A pure fraction of **31** was obtained for characterization by column chromatography (**31**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.29

(m, 5H), 6.62 (bs, 1H), 5.33 (t, J = 7.0 Hz, 1H), 5.18 (s, 2H), 4.93 (s, 2H), 4.61 – 4.49 (m, 2H), 4.44 – 4.40 (m, 1H), 2.13 – 2.03 (m, 2H), 2.02 (s, 3H), 1.83 – 1.76 (m, 1H), 1.74 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 157.4, 143.2, 141.8, 136.2, 128.8, 128.5, 128.3, 119.0, 113.5, 68.2, 62.9, 61.5, 36.3, 27.3, 21.2, 20.9, 16.7 ppm. The mixture of isomers is enriched in **32** because a fraction of **31** was removed by column chromatography, see above. **Mixture of isomers (31 and 32)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.10 (s, 1H), 5.70 (d, J = 15.7 Hz, 1H), 5.46 (dt, J = 15.6, 7.0 Hz, 1H), 5.33 (dt, J = 7.1, 1.2 Hz, 1H), 5.20 (s, 2H), 5.17 (s, 2H), 5.03 (d, J = 12.1 Hz, 1H), 4.94 (d, J = 4.2 Hz, 1H), 4.57 (d, J = 7.1 Hz, 2H), 4.46 – 4.39 (m, 1H), 2.69 (d, J = 6.9 Hz, 2H), 2.04 (s, 3H), 2.03 (s, 2H), 1.74 (s, 3H), 1.68 (s, *3*H), 1.47 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 158.7, 157.6, 143.3, 143.3, 141.8, 136.1, 128.7, 128.7, 128.5, 128.5, 128.3, 128.2, 128.2, 119.2, 118.9, 113.4, 113.3, 68.1, 63.4, 62.9, 61.6, 61.5, 42.4, 36.3, 27.9, 27.3, 26.3, 23.6, 21.2, 20.8, 16.7, 16.6 ppm; IR (thin film) 3305, 2941, 1698, 1454, 1234, 1097 cm^{-1}; HRMS (ESI) *m/z* 384.1755 (384.1789 calcd for $C_{20}H_{27}NNaO_5^+$ $[MNa]^+$).

(36) Benzyl hydroxy(2-methylcyclohex-2-en-1-yl)carbamate



According to the general procedure CuCl (4.5 mg, 0.045 mmol, 0.05 equiv) and pyridine (0.91 μL, 0.011 mmol, 0.0125 equiv) were added to benzyl hydroxycarbamate **16** (151 mg, 0.9 mmol, 1.0 equiv) and 1- methylcyclohex-1-ene **35** (104 mg, 1.1 mmol, 1.2 equiv) in 9 mL THF. The resulting reaction mixture was stirred for 46 h at 23 ˚C. The reaction was quenched with 9 mL EDTA (0.5 M, pH 7) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford hydroxycarbamate **36** and **37** (155 mg, 66%) as a 6:1 mixture. Hydroxycarbamate **38** was also isolated (12.7 mg, 5%) as a colorless solid. A pure fraction of **36** was obtained for characterization by column chromatography. **(36)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 5H), 5.68 (s, 1H), 5.22 – 5.21 (m, 2H), 4.56 (bs, 1H), 2.10 – 1.98 (m, 1H), 1.98 – 1.87 (m, 2H), 1.86 – 1.75 (m, 2H), 1.62 (s, 3H), 1.60 – 1.50 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6, 157.6, 136.2, 131.9, 128.8, 128.5, 128.3, 127.9, 68.2, 58.3, 27.0, 25.2, 21.3, 20.3 ppm. IR (thin film) 3269, 2939, 1696, 1454, 1297, 1102 cm^{-1}; HRMS (ESI) *m/z* 284.1222 (284.1265 calcd for $C_{15}H_{19}NNaO_3^+$ $[MNa]^+$). The mixture of isomers is enriched in **37** because a fraction of **36** was removed by column chromatography, see above. **Mixture of isomers (36 and 37)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 5H), 5.70 – 5.63 (m, 1H), 5.26 – 5.16 (m, 4H), 4.80 (s, 1H), 4.71 (s, 1H), 4.57 – 4.45 (m, 2H), 2.12 – 1.76 (m, 6H), 1.62 (s, 3H) ppm. A pure fraction of **38** was obtained for characterization by column chromatography. (**38**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H), 5.87 (s, 1H), 5.83 – 5.77 (m, 1H), 5.77 – 5.65 (m, 1H), 5.26 – 5.16 (m, 2H), 2.10 – 1.89 (m, 2H), 1.73 – 1.52 (m, 4H), 1.40 (s, 3H) ppm. **Mixture of isomers (36, 37, and 38)**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8, 156.7, 155.5, 145.6, 136.3, 136.2, 135.1, 134.2, 132.0, 129.1, 128.8, 128.7, 128.7, 128.7, 128.6,

128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.1, 106.5, 71.7, 68.5, 68.1, 68.0, 61.8, 58.3, 35.2, 30.5, 27.2, 27.0, 25.6, 25.1, 21.3, 20.2 ppm.

6.1.2 Supporting Information for the Nitroso Diels–Alder Reaction

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). 1H NMR spectra were recorded on Varian Spectrometers (at 400, 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{31}P NMR spectra were recorded on a Varian Spectrometer (162 MHz) and are reported in terms of chemical shift. Data for ^{31}P NMR spectra are reported relative to H_3PO_4. IR spectra were recorded on a Perkin Elmer Spectrum Two FT/IR and are reported in terms of frequency of absorption (cm^{-1}). Low resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility.

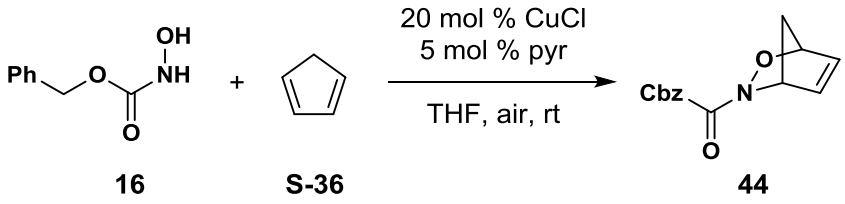
Starting Materials

Hydroxamic acids **S-18**, **S-19**, **S-20**, and **S-21** were purchased from commercial sources and used as received. *N*-hydroxycarbamates **16**, **S-5**, and **S-6** were purchased from commercial sources and used as received. *N*-hydroxycarbamates **S-7**, **S-22**, **S-23**, **S-24**, **S-25**, **S-26** and **1** were prepared from the corresponding alcohol according to literature precedent.[4] Starting *N*-hydroxyureas **S-28**, **S-29**, and **S-30** were prepared according to the same procedure from the corresponding amine. Hydroxyurea (**S-27**) was purchased from a commercial source and used as received. Hydroxylamine **S-17** was prepared according to literature precedent.[5] Hydroxylamine **S-18** was prepared according to literature precedent.[6] Hydroxylamine **S-19** and **S-20** were prepared according to literature precedent.[7] Hydroxylamine **S-21** was prepared according to literature precedent.[8]

Substrate scope for Nitroso Hetero–Diels–Alder Reaction

General Procedure for the Diels–Alder Reaction: To a stirred solution of hydroxamic acid **63** and cyclohexa-1,3-diene **64** in THF was added 20 mol % CuCl and 5 mol % pyridine. The reaction was stirred at room temperature open to the air until complete by TLC. Upon completion, the reaction was quenched with EDTA (0.5 M, pH 7.0), diluted with ethyl acetate and stirred until color no longer persisted in organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **65**.

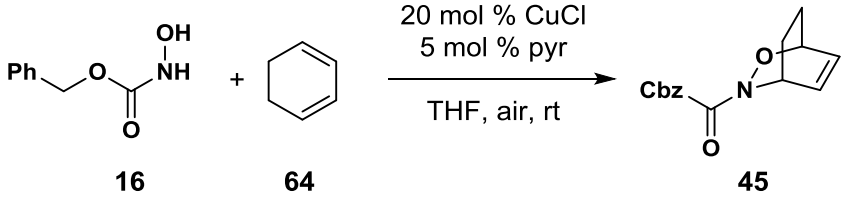
(44) Benzyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate



16 **S-36** **44**

According to the general procedure, CuCl (11 mg, 0.11 mmol, 0.20 equiv) and pyridine (2.2 μL, 0.027 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (90 mg, 0.54 mmol, 1.0 equiv) and cyclopentadiene **S-36** (50 μL, 0.59 mmol, 1.1 equiv) in 5 mL THF. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **44** (117 mg, 94%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 6.37 (s, 2H), 5.23 (s, 1H), 5.19 (dd, J = 12.3, 1.7 Hz, 1H), 5.12 (dd, J = 12.3, 1.8 Hz, 1H), 5.04 (s, 1H), 2.00 (dd, J = 8.7, 1.7 Hz, 1H), 1.74 (d, J = 8.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 135.8, 134.6, 133.1, 128.6, 128.4, 128.3, 84.0, 67.9, 65.2, 48.3 ppm; IR (thin film) 3032, 2961, 1741, 1386, 1177, 1090 cm^{-1}; MS (ESI) *m/z* 254.04 (254.08 calcd for $C_{13}H_{13}NNaO_3^+$ $[MNa]^+$).

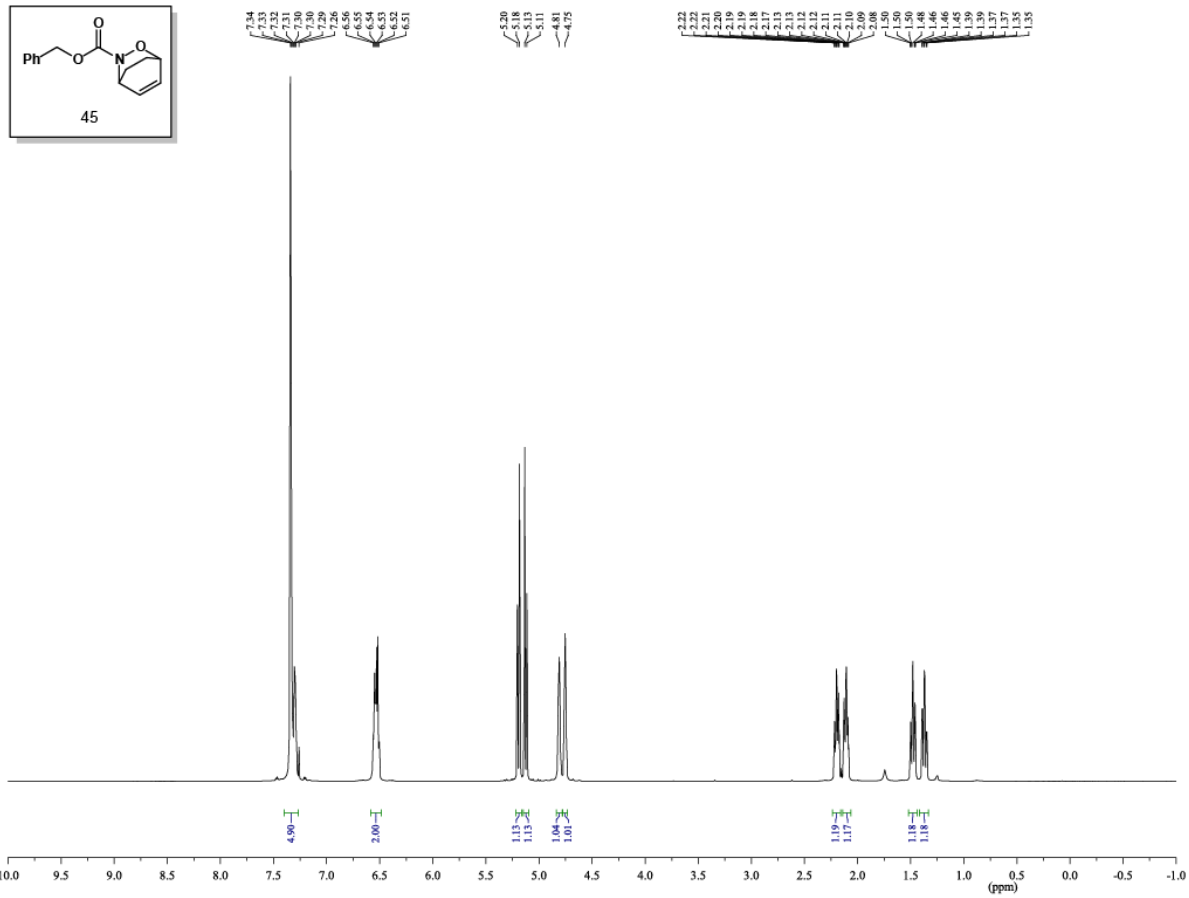
(45) Benzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



16 **64** **45**

According to the general procedure, CuCl (6.0 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30

mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (34 μL, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 4 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **45** (70 mg, 96%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.53 (ddd, *J* = 13.7, 7.1, 7.1 Hz, 2H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 2.20 (dddd, *J* = 13.0, 8.2, 3.6, 3.6 Hz, 1H), 2.11 (dddd, *J* = 12.7, 9.3, 3.3, 3.3 Hz, 1H), 1.48 (dddd, *J* = 12.3, 12.3, 2.9, 2.9 Hz 1H), 1.37 (ddd, *J* = 12.5, 12.5, 3.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 136.1, 132.1, 131.8, 128.6, 128.3, 128.2, 71.2, 67.8, 50.3, 23.6, 20.7 ppm; IR (thin film) 3061, 2939, 1701, 1455, 1264, 1074 cm^{-1}; MS (ESI) *m/z* 268.11 (268.09 calcd for $C_{14}H_{15}NNaO_3^+$ $[MNa]^+$).


Ph
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O
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6.56
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5.0
4.5
4.0
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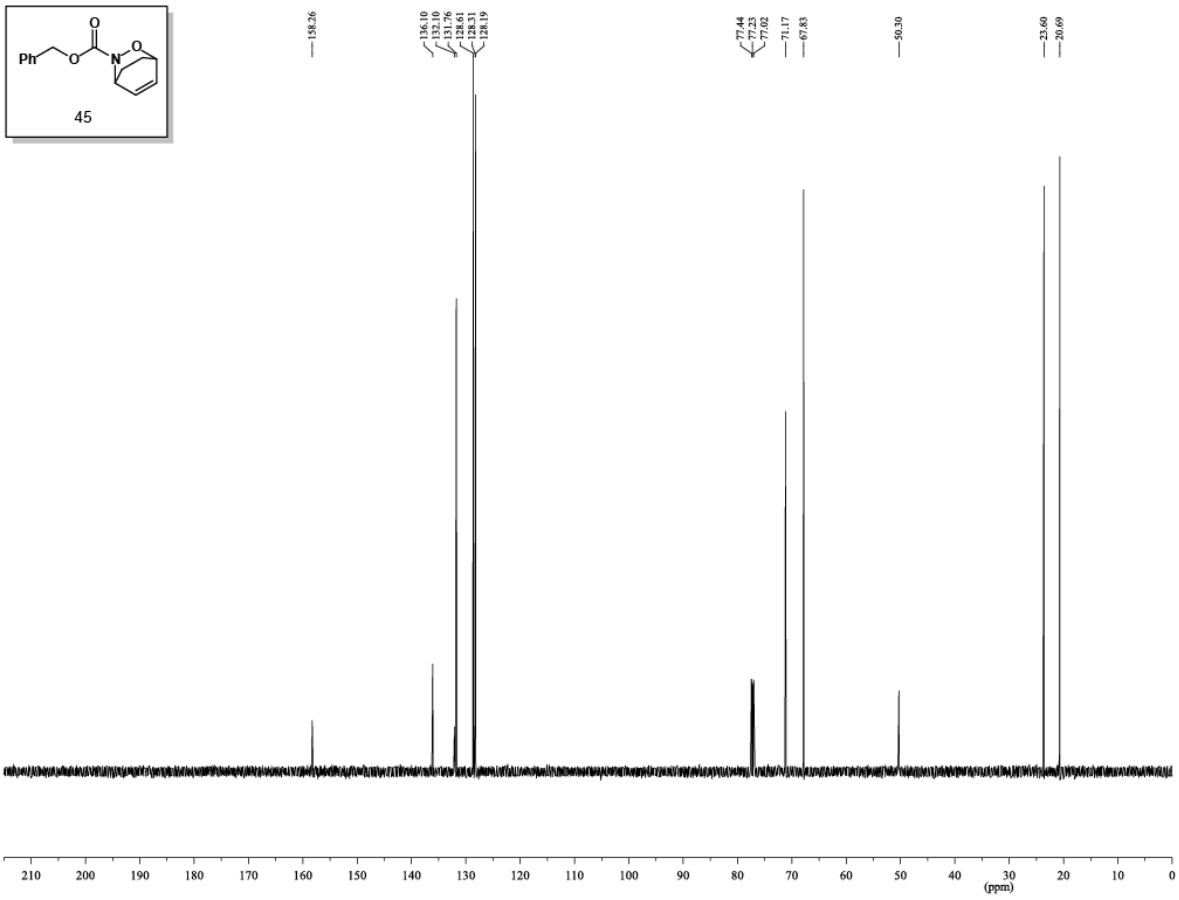
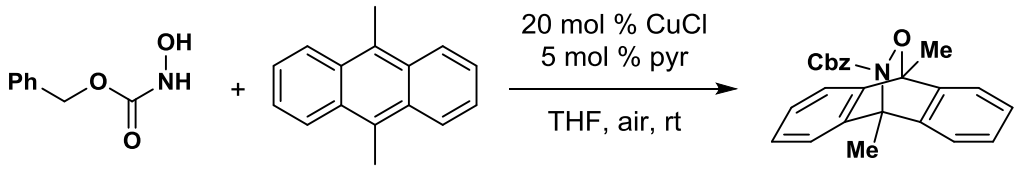
0.0
-0.5
-1.0
(ppm)



(46) Benzyl 9,10-dimethyl-9,10-dihydro-9,10-(epoxyimino)anthracene-11 carboxylate

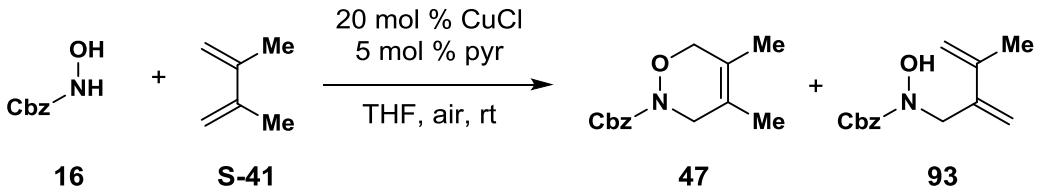


16 **S-38** **46**

According to the general procedure, CuCl (5.8 mg, 0.058 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (49 mg, 0.29 mmol, 1.0 equiv) and 9,10-dimethylanthracene **S-38** (72 mg, 0.35 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 5 h at rt. The reaction was quenched with 6 mL

EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **46** (104 mg, 96%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 7.43 – 7.36 (m, 2H), 7.31 – 7.19 (m, 7H), 6.98 (m, 2H), 5.00 (s, 2H), 2.63 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 141.9, 140.6, 136.3, 128.4, 127.8, 127.4, 127.4, 127.1, 121.7, 120.8, 79.3, 67.3, 64.2, 16.7, 15.2 ppm; IR (thin film) 3033, 2984, 1713, 1460, 1276, 1070 cm^{-1}; MS (ESI) *m/z* 394.17 (394.14 calcd for $C_{24}H_{21}NNaO_3^+$ $[MNa]^+$).

(47) Benzyl 4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate

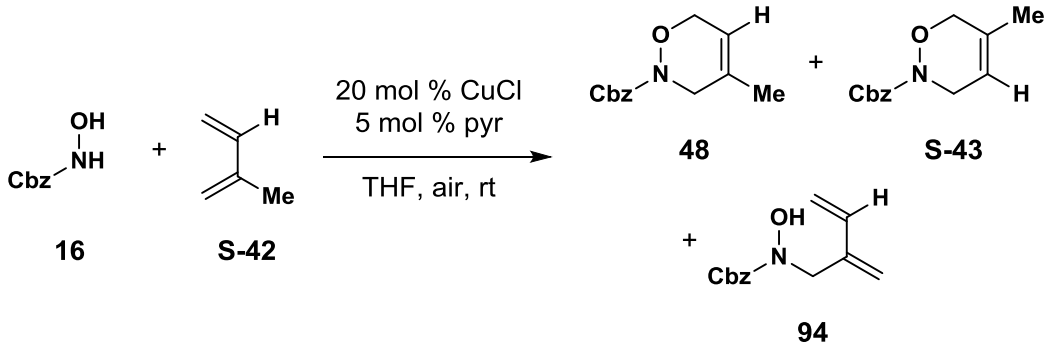


16 **S-41** **47** **93**

According to the general procedure, CuCl (12 mg, 0.12 mmol, 0.20 equiv) and pyridine (2.4 μL, 0.030 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (100 mg, 0.60 mmol, 1.0 equiv) and 2,3- dimethylbuta-1,3-diene **S-41** (83 μL, 0.72 mmol, 1.2 equiv) in 6 mL THF. The resulting mixture was stirred for 8 h at rt. The reaction was quenched with 12 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 12 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **47** (88 mg, 71%) as a colorless solid and carbamate **93** (21 mg, 17%) as a colorless oil. **(47)**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 5.21 (s, 2H), 4.22 (s, 2H), 3.97 (s, 2H), 1.66 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 136.2, 128.7, 128.4, 128.3, 123.3, 121.9, 71.8, 67.8, 48.6, 15.4, 14.0 ppm; IR (thin film) 2916, 2847, 1710, 1411, 1219, 1089 cm^{-1}; MS (ESI) *m/z*

270.13 (270.11 calcd for $C_{14}H_{17}NNaO_3^+$ $[MNa]^+$). **Benzyl hydroxy(3-methyl-2-methylenebut-3-en-1-yl)carbamate (93)**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 6.39 (bs, 1H), 5.29 (s, 1H), 5.20 (s, 2H), 5.17 (s, 1H), 5.09 (s, 1H), 5.00 (s, 1H), 4.40 (s, 2H), 1.93 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 141.5, 141.1, 136.0, 128.8, 128.6, 128.4, 115.1, 113.7, 68.3, 53.2, 21.4 ppm; IR (thin film) 3292, 2950, 1793, 1456, 1246, 1102 cm^{-1}; MS (ESI) *m/z* 270.14 (270.11 calcd for $C_{14}H_{17}NNaO_3^+$ $[MNa]^+$).

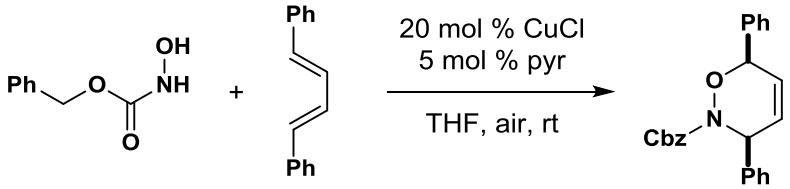
(48) Benzyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate



According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and 2- methylbuta-1,3-diene **S-42** (36 μL, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **48** and **S-43** (25 mg, 43%. 2:1 mixture, inseparable) as a colorless solid and carbamate **94** (21 mg, 36%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) **(48)**: δ 7.47 – 7.29 (m, 5H), 5.53 (s, 1H), 5.22 (s, 2H), 4.39 (s, 2H), 4.02 (s, 2H), 1.73 (s, 3H) ppm (**S-43):** δ 7.47 – 7.29 (m, 5H), 5.52 (s, 1H), 5.21 (s, 2H),

4.28 (s, 2H), 4.11 (s, 2H), 1.66 (s, 3H) ppm; **(Mixture):** ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 155.7, 136.2, 136.2, 131.8, 130.3, 128.8, 128.5, 128.4, 128.4, 118.2, 116.5, 71.9, 68.8, 67.9, 67.9, 48.7, 45.0, 19.9, 18.5 ppm; IR (thin film) 3034, 2914, 1708, 1410, 1217, 1099 cm^{-1}; MS (ESI) *m/z* 256.10 (256.09 calcd for $C_{13}H_{15}NNaO_3^+$ $[MNa]^+$). **Benzyl hydroxy(2-methylenebut-3-en-1-yl)carbamate (94):** ^{1}H NMR (600 MHz, $CDCl^3$) δ 7.40 – 7.30 (m, 5H), 6.39 (dd, *J* = 17.8, 11.1 Hz, 1H), 6.39 (bs, 1H), 5.29 (d, *J* = 17.8 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 3H), 5.20 (d, *J* = 10.0 Hz, 1H), 5.10 (d, *J* = 11.1 Hz, 1H), 4.35 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 140.1, 136.7, 136.0, 128.8, 128.6, 128.4, 118.3, 114.9, 68.4, 51.8 ppm; IR (thin film) 3293, 2933, 1702, 1455, 1250, 1104 cm^{-1}; MS (ESI) *m/z* 256.10 (256.09 calcd for $C_{13}H_{15}NNaO_3^+$ $[MNa]^+$).

(49) Benzyl 3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate

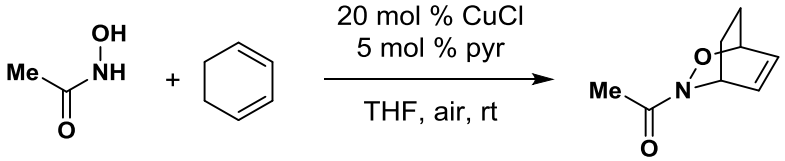


16 **S-37** **49**

According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene **S-37** (74 mg, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 12 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **49** (89 mg, 80%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.49 – 7.30 (m, 12H),

6.17 (ddd, J = 10.1, 4.3, 2.0 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H), 5.68 (s, 1H), 5.63 (s, 1H), 5.33 (d, J = 12.3 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0, 138.9, 137.1, 136.3, 129.2, 128.9, 128.8, 128.7, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 126.2, 79.9, 67.8, 29.6 ppm; IR (thin film) 3032, 2956, 1701, 1412, 1273, 1092 cm^{-1}; MS (ESI) *m/z* 394.16 (394.14 calcd for $C_{24}H_{21}NNaO_3^+$ $[MNa]^+$).

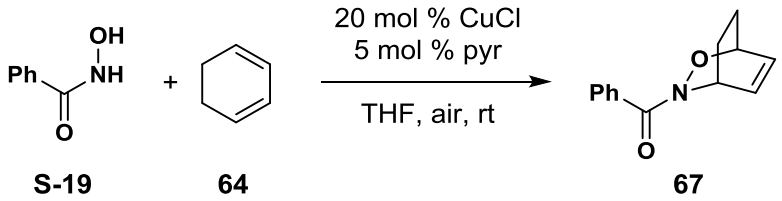
(66) 1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3- yl)ethanone



S-18 **64** **66**

As modified from the general procedure, CuCl (13 mg, 0.14 mmol, 0.20 equiv) and pyridine (2.6 µL, 0.033 mmol, 0.05 equiv) were added to *N*-hydroxyacetamide **S-18** (50 mg, 0.37 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (76 µL, 0.80 mmol, 1.2 equiv) in 6 mL THF. The resulting mixture was stirred for 27 h at 50 ºC. The reaction was quenched with 12 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 12 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **66** (59 mg, 58%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.62 (dd, J = 6.9, 6.9 Hz, 1H), 6.50 (dd, J = 6.6, 6.6 Hz, 1H), 5.32 – 5.20 (m, 1H), 4.80 – 4.68 (m, 1H), 2.24 – 2.15 (m, 1H), 2.08 (ddd, J = 9.2, 9.2, 3.3 Hz, 1H), 1.95 (s, 3H), 1.52 – 1.44 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 133.2, 131.5, 72.0, 46.4, 23.7, 21.3, 21.1 ppm; IR (thin film) 2939, 2865, 1655, 1366, 1268, 1049 cm^{-1}; MS (ESI) *m/z* 176.06 (176.07 calcd for $C_8H_{11}NNaO_2^+$ $[MNa]^+$).

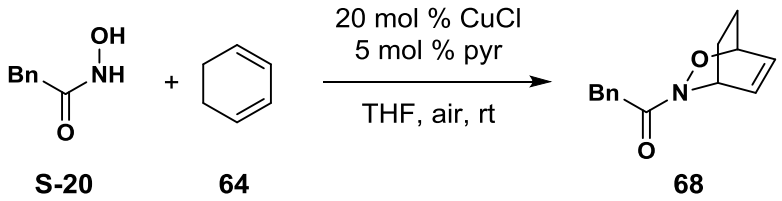
(67) 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl(phenyl)methanone



S-19 **64** **67**

According to the general procedure, CuCl (7.3 mg, 0.074 mmol, 0.20 equiv) and pyridine (1.5 μL, 0.018 mmol, 0.05 equiv) were added to *N*-hydroxybenzamide **S-19** (50 mg, 0.37 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (42 μL, 0.44 mmol, 1.2 equiv) in 4 mL THF. The resulting mixture was stirred for 96 h at rt. The reaction was quenched with 8 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **67** (63 mg, 80%) as a colorless solid. By low temperature NMR, two conformational isomers were observed in a 2:1 ratio. **Major:** ^{1}H NMR (500 MHz, CD_3OD, -68 ºC) δ 7.67 – 7.37 (m, 5H), 6.67 (ddd, *J* = 7.7, 5.7, 1.2 Hz, 1H), 6.52 (ddd, *J* = 7.9, 6.3, 1.4 Hz, 1H), 5.07 – 5.02 (m, 1H), 4.81 – 4.77 (m, 1H), 2.37 – 2.23 (m, 2H), 1.69 – 1.47 (m, 2H) ppm; **Minor:** ^{1}H NMR (500 MHz, CD_3OD, -68 ºC) δ 7.67 – 7.37 (m, 5H), 6.79 (ddd, *J* = 7.8, 6.2, 1.4 Hz, 1H), 6.61 (ddd, *J* = 8.0, 5.6, 1.5 Hz, 1H), 5.45 – 5.40 (m, 1H), 4.85 – 4.81 (m, 1H), 2.37 – 2.23 (m, 1H), 2.21 – 2.15 (m, 1H), 1.69 – 1.47 (m, 2H) ppm; **Mixed:** ^{13}C NMR (125 MHz, CD_3OD, -68 ºC) δ 169.4, 167.7, 134.8, 134.6, 134.1, 133.3, 132.5, 132.3, 131.8, 130.2, 130.0, 128.9, 128.8, 73.8, 73.6, 53.8, 53.7, 48.1, 48.1, 24.2, 24.1, 22.4, 21.6 ppm; IR (thin film) 3060, 2938, 1642, 1449, 1270, 1084 cm^{-1}; MS (ESI) *m/z* 238.11 (238.08 calcd for $C_{13}H_{13}NNaO_2^+$ $[MNa]^+$).

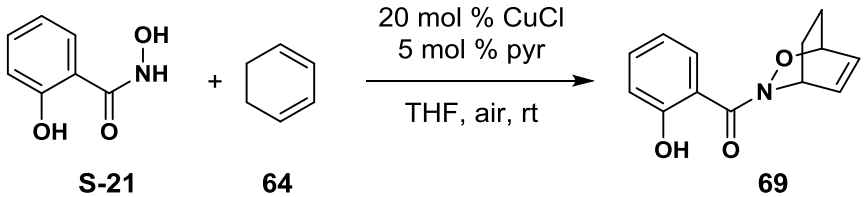
(68) 1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-2-phenylethanone



S-20 **64** **68**

According to the general procedure, CuCl (6.7 mg, 0.067 mmol, 0.20 equiv) and pyridine (1.4 μL, 0.017 mmol, 0.05 equiv) were added to *N*-hydroxy-2-phenylacetamide **S-20** (51 mg, 0.34 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (39 μL, 0.40 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 12 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **68** (72 mg, 93%) as a light brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.58 – 6.50 (m, 2H), 5.19 (d, J = 12.3 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 4.85 – 4.80 (m, 1H), 4.77 – 4.73 (m, 1H), 2.20 (dddd, J = 12.8, 9.0, 3.5, 3.5 Hz, 1H), 2.11 (dddd, J = 12.7, 9.2, 3.2, 3.2 Hz, 1H), 1.48 (dddd, J = 12.2, 12.2, 2.8, 2.8, 1H), 1.37 (ddd, J = 12.7, 12.7, 3.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 136.1, 132.1, 131.8, 128.6, 128.3, 128.2, 71.2, 67.8, 50.3, 23.6, 20.7 ppm; IR (thin film) 3062, 2939, 1700, 1455, 1265, 1074 cm^{-1}; MS (ESI) *m/z* 268.09 (268.07 calcd for $C_{14}H_{15}KNO_2^+$ $[MK]^+$).

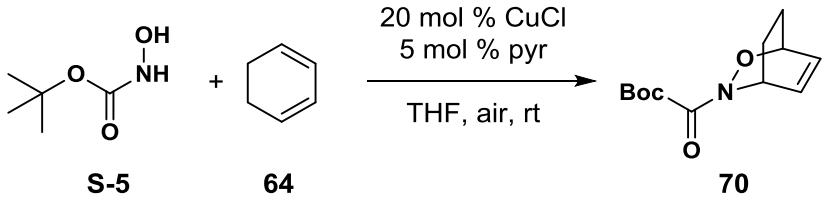
(69) 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl(2-hydroxyphenyl)methanone



S-21 **64** **69**

As modified from the general procedure, CuCl (6.5 mg, 0.065 mmol, 0.20 equiv) and pyridine (1.3 μL, 0.016 mmol, 0.05 equiv) were added to *N*,2-dihydroxybenzamide **S-21** (50 mg, 0.33 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (37 μL, 0.39 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 120 h at 50 ºC. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **69** (55 mg, 73%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.33 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.70 (dd, *J* = 6.9, 6.9 Hz, 1H), 6.58 (dd, *J* = 6.3, 6.3 Hz, 1H), 5.48 – 5.41 (m, 1H), 4.92 – 4.88 (m, 1H), 2.37 – 2.29 (m, 1H), 2.28 – 2.19 (m, 1H), 1.62 – 1.52 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 161.1, 133.8, 132.8, 132.2, 130.6, 120.7, 118.3, 117.8, 115.1, 72.8, 23.6, 21.1 ppm; IR (thin film) 2939, 1627, 1486, 1253, 1087 cm^{-1}; MS (ESI) *m/z* 254.11 (254.08 calcd for $C_{13}H_{13}NNaO_3^+$ $[MNa]^+$).

(70) *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate

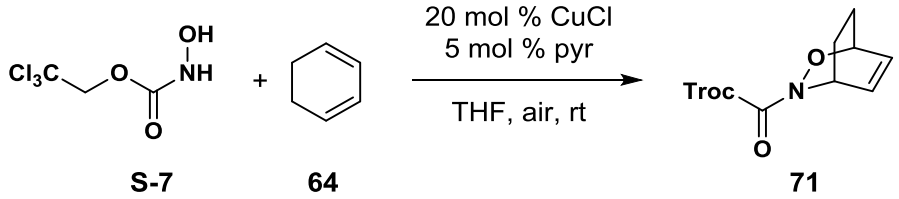


S-5 **64** **70**

According to the general procedure, CuCl (7.5 mg, 0.076 mmol, 0.20 equiv) and pyridine (1.5 μL, 0.019 mmol, 0.05 equiv) were added to *tert*-butyl hydroxycarbamate **S-5** (51 mg, 0.38 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (44 μL, 0.46 mmol, 1.2 equiv) in 4 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 8 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 8 mL). The combined organic

layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **70** (77 mg, 96%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 – 6.45 (m, 2H), 4.75 – 4.64 (m, 2H), 2.15 (dddd, *J* = 12.9, 9.3, 3.7, 3.7 Hz, 1H), 2.06 (dddd, *J* = 12.9, 9.4, 3.5, 3.5 Hz, 1H), 1.48 – 1.40 (m, 10H), 1.35 – 1.29 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8, 131.9, 131.7, 81.7, 70.8, 50.3, 28.3, 23.7, 20.7 ppm; IR (thin film) 2976, 2865, 1698, 1367, 1162, 1074 cm^{-1}; MS (ESI) *m/z* 234.13 (234.11 calcd for $C_{11}H_{17}NNaO_3^+$ $[MNa]^+$).

(71) 2,2,2-Trichloroethyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate

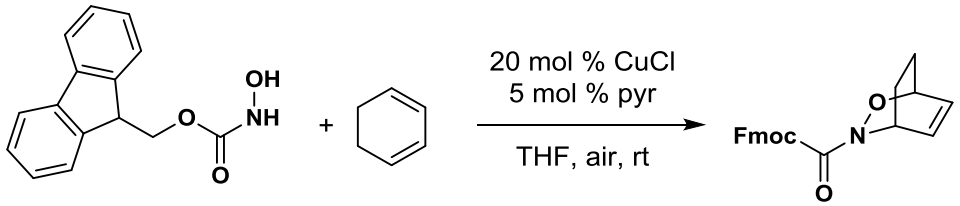


S-7 **64** **71**

According to the general procedure, CuCl (4.8 mg, 0.048 mmol, 0.20 equiv) and pyridine (1.0 μL, 0.012 mmol, 0.05 equiv) were added to 2,2,2-trichloroethyl hydroxycarbamate **S-7** (50 mg, 0.24 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (28 μL, 0.29 mmol, 1.2 equiv) in 2.5 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 5 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **71** (60 mg, 87%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.61 (ddd, *J* = 7.7, 5.7, 1.1, 1H), 6.55 (ddd, *J* = 7.7, 5.7, 1.7, 1H), 4.89 – 4.79 (m, 3H), 4.68 (d, *J* = 12.0 Hz, 1H), 2.25 (dddd, *J* = 13.0, 9.4, 3.7, 3.7 Hz, 1H), 2.17 (dddd, *J* = 12.8, 9.3, 3.4, 3.4 Hz, 1H), 1.53 (dddd, *J* = 12.8, 12.8, 3.2, 3.2 Hz, 1H), 1.44 – 1.39 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 131.9, 95.3, 75.1, 71.6, 50.6, 28.4, 23.5, 20.8 ppm; IR (thin film) 2940, 2864, 1708, 1392, 1261, 1051 cm^{-1}; MS

(ESI) *m/z* 307.98 (98%), 309.98 (100%), 311.98 (35%) (307.96, 309.96, 311.96 calcd for $C_9H_{10}Cl_3NNaO_3^+$ $[MNa]^+$).

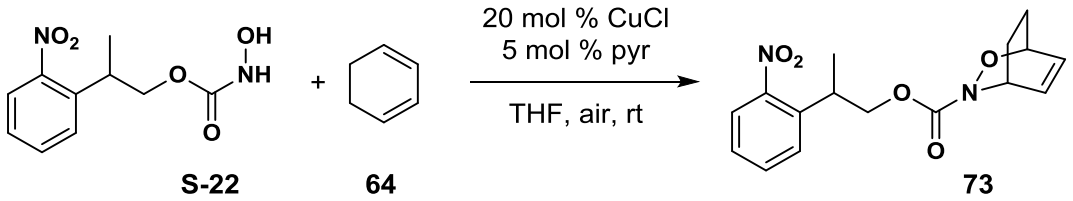
(72) 9H-fluoren-9-yl)methyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-6 **64** **72**

According to the general procedure, CuCl (4 mg, 0.040 mmol, 0.20 equiv) and pyridine (0.8 µL, 0.010 mmol, 0.05 equiv) were added to (9H-fluoren-9-yl)methyl hydroxycarbamate **S-6** (51 mg, 0.20 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (23 µL, 0.24 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 6 h at rt. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **72** (66 mg, 99%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 6.2, 6.2 Hz, 2H), 7.39 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.31 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 2H), 6.55 – 6.36 (m, 2H), 4.82 – 4.68 (m, 2H), 4.48 – 4.68 (m, 2H), 4.25 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.17 – 2.18 (m, 1H), 1.49 (dd, *J* = 12.2, 12.2 Hz, 1H), 1.39 (dd, *J* = 11.9, 11.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4, 143.9, 143.8, 141.5, 132.2, 131.7, 127.9, 127.3, 127.3, 125.3, 125.3, 120.1, 120.1, 71.2, 67.9, 50.4, 47.2, 23.7, 20.7 ppm; IR (thin film) 3063, 2940, 1704, 1451, 1265, 1078 cm^{-1}; MS (ESI) *m/z* 356.13 (356.13 calcd for $C_{21}H_{19}NNaO_3^+$ $[MNa]^+$).

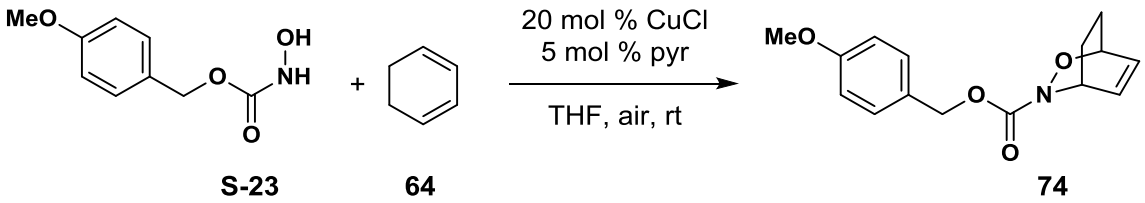
(73) 2-(2-Nitrophenyl)propyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-22 **64** **73**

According to the general procedure, CuCl (4.2 mg, 0.043 mmol, 0.20 equiv) and pyridine (0.87 μL, 0.011 mmol, 0.05 equiv) were added to 2-(2-nitrophenyl)propyl hydroxycarbamate **S-22** (51 mg, 0.21 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (25 μL, 0.26 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 6 h at rt. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **73** (66 mg, 96%, 1:1 dr, inseparable) as a brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 6.47 – 6.33 (m, 2H), 4.72 – 4.64 (m, 1H), 4.63 – 4.55 (m, 1H), 4.33 – 4.17 (m, 2H), 3.71 – 3.61 (m, 1H), 2.15 – 2.09 (m, 1H), 2.06 – 1.94 (m, 1H), 1.41 (dddd, *J* = 12.9, 12.9, 3.1, 3.1 Hz, 1H), 1.36 – 1.25 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.1, 150.5, 137.4, 137.4, 132.8, 132.0, 131.7, 131.6, 128.5, 127.6, 127.6, 124.2, 124.2, 71.1, 71.1, 69.8, 69.7, 50.4, 33.6, 23.6, 20.6, 20.6, 18.1, 18.1 ppm; IR (thin film) 2973, 2939, 1738, 1512, 1263, 1077 cm^{-1}; MS (ESI) *m/z* 341.12 (341.11 calcd for $C_{16}H_{18}N_2NaO_5^+$ $[MNa]^+$).

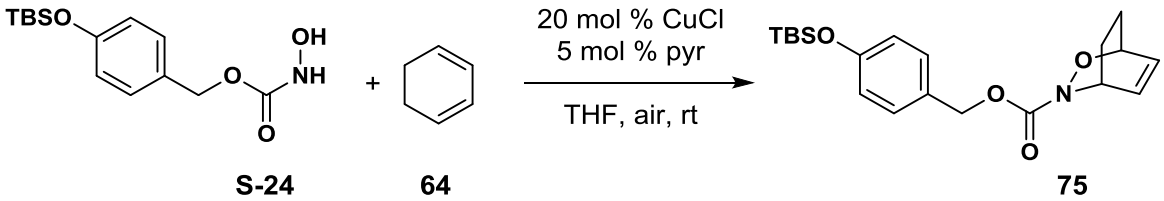
(74) 4-methoxybenzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-23 **64** **74**

According to the general procedure, CuCl (5.0 mg, 0.051 mmol, 0.20 equiv) and pyridine (1.0 μL, 0.013 mmol, 0.05 equiv) were added to 4-methoxybenzyl hydroxycarbamate **S-23** (50 mg, 0.25 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (29 μL, 0.30 mmol, 1.2 equiv) in 2.5 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 5 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **74** (68 mg, 97%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.56 – 6.46 (m, 2H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.79 (s, 1H), 4.74 (s, 1H), 3.79 (s, 3H), 2.19 (dddd, *J* = 13.1, 9.3, 3.7, 3.7 Hz, 1H), 2.09 (dddd, *J* = 12.8, 9.2, 3.3, 3.3 Hz, 1H), 1.47 (dddd, *J* = 12.3, 12.3, 3.0, 3.0 Hz, 1H), 1.40 – 1.33 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 158.4, 132.1, 131.8, 130.2, 128.3, 114.0, 71.2, 67.8, 55.4, 50.3, 23.6, 20.7 ppm; IR (thin film) 3060, 2939, 1737, 1516, 1249, 1075 cm^{-1}; MS (ESI) *m/z* 298.13 (298.11 calcd for $C_{15}H_{17}NNaO_4^+$ $[MNa]^+$).

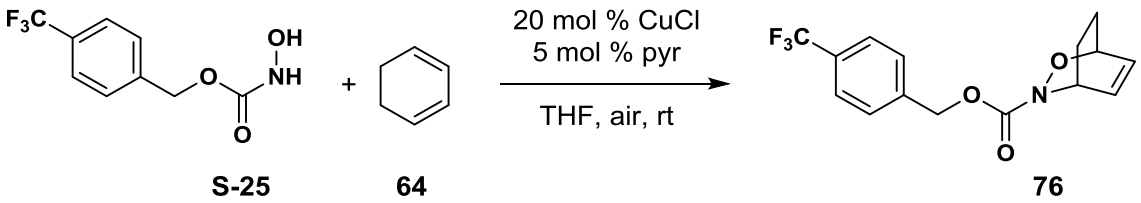
(75) 4-((*tert*-butyldimethylsilyl)oxy)benzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-24 **64** **75**

According to the general procedure, CuCl (4.9 mg, 0.050 mmol, 0.20 equiv) and pyridine (1.0 μL, 0.012 mmol, 0.05 equiv) were added to 4-((*tert*-butyldimethylsilyl)oxy)benzyl hydroxycarbamate **S-24** (73 mg, 0.24 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (26 μL, 0.27 mmol, 1.2 equiv) in 2.5 mL THF. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with 5 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **75** (78 mg, 85%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.56 – 6.49 (m, 2H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.80 (s, 1H), 4.75 (s, 1H), 2.20 (dddd, *J* = 13.0, 9.1, 3.7, 3.7 Hz, 1H), 2.11 (dddd, *J* = 12.7, 9.2, 3.3, 3.3 Hz, 1H), 1.48 (dddd, *J* = 12.2, 12.2, 3.0, 3.0 1H), 1.37 (ddd, *J* = 11.8, 11.8, 3.3 Hz, 1H), 0.97 (s, 9H), 0.18 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5, 156.0, 132.2, 131.8, 130.1, 128.9, 120.2, 71.2, 67.8, 50.4, 25.9, 23.7, 20.8, 18.4, -4.2 ppm; IR (thin film) 2955, 2858, 1701, 1512, 1260, 1075 cm^{-1}; MS (ESI) *m/z* 398.20 (398.18 calcd for $C_{20}H_{29}NNaO_4Si^+$ $[MNa]^+$).

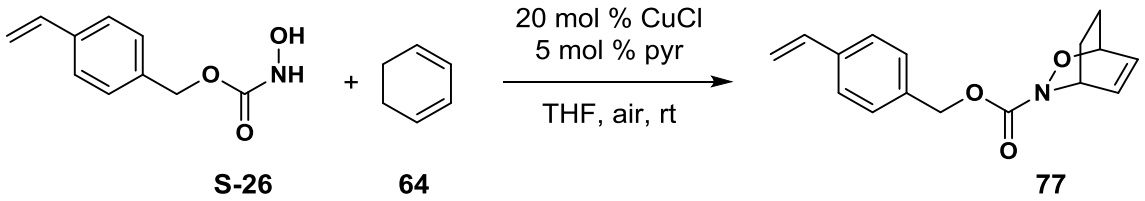
(76) 4-(trifluoromethyl)benzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-25 **64** **76**

According to the general procedure, CuCl (4.2 mg, 0.043 mmol, 0.20 equiv) and pyridine (0.85 μL, 0.011 mmol, 0.05 equiv) were added to 4-(trifluoromethyl)benzyl hydroxycarbamate **S-25** (50 mg, 0.21 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (24 μL, 0.26 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 4 h at rt. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **76** (64 mg, 97%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 6.61 – 6.49 (m, 2H), 5.24 (d, *J* = 12.9 Hz, 1H), 5.18 (d, *J* = 12.9 Hz, 1H), 4.84 – 4.81 (m, 1H), 4.79 – 4.76 (m, 1H), 2.22 (dddd, *J* = 13.0, 9.4, 3.7, 3.7 Hz, 1H), 2.13 (dddd, *J* = 12.8, 9.3, 3.4, 3.4 Hz, 1H), 1.51 (dddd, *J* = 12.8, 12.8, 3.1, 3.1 Hz, 1H), 1.44 – 1.36 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 140.3, 132.2, 131.9, 130.5 (q, *J* = 32.6 Hz), 128.1, 125.7 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.1 Hz), 71.4, 66.8, 50.3, 23.6, 20.8 ppm; IR (thin film) 3063, 2942, 1705, 1392, 1126, 1067 cm^{-1}; MS (ESI) *m/z* 336.10 (336.08 calcd for $C_{15}H_{17}NNaO_4^+$ $[MNa]^+$).

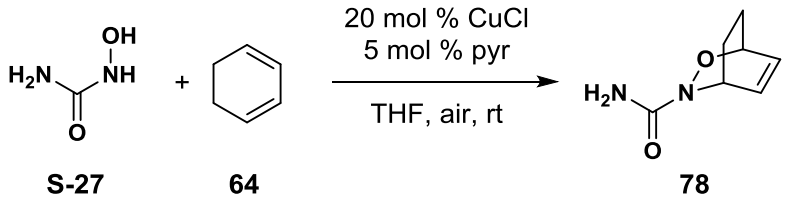
(77) 4-Vinylbenzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-26 **64** **77**

According to the general procedure, CuCl (11 mg, 0.11 mmol, 0.20 equiv) and pyridine (2.2μL, 0.027 mmol, 0.05 equiv) were added to 4-vinylbenzyl hydroxycarbamate **S-26** (105 mg, 0.25 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (57 μL, 0.60 mmol, 1.2 equiv) in 5 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **77** (139 mg, 94%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.58 – 6.48 (m, 2H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.24 (d, *J* = 10.9 Hz, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 4.82 – 4.79 (m, 1H), 4.77 – 4.74 (m, 1H), 2.20 (dddd, *J* = 13.0, 9.4, 3.7, 3.7 Hz, 1H), 2.11 (dddd, *J* = 12.8, 9.3, 3.4, 3.4 Hz, 1H), 1.48 (dddd, *J* = 12.3, 12.3, 3.1, 3.1 Hz, 1H), 1.41 – 1.33 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 137.7, 136.5, 135.6, 132.1, 131.8, 128.5, 126.4, 114.4, 71.2, 67.6, 50.3, 23.6, 20.7 ppm; IR (thin film) 2967, 2939, 1701, 1513, 1264, 1075 cm^{-1}; MS (ESI) *m/z* 294.13 (294.11 calcd for $C_{16}H_{17}NNaO_3^+$ $[MNa]^+$).

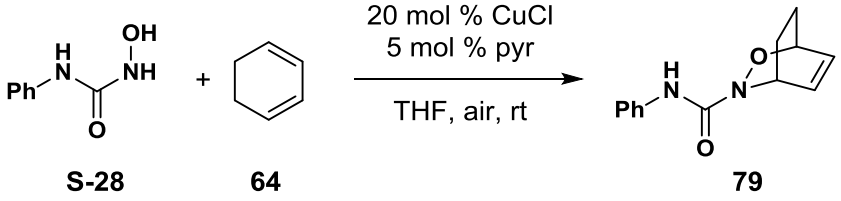
(78) 2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide



S-27 **64** **78**

According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to hydroxyurea **S-27** (23 mg, 0.30 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (34 μL, 0.36 mmol, 1.1 equiv) in 3 mL THF. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over MgSO4, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **78** (41 mg, 89%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (dd, J = 6.3, 6.3 Hz, 1H), 6.48 (dd, J = 6.5, 6.5 Hz, 1H), 5.33 (bs, 2H), 4.92 – 4.83 (m, 1H), 4.70 – 4.61 (m, 1H), 2.22 – 2.05 (m, 2H), 1.50 (dd, J = 12.0, 12.0 Hz, 1H), 1.34 (dd, J = 11.7, 11.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 132.5, 130.7, 71.0, 49.8, 23.9, 20.3 ppm; IR (thin film) 3455, 2938, 2860, 1667, 1371, 1171, 1053 cm^{-1}; MS (ESI) *m/z* 177.06 (177.06 calcd for $C_7H_{10}N_2NaO_2^+$ $[MNa]^+$).

(79) N-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide

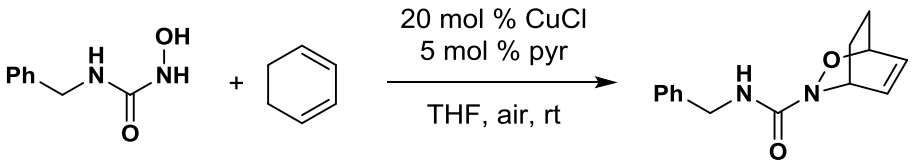


S-28 **64** **79**

According to the general procedure, CuCl (6.5 mg, 0.066 mmol, 0.20 equiv) and pyridine (1.3 μL, 0.016 mmol, 0.05 equiv) were added to 1-hydroxy-3-phenylurea **S-28** (50 mg, 0.33

mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (38 μL, 0.39 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 4 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **79** (71 mg, 94%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.28 (dd, J = 8.0, 8.0 Hz, 2H), 7.04 (dd J = 7.4, 7.4 Hz, 1H), 6.59 (ddd, J = 7.4, 5.9, 1.3 Hz, 1H), 6.51 (ddd, J = 7.8, 5.8, 1.7 Hz, 1H), 5.06 – 4.99 (m, 1H), 4.82 – 4.76 (m, 1H), 2.26 – 2.11 (m, 2H), 1.57 (dddd, J = 12.3, 12.3, 3.0, 3.0 Hz, 1H), 1.44 – 1.34 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 137.9, 132.8, 130.6, 129.1, 123.7, 119.4, 71.3, 50.1, 24.0, 20.19 ppm; IR(thin film) 3394, 3059, 2938, 1679, 1527, 1217, 1050 cm^{-1}, MS (ESI) *m/z* 253.12 (253.09 calcd for $C_{13}H_{14}N_2NaO_4^+$ $[MNa]^+$).

(80) N-benzyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide

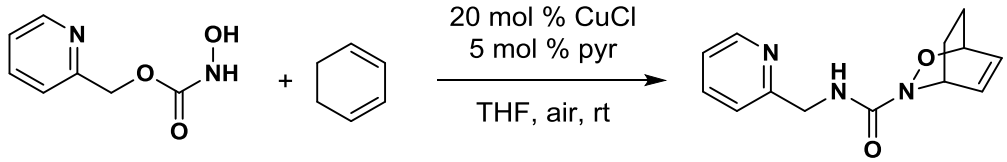


S-29 **64** **80**

According to the general procedure, CuCl (6.0 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to 1-hydroxy-3-benzylurea **S-29** (50 mg, 0.30 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (34 μL, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 5 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **80** (73 mg, 99%) as a colorless solid. ^{1}H NMR

(600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.26 – 7.21 (m, 3H), 6.56 (ddd, *J* = 8.2, 5.9, 1.4, 1H), 6.49 (ddd, *J* = 7.8, 5.8, 1.7, 1H), 6.10 (bs, 1H), 4.97 – 4.93 (m, 1H), 4.66 – 4.63 (m, 1H), 4.42 – 4.33 (m, 2H), 2.19 – 2.09 (m, 2H), 1.58 – 1.49 (m, 1H), 1.38 – 1.30 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 138.9, 132.4, 130.5, 128.7, 127.6, 127.4, 70.7, 50.5, 43.9, 24.1, 20.2 ppm; IR (thin film) 3339, 3061, 2934, 1669, 1524, 1251, 1018 cm^{-1}; MS (ESI) *m/z* 267.13 (267.11 calcd for $C_{14}H_{16}N_2NaO_2^+$ $[MNa]^+$).

(81) N-(pyridin-2-ylmethyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide

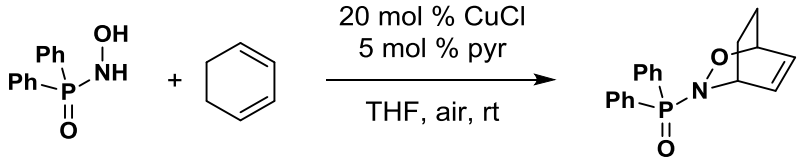


S-30 **64** **81**

According to the general procedure, CuCl (3.6 mg, 0.036 mmol, 0.20 equiv) and pyridine (0.72 μL, 0.0090 mmol, 0.05 equiv) were added to 1-hydroxy-3-(pyridin-2-ylmethyl)urea **S-30** (30 mg, 0.18 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (21 μL, 0.22 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **81** (34 mg, 77%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.6 Hz, 1H), 7.63 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.1, 5.2 Hz, 1H), 6.65 (bs, 1H), 6.55 (ddd, *J* = 7.9, 6.3, 1.2 Hz, 1H), 6.50 (ddd, *J* = 7.8, 5.9, 1.7 Hz, 1H), 4.96 – 4.92 (m, 1H), 4.73 – 4.70 (m, 1H), 4.55 (dd, *J* = 16.0, 5.7 Hz, 1H), 4.44 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.22 – 2.10 (m, 2H), 1.54 (dddd, *J* = 12.2, 12.2 3.0, 3.0 Hz 1H), 1.39 – 1.32 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.56, 157.8, 149.3, 136.9, 132.4, 130.7, 122.4, 121.8, 70.8, 50.5, 45.4,

24.1, 20.3 ppm; IR (thin film) 3347, 3057, 2936, 1674, 1512, 1260, 1018 cm^{-1}; MS (ESI) *m/z* 268.09 (268.11 calcd for $C_{13}H_{15}N_3NaO_2^+$ $[MNa]^+$).

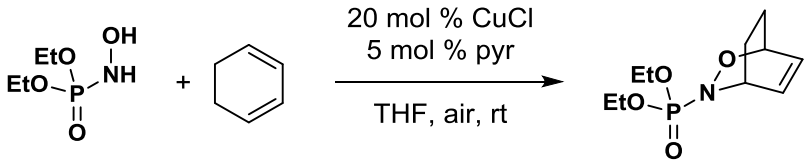
(83) 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yldiphenylphosphine oxide



S-31 **64** **83**

According to the general procedure, CuCl (4.2 mg, 0.043 mmol, 0.20 equiv) and pyridine (0.86 μL, 0.011 mmol, 0.05 equiv) were added to *N*-hydroxy-*P*,*P*-diphenylphosphinic amide **S-31** (50 mg, 0.21 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (24 μL, 0.26 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **83** (66 mg, 99%) as a colorless solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.88 – 7.80 (m, 4H), 7.55 (dddd, *J* = 20.4, 7.4, 7.4, 1.3 Hz, 2H), 7.47 (dddd, *J* = 18.8, 7.6, 7.6, 3.5 Hz, 4H), 6.44 (ddd, *J* = 7.8, 6.3, 1.3 Hz, 1H), 6.35 (ddd, *J* = 7.8, 5.8, 1.4 Hz,1H), 4.55 – 4.50 (m, 1H), 4.02 – 3.96 (m, 1H), 2.25 – 2.13 (m, 2H), 1.43 – 1.34 (m, 2H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 133.7 (d, *J* = 2.7 Hz), 133.7 (d, *J* = 9.3 Hz), 133.5 (d, *J* = 4.7 Hz), 133.4 (d, *J* = 2.7 Hz), 133.4 (d, *J* = 9.3 Hz), 71.5, 49.9, 49.5 (d, *J* = 2.9 Hz), 24.8, 23.5 (d, *J* = 11.1 Hz) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 28.6 ppm; IR (thin film) 3058, 2934, 1440, 1213, 1119 cm^{-1}; MS (ESI) *m/z* 334.12 (334.10 calcd for $C_{18}H_{18}NNaO_2P^+$ $[MNa]^+$).

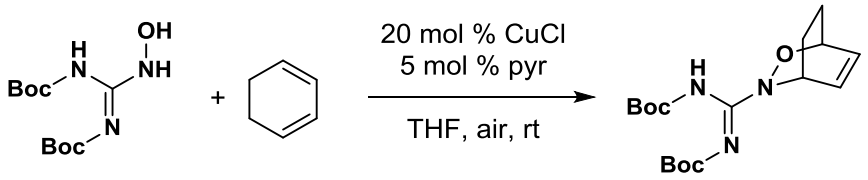
(84) Diethyl 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-ylphosphonate



S-32 **64** **84**

As modified from the general procedure, CuCl (4.1 mg, 0.041 mmol, 0.20 equiv) and pyridine (0.83 μL, 0.010 mmol, 0.05 equiv) were added to diethyl (trimethylsilyl)oxyphosphoramidate **S-32** (50 mg, 0.21 mmol,1.0 equiv) and cyclohexa-1,3-diene **64** (24 μL, 0.25 mmol, 1.2 equiv) in 2 mL THF. The resulting mixture was stirred for 5 h at rt. The reaction was filtered through a plug of neutral alumina and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **84** (25 mg, 49%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60 (ddd, J = 7.9, 6.8, 1.1 Hz, 1H), 6.48 (ddd, J = 7.5, 6.4, 1.1 Hz, 1H), 4.59 – 4.56 (m, 1H), 4.32 – 4.28 (m, 1H), 4.18 – 4.12 (m, 2H), 4.11 – 4.01 (m, 2H), 2.24 – 2.10 (m, 1H), 2.18 – 2.10 (m, 1H), 1.47 – 1.35 (m, 2H), 1.33 (t, J = 6.7 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 132.5 (d, J = 3.7 Hz), 131.0, 70.0, 64.2 (d, J = 7.1 Hz), 63.8 (d, J = 6.4 Hz), 48.9, 23.83 (d, J = 1.6 Hz), 22.7 (d, J = 12.0 Hz), 16.4 (d, J = 6.5 Hz), 16.4 (d, J = 6.7 Hz) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 5.4 ppm; IR (thin film) 2981, 2934, 1258, 1028, 977 cm^{-1}; MS (ESI) *m/z* 270.11 (270.09 calcd for $C_{10}H_{18}NNaO_4P^+$ $[MNa]^+$).

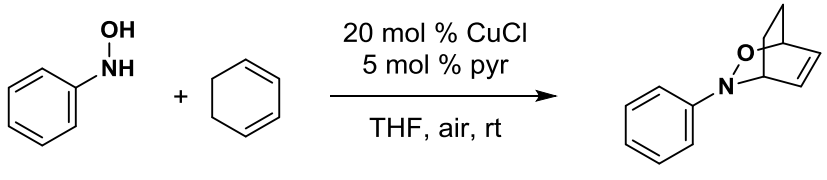
(85) (*E*)-*tert*-butyl (2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl((*tert* butoxycarbonyl)imino)methyl) carbamate



S-33 **64** **85**

As modified from the general procedure, *N*,*N*'-di-*tert*-butoxycarbonyl-*N*''hydroxylguanidine **S-33** (10 mg, 0.036 mmol, 1.0 equiv) was added to a solution of CuCl (0.7 mg, 0.0072 mmol, 0.20 equiv), pyridine (0.19 μL, 0.0018 mmol, 0.05 equiv) and cyclohexa-1,3- diene **64** (4 μL, 0.043 mmol, 1.2 equiv) in 1 mL of THF . The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **85** (8.4 mg, 66%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 6.66 (ddd, *J* = 7.6, 6.5, 1.1 Hz, 1H), 6.52 (ddd, *J* = 7.5, 6.2, 1.3 Hz, 1H), 5.23 – 5.13 (m, 1H), 4.84 – 4.77 (m, 1H), 2.27 – 2.12 (m, 2H), 1.53 – 1.45 (m, 20H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.3, 131.4, 72.6, 50.4, 28.3, 28.2, 23.7, 20.4 ppm (carbonyl and guanidine carbons not observed); IR (thin film) 3282, 2979, 1720, 1369, 1136, 1059 cm^{-1}; MS (ESI) *m/z* 376.19 (376.18 calcd for $C_{17}H_{27}N_3NaO_5^+$ $[MNa]^+$).

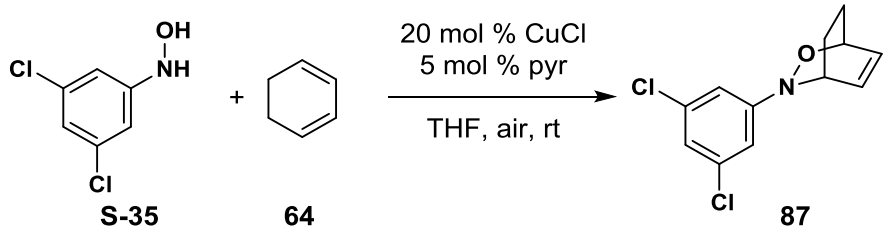
(86) 3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene



S-34 **64** **86**

As modified from the general procedure, *N*-phenylhydroxylamine **S-34** (50 mg, 0.46 mmol, 1.0 equiv) in 1 mL THF was added to a solution of CuCl (9.1 mg, 0.092 mmol, 0.20 equiv), pyridine (1.8 μL, 0.023 mmol, 0.05 equiv) and cyclohexa-1,3-diene **64** (261 μL, 2.75 mmol, 6.0 equiv) in 4 mL THF *via* syringe pump (0.5 ml/min). After completion of addition, the resulting mixture was stirred for 1 h at rt. The reaction was quenched with 10 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **86** (72 mg, 84%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.93 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.58 (ddd, *J* = 7.8, 6.0, 1.5 Hz, 1H), 6.15 (ddd, *J* = 7.6, 6.5, 1.1 Hz, 1H), 4.73 – 4.68 (m, 1H), 4.46 – 4.41 (m, 1H), 2.30 (dddd, *J* = 12.6, 9.6, 3.3, 3.3 Hz, 1H), 2.23 (dddd, *J* = 13.0, 9.5, 3.7, 3.7 Hz, 1H), 1.58 (dddd, *J* = 12.3, 12.3, 3.0, 3.0 Hz, 1H), 1.37 (dddd, *J* = 12.3, 12.3, 3.6, 1.3 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 131.8, 130.1, 128.5, 122.2, 117.6, 69.3, 56.7, 24.2, 21.6 ppm; IR (thin film) 2961, 2858, 1596, 1490, 1225, 940 cm^{-1}; MS (ESI) *m/z* 188.10 (188.11 calcd for $C_{12}H_{14}NO^+$ $[MH]^+$).

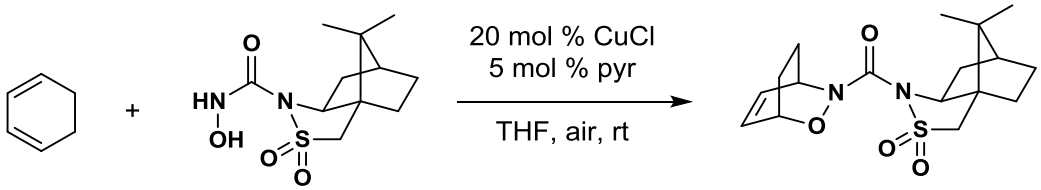
(87) 3-(3,5-dichlorophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene



As modified from the general procedure, *N*-(3,5-dichlorophenyl)hydroxylamine **S-35** (50 mg, 0.28 mmol, 1.0 equiv) in 1 mL THF was added to a solution of CuCl (5.6 mg, 0.056 mmol, 0.20 equiv), pyridine (1.1 μL, 0.014 mmol, 0.05 equiv) and cyclohexa-1,3-diene **64**

(160 μL, 1.69 mmol, 6.0 equiv) in 2 mL THF *via* syringe pump (0.5 ml/min). After completion of addition, the resulting mixture was stirred for 1 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **87** (58 mg, 81%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 – 6.84 (m, 3H), 6.56 (ddd, *J* = 7.6, 6.5, 1.1 Hz, 1H), 6.17 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.73 – 4.68 (m, 1H), 4.43 – 4.37 (m, 1H), 2.28 – 2.16 (m, 2H), 1.57 (dddd, *J* = 12.8, 12.8, 2.9, 2.9 Hz, 1H), 1.39 – 1.32 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 135.0, 131.9, 129.9, 121.8, 115.8, 69.8, 56.5, 24.0, 21.2 ppm; IR (thin film) 2937, 2860, 1583, 1420, 1112, 901 cm^{-1}; MS (ESI) *m/z* 256.02 (100%), 258.02 (64%) (256.03, 258.03 calcd for $C_{12}H_{12}Cl_2NO^+$ $[MH]^+$).

(89) 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl((3aR,6S)-8,8-dimethyl-2,2 dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)methanone

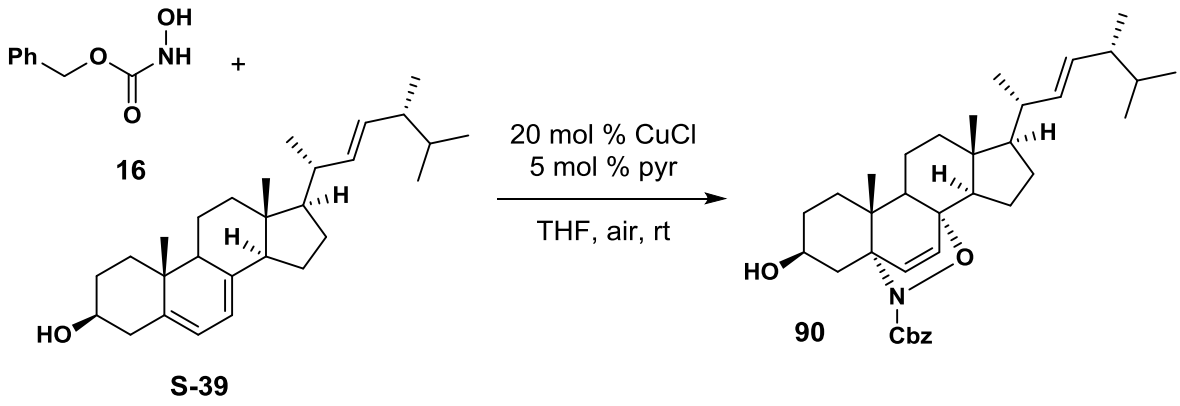


64 **88** **89**

According to the general procedure, CuCl (2.2 mg, 0.022 mmol, 0.20 equiv) and pyridine (0.44 μL, 0.0055 mmol, 0.05 equiv) were added to (3a*R*,6*S*)-N-hydroxy-8,8-dimethylhexahydro-1H-3a,6-methanobenzo[c]isothiazole-1- carboxamide 2,2-dioxide **88** (30 mg, 0.11 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (13 μL, 0.13 mmol, 1.2 equiv) in 1 mL THF. The resulting mixture was stirred for 6 h at rt. The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined

organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **89** (39 mg, 99%, >20:1 dr) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (ddd, *J* = 7.7, 5.9, 1.5, 1H), 6.37 (ddd, *J* = 7.6, 6.1, 1.1, 1H), 4.99 – 4.94 (m, 1H), 4.87 – 4.83 (m, 1H), 3.99 (dd, *J* = 7.7, 4.3 Hz, 1H), 3.37 (s, 2H), 2.32 – 2.20 (m, 2H), 1.93 – 1.76 (m, 5H), 1.50 – 1.42 (m, 2H), 1.38 – 1.29 (m, 2H), 1.18 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 132.5, 129.6, 71.8, 65.2, 54.3, 52.9, 48.7, 48.1, 44.9, 37.5, 32.7, 26.9, 23.4, 20.9, 20.6, 20.1 ppm; IR (thin film) 2936, 1708, 1336, 1166, 1060 cm^{-1}; MS (ESI) *m/z* 375.17 (375.13 calcd for $C_{17}H_{24}N_2NaO_4S^+$ $[MNa]^+$); $[\alpha]_D^{25}$ +63.7° (1.00, $CHCl_3$).

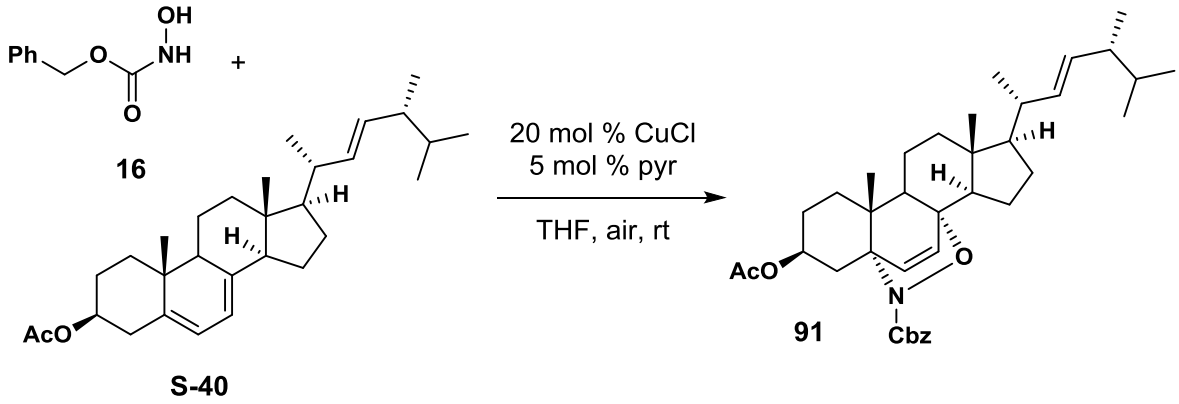
(90) (3S,5S,8S,9R,10R,13R,14R,17R)-Benzyl 17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-3-hydroxy-10,13-dimethyl-2,3,4,9,10,11,12,13,14,15,16,17-dodecahydro-1H-8,5 (epoxyimino)cyclopenta[a]phenanthrene-19-carboxylate



According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and ergosterol **S-39** (143 mg, 0.36 mmol, 1.2 equiv) in 3 mL THF. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3x 6 mL). The combined organic layers were

dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **90** (168 mg, 99%, 16:1 mixture of regioisomers, inseparable) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 5H), 6.25 (d, J = 8.3 Hz, 1H), 6.20 (d, J = 8.4 Hz, 1H), 5.24 – 5.10 (m, 3H), 4.95 (d, J = 12.8 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.27 (dd, J = 13.4, 3.0 Hz, 1H), 2.07 – 1.80 (m, 7H), 1.78 – 1.66 (m, 3H), 1.66 – 1.56 (m, 2H), 1.50 – 1.41 (m, 3H), 1.40 – 1.29 (m, 2H), 1.26 – 1.08 (m, 3H), 0.98 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H), 0.85 – 0.76 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 136.9, 136.6, 135.5, 132.4, 128.5, 127.9, 127.7, 127.4, 79.7, 67.4, 67.3, 67.1, 56.6, 53.7, 53.1, 44.4, 43.0, 40.0, 39.7, 39.1, 36.6, 35.1, 33.3, 30.0, 28.7, 24.2, 21.1, 21.0, 20.2, 19.8, 18.1, 17.9, 13.3 ppm; MS (ESI) *m/z* 584.38 (584.37 calcd for $C_{36}H_{51}NNaO_4^+$ $[MNa]^+$); $[\alpha]_D^{25}$ -4.1° (1.00, $CHCl_3$).

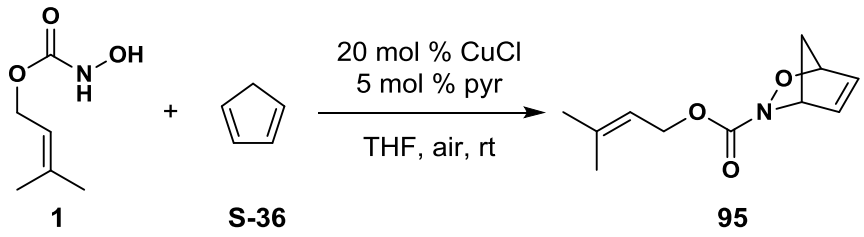
(91) (3S,5S,8S,9R,10R,13R,14R,17R)-benzyl 3-acetoxy-17-((2R,5R,E)-5,6-dimethylhept-3-en-2- yl)-10,13-dimethyl-2,3,4,9,10,11,12,13,14,15,16,17-dodecahydro-1H-8,5-(epoxyimino)cyclopenta[a]phenanthrene-19-carboxylate



According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 μL, 0.015 mmol, 0.05 equiv) were added to benzyl hydroxycarbamate **16** (50 mg, 0.30 mmol, 1.0 equiv) and ergosteryl acetate **S-40** (158 mg, 0.36 mmol, 1.2 equiv) in 3 mL THF.

The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **91** (155 mg, 86%, 35:1 mixture of regioisomers, inseparable) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 5H), 6.25 (d, J = 8.4 Hz, 1H), 6.21 (d, J = 8.5 Hz, 1H), 5.23 – 5.11 (m, 4H), 4.96 (d, J = 12.7 Hz, 1H), 3.32 (dd, J = 13.6, 3.6 Hz, 1H), 2.15 – 2.08 (m, 1H), 2.08 – 1.96 (m, 5H), 1.96 – 1.88 (m, 2H), 1.88 – 1.80 (m, 1H), 1.77 – 1.64 (m, 3H), 1.63 – 1.54 (m, 2H), 1.49 – 1.40 (m, 3H), 1.39 – 1.28 (m, 2H), 1.27 – 1.08 (m, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.93 – 0.86 (m, 6H), 0.86 – 0.74 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 159.4, 136.6, 136.6, 135.5, 132.4, 128.7, 128.5, 127.9, 127.6, 79.6, 70.4, 67.4, 67.0, 56.6, 53.7, 53.0, 44.4, 43.0, 40.0, 39.7, 39.0, 34.7, 33.3, 32.8, 28.6, 26.8, 24.2, 21.6, 21.1, 21.0, 20.2, 19.8, 17.9, 17.9, 13.3 ppm; IR (thin film) 2957, 2872, 1737, 1457, 1245, 1030 cm^{-1}; (ESI) *m/z* 626.38 (626.38 calcd for $C_{38}H_{53}NNaO_5^+$ $[MNa]^+$); $[\alpha]_D^{25}$ +5.6° (1.00, $CHCl_3$).

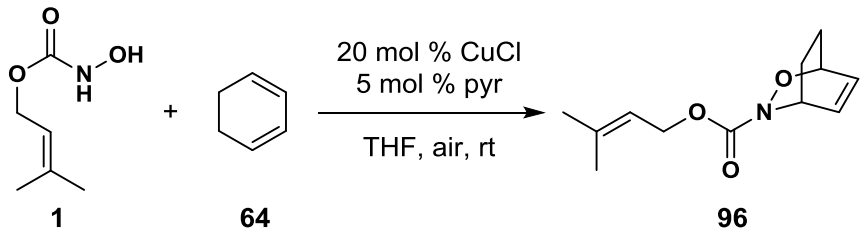
(95) 3-Methylbut-2-en-1-yl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate



According to the general procedure, CuCl (14 mg, 0.14 mmol, 0.20 equiv) and pyridine (2.9 µL, 0.036 mmol, 0.05 equiv) were added to 3-methylbut-2-en-1-yl hydroxycarbamate **1** (104 mg, 0.72 mmol, 1.0 equiv) and cyclopentadiene **S-36** (66 µL, 0.79 mmol, 1.1 equiv) in 7 mL THF. The resulting mixture was stirred for 3 h at rt. The reaction was quenched with 14 mL

EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 14 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **95** (117 mg, 78%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.42 – 6.39 (m, 1H), 6.37 – 6.33 (m, 1H), 5.33 – 5.26 (m, 1H), 5.19 (s, 1H), 5.00 (s, 1H), 4.59 (dd, *J* = 12.1, 7.3 Hz, 1H), 4.54 (dd, *J* = 12.1, 7.3 Hz, 1H), 1.96 (ddd, *J* = 8.6, 1.8, 1.8 Hz, 1H), 1.72 (d, *J* = 9.2 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 139.6, 134.6, 133.1, 118.5, 83.9, 65.1, 63.3, 48.3, 25.9, 18.1 ppm; IR (thin film) 3019, 2968, 1701, 1444, 1178, 1032 cm^{-1}; MS (ESI) *m/z* 232.09 (232.09 calcd for $C_{11}H_{15}NNaO_3^+$ $[MNa]^+$).

(96) 3-Methylbut-2-en-1-yl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



According to the general procedure, CuCl (5.9 mg, 0.060 mmol, 0.20 equiv) and pyridine (1.2 µL, 0.015 mmol, 0.05 equiv) were added to 3-methylbut-2-en-1-yl hydroxycarbamate **1** (44 mg, 0.30 mmol, 1.0 equiv) and cyclohexa-1,3-diene **64** (34 µL, 0.36 mmol, 1.1 equiv) in 3 mL THF. The resulting mixture was stirred for 4 h at rt. The reaction was quenched with 6 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford oxazine **96** (61 mg, 91%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 6.7, 6.7 Hz, 1H), 6.52 (ddd, *J* = 7.3, 6.0, 1.3 Hz, 1H), 5.34 (t, *J* = 7.2 Hz, 1H), 4.83 – 4.77 (m, 1H), 4.77 – 4.72 (m, 1H), 4.64 (dd, *J* =

12.0, 7.4 Hz, 1H), 4.58 (dd, *J* = 12.1, 7.3 Hz, 1H), 2.20 (dddd, *J* = 12.9, 9.0, 3.6, 3.6 Hz, 1H), 2.11 (dddd, *J* = 12.7, 9.5, 3.2, 3.2 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.49 (dddd, *J* = 12.9, 12.9, 2.9, 2.9 Hz, 1H), 1.41 – 1.34 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 139.3, 132.2, 131.8, 118.8, 71.2, 63.3, 50.2, 26.0, 23.7, 20.8, 18.3 ppm; IR (thin film) 2937, 2862, 1701, 1447, 1264, 1075 cm^{-1}; MS (ESI) *m/z* 246.11 (246.11 calcd for $C_{12}H_{17}NNaO_3^+$ $[MNa]^+$).

6.2 Chapter 3 Supporting Information

6.2.1 Supporting Information for the *N*-Selective Nitrosocarbonyl Aldol Reaction

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). ^{1}H NMR spectra were recorded on Varian Spectrometers (at 400, 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum Two FT/IR and are reported in terms of frequency of absorption

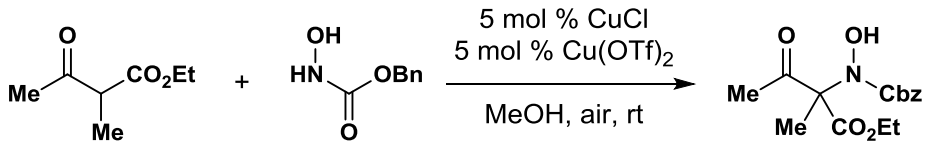
(cm^{-1}). Low resolution mass spectra and X-Ray analyses were obtained from the UC Santa Barbara Mass Spectrometry and X-Ray Facilities.

Starting Materials

Hydroxycarbamates **S-5**, **S-6**, **S-7**, and **S-8** were prepared according to literature precedent.[4] Hydroxycarbamates **S-4** and **30** were prepared according to literature precedent. Hydroxycarbamates **2**, and **42** were purchased from commercial sources. β-Keto esters **S-9**, **S-12**, **S-13**, **S-14**, **S-15**, and **S-16** were prepared by acylation of ethyl propionate with the corresponding *N*-methoxy-*N*-methylamides.[9] β-Keto esters **S-1**, **S-2**, and **S-3** were prepared by alkylation of the corresponding acetoacetate with methyl iodide.[10] β-Keto esters **S-10** and **S-11** were prepared from ethyl-2-bromopropionate and the corresponding nitrile.[11] β-Keto esters **1, S-17**, **S-18**, and **S-19** were purchased from commercial sources**.** Copper(II) trifluoromethanesulfonate was used as received. Copper(I) chloride was purified prior to use according to literature precedent.[12] Note, the use of commercially available copper(I) chloride can result in extended reaction times. The crystal structure data for *tert*-butyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate **9** and ethyl 4,5-dimethyl-3-((4-nitrobenzoyl)oxy)-2-oxooxazolidine-4-carboxylate **S-23** can be obtained free of charge from the Cambridge Crystallographic Data Centre with deposition numbers CCDC 883296 and CCDC 891932 respectively.

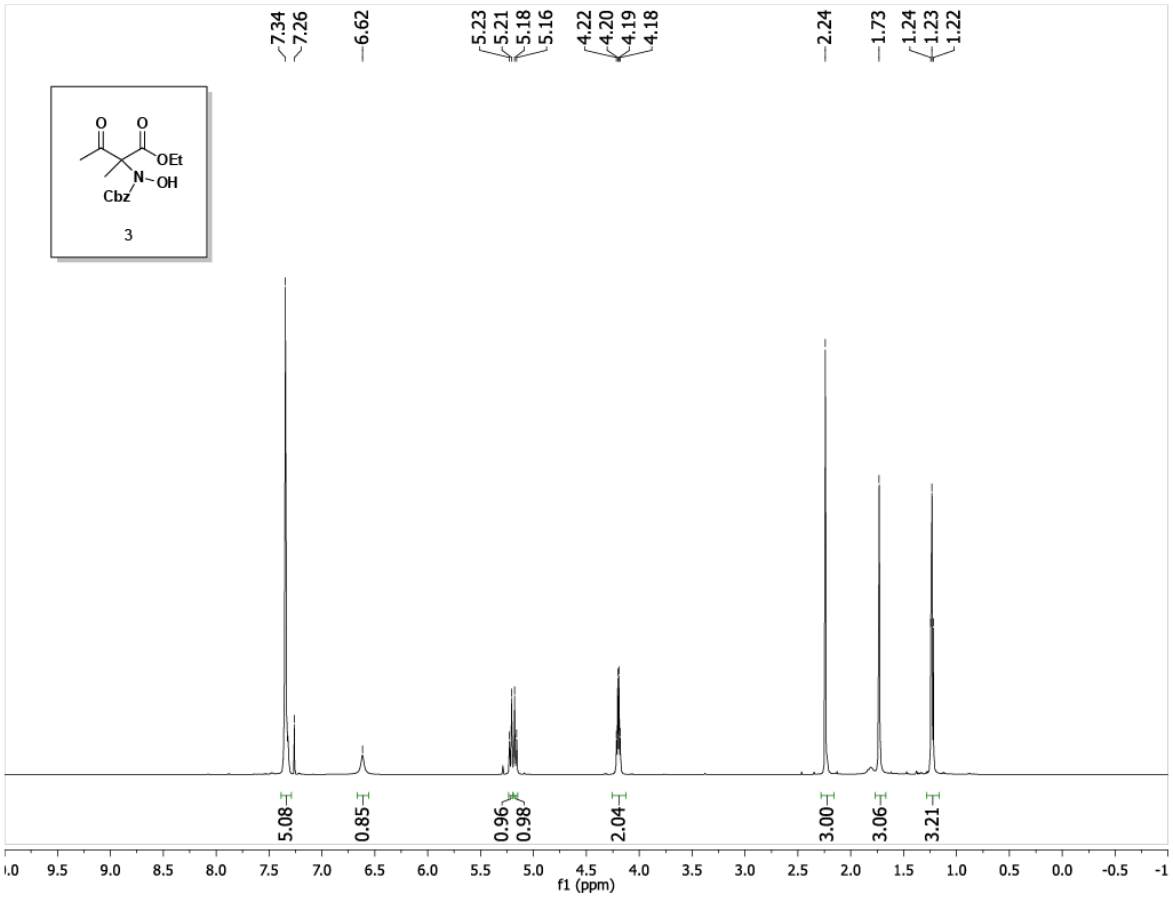
Substrate Scope

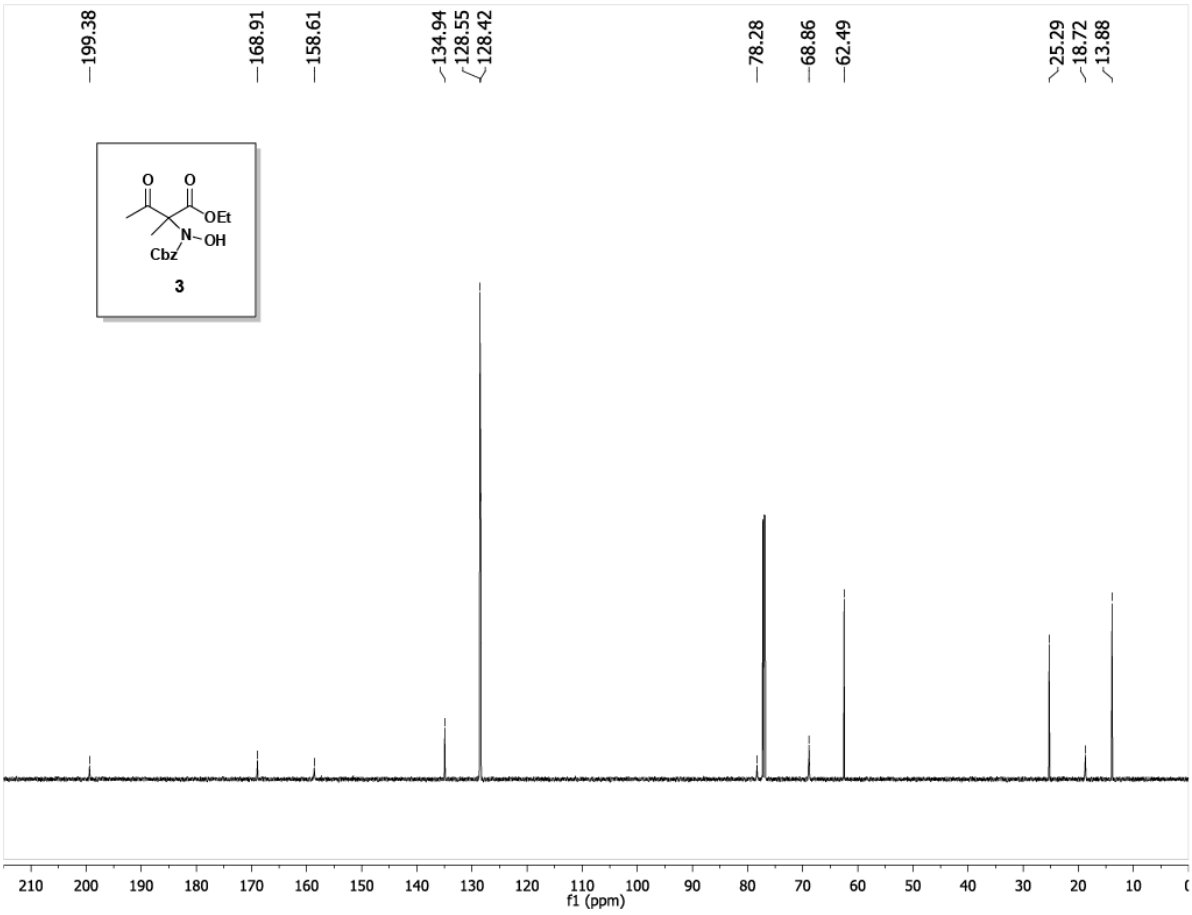
(3) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate



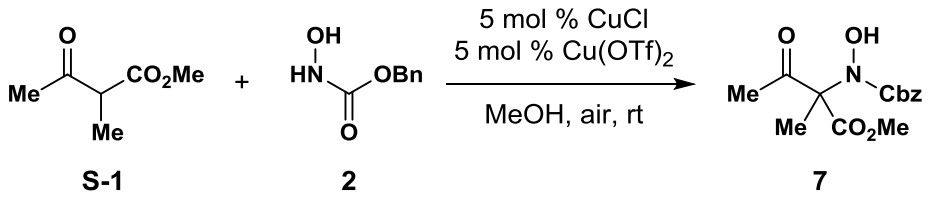
1 **2** **3**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (24 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **3** (80 mg, 92%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.62 (s, 1H), 5.22 (d, J = 12.0 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 2.24 (s, 3H), 1.73 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 168.9, 158.6, 134.9, 128.6, 128.4, 78.3, 68.9, 62.5, 25.3, 18.7, 13.9 ppm; IR (thin film) 3365, 2984, 1725, 1326, 1264, 1100 cm^{-1}; MS (ESI) *m/z* 332.11 (332.11 calcd for $C_{15}H_{19}NNaO_6^+$ $[MNa]^+$)


7.34
7.26
6.62
5.23
5.21
5.18
5.16
4.22
4.20
4.19
4.18
2.24
1.73
1.24
1.23
1.22
OEt
N
OH
Cbz
3
5.08
0.85
0.96
0.98
2.04
3.00
3.06
3.21
f1 (ppm)



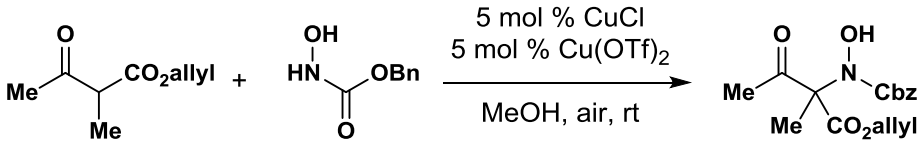
(7) Methyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate



To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-1** (44 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (24 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and

the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **7** (72 mg, 87%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 6.64 (s, 1H), 5.22 (d, J = 12.1 Hz, 1H), 5.18 (d, J = 12.1 Hz, 1H), 3.72 (s, 3H), 2.24 (s, 3H), 1.73 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 169.4, 158.6, 134.9, 128.6, 128.6, 128.4, 78.2, 68.9, 53.1, 25.3, 18.8 ppm; IR (thin film) 3396, 2955, 1748, 1270, 1216, 1085, 795 cm^{-1}; MS (ESI) *m/z* 318.09 (318.09 calcd for $C_{14}H_{17}NNaO_6^+$ $[MNa]^+$).

(8) Allyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate

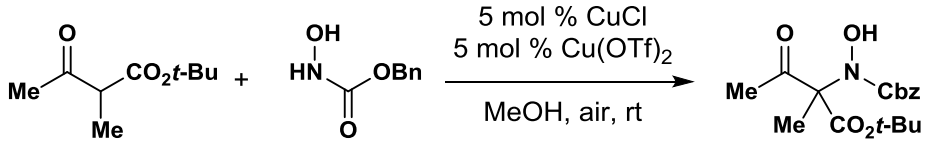


S-2 **2** **8**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-2** (53 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (20 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The

residue was purified by column chromatography to afford **8** (81 mg, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 6.55 (s, 1H), 5.85 (ddd, *J* = 16.6, 11.0, 5.7 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 11.1 Hz, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 5.5 Hz, 2H), 2.24 (s, 3H), 1.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.2, 168.6, 158.6, 134.9, 131.0, 128.6, 128.4, 119.1, 78.4, 68.9, 66.8, 25.3, 18.8 ppm; IR (thin film) 3364, 2950, 1724, 1498, 1455, 1393, 1325 cm^{-1}; MS (ESI) *m/z* 344.12 (344.11 calcd for $C_{16}H_{19}NNaO_6^+$ $[MNa]^+$).

(9) *Tert*-butyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate

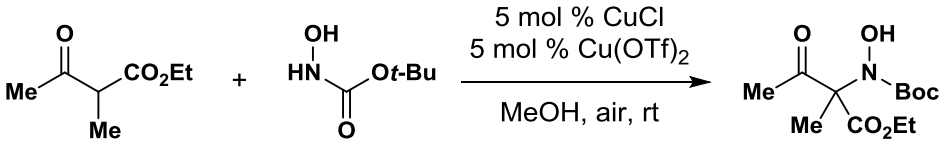


S-3 **2** **9**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-3** (59 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (24 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **9** (78 mg, 82%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 6.61 (s, 1H), 5.19 (s, 2H), 2.22 (s, 3H), 1.68 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 167.8, 158.6,

135.0, 128.5, 128.5, 128.4, 83.7, 78.7, 68.7, 27.7, 25.4, 18.7 ppm; IR (thin film) 3365, 2979, 1722, 1499, 1456, 1326 cm^{-1}; MS (ESI) *m/z* 360.13 (360.14 calcd for $C_{17}H_{23}NNaO_6^+$ $[MNa]^+$).

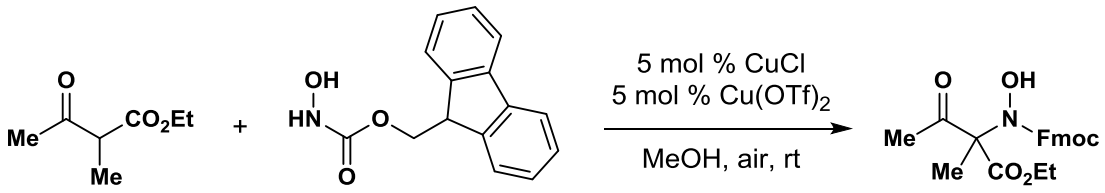
(10) Ethyl 2-((*tert*-butoxycarbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate



1 **42** **10**

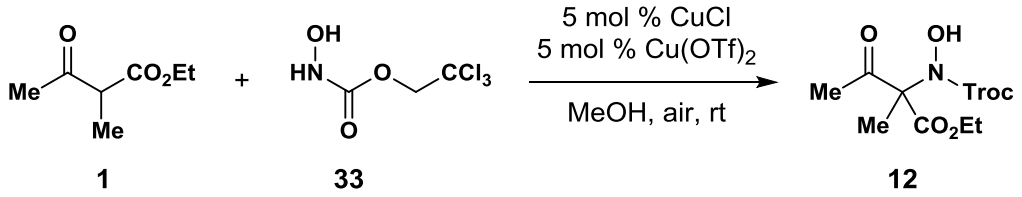
To a round bottom flask containing hydroxycarbamate **42** (37 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (23 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **10** (61 mg, 79%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 6.26 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.72 (s, 3H), 1.47 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7, 168.9, 157.9, 84.5, 78.4, 62.2, 27.9, 25.2, 19.1, 14.0 ppm; IR (thin film) 3363, 2982, 2936, 1747, 1752, 1449, 1370, 1260 cm^{-1}; MS (ESI) *m/z* 298.13 (298.13 calcd for $C_{12}H_{21}NNaO_6^+$ $[MNa]^+$).

(11) Ethyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxobutanoate



To a round bottom flask containing hydroxycarbamate **S-4** (72 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (27 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **11** (98 mg, 87%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 8.1 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (tdd, J = 7.5, 2.4, 0.9 Hz, 2H), 6.28 (s, 1H), 4.53 (dd, J = 10.6, 6.9 Hz, 1H), 4.47 (dd, J = 10.6, 7.0 Hz, 1H), 4.28 – 4.19 (m, 3H), 2.19 (s, 3H), 1.69 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.0, 169.0, 158.6, 143.3, 143.3, 141.3, 127.9, 127.2, 127.2, 125.1, 125.0, 120.0, 78.4, 68.8, 62.6, 46.8, 25.1, 18.5, 14.0 ppm; IR (thin film) 3373, 2982, 2257, 1744, 1726, 1527, 1376 1355 cm^{-1}; MS (ESI) *m/z* 420.15 (420.14 calcd for $C_{22}H_{23}NNaO_6^+$ $[MNa]^+$).

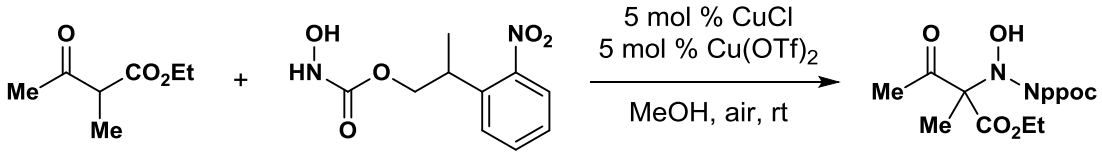
(12) Ethyl 2-(hydroxy((2,2,2-trichloroethoxy)carbonyl)amino)-2-methyl-3-oxobutanoate



To a round bottom flask containing hydroxycarbamate **33** (58 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (26 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **12** (89 mg, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (s, 1H), 4.84 (d, J = 11.9 Hz, 1H), 4.77 (d, J = 11.9 Hz, 1H), 4.33 – 4.24 (m, 2H), 2.33 (s, 3H), 1.80 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.9, 168.7, 156.8, 94.3, 78.5, 75.8, 62.8, 25.3, 18.8, 14.0 ppm; IR (thin film) 3373, 2985, 2955, 1729, 1447, 1391, 1357, 1327, 1267 cm^{-1}; MS (ESI) *m/z* 371.98 (100%), 373.98 (100%), 375.98 (34%) (371.98, 373.98, 375.97 calcd for $C_{10}H_{14}Cl_3NNaO_6^+$ $[MNa]^+$). **1 gram scale at 5 mol % catalyst loading:** To a round bottom flask containing hydroxycarbamate **33** (1.00g, 4.80 mmol, 1.0 equiv), $Cu(OTf)_2$ (87 mg, 0.24 mmol, 0.05 equiv), and CuCl (24 mg, 0.24 mmol, 0.05 equiv), was added a solution of β-

ketoester **1** (804 mg, 5.76 mmol, 1.2 equiv) in MeOH (34 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (26 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **12** (1.45 g, 86%) as a colorless oil. Spectral data was consistent with **12**. **1 gram scale at 1 mol % catalyst loading:** To a round bottom flask containing hydroxycarbamate **33** (1.00 g, 4.80 mmol, 1.0 equiv), $Cu(OTf)_2$ (17.4 mg, 0.048 mmol, 0.05 equiv), and CuCl (4.8 mg, 0.048 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (804 mg, 5.76 mmol, 1.2 equiv) in MeOH (34 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (240 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **12** (1.38 g, 82%) as a colorless oil. Spectral data was consistent with **12**.

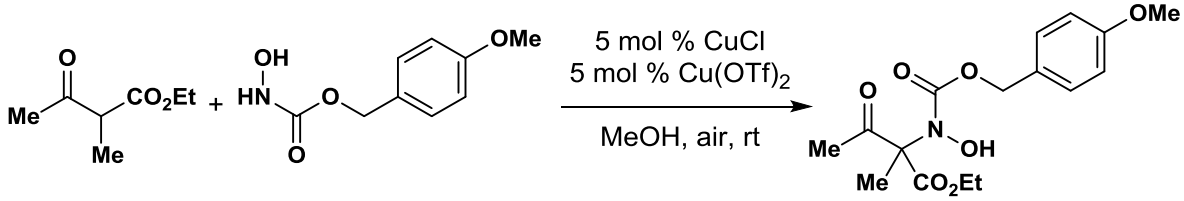
(13) Ethyl 2-(hydroxy((2-(2-nitrophenyl)propoxy)carbonyl)amino)-2-methyl-3-oxobutanoate



To a round bottom flask containing hydroxycarbamate **S-5** (67 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (36 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **13** (104 mg, 96%, 1;1 dr, inseparable mixture) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (td, J = 8.1, 1.1 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.37 (td, J = 7.6, 1.1 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 4.37 – 4.29 (m, 2H), 4.25 – 4.17 (m, 2H), 3.74 – 3.67 (m, 1H), 2.16 (d, J = 6.0 Hz, 3H), 1.66 (d, J = 4.5 Hz, 3H), 1.34 (d, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.2, 199.2, 168.7, 168.7, 158.4, 150.3, 150.2, 136.9, 136.8, 132.8, 132.8, 128.2, 128.2, 127.6, 124.3, 124.2, 78.1, 78.1, 70.7, 70.6, 62.5, 62.4, 33.3, 33.3, 25.1, 25.1, 18.5, 17.7, 17.7, 13.9 ppm; IR (thin film) 3373, 2982,

2257, 1744, 1726, 1609, 1527, 1447, 1355 cm^{-1}; MS (ESI) *m/z* 405.13 (405.13 calcd for $C_{17}H_{22}N_2NaO_8^+$ $[MNa]^+$).

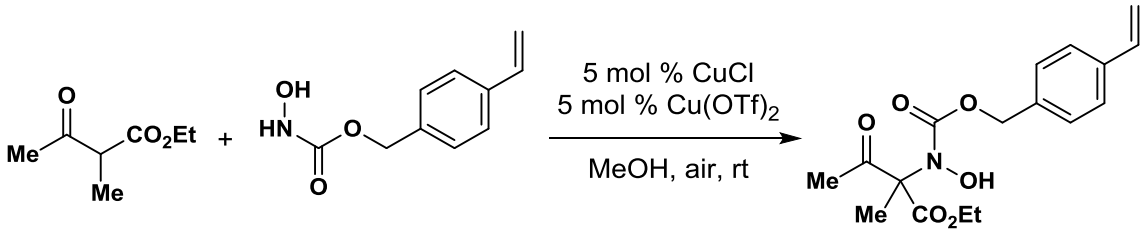
(14) Ethyl 2-(hydroxy(((4-methoxybenzyl)oxy)carbonyl)amino)-2-methyl-3-oxobutanoate



1 **S-6** **14**

To a round bottom flask containing hydroxycarbamate **S-6** (55 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (24 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **14** (65 mg, 69%) as a colorless oil after. ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.15 (d, J = 11.8 Hz, 1H), 5.09 (d, J = 11.8 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 168.9, 159.8, 158.7, 130.4, 127.1, 113.9, 78.2, 68.7, 62.4, 55.3, 25.3, 18.7, 13.9 ppm; IR (thin film) 3346, 2981, 2841, 1743, 1716, 1600, 1456, 1259 cm^{-1}; MS (ESI) *m/z* 362.13 (362.12 calcd for $C_{16}H_{21}NNaO_7^+$ $[MNa]^+$).

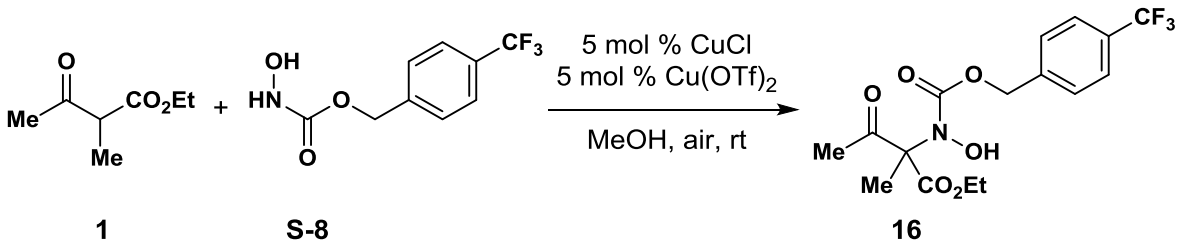
(15) Ethyl 2-(hydroxy(((4-vinylbenzyl)oxy)carbonyl)amino)-2-methyl-3-oxobutanoate



1 S-7 15

To a round bottom flask containing hydroxycarbamate **S-7** (54 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (48 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **15** (88 mg, 86%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.71 (dd, J = 17.6, 10.9 Hz, 1H), 6.29 (s, 1H), 5.76 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 5.21 (d, J = 12.1 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 4.22 (qd, J = 7.1, 2.4 Hz, 2H), 2.25 (s, 3H), 1.74 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.2, 168.9, 158.5, 137.9, 136.2, 134.4, 128.7, 126.4, 114.5, 78.4, 68.6, 62.5, 25.3, 18.7, 13.9 ppm; IR (thin film) 3375, 3090, 3983, 2257, 1744, 1725, 1515, 1448, 1328, 1264 cm^{-1}; MS (ESI) *m/z* 358.13 (358.13 calcd for $C_{17}H_{21}NNaO_6^+$ $[MNa]^+$).

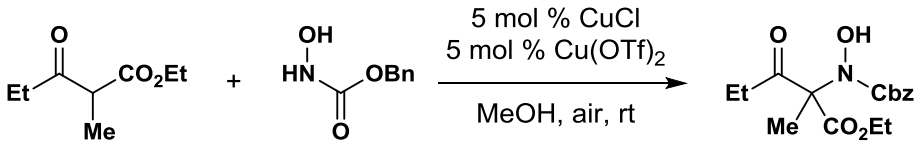
(16) Ethyl 2-(hydroxy(((4-(trifluoromethyl)benzyl)oxy)carbonyl)amino)-2-methyl-3-oxobutanoate



1 S-8 16

To a round bottom flask containing hydroxycarbamate **S-8** (66 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **1** (49 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (36 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **16** (93 mg, 87%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 5.25 (d, J = 12.7 Hz, 1H), 5.22 (d, J = 12.8 Hz, 1H), 4.24 – 4.18 (m, 2H), 2.25 (s, 3H), 1.74 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 168.9, 158.4, 139.0, 130.6 (q, J = 32.5 Hz), 128.2, 125.5 (q, J = 3.7 Hz), 124.7 (q, J = 271.6 Hz), 78.2, 67.6, 62.6, 25.3, 18.8, 13.8 ppm; IR (thin film) 3373, 2986, 2950, 1726, 1623, 1448, 1420, 1326, 1166, 1126 cm^{-1}; MS (ESI) *m/z* 400.11 (400.10 calcd for $C_{16}H_{18}F_3NNaO_6^+$ $[MNa]^+$).

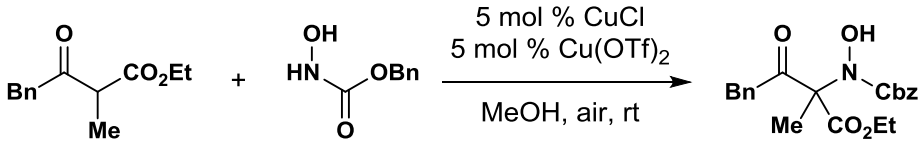
(19) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxopentanoate



S-9 **2** **19**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-9** (54 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (30 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **19** (78 mg, 86%%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 6.80 (s, 1H), 5.20 (d, J = 12.1 Hz, 1H), 5.15 (d, J = 12.1 Hz, 1H), 4.19 (qd, J = 7.1, 1.7 Hz, 2H), 2.65 – 2.52 (m, 2H), 1.72 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.7, 169.2, 158.7, 135.0, 128.5, 128.5, 128.4, 78.0, 68.8, 62.4, 30.8, 19.1, 13.9, 8.0 ppm; IR (thin film) 3375, 3066, 3034, 1745, 1722, 1587, 1456, 1187 cm^{-1}; MS (ESI) *m/z* 362.12 (362.10 calcd for $C_{16}H_{21}KNO_6^+$ $[MK]^+$).

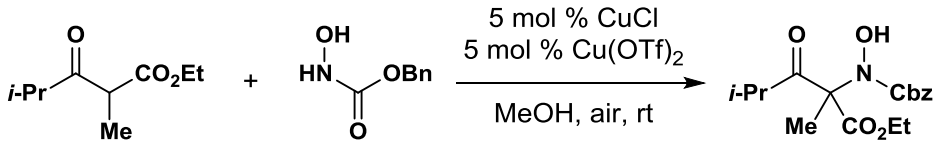
(20) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxo-4-phenylbutanoate



S-10 **2** **20**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-10** (75 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (96 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **20** (97 mg, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 5H), 7.30 – 7.21 (m, 3H), 7.17 (d, J = 7.1 Hz, 2H), 6.61 (s, 1H), 5.22 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.1 Hz, 1H), 4.19 – 4.08 (m, 2H), 3.94 (d, J = 16.5 Hz, 1H), 3.90 (d, J = 16.5 Hz, 1H), 1.79 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.9, 168.9, 158.7, 134.9, 133.8, 129.7, 128.6, 128.6, 128.5, 128.3, 126.9, 78.5, 69.0, 62.6, 43.8, 18.7, 13.8 ppm; IR (thin film) 3379, 3064, 2983, 1726, 1586, 1497, 1455, 1263, 1028 cm^{-1}; MS (ESI) *m/z* 408.15 (408.14 calcd for $C_{21}H_{23}NNaO_6^+$ $[MNa]^+$).

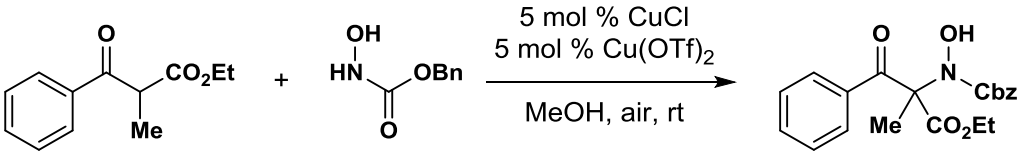
(21) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2,4-dimethyl-3-oxopentanoate



S-11 **2** **21**

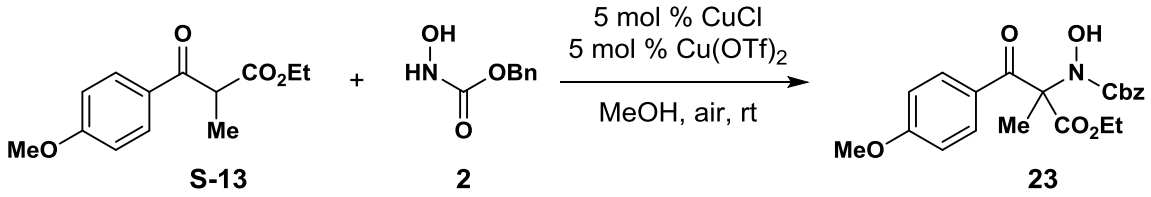
To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β -ketoester **S-11** (59 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (32 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **21** (87 mg, 91%) as a colorless. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 6.70 (s, 1H), 5.19 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.16 (qd, J = 7.1, 3.0 Hz, 2H), 3.11 (h, J = 6.6 Hz, 1H), 1.79 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 169.2, 158.6, 135.1, 128.5, 128.4, 128.4, 78.3, 68.6, 62.4, 36.3, 20.5, 20.5, 19.1, 13.9 ppm; IR (thin film) 3375, 2980, 2875, 1722, 1499, 1456, 1326, 1261, 1010 cm^{-1}; MS (ESI) *m/z* 360.15 (360.14 calcd for $C_{17}H_{23}NNaO_6^+$ $[MNa]^+$).

(22) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-oxo-3-phenylpropanoate



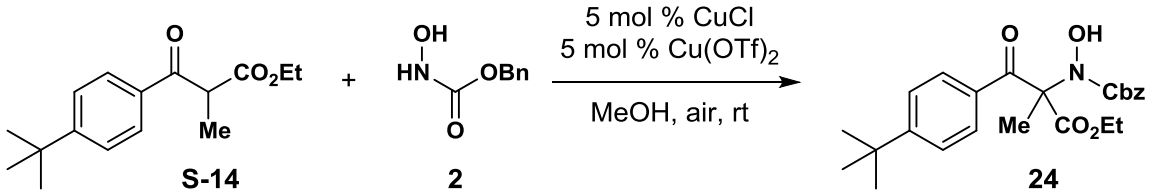
To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-12** (70 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (72 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **22** (90 mg, 87%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.4, 1.1 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.18 (d, J = 3.6 Hz, 2H), 6.66 (s, 1H), 5.15 (d, J = 12.1 Hz, 1H), 5.08 (d, J = 12.1 Hz, 1H), 4.24 (qd, J = 7.1, 1.2 Hz, 2H), 1.92 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 169.8, 158.4, 134.8, 134.5, 133.0, 129.3, 128.4, 128.4, 128.3, 128.3, 78.3, 68.9, 62.6, 19.9, 13.9 ppm; IR (thin film) 3363, 3066, 2983, 1744, 1715, 1688, 1578, 1498, 1264 cm^{-1}; MS (ESI) *m/z* 394.13 (394.13 calcd for $C_{20}H_{21}NNaO_6^+$ $[MNa]^+$).

(23) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-3-(4-methoxyphenyl)-2-methyl-3-oxopropanoate



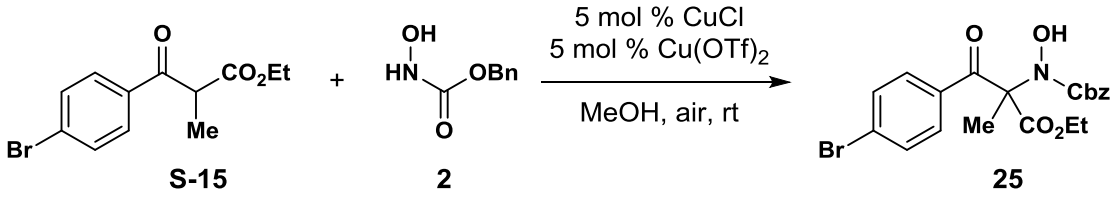
To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-13** (80 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (96 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **23** (101 mg, 90%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 9.0 Hz, 2H), 7.27 – 7.21 (m, 3H), 7.15 (s, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.13 (d, J = 12.1 Hz, 1H), 5.05 (d, J = 12.2 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.91 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H) ppm**;** ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.8, 170.0, 163.4, 158.8, 135.0, 131.8, 128.5, 128.4, 128.4, 127.4, 113.6, 78.4, 68.9, 62.6, 55.5, 20.3, 14.0 ppm**;** IR (thin film) 3364, 2958, 2839, 1745, 1725, 1587, 1516, 1251 cm^{-1}; MS (ESI) *m/z* 424.14 (424.14 calcd for $C_{21}H_{23}NNaO_7^+$ $[MNa]^+$).

(24) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-3-(4-(tert-butyl)phenyl)-2-methyl-3-oxopropanoate



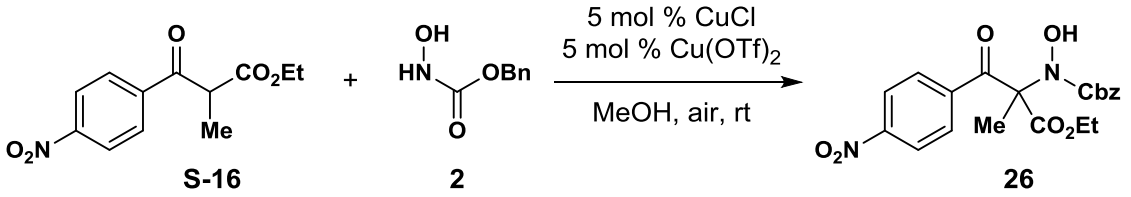
To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-14** (89 mg, 0.34 mmol, 0.05 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (96 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **24** (104 mg, 87%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.17 (s, 2H), 6.69 (s, 1H), 5.16 (d, J = 12.1 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.92 (s, 3H), 1.32 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.5, 169.9, 158.5, 156.7, 134.9, 131.7, 129.3, 128.4, 128.3, 128.3, 125.3, 78.4, 7.8, 62.6, 35.1, 31.0, 20.2, 13.9 ppm; IR (thin film) 3358, 2965, 1745, 1716, 1685, 1321, 1268 cm^{-1}; MS (ESI) *m/z* 450.19 (450.19 calcd for $C_{24}H_{29}NNaO_6^+$ $[MNa]^+$).

(25) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-3-(4-bromophenyl)-2-methyl-3-oxopropanoate



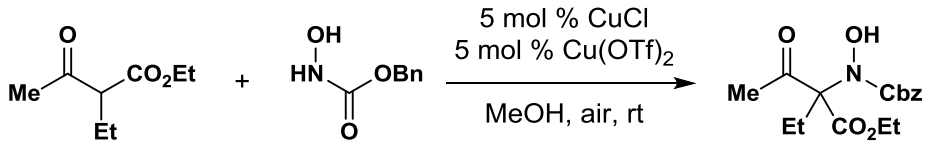
To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-15** (97 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (72 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **25** (100 mg, 79%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.30 – 7.24 (m, 3H), 7.14 (d, J = 6.7 Hz, 2H), 6.87 (s, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.22 (qd, J = 7.1, 0.8 Hz, 2H), 1.88 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.6, 169.5, 158.4, 134.6, 133.3, 131.6, 130.7, 128.5, 128.5, 128.4, 128.2, 78.2, 69.0, 62.8, 19.7, 13.9 ppm; IR (thin film) 3358, 3034, 2982, 1744, 1713, 1691, 1583, 1264 cm^{-1}; MS (ESI) *m/z* 472.06 (100%), 474.06 (100%) (472.04, 474.03 calcd for $C_{20}H_{20}BrNNaO_6^+$ $[MNa]^+$).

(26) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methyl-3-(4-nitrophenyl)-3-oxopropanoate



To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-16** (85 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (72 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **26** (74 mg, 63%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H), 7.33 – 7.26 (m, 3H), 7.19 (d, J = 6.8 Hz, 2H), 6.54 (s, 1H), 5.15 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.91 (s, 3H), 1.55 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.4, 169.1, 158.3, 149.9, 139.5, 134.5, 130.1, 128.7, 128.5, 128.5, 123.4, 78.2, 69.2, 63.1, 19.1, 13.9 ppm; IR (thin film) 3373, 2984, 1744, 1699, 1525, 1348 cm^{-1}; MS (ESI) *m/z* 439.12 (439.11 calcd for $C_{20}H_{20}N_2NaO_8^+$ $[MNa]^+$).

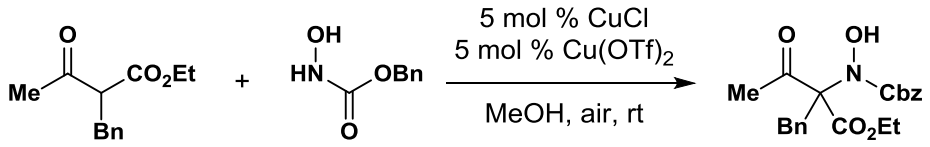
(27) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-ethyl-3-oxobutanoate



S-17 **2** **27**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-17** (54 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (48 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **27** (76 mg, 84%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 6.71 (s, 1H), 5.19 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.26 (dq, J = 14.8, 7.5 Hz, 1H), 2.24 (s, 3H), 2.16 (dq, J = 14.8, 7.5 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.2, 168.5, 158.5, 135.1, 128.5, 128.5, 128.4, 81.1, 68.7, 62.3, 26.6, 26.6, 13.9, 9.2 ppm ; IR (thin film) 3374, 3066, 3034, 1722, 1456, 1393, 1326, 1243 cm^{-1}; MS (ESI) *m/z* 346.15 (346.13 calcd for $C_{16}H_{21}NNaO_6^+$ $[MNa]^+$).

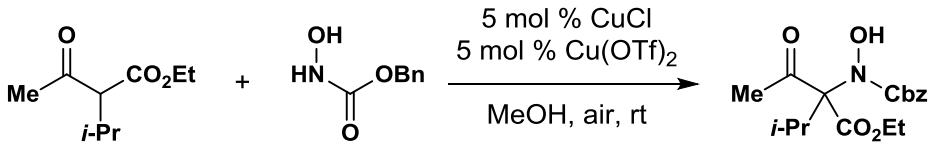
(28) Ethyl 2-benzyl-2-(((benzyloxy)carbonyl)(hydroxy)amino)-3-oxobutanoate



S-18 **2** **28**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (5 mg, 0.014 mmol, 0.05 equiv), and CuCl (1.4 mg, 0.014 mmol, 0.05 equiv), was added a solution of β-ketoester **S-18** (75 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (120 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **28** (85 mg, 79%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 5H), 7.30 (d, J = 7.5 Hz, 2H), 7.24 – 7.19 (m, 3H), 6.46 (s, 1H), 4.93 (d, J = 12.0 Hz, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.25 – 4.15 (m, 2H), 3.64 (d, J = 14.1 Hz, 1H), 3.49 (d, J = 14.1 Hz, 1H), 2.13 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 167.4, 157.4, 134.9, 131.0, 128.6, 128.6, 128.5, 128.1, 127.2, 82.4, 68.5, 62.8, 36.2, 26.4, 13.8 ppm; IR (thin film) 3388, 3033, 2983, 1718, 1497, 1455, 1310, 1117 cm^{-1}; MS (ESI) *m/z* 408.15 (408.14 calcd for $C_{21}H_{23}NNaO_6^+$ $[MNa]^+$).

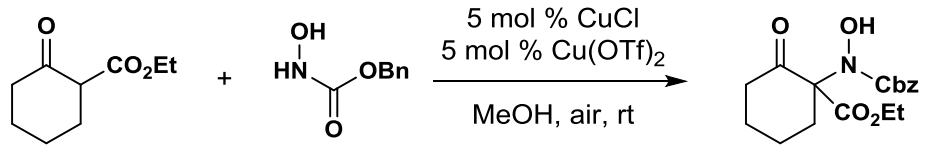
(29) Ethyl 2-acetyl-2-(((benzyloxy)carbonyl)(hydroxy)amino)-3-methylbutanoate



S-19 **2** **29**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (20 mg, 0.056 mmol, 0.20 equiv), and CuCl (5.5 mg, 0.056 mmol, 0.20 equiv), was added a solution of β-ketoester **S-19** (59 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (96 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **29** (40 mg, 42%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 6.65 (s, 1H), 5.19 (s, 2H), 4.26 – 4.17 (m, 2H), 2.79 (h, J = 6.9 Hz, 1H), 2.22 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.9, 168.8, 157.7, 135.2, 128.5, 128.5, 128.4, 83.2, 68.5, 62.3, 32.7, 27.6, 19.2, 18.6, 13.9 ppm; IR (thin film) 3385, 2975, 1721, 1498, 1456, 1393, 1323 cm^{-1}; MS (ESI) *m/z* 360.16 (360.14 calcd for $C_{17}H_{23}NNaO_6^+$ $[MNa]^+$).

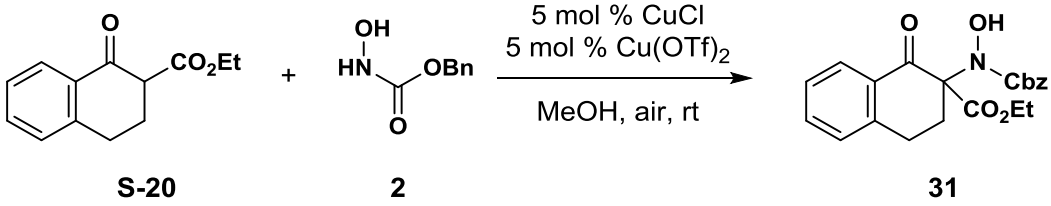
(30) Ethyl 1-(((benzyloxy)carbonyl)(hydroxy)amino)-2-oxocyclohexanecarboxylate



72 **2** **30**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (20 mg, 0.056 mmol, 0.20 equiv), and CuCl (5.5 mg, 0.056 mmol, 0.20 equiv), was added a solution of β-ketoester **72** (58 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (120 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **30** (40 mg, 43%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 6.38 (s, 1H), 5.24 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.25 – 4.15 (m, 2H), 2.75 (td, J = 12.4, 6.1 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.46 (dt, J = 12.8, 4.2 Hz, 1H), 2.26 (ddd, J = 15.0, 11.6, 3.4 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.94 – 1.85 (m, 1H), 1.84 – 1.74 (m, 1H), 1.72 – 1.65 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.3, 168.7, 159.3, 135.0, 128.6, 128.5, 128.5, 79.9, 68.9, 62.3, 39.9, 34.7, 28.2, 20.6, 14.0 ppm; IR (thin film) 3364, 2947, 1724, 1324 cm^{-1}; MS (ESI) *m/z* 358.11 (358.13 calcd for $C_{17}H_{21}NNaO_6^+$ $[MNa]^+$).

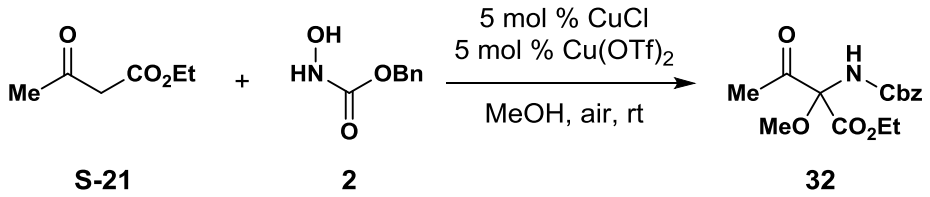
(31) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate



S-20 **2** **31**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (20 mg, 0.056 mmol, 0.20 equiv), and CuCl (5.5 mg, 0.056 mmol, 0.20 equiv), was added a solution of β-ketoester **S-20** (74 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (144 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **29** (75 mg, 70%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 1H), 7.46 (td, J = 7.6, 1.3 Hz, 1H), 7.36 – 7.26 (m, 6H), 7.21 (d, J = 7.7 Hz, 1H), 6.52 (s, 1H), 5.18 (d, J = 12.4 Hz, 1H), 5.16 (d, J = 12.8 Hz, 1H), 4.20 – 4.09 (m, 2H), 3.19 – 3.11 (m, 1H), 2.97 – 2.89 (m, 2H), 2.71 – 2.64 (m, 1H), 1.15 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.6, 168.5, 159.0, 142.7, 135.0, 133.6, 132.0, 128.5, 128.4, 128.4, 128.2, 126.8, 76.4, 68.8, 62.3, 31.2, 25.6, 13.8 ppm; IR (thin film) 3373, 3066, 1743, 1701, 1297 cm^{-1}; MS (ESI) *m/z* 406.15 (406.13 calcd for $C_{21}H_{21}NNaO_6^+$ $[MNa]^+$).

(32) Ethyl 2-(((benzyloxy)carbonyl)(hydroxy)amino)-2-methoxy-3-oxobutanoate

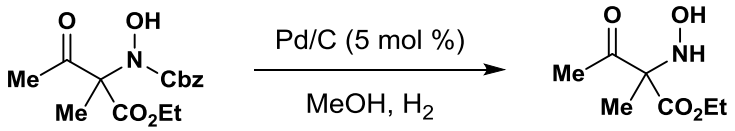


S-21 **2** **32**

To a round bottom flask containing hydroxycarbamate **2** (47 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (20 mg, 0.056 mmol, 0.20 equiv), and CuCl (5.5 mg, 0.056 mmol, 0.20 equiv), was added a solution of β-ketoester **S-21** (44 mg, 0.34 mmol, 1.2 equiv) in MeOH (2 mL). The reaction was stirred at room temperature open to the atmosphere, using a 24-gauge needle, until completion as indicated by TLC (72 h). Upon completion, solvent removal *in vacuo* and dilution with ethyl acetate was followed by quenching with EDTA (0.5 M, pH 7.0), and the solution was stirred until color no longer persisted in the organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford **32** (51 mg, 61%) as a colorless oil. ^{1}H NMR (600 MHz, CD_3OD) δ 7.38 – 7.28 (m, 5H), 5.11 (d, J = 12.8 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 4.27 – 4.17 (m, 2H), 3.25 (s, 3H), 2.30 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 200.6, 165.9, 155.2, 136.3, 128.1, 127.8, 127.6, 89.4, 66.7, 62.6, 50.3, 24.0, 12.7 ppm; IR (thin film) 3378, 2983, 1730, 1273 cm^{-1}; MS (ESI) *m/z* 332.13 (332.11 calcd for $C_{15}H_{19}NNaO_6^+$ $[MNa]^+$).

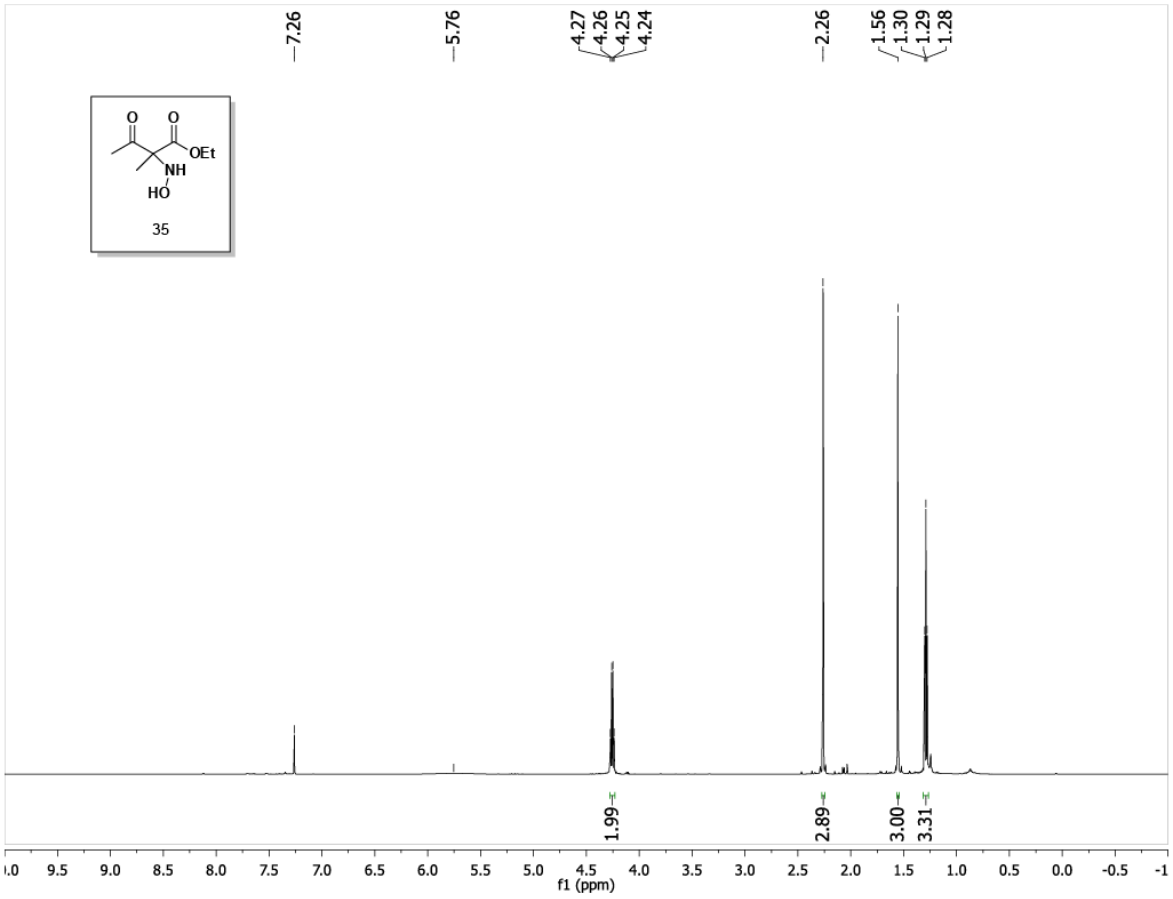
Post–Functionalization of *N*-Aldol Products

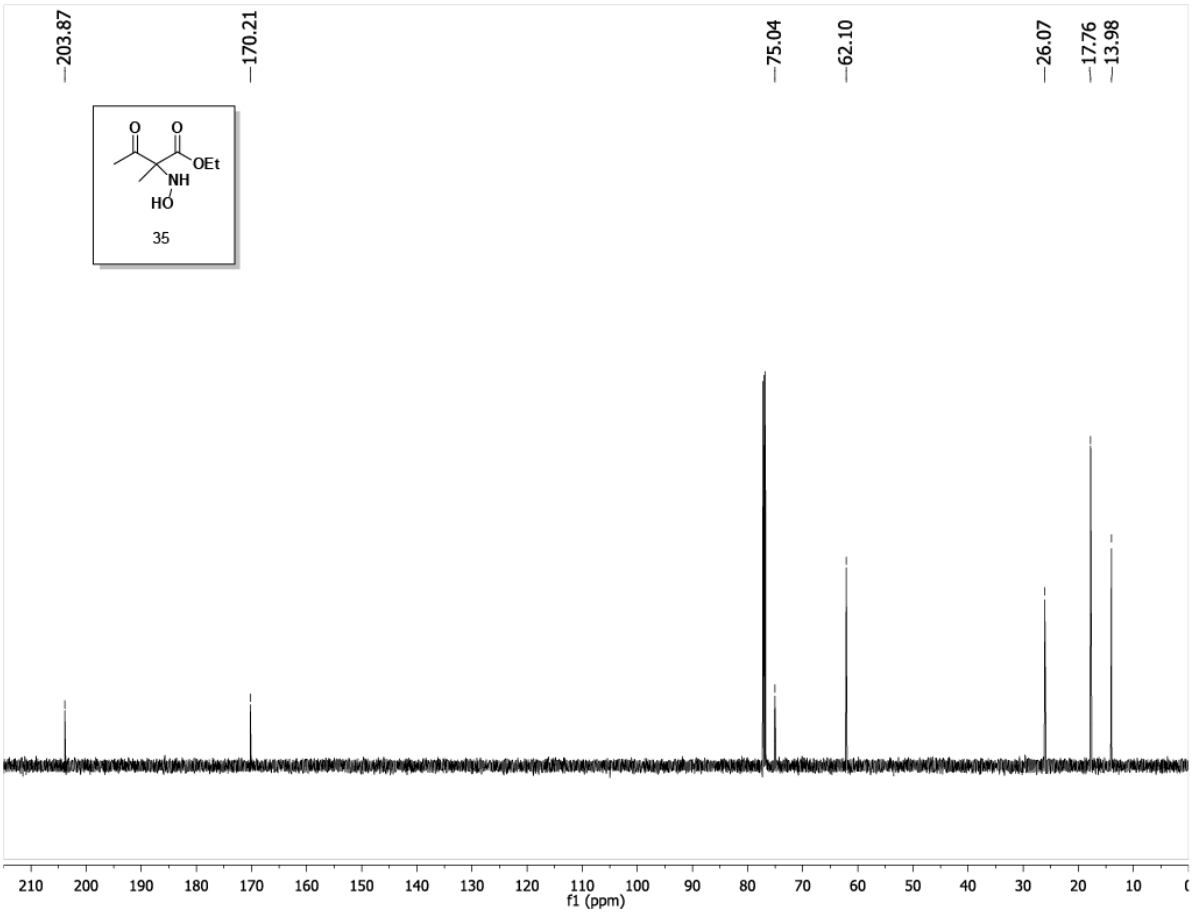
(35) Ethyl 2-(hydroxyamino)-2-methyl-3-oxobutanoate



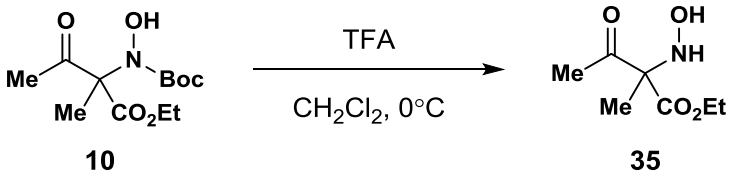
3 **35**

To a stirred solution of oxobutanoate **3** (59 mg, 0.192 mmol, 1.0 equiv) in methanol (2 mL), was added Pd/C (10%) (10 mg, 0.096 mmol, 0.05 equiv). The flask was charged with hydrogen gas and left to stir until complete as indicated by TLC (15 min). Filtration and removal of the solvent *in vacuo* was followed with column chromatography to afford **35** (25 mg, 73%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.25 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 1.56 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.9, 170.2, 75.0, 62.1, 26.1, 17.8, 14.0 ppm; IR (thin film) 3280, 2986, 2939, 1718, 1448, 1359 cm^{-1}; MS (ESI) *m/z* 198.07 (198.07 calcd for $C_7H_{13}NNaO_4^+$ $[MNa]^+$).


7.26
5.76
4.27
4.26
4.25
4.24
2.26
1.56
1.30
1.29
1.28
O
O
OEt
NH
HO
35
1.99
2.89
3.00
3.31
f1 (ppm)



(35) Ethyl 2-(hydroxyamino)-2-methyl-3-oxobutanoate

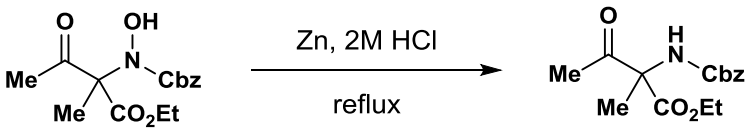


10 **35**

To a stirred solution of oxobutanoate **10** (26 mg, 0.094 mmol, 1.0 equiv) in dichloromethane (0.94 mL) at 0 °C, was added trifluoroacetic acid (0.08 mL, 1.13 mmol, 12.0 equiv) dropwise. The reaction was left to stir until complete as indicated by TLC (10 min). The reaction was transferred to a separatory funnel containing dichloromethane and saturated $NaHCO_3$. The reaction was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* was

followed with the isolation of **35** (16 mg, 95%) as a colorless oil. ^{1}H NMR (600 MHz, CD_3OD) δ 4.21 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H), 1.48 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 204.5, 170.1, 75.0, 61.4, 24.6, 16.6, 12.9 ppm. Additional spectral data were consistent with the previous entry.

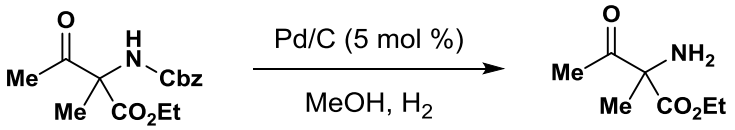
(36) Ethyl 2-(((benzyloxy)carbonyl)amino)-2-methyl-3-oxobutanoate



3 **36**

Oxobutanoate **3** (192 mg, 0.62 mmol, 1.0 equiv) was heated under reflux in 2 M HCl (4.30 mL) with powdered zinc (203 mg, 3.1 mmol, 5 equiv) for 2 hours and 15 minutes. The reaction was transferred to a separatory funnel containing dichloromethane and saturated $NaHCO_3$. The reaction was extracted with dichloromethane (7 x 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and solvent removal *in vacuo,* the crude material was purified by column chromatography to afford **36** (144 mg, 79%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 6.38 (s, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.21 (dd, *J* = 11.9, 6.9 Hz, 2H), 2.19 (s, 3H), 1.73 (s, 3H), 1.21 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.9, 169.0, 154.5, 136.2, 128.5, 128.2, 128.1, 68.6, 66.9, 62.7, 24.1, 20.4, 13.9 ppm; IR (thin film) 3408, 3034, 2984, 1722, 1492, 1269, 1065 cm^{-1}; MS (ESI) *m/z* 316.13 (316.12 calcd for $C_{15}H_{19}NNaO_5^+$ $[MNa]^+$).

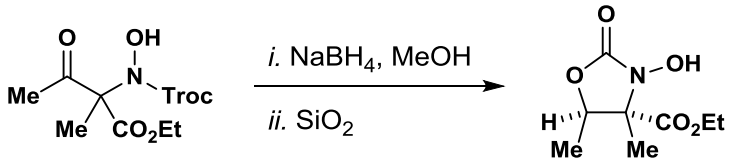
(37) Ethyl 2-amino-2-methyl-3-oxobutanoate



36 **37**

To a stirred solution of oxobutanoate **36** (92 mg, 0.31 mmol, 1.0 equiv) in methanol (2 mL), was added Pd/C (10%) (25 mg, 0.016 mmol, 0.05 equiv). The flask was charged with hydrogen gas and left to stir until complete as indicated by TLC (10 min). Filtration and removal of the solvent *in vacuo* was followed with the isolation of **37** (44 mg, 90%) as a colorless oil. ^{1}H NMR (600 MHz, CD_3OD) δ 4.22 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.48 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).**;** ^{13}C NMR (151 MHz, CD_3OD) δ 205.4, 172.1, 66.9, 61.6, 23.5, 20.8, 12.9.**;** IR (thin film) 3279, 2926, 1717, 1263, 1106 cm^{-1}; MS (ESI) *m/z* 182.07 (182.09 calcd for $C_7H_{13}NNaO_3^+$ $[MNa]^+$).

(38) Ethyl 3-hydroxy-4,5-dimethyl-2-oxooxazolidine-4-carboxylate

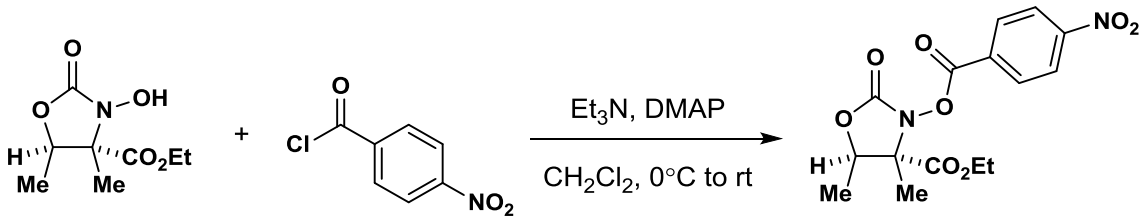


12 **38**

To a round bottom flask was added oxobutanoate **12** (105 mg, 0.30 mmol, 1.0 equiv) and flushed with nitrogen gas, followed by the addition of methanol (4 mL). A solution of sodium borohydride (13 mg, 0.33 mmol, 1.1 equiv) in methanol (1 mL) was then added at 0 ^{o}C and stirred for 20 min, followed by the addition of silica gel (1 g) and stirred for 2 hr. The solvent was removed *in vacuo* and the sample was loaded for column chromatography to afford **38** (43mg, 71%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.56

(q, J = 6.5 Hz, 1H), 4.27 (qd, J = 7.1, 1.1 Hz, 2H), 1.48 (s, 3H), 1.43 (d, J = 6.5 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 157.8, 74.7, 68.9, 62.5, 14.8, 14.0, 13.2 ppm; IR (thin film) 3269, 2988, 2943, 1770, 1465, 1388 cm^{-1}; MS (ESI) *m/z* 242.05 (242.04 calcd for $C_8H_{13}KNO_5^+$ $[MK]^+$).

(S-23) Ethyl 4,5-dimethyl-3-((4-nitrobenzoyl)oxy)-2-oxooxazolidine-4-carboxylate



38 **S-22** **S-23**

To a stirred solution of **38** (40.0 mg, 0.20 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.24 mg, 0.002 mmol, 0.01 equiv), and triethylamine (22.2 mg, 0.22 mmol, 1.1 equiv) in dichloromethane (6 mL) at 0 ^{o}C was slowly added 4-nitrobenzoylchloride **S-22** (41 mg, 0.22 mmol, 1.1 equiv), under nitrogen gas. Removal of the solvent *in vacuo* was then followed by column chromatography to afford **S-23** (57 mg, 88%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J = 8.9 Hz, 2H), 8.25 (d, J = 8.9 Hz, 2H), 4.92 (q, J = 6.5 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.59 (s, 3H), 1.56 (d, J = 6.5 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 161.6, 154.9, 151.1, 132.3, 131.2, 123.8, 75.1, 68.8, 62.6, 14.8, 13.9, 13.8 ppm; IR (thin film) 1807, 1780, 1739, 1529, 1387, 1347, 1249 cm^{-1}; MS (ESI) *m/z* 375.09 (375.08 calcd for $C_{15}H_{16}N_2NaO_8^+$ $[MK]^+$).

6.2.2. Supporting Information for the *O*-Selective Nitrosocarbonyl Aldol Reaction

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially

obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). ^{1}H NMR spectra were recorded on Varian Spectrometers (at 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift, and where relevant, multiplicity and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum Two FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra and X-Ray analyses were obtained from the UC Santa Barbara Mass Spectrometry and X-Ray Facilities.

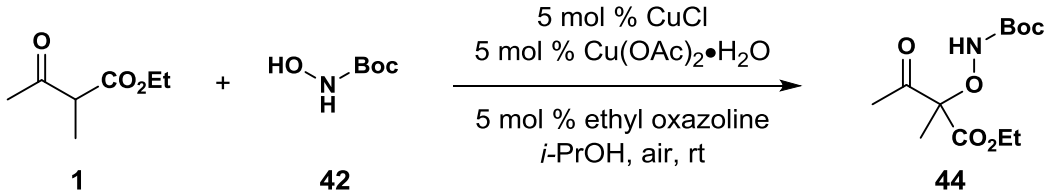
Starting Materials

Hydroxycarbamates **2**, **42**, **S-5**, **S-6**, **S-7**, and **S-8** were purchased from commercial sources, or prepared according to literature precedent.[1] β-Ketoesters **1**, **72**, **S-17**, **S-18**, **S-19**, **S-24**, **S-25**, and **S-26** were purchased from commercial sources and used as received. β-Ketoesters **S-1**, **S-2**, and **S-3** were prepared by alkylation of the corresponding acetoacetate with methyl iodide.[10] β-Ketoesters **S-9**, **S-10**, and **S-11** were prepared from ethyl-2-bromopropionate and the corresponding nitrile. β-Ketoesters **S-20**, and **S-27** were prepared by acylation of the ketone with the corresponding carbonate.[13] β-Ketoesters **S-28** and **S-29** were prepared by

esterification from the corresponding acid.[14] β-Ketoester **S-30** was prepared according to literature precedent. Annulation reagent **S-32** was purchased from commercial vendors and used as received. Annulation reagent **S-33** was prepared according to the Aggarwal method.[15] The crystal structures of compounds **85** and **S-31** are available free of charge from the Cambridge Crystallographic Data Centre via www.cdcc.cam.ac.uk/data_request/cif CCDC 907696 (**85**) and CCDC 932616 (**S-31**).

Substrate Scope for the *O*-Selective Nitrosocarbonyl Aldol

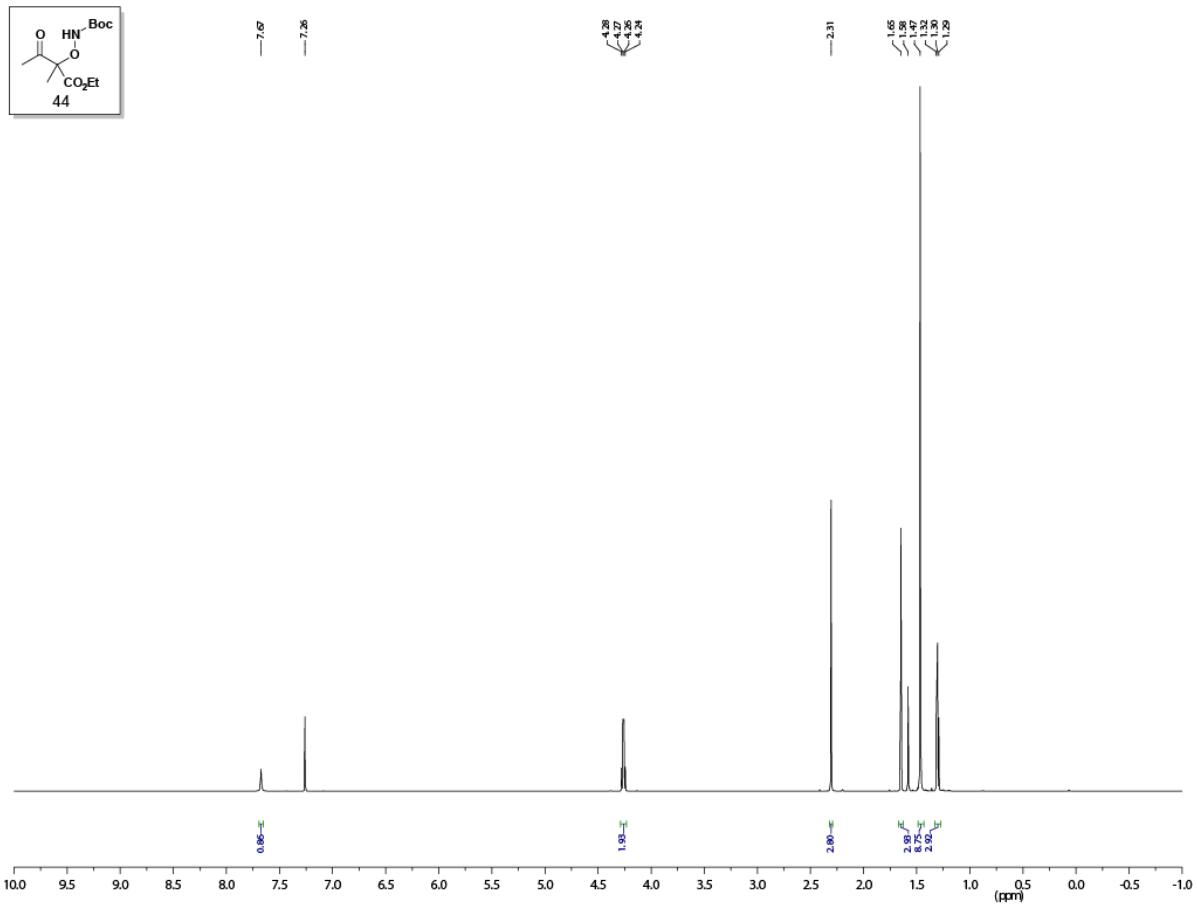
(44) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxobutanoate

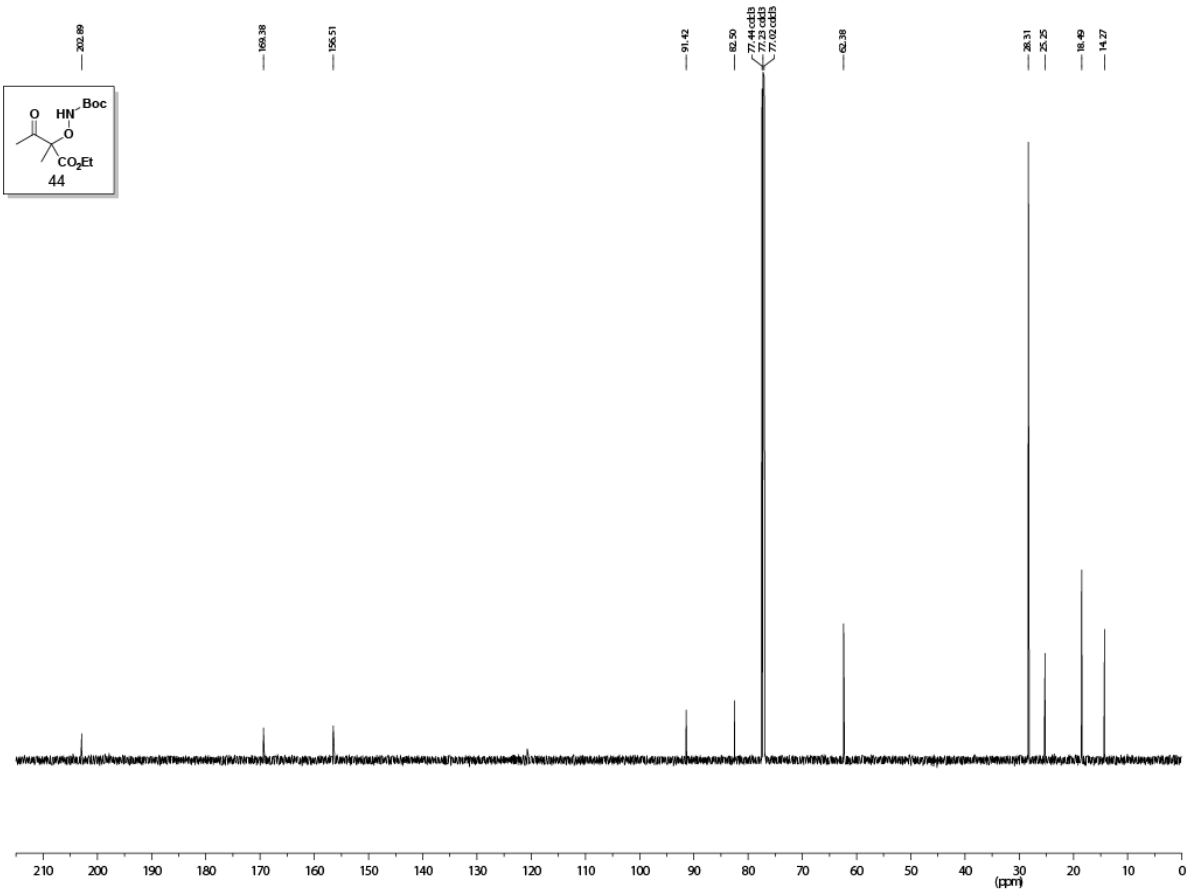


1 **42** **44**

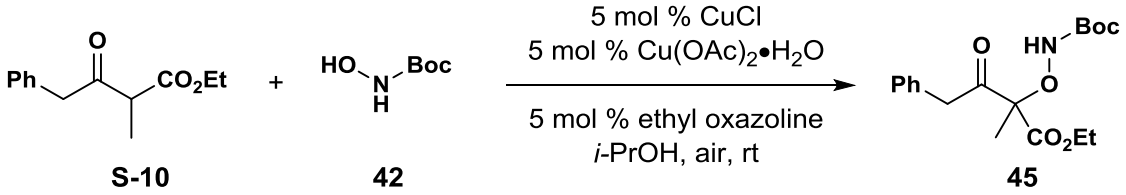
According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 17 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **44** (70 mg, 84%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.65 (s, 3H), 1.47 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9, 169.4, 156.5, 91.4, 82.5, 62.4, 28.3, 25.3, 18.5, 14.3 ppm; IR (thin

film) 3297, 2958, 1727, 1370, 1248, 1131 cm^{-1}; HRMS (ESI) *m/z* 298.1259 (298.1261 calcd for $C_{12}H_{21}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (8 mg, 10%).





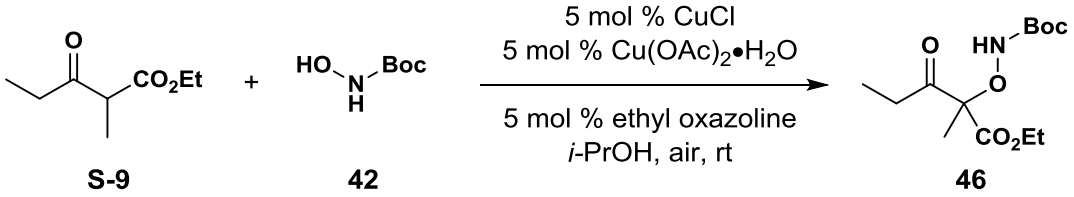
(45) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxo-4-phenylbutanoate



According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxo-4-phenylbutanoate **S-10** (133 mg, 0.60 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with

ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **45** (77 mg, 73%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.30 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.10 (d, J = 17.1 Hz, 1H), 3.97 (d, J = 17.1 Hz, 1H), 1.10 (s, 3H), 1.48 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.4, 169.4, 156.5, 133.5, 130.0, 128.6, 127.2, 91.4, 82.5, 62.4, 43.6, 28.3, 18.6, 14.2 ppm; IR (thin film) 3301, 2982, 1729, 1456, 1370, 1249, 1135 cm^{-1}; HRMS (ESI) *m/z* 374.1571 (374.1574 calcd for $C_{18}H_{25}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (16 mg, 15%).

(46) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxopentanoate

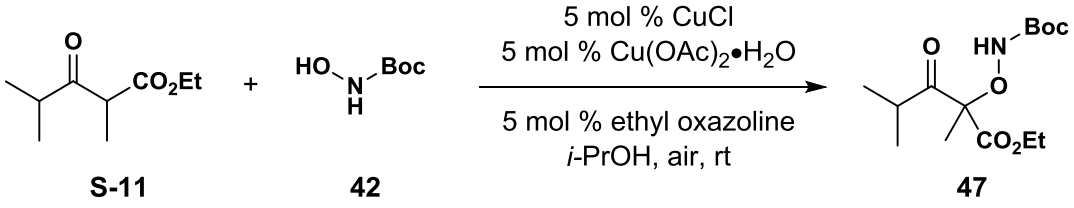


S-9 **42** **46**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxopentanoate **S-9** (95 mg, 0.60 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **46** (54 mg, 62%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 4.24

(qd, J = 7.1, 1.0 Hz, 2H), 2.76 (dq, J = 18.6, 7.2 Hz, 1H), 2.65 (dq, J = 18.6, 7.2 Hz, 1H), 1.63 (s, 3H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 169.6, 156.5, 91.4, 82.4, 62.3, 30.6, 28.3, 18.6, 14.2, 7.6 ppm; IR (thin film) 3300, 2982, 1726, 1370, 1247, 1131 cm^{-1}; HRMS (ESI) *m/z* 312.1417 (312.1418 calcd for $C_{13}H_{23}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (13 mg, 19%).

(47) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2,4-dimethyl-3-oxopentanoate

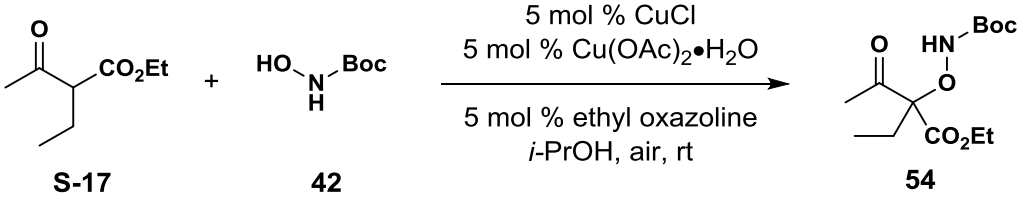


S-11 **42** **47**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2,4-dimethyl-3-oxopentanoate **S-11** (103 mg, 0.60 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **47** (52 mg, 57%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.28 (h, J = 6.8 Hz, 1H), 1.66 (s, 3H), 1.46 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.7, 169.6, 156.5, 91.9, 82.4, 62.3, 35.5, 28.3, 19.9, 19.2, 18.8, 14.3 ppm; IR (thin film) 3300, 2980, 1754, 1370, 1248, 1133 cm^{-1}; HRMS (ESI) *m/z* 326.1574 (326.1574 calcd for

$C_{14}H_{25}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (17 mg, 19%).

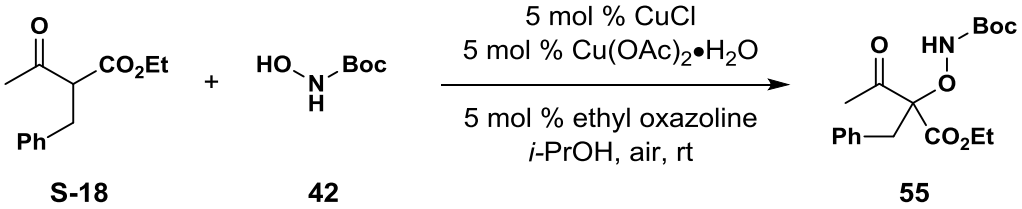
(54) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-ethyl-3-oxobutanoate



S-17 **42** **54**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-ethyl-3-oxobutanoate **S-17** (142 mg, 0.90 mmol, 3.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 15 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **54** (78 mg, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 4.26 (qd, J = 7.1, 1.5 Hz, 2H), 2.29 (s, 3H), 2.13 (dq, J = 14.7, 7.4 Hz, 1H), 2.06 (dq, J = 14.7, 7.5 Hz, 1H), 1.44 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.5, 169.1, 156.2, 94.3, 82.4, 62.2, 28.3, 26.1, 26.1, 14.3, 8.0 ppm; IR (thin film) 3297, 2981, 1725, 1370, 1248, 1148 cm^{-1}; HRMS (ESI) *m/z* 312.1414 (312.1418 calcd for $C_{13}H_{23}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

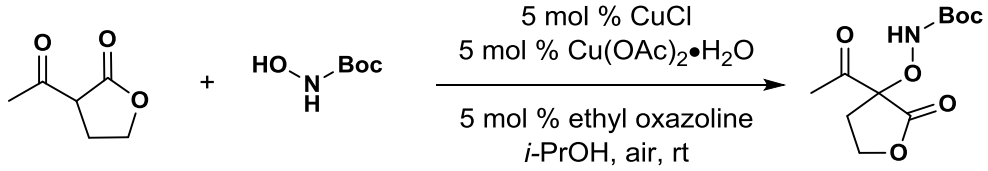
(55) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-benzyl-3-oxobutanoate



S-18 **42** **55**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-benzyl-3-oxobutanoate **S-18** (198 mg, 0.90 mmol, 3.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 15 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **55** (102 mg, 96%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.28 – 7.18 (m, 5H), 4.36 – 4.01 (m, 2H), 3.41 (d, J = 14.6 Hz, 1H), 3.30 (d, J = 14.6 Hz, 1H), 2.25 (s, 3H), 1.45 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9, 168.5, 155.9, 134.0, 130.4, 128.2, 127.2, 93.5, 82.3, 62.0, 38.7, 28.1, 25.9, 13.9 ppm; IR (thin film) 3297, 2982, 1725, 1369, 1246, 1161 cm^{-1}; HRMS (ESI) *m/z* 374.1580 (374.1574 calcd for $C_{18}H_{25}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

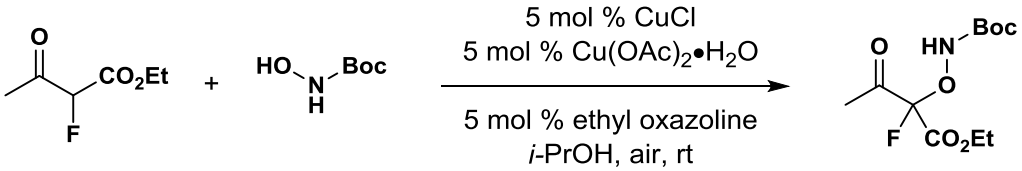
(56) *Tert*-butyl (3-acetyl-2-oxotetrahydrofuran-3-yl)oxycarbamate



S-24 **42** **56**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to 3-acetyldihydrofuran-2(3H)-one **S-24** (46 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 16 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **56** (73 mg, 93%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 4.43 (ddd, J = 8.7, 7.5, 4.7 Hz, 1H), 4.33 (q, J = 8.5 Hz, 1H), 2.71 – 2.61 (m, 2H), 2.38 (s, 3H), 1.47 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.1, 170.9, 156.8, 92.1, 83.3, 66.2, 29.3, 28.2, 26.0 ppm; IR (thin film) 3277, 2982, 1723, 1371, 1250, 1162 cm^{-1}; HRMS (ESI) *m/z* 282.0945 (282.0948 calcd for $C_{11}H_{17}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

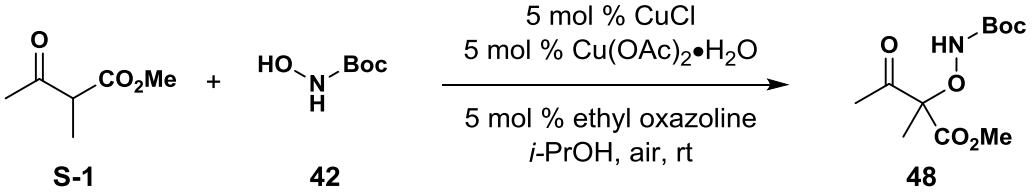
(57) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-fluoro-3-oxobutanoate



S-25 **42** **57**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-fluoro-3-oxobutanoate **S-25** (53 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 16 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **57** (81 mg, 96%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 4.32 (qq, J = 8.1, 3.6 Hz, 2H), 2.40 (d, J = 1.7 Hz, 3H), 1.48 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9 (d, J = 29 Hz), 162.4 (d, J = 35 Hz), 155.7, 108.9 (d, J = 252 Hz), 83.7, 63.5, 28.2, 25.4, 14.1 ppm; IR (thin film) 3275, 2984, 1745, 1371, 1250, 1138 cm^{-1}; HRMS (ESI) *m/z* 302.1013 (302.1010 calcd for $C_{11}H_{18}FNNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(48) Methyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxobutanoate

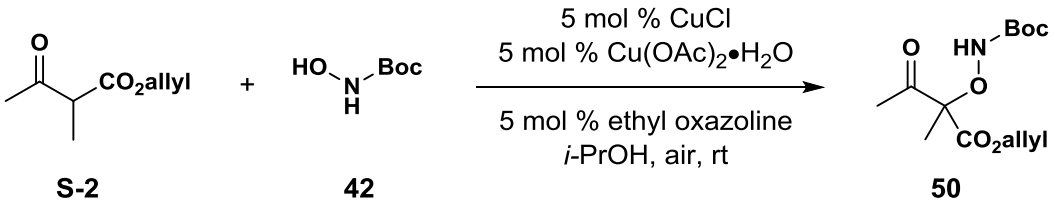


S-1 **42** **48**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to methyl 2-methyl-3-oxobutanoate **S-1** (47 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction

was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **49** (67 mg, 86%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 3.78 (s, 3H), 2.29 (s, 3H), 1.63 (s, 3H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8, 169.8, 156.5, 91.5, 82.5, 53.1, 28.3, 25.2, 18.5 ppm; IR (thin film) 3230, 2981, 1728, 1370, 1248, 1131 cm^{-1}; HRMS (ESI) *m/z* 284.1103 (284.1105 calcd for $C_{11}H_{19}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (8 mg, 10%).

(50) Allyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxobutanoate

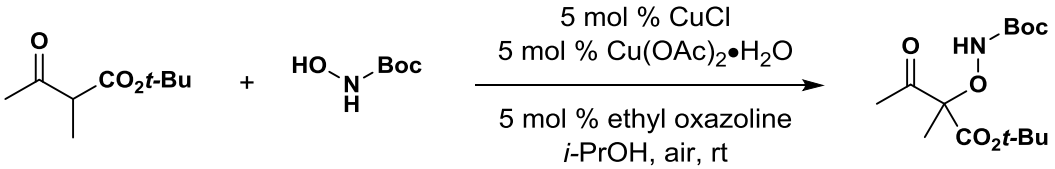


S-2 **42** **50**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to allyl 2-methyl-3-oxobutanoate **S-2** (56 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 15 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **50** (70 mg, 81%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 5.90 (ddt, J = 16.3, 11.6, 5.8 Hz, 1H), 5.33 (dq, J = 17.1, 1.3 Hz, 1H), 5.26 (dq, J = 10.4, 1.0 Hz, 1H), 4.67 (dt, J = 5.8, 1.2 Hz, 2H), 2.29 (s, 3H), 1.65 (s, 3H), 1.45 (s, 9H) ppm. ^{13}C NMR (150 MHz,

$CDCl_3$) δ 202.7, 169.0, 156.5, 131.3, 119.4, 91.5, 82.5, 66.7, 28.3, 25.2, 18.5 ppm. IR (thin film) 3302, 2982, 1728, 1370, 1248, 1130 cm^{-1}; HRMS (ESI) *m/z* 310.1261 (310.1261 calcd for $C_{13}H_{21}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (8 mg, 9%).

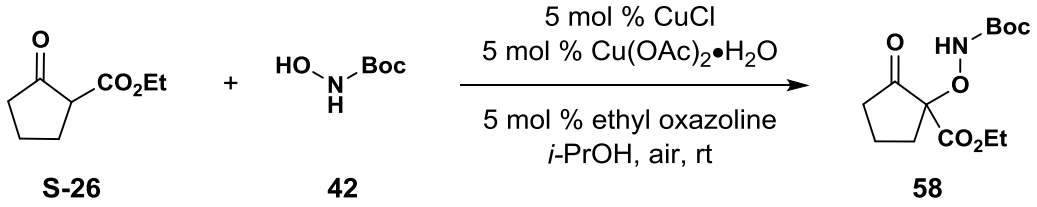
(51) *Tert*-butyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxobutanoate



S-3 **42** **51**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to *tert*-butyl 2-methyl-3-oxobutanoate **S-3** (62 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 17 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **51** (65 mg, 71%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 7.71 (s, 1H), 2.27 (s, 3H), 1.59 (s, 3H), 1.48 (s, 9H), 1.45 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1, 168.5, 156.5, 91.4, 83.6, 82.3, 28.3, 28.1, 25.3, 18.4 ppm; IR (thin film) 3293, 2981, 1726, 1370, 1248, 1131 cm^{-1}; HRMS (ESI) *m/z* 326.1566 (326.1574 calcd for $C_{14}H_{25}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (13 mg, 14%).

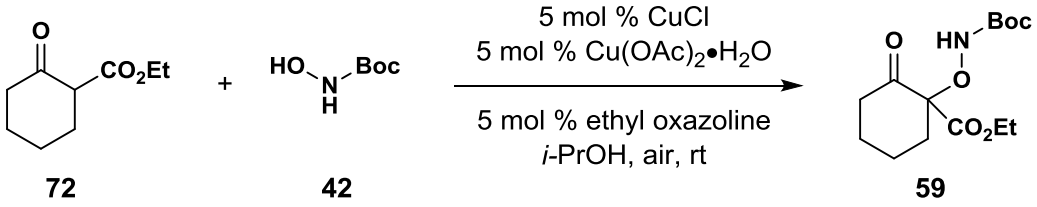
(58) Ethyl 1-(((*tert*-butoxycarbonyl)amino)oxy)-2-oxocyclopentanecarboxylate



S-26 **42** **58**

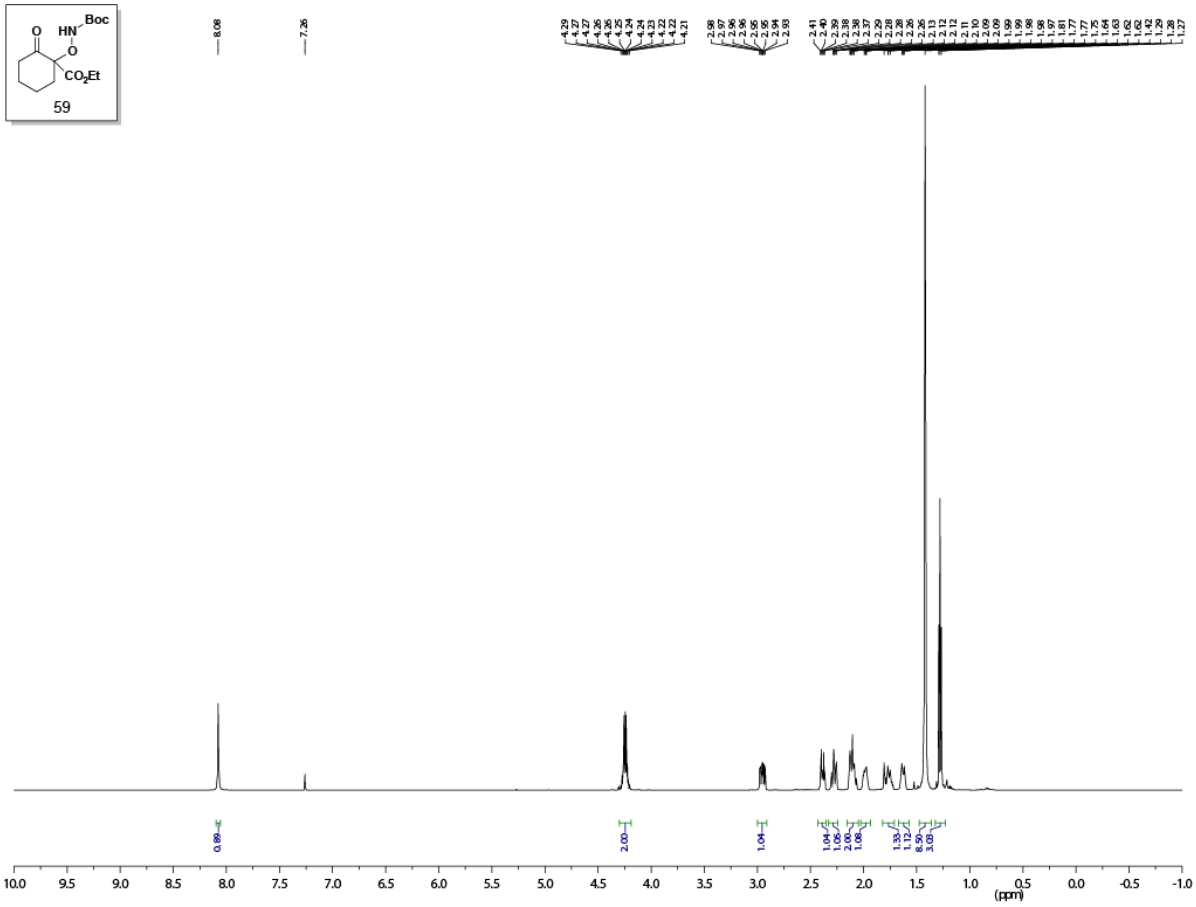
According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclopentanecarboxylate **S-26** (56 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 16 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **58** (77 mg, 89%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 4.25 (qd, J = 7.1, 1.1 Hz, 2H), 2.73 – 2.52 (m, 1H), 2.42 – 2.22 (m, 4H), 2.12 – 1.97 (m, 1H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 169.7, 156.4, 89.0, 82.3, 62.3, 36.9, 33.7, 28.3, 19.0, 14.3 ppm; IR (thin film) 3325, 2980, 1746, 1369, 1268, 1165 cm^{-1}; HRMS (ESI) *m/z* 310.1245 (310.1261 calcd for $C_{13}H_{21}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(59) Ethyl 1-(((*tert*-butoxycarbonyl)amino)oxy)-2-oxocyclohexanecarboxylate



72 **42** **59**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 16 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **59** (85 mg, 94%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (s, 1H), 4.33 – 4.13 (m, 2H), 2.95 (ddd, *J* = 13.8, 11.3, 5.8 Hz, 1H), 2.39 (dt, *J* = 13.8, 4.9 Hz, 1H), 2.28 (ddd, *J* = 15.6, 11.4, 3.9 Hz, 1H), 2.17 – 2.04 (m, 2H), 2.03 – 1.94 (m, 1H), 1.86 – 1.70 (m, 1H), 1.63 (dt, *J* = 13.5, 4.6 Hz, 1H), 1.42 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 170.1, 156.2, 90.6, 82.3, 62.1, 39.5, 34.6, 28.3, 27.3, 20.4, 14.3 ppm; IR (thin film) 3310, 2980, 1726, 1369, 1251, 1160 cm^{-1}; HRMS (ESI) *m/z* 324.1397 (324.1418 calcd for $C_{14}H_{23}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.


Boc
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O
O
CO2Et
59
8.08
7.25
4.29
4.27
4.27
4.27
4.26
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4.25
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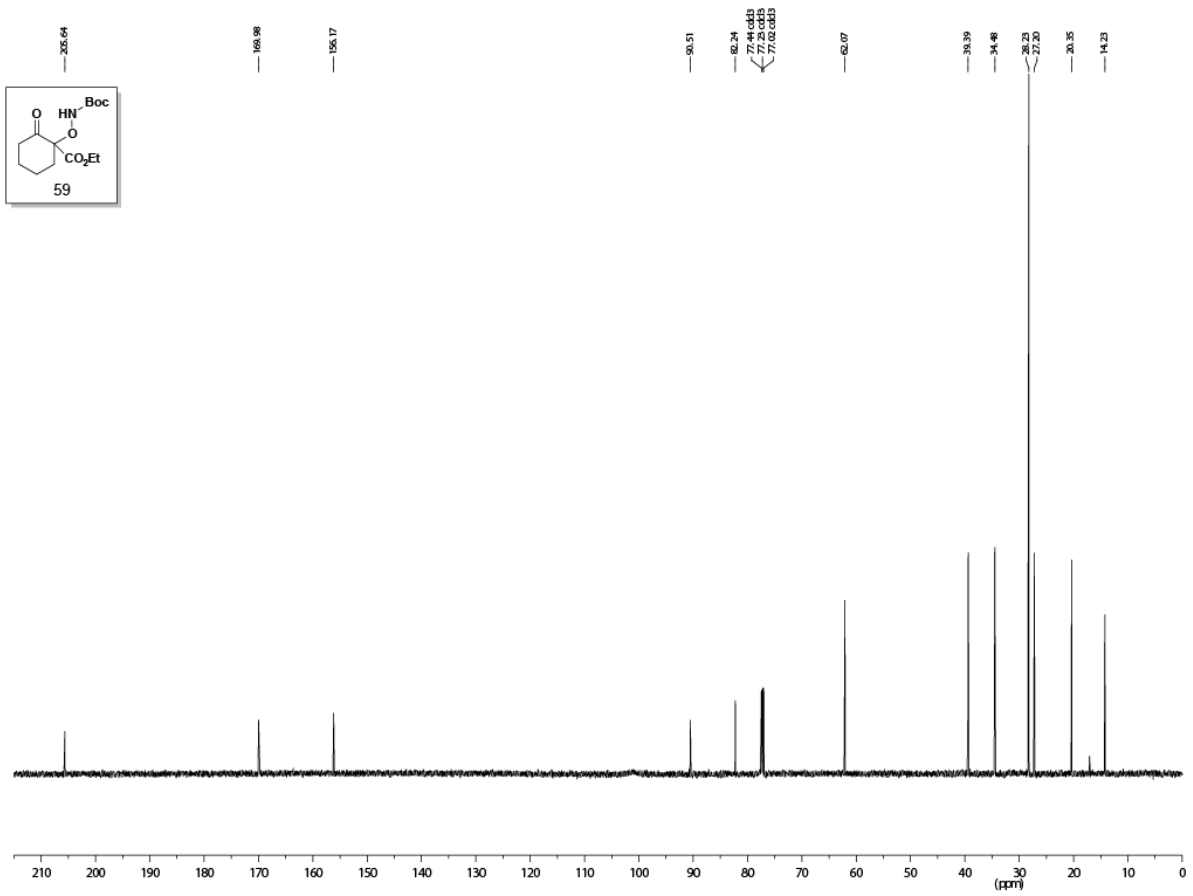
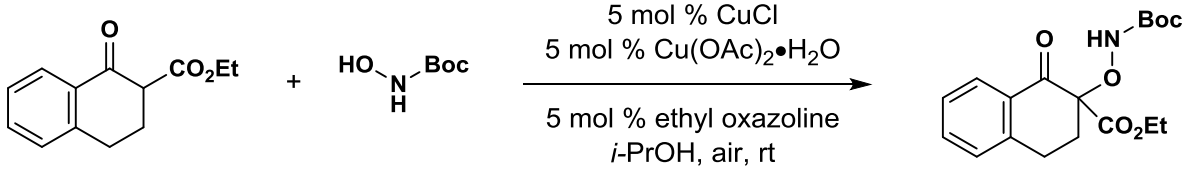
(ppm)



(60) Ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate

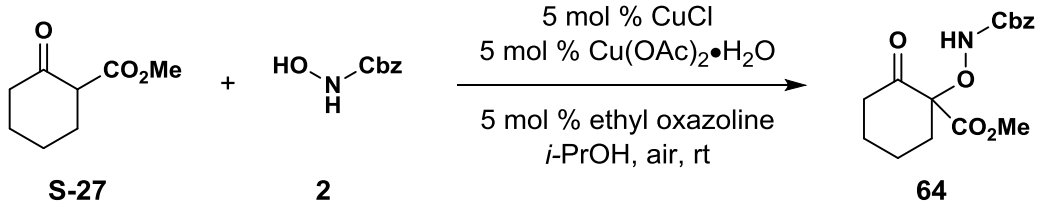


S-20 **42** **60**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **S-20** (79 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in

2 mL of *iso*propyl alcohol. The reaction was stirred for 15 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **60** (102 mg, 97%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 – 7.95 (m, 2H), 7.50 (td, *J* = 7.5, 1.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.42 (ddd, *J* = 16.5, 9.6, 4.8 Hz, 1H), 2.89 (dt, *J* = 16.9, 5.1 Hz, 1H), 2.69 (ddd, *J* = 14.4, 9.7, 4.9 Hz, 1H), 2.49 (dt, *J* = 14.2, 5.1 Hz, 1H), 1.32 – 1.22 (m, 12H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.8, 169.6, 155.9, 143.8, 134.3, 131.3, 128.9, 128.2, 127.0, 87.6, 81.9, 62.2, 30.7, 28.0, 24.9, 14.2 ppm; IR (thin film) 3325, 3068, 2936, 1747, 1368, 1268, 1165 cm^{-1}; HRMS (ESI) *m/z* 372.1436 (372.1418 calcd for $C_{18}H_{23}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(64) Methyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate

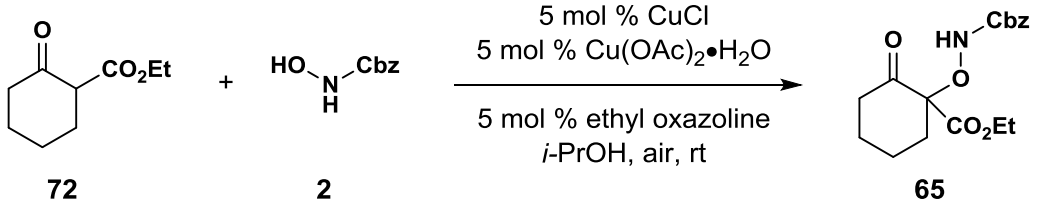


S-27 **2** **64**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to methyl 2-oxocyclohexane-1-carboxylate **S-27** (56 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then

concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **64** (71 mg, 74%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.41 – 7.30 (m, 5H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 3.78 (s, 3H), 2.95 (ddd, *J* = 13.9, 11.2, 5.7 Hz, 1H), 2.42 (dt, *J* = 13.9, 4.9 Hz, 1H), 2.32 (ddd, *J* = 15.3, 11.3, 4.5 Hz, 1H), 2.21 – 2.06 (m, 2H), 2.03 – 1.94 (m, 1H), 1.85 – 1.73 (m, 1H), 1.71 – 1.61 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.2, 170.2, 156.9, 135.5, 128.8, 128.7, 128.5, 90.9, 67.9, 52.9, 39.5, 34.5, 27.2, 20.4 ppm; IR (thin film) 3299, 3034, 2954, 1723, 1437, 1226, 1103 cm^{-1}; HRMS (ESI) *m/z* 344.1106 (344.1105 calcd for $C_{16}H_{19}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(65) Ethyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexanecarboxylate

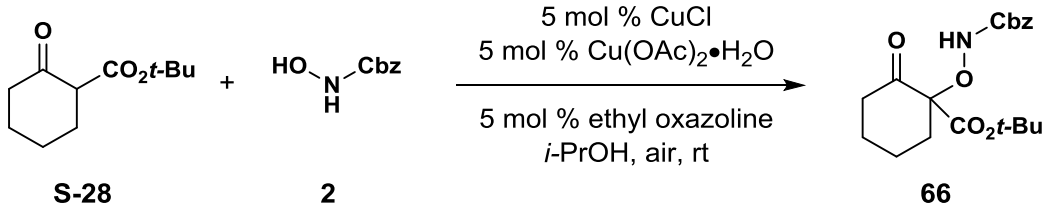


72 **2** **65**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **65** (82 mg, 81%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.41 – 7.28 (m, 5H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.28 – 4.20 (m,

2H), 2.92 (ddd, J = 14.1, 10.8, 5.7 Hz, 1H), 2.42 (dt, J = 13.9, 5.2 Hz, 1H), 2.33 (ddd, J = 14.7, 10.8, 3.8 Hz, 1H), 2.17 – 2.04 (m, 2H), 2.00 – 1.91 (m, 1H), 1.84 – 1.72 (m, 1H), 1.69 – 1.59 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 169.5, 156.9, 135.5, 128.7, 128.6, 128.4, 90.7, 67.8, 62.2, 39.6, 34.4, 27.1, 20.4, 14.2 ppm; IR (thin film) 3301, 2944, 1724, 1453, 1225, 1102 cm^{-1}; HRMS (ESI) *m/z* 358.1260 (358.1261 calcd for $C_{17}H_{21}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(66) *Tert*-butyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate

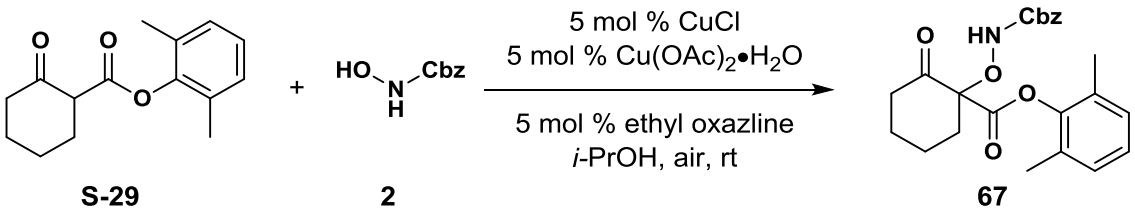


S-28 **2** **66**

According to the general procedure, CuCl (0.8 mg, 0.0075 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (25 mg, 0.15 mmol, 1 equiv) were added to *tert*-butyl 2-oxocyclohexane-1-carboxylate **S-28** (36 mg, 0.18 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol, 0.05 equiv), and ethyl oxazoline (0.8 mg, 0.0075 mmol, 0.05 equiv) in 1 mL of *iso*propyl alcohol. The reaction was stirred for 24 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **66** (40 mg, 77%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.40 – 7.28 (m, 5H), 5.19 (d, J = 12.1 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 2.86 (ddd, J = 14.7, 9.6, 5.6 Hz, 1H), 2.45 (dt, J = 13.9, 5.8 Hz, 1H), 2.37 – 2.28 (m, 1H), 2.12 – 2.01 (m,

2H), 1.95 – 1.87 (m, 1H), 1.87 – 1.76 (m, 1H), 1.68 – 1.58 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 168.7, 156.8, 135.6, 128.8, 128.6, 128.5, 90.8, 83.7, 67.8, 40.0, 34.7, 28.1, 27.1, 20.8 ppm; IR (thin film) 3329, 3035, 2942, 1724, 1456, 1301, 1223, 1103 cm^{-1}; HRMS (ESI) *m/z* 386.1587 (386.1574 calcd for $C_{19}H_{25}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(67) 2,6-Dimethylphenyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate

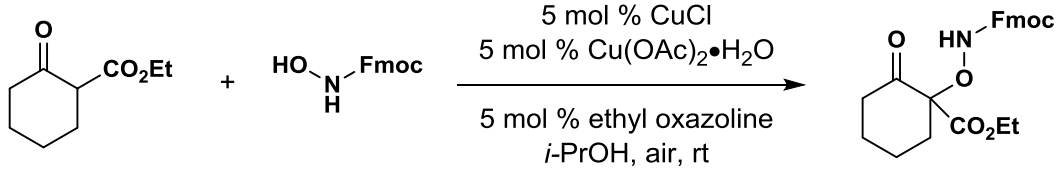


S-29 **2** **67**

According to the general procedure, CuCl (0.8 mg, 0.0075 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (25 mg, 0.15 mmol, 1 equiv) were added to 2,6-dimethylphenyl 2-oxocyclohexane-1-carboxylate **S-29** (44 mg, 0.18 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol, 0.05 equiv), and ethyl oxazoline (0.8 mg, 0.0075 mmol, 0.05 equiv) in 1 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **67** (50 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.42 – 7.31 (m, 5H), 7.07 (s, 3H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 3.12 (td, *J* = 13.2, 5.9 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.51 – 2.42 (m, 2H), 2.30 – 2.17 (m, 7H), 2.16 – 2.07 (m, 1H), 1.90 – 1.76 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.6, 168.2, 157.1, 147.8, 135.4, 130.4, 129.0, 128.8, 128.8, 128.5, 126.6, 91.0, 68.1, 39.4, 35.0, 27.2,

20.2, 16.8 ppm; IR (thin film) 3323, 3034, 2951, 1760, 1473, 1318, 1223, 1099 cm^{-1}; HRMS (ESI) *m/z* 434.1570 (434.1574 calcd for $C_{23}H_{25}NNaO_6^+$ $[MNa]^+$). A minor amount of the *N*-selective product was also isolated (2 mg, 3%).

(68) Ethyl 1-(((((9H-fluoren-9-yl)methoxy)carbonyl)amino)oxy)-2-oxocyclohexanecarboxylate

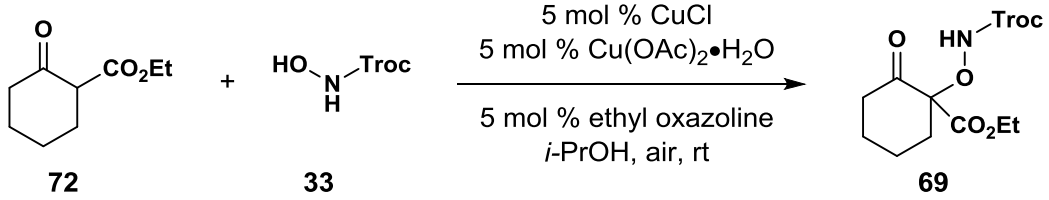


72 **S-4** **68**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and (9H-fluoren-9-yl)methyl hydroxycarbamate **S-4** (77 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 19 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **68** (102 mg, 80%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.41 (td, *J* = 7.5, 1.3 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 4.51 (d, *J* = 6.7 Hz, 2H), 4.29 (qd, *J* = 7.2, 4.9 Hz, 2H), 4.22 (t, *J* = 6.8 Hz, 1H), 2.87 – 2.74 (m, 1H), 2.39 (dt, *J* = 14.0, 4.9 Hz, 1H), 2.33 (ddd, *J* = 14.7, 10.8, 4.1 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.03 – 1.89 (m, 2H), 1.83 – 1.70 (m, 1H), 1.65 – 1.57 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 169.8, 157.0, 143.5,

143.5, 141.5, 128.0, 127.4, 127.3, 125.1, 125.1, 120.2, 90.7, 67.7, 62.3, 47.1, 39.6, 34.5, 27.2, 20.4, 14.3 ppm; IR (thin film) 3303, 2929, 1724, 1451, 1224, 1103 cm^{-1}; HRMS (ESI) *m/z* 446.1572 (446.1574 calcd for $C_{24}H_{25}NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(69) Ethyl 2-oxo-1-((((2,2,2-trichloroethoxy)carbonyl)amino)oxy)cyclohexanecarboxylate

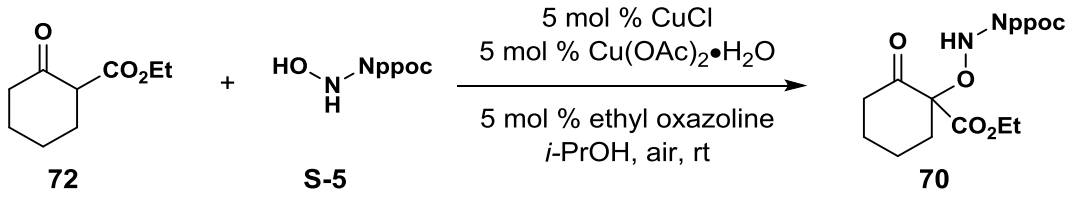


72 **33** **69**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and 2,2,2-trichloroethyl hydroxycarbamate **33** (63 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 19 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **69** (101 mg, 89%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.38 – 4.22 (m, 2H), 2.93 (ddd, *J* = 14.1, 10.6, 5.7 Hz, 1H), 2.47 (dt, *J* = 14.1, 5.3 Hz, 1H), 2.37 (ddd, *J* = 15.0, 10.9, 4.5 Hz, 1H), 2.20 – 2.05 (m, 2H), 2.03 – 1.93 (m, 1H), 1.89 – 1.77 (m, 1H), 1.74 – 1.61 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.2, 169.6, 155.1, 94.9, 90.8, 75.0, 62.5, 39.7, 34.4, 27.1, 20.5, 14.3 ppm; IR (thin film) 3294, 2958, 1726, 1369, 1252,

1124 cm^{-1}; HRMS (ESI) *m/z* 397.9937 (397.9935 calcd for $C_{12}H_{16}Cl_3NNaO_6^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(70) Ethyl 1-((((2-(2-nitrophenyl)propoxy)carbonyl)amino)oxy)-2-oxocyclohexanecarboxylate

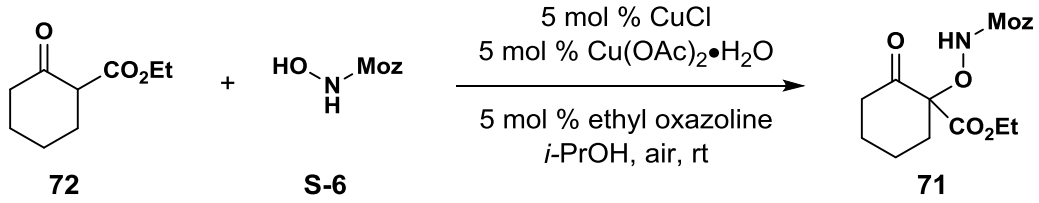


72 **S-5** **70**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and 2-(2-nitrophenyl)propyl hydroxycarbamate **S-5**(72 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 14 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **70** (107 mg, 87%, 1:1 dr, inseparable) as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.22 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.46 – 7.40 (m, 1H), 7.39 – 7.33 (m, 1H), 4.54 – 4.02 (m, 4H), 3.68 (h, *J* = 6.7 Hz, 1H), 2.90 – 2.70 (m, 1H), 2.44 – 2.23 (m, 2H), 2.13 – 2.05 (m, 1H), 2.05 – 1.96 (m, 1H), 1.96 – 1.87 (m, 1H), 1.81 – 1.70 (m, 1H), 1.66 – 1.57 (m, 1H), 1.33 (d, *J* = 2.0 Hz, 3H), 1.32 (d, *J* = 2.0 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.3, 205.2, 169.7, 169.6, 156.7, 150.5, 150.5, 137.0, 137.0, 132.9, 132.9, 128.3, 128.2, 127.7, 127.7, 124.4, 124.4, 90.7, 90.6, 69.6, 69.6, 62.2, 39.6 , 39.5, 34.4, 34.4, 27.1, 20.4, 20.4, 17.8, 17.8, 14.2 ppm; IR

(thin film) 3318, 2962, 1724, 1527, 1355, 1226, 1102 cm^{-1}; HRMS (ESI) *m/z* 431.1418 (431.1425 calcd for $C_{19}H_{24}N_2NaO_8^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

(71) Ethyl 1-(((((4-methoxybenzyl)oxy)carbonyl)amino)oxy)-2-oxocyclohexanecarboxylate



72 **S-6** **71**

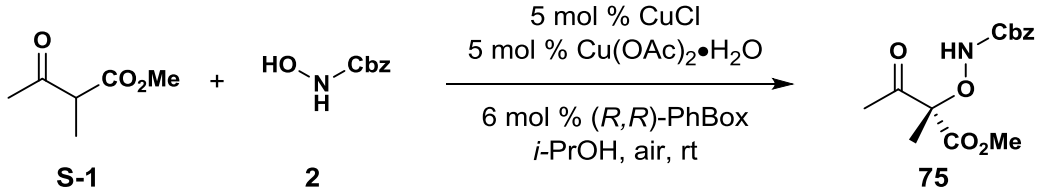
According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and 4-methoxybenzyl hydroxycarbamate **S-6** (59 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexanecarboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 15 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **71** (93 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.11 (d, *J* = 11.8 Hz, 1H), 5.03 (d, *J* = 11.8 Hz, 1H), 4.28 – 4.20 (m, 2H), 3.79 (s, 3H), 2.92 (ddd, *J* = 14.1, 10.9, 5.7 Hz, 1H), 2.41 (dt, *J* = 13.9, 5.1 Hz, 1H), 2.32 (ddd, *J* = 14.8, 10.9, 3.7 Hz, 1H), 2.18 – 2.03 (m, 2H), 2.00 – 1.90 (m, 1H), 1.85 – 1.74 (m, 1H), 1.70 – 1.57 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 169.7, 160.0, 157.0, 130.4, 127.6, 114.1, 90.7, 67.7, 62.2, 55.4, 39.6, 34.5, 27.1, 20.4, 14.2 ppm; IR (thin film) 3302, 2942, 1725, 1516, 1250, 1101

cm^{-1}; HRMS (ESI) *m/z* 388.1364 (388.1367 calcd for $C_{18}H_{23}NNaO_7^+$ $[MNa]^+$). Less than 2% of the *N*-selective product was observed.

Asymmetric *O*-Selective Nitrosocarbonyl Aldol Reaction

General Procedure for the Asymmetric Aldol Reaction: To a stirred solution of β-ketoester **4**, 5 mol % $Cu(OAc)_2 \cdot H_2O$, and 6 mol % (+)-2,2′-*Iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] in *iso*propyl alcohol (0.15 M) was added 5 mol % CuCl and benzyl hydroxycarbamate **30**. The reaction was stirred at room temperature open to the air until complete by TLC and the *iso*propyl alcohol was removed *in vacuo*. The reaction was quenched with EDTA (0.5 M, pH 7.0), diluted with ethyl acetate and stirred until color no longer persisted in organic layer (approx 30 mins). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over $MgSO_4$. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford the corresponding aldol product.

(75) Methyl 2-((((benzyloxy)carbonyl)amino)oxy)-2-methyl-3-oxobutanoate

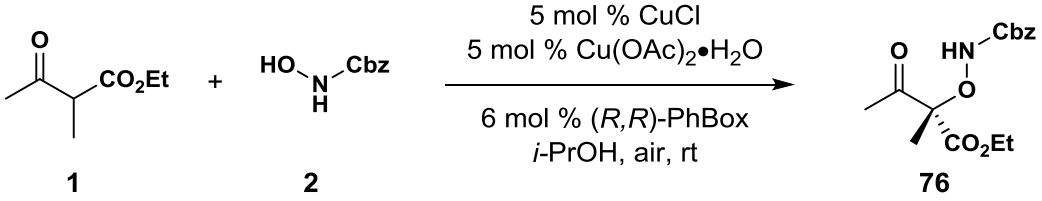


S-1 **2** **75**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to methyl 2-methyl-3-oxobutanoate **S-1** (47 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.018 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the

solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **75** (69 mg, 78%, 93:7 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 43.3 min (major), (*X*) Rt = 45.0 min (minor)); $[\alpha]_D^{25}$ +3.8° (c 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.40 – 7.30 (m, 5H), 5.17 (s, 2H), 3.77 (s, 3H), 2.29 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 169.7, 158.8, 135.2, 128.8, 128.8, 128.7, 78.7, 69.2, 53.4, 25.5, 19.0 ppm; IR (thin film) 3289, 2956, 1727, 1456, 1232, 1106 cm^{-1}; HRMS (ESI) *m/z* 318.0945 (318.0948 calcd for $C_{14}H_{17}NNaO_6^+$ $[MNa]^+$).

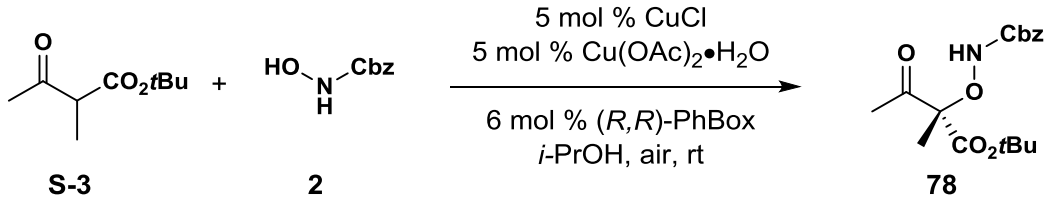
(76) Ethyl 2-((((benzyloxy)carbonyl)amino)oxy)-2-methyl-3-oxobutanoate



According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.018 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column

chromatography to afford aldol product **76** (69 mg, 74%, 92:8 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 38.4 min (major), (*X*) Rt = 41.2 min (minor)); $[\alpha]_D^{25}$ +2.8° (c 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.39 – 7.29 (m, 5H), 5.17 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 3H), 1.65 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.4, 169.1, 157.3, 135.5, 128.8, 128.8, 128.5, 91.6, 68.1, 62.5, 25.3, 18.4, 14.2 ppm; IR (thin film) 3290, 2985, 1727, 1456, 1231, 1105 cm^{-1}; HRMS (ESI) *m/z* 332.1107 (332.1105 calcd for $C_{15}H_{19}NNaO_6^+$ $[MNa]^+$).

(78) *Tert*-butyl 2-((((benzyloxy)carbonyl)amino)oxy)-2-methyl-3-oxobutanoate

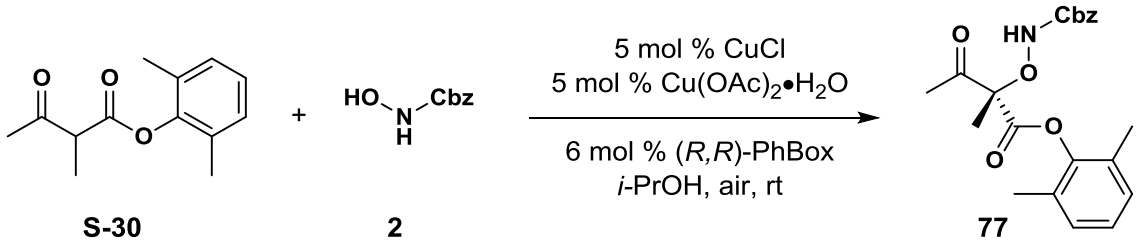


S-3 **2** **78**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to *tert*-butyl 2-methyl-3-oxobutanoate **S-3** (62 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.015 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **78** (77 mg, 76%, 99:1 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm,

step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 29.5 min (major), (*X*) Rt = 31.9 min (minor)); $[\alpha]_D^{25}$ +3.3° (c 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.41 – 7.29 (m, 5H), 5.19 – 5.13 (m, 2H), 2.26 (s, 3H), 1.60 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 168.2, 157.2, 135.5, 128.8, 128.7, 128.5, 91.5, 83.7, 68.0, 28.0, 25.3, 18.3 ppm; IR (thin film) 3290, 2979, 1725, 1456, 1227, 1104 cm^{-1}; HRMS (ESI) *m/z* 360.1420 (360.1418 calcd for $C_{17}H_{23}NNaO_6^+$ $[MNa]^+$).

(77) 2,6-Dimethylphenyl 2-((((benzyloxy)carbonyl)amino)oxy)-2-methyl-3-oxobutanoate

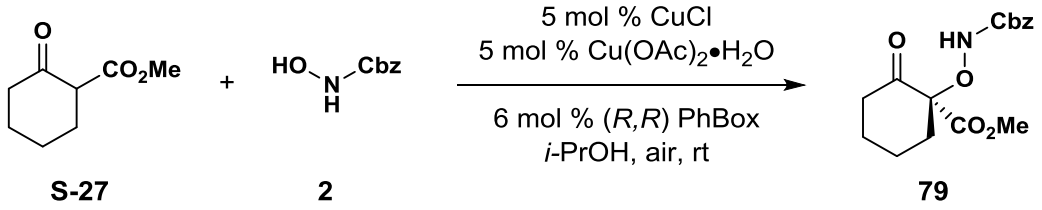


S-30 **2** **77**

According to the general procedure, CuCl (0.7 mg, 0.0075 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (25 mg, 0.15 mmol, 1 equiv) were added to 2,6-dimethylphenyl 2-methyl-3-oxobutanoate **S-30** (40 mg, 0.18 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 0.0075 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (3.0 mg, 0.0090 mmol, 0.06 equiv) in 1 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **77** (49 mg, 85%, 99:1 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm,

step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 39.7 min (major), (*X*) Rt = 42.2 min (minor)); $[\alpha]_D^{25}$ +16.5° (c 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.42 – 7.30 (m, 5H), 7.12 – 7.00 (m, 3H), 5.20 (s, 2H), 2.41 (s, 3H), 2.15 (s, 6H), 1.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.1, 167.3, 157.4, 147.8, 135.4, 130.2, 129.0, 128.9, 128.8, 128.6, 126.6, 92.1, 68.2, 25.4, 19.0, 16.6 ppm; IR (thin film) 3281, 3034, 2927, 1728, 1456, 1231, 1101 cm^{-1}; HRMS (ESI) *m/z* 408.1415 (408.1418 calcd for $C_{21}H_{23}NNaO_6^+$ $[MNa]^+$).

(79) Methyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate

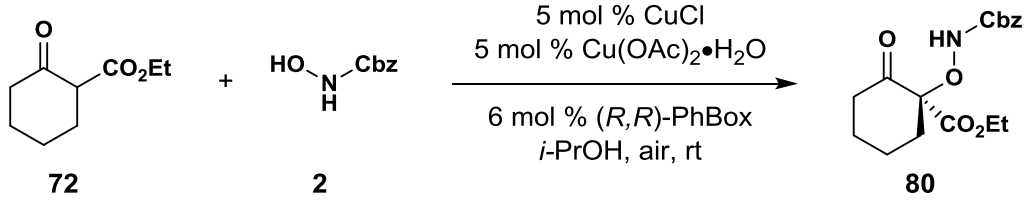


S-27 **2** **79**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to methyl 2-oxocyclohexane-1-carboxylate **S-27** (56 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.018 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **79** (78 mg, 81%, 91:9 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min,

(*X*) Rt = 43.2 min (major), (*X*) Rt = 45.8 min (minor)); $[\alpha]_D^{25}$ +38.5° (c 1.00, $CHCl_3$); Spectral data consistent with compound **64**.

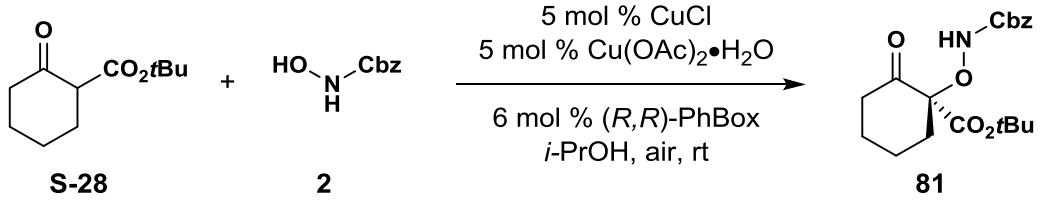
(80) Ethyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate



72 **2** **80**

According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-oxocyclohexane-1-carboxylate **72** (61 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.018 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **80** (83 mg, 82%, 90:10 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 37.7 min (major), (*X*) Rt = 40.7 min (minor)); $[\alpha]_D^{25}$ +35.4° (c 1.00, $CHCl_3$); Spectral data consistent with compound **65**.

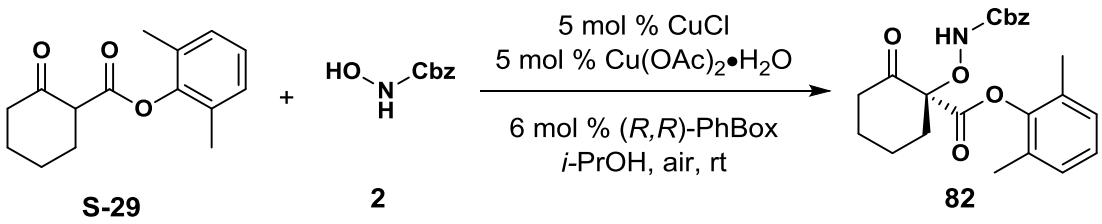
(81) *Tert*-butyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate



S-28 **2** **81**

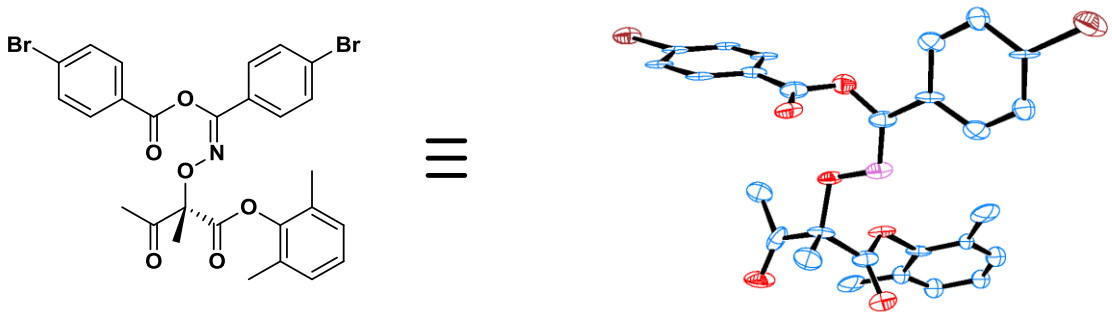
According to the general procedure, CuCl (0.6 mg, 0.0065 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (22 mg, 0.13 mmol, 1 equiv) were added to *tert*-butyl 2-oxocyclohexane-1-carboxylate **S-28** (31 mg, 0.16 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.3 mg, 0.0065 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (2.6 mg, 0.0078 mmol, 0.06 equiv) in 1 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 2 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **81** (40 mg, 85%. 99:1 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 27.1 min (major), (*X*) Rt = 42.2 min (minor)); $[\alpha]_D^{25}$ +20.6° (c 1.00, $CHCl_3$); Spectral data consistent with compound **66**.

(82) 2,6-Dimethylphenyl 1-((((benzyloxy)carbonyl)amino)oxy)-2-oxocyclohexane-1-carboxylate



According to the general procedure, CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and benzyl hydroxycarbamate **2** (50 mg, 0.30 mmol, 1 equiv) were added to 2,6-dimethylphenyl 2-oxocyclohexane-1-carboxylate **S-29** (87 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and (+)-2,2′-*iso*propylidenebis[(4*R*)-4-phenyl-2-oxazoline] (6.0 mg, 0.018 mmol, 0.06 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 8 h at rt, and the solvent was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol product **82** (105 mg, 88%, 91:9 er) as a colorless oil. Enantiomeric ratio determined by chiral HPLC (Chiralpak IA column, 4.6 mm x 250 mm, step gradient (95.5/0.5 hexanes/*i*-PrOH, 30 min; 97/3 hexanes/*i*-PrOH, 30 min), 1 mL/min, (*X*) Rt = 41.1 min (minor), (*X*) Rt = 45.4 min (major)); $[\alpha]_D^{25}$ +70.2° (c 1.00, $CHCl_3$); Spectral data consistent with compound **67**.

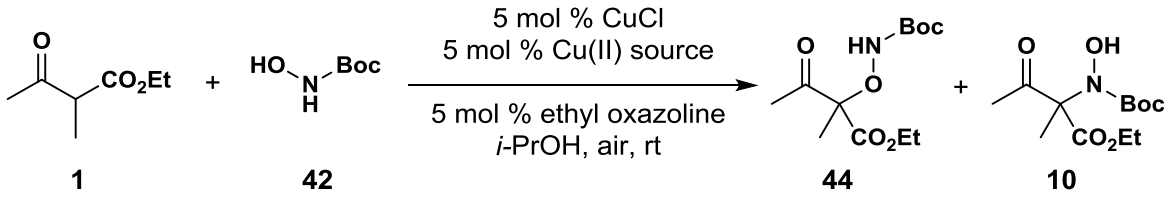
(S-31) (S,Z)-(S,Z)-4-bromo-N-((1-(2,6-dimethylphenoxy)-2-methyl-1,3-dioxobutan-2-yl)oxy)benzimidic 4-bromobenzoic anhydride



Single crystal X-ray crystallography of **S-31** was used to determine the absolute stereochemistry of asymmetric aldol products. See CDCC 932616 for more information.

Mechanistic Studies

General Procedure for the Cu(II) Counterion Screen:

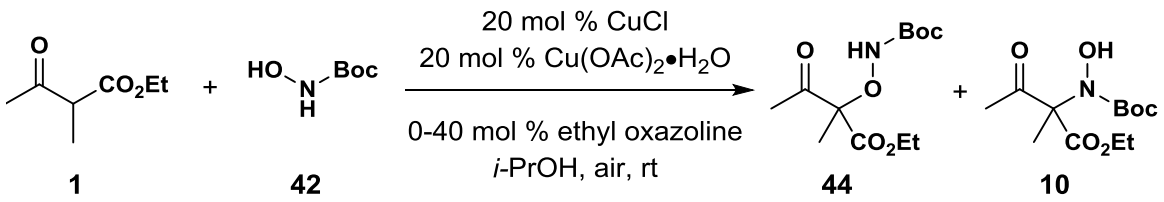


To a stirred solution of ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), the corresponding Cu(II) source (0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL *iso*propyl alcohol was added CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv). The reaction was stirred at room temperature open to the air until complete as judged by TLC, and the *iso*propyl alcohol was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were

dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol products **44** and **10**. The regioselectivity of the reaction was determined by ^{1}HNMR analysis of the crude reaction mixture.

Cu(II) Source	Regioselectivity (O:N)
$Cu(OTf)_2$	1.5:1
$Cu(BF_4)_2•H_2O$	1.5:1
$CuCl_2$	6:1
$CuCO_3$	8:1
$Cu(OAc)_2•H_2O$	10:1
$Cu(2\text{-EtHex})_2$	14:1

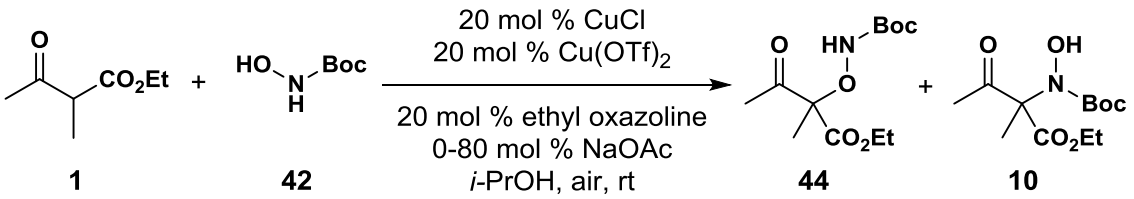
General Procedure for the Screen of Ethyl Oxazoline Loading:



To a stirred solution of ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2•H_2O$ (12 mg, 0.060 mmol, 0.20 equiv), and ethyl oxazoline (0–40 mol %) in 2 mL *iso*propyl alcohol was added CuCl (6 mg, 0.060 mmol, 0.20 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv). The reaction was stirred at room temperature open to the air until complete as judged by TLC, and the *iso*propyl alcohol was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol products **44** and **10**. The regioselectivity of the reaction was determined by ^{1}HNMR analysis of the crude reaction mixture.

mol % ethyl oxazoline	Regioselectivity (O:N)
0	3:1
5	6:1
10	14:1
20	18:1
40	>20:1

General Procedure for the Screen of NaOAc loading:



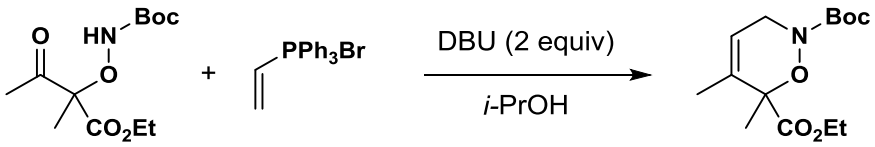
To a stirred solution of ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), $Cu(OTf)_2$ (22 mg, 0.060 mmol, 0.20 equiv), and ethyl oxazoline (6 mg, 0.060 mmol, 0.20 equiv) in 2 mL *iso*propyl alcohol was added CuCl (6 mg, 0.060 mmol, 0.20 equiv), NaOAc (0–80 mol %) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv). The reaction was stirred at room temperature open to the air until complete as judged by TLC, and the *iso*propyl alcohol was removed *in vacuo*. The reaction was quenched with 4 mL EDTA (0.5 M, pH 7.0) and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford aldol products **44** and **10**. The regioselectivity of the reaction was determined by ^{1}HNMR analysis of the crude reaction mixture.

mol % NaOAc	Regioselectivity (O:N)
0	2:1
5	2:1
10	2:1
15	2:1
20	3:1

25	4:1
30	5:1
35	6:1
40	7:1
80	7:1

Post–Functionalization of *O*-Aldol Products

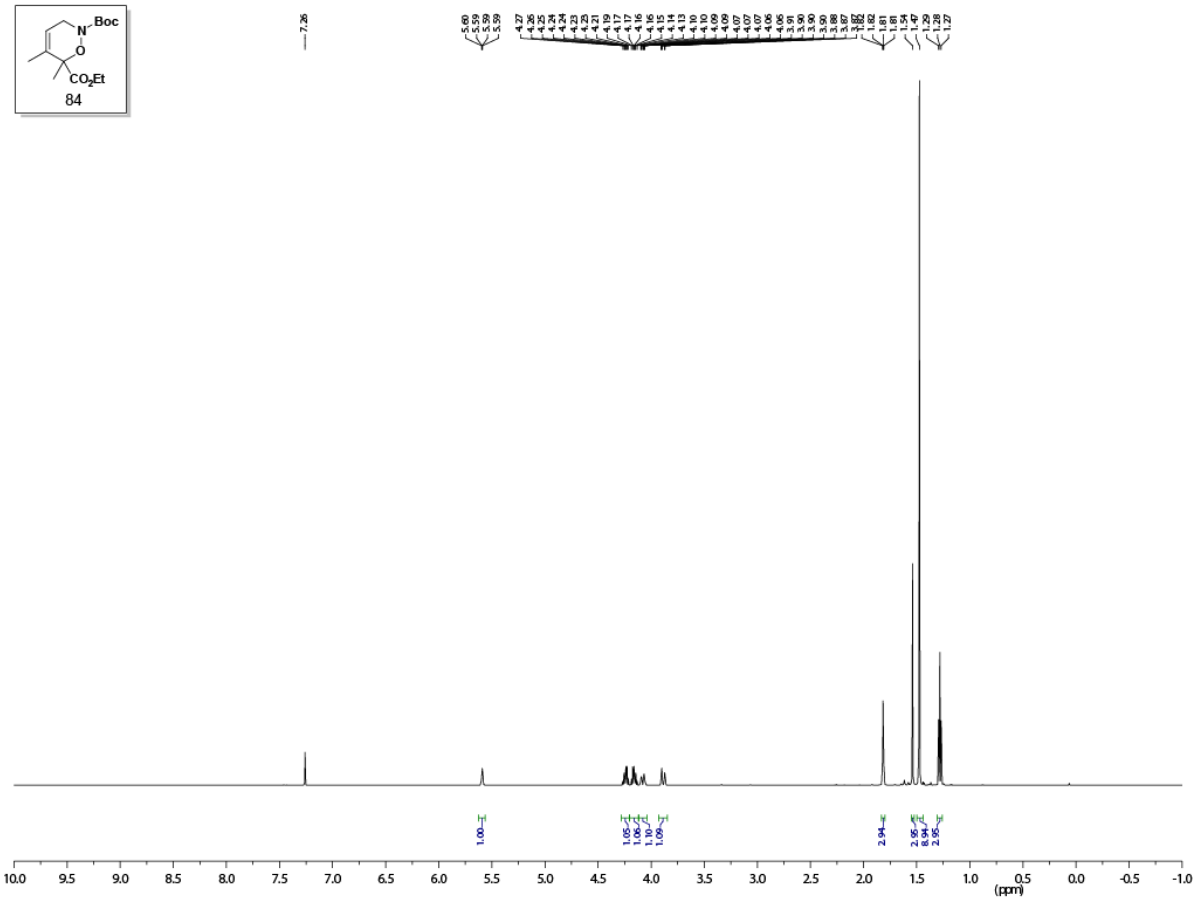
(84) 2-(*Tert*-butyl) 6-ethyl 5,6-dimethyl-3,6-dihydro-2H-1,2-oxazine-2,6-dicarboxylate

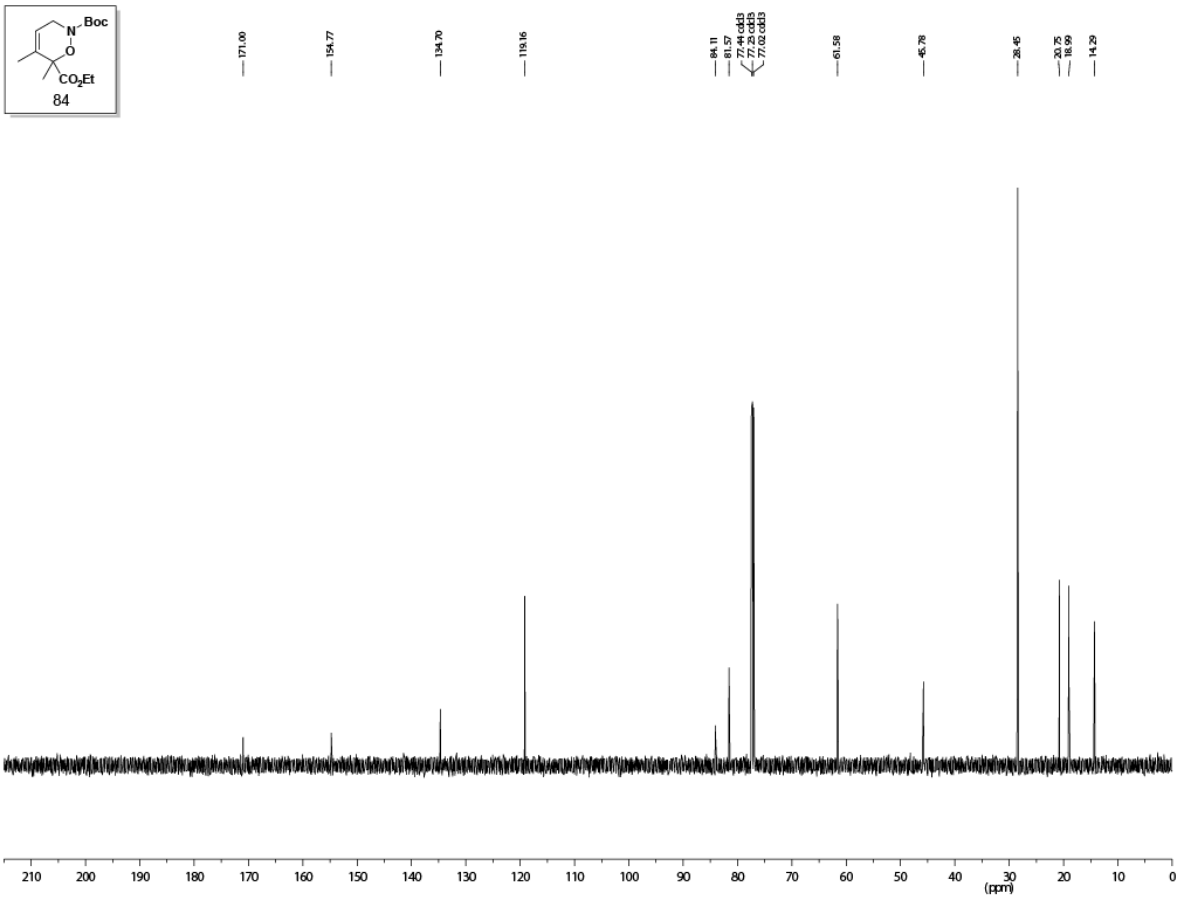


44 **S-32** **84**

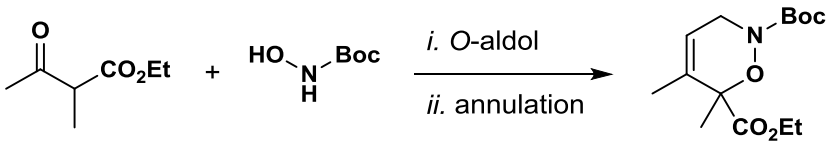
Vinyltriphenylphosphonium bromide **S-32** (134 mg, 0.36 mmol, 2.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (54 µL, 0.36 mmol, 2.0 equiv) were added to ethyl 2-(((*tert*-butoxycarbonyl)amino)oxy)-2-methyl-3-oxobutanoate **44** (50 mg, 0.18 mmol, 1 equiv) in 1 mL of *iso*propyl alcohol. The reaction was heated to reflux, stirred for 2 h and cooled to rt. The reaction was quenched with H_2O (10 mL) and diluted with ethyl acetate (10 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford annulation product **84** (42 mg, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 – 5.57 (m, 1H), 4.24 (dq, J = 10.8, 7.1 Hz, 1H), 4.16 (dq, J = 10.8, 7.1 Hz, 1H), 4.08 (ddq, J = 16.8, 3.6, 1.7 Hz, 1H), 3.89 (dp, J = 16.8, 2.2 Hz, 1H), 1.82 (q, J = 1.8 Hz, 3H), 1.54 (s, 3H), 1.47 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ

171.0, 154.8, 134.7, 119.2, 84.1, 81.6, 61.6, 45.8, 28.5, 20.8, 19.0, 14.3 ppm; IR (thin film) 2980, 1736, 1367, 1265, 1109 cm^{-1}; HRMS (ESI) *m/z* 308.1469 (308.1468 calcd for $C_{14}H_{23}NNaO_5^+$ $[MNa]^+$).





(84) 2-(*Tert*-butyl) 6-ethyl 5,6-dimethyl-3,6-dihydro-2H-1,2-oxazine-2,6-dicarboxylate

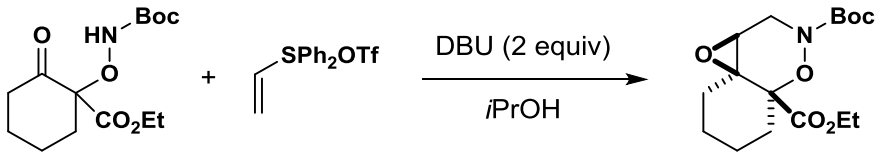


1 **42** **84**

CuCl (1.5 mg, 0.015 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (40 mg, 0.30 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxobutanoate **1** (52 mg, 0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol, 0.05 equiv), and ethyl oxazoline (1.5 mg, 0.015 mmol, 0.05 equiv) in 2 mL of *iso*propyl alcohol. The reaction was stirred for 17 h at rt, and then vinyltriphenylphosphonium bromide **S-32** (222 mg, 0.60 mmol, 2.0 equiv) and 1,8-

diazabicyclo[5.4.0]undec-7-ene (90 μL, 0.60 mmol, 2.0 equiv) were added to the solution. The reaction was heated to reflux for an additional 2 h, cooled to rt, and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford annulation product **84** (56 mg, 65%) as a colorless oil.

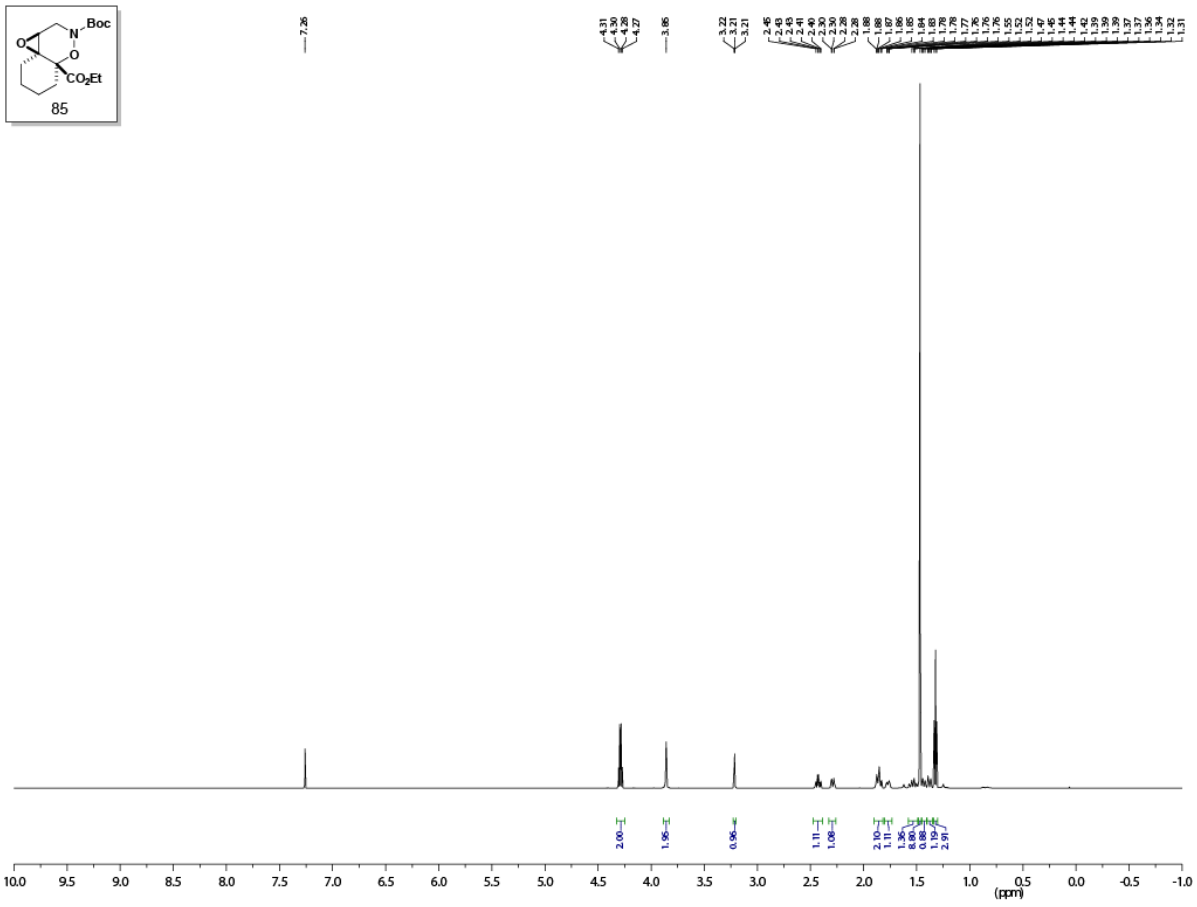
(85) 3-(*Tert*-butyl) 4a-ethyl hexahydro-3H,4aH-benzo[e]oxireno[2,3-d][1,2]oxazine-3,4a-dicarboxylate

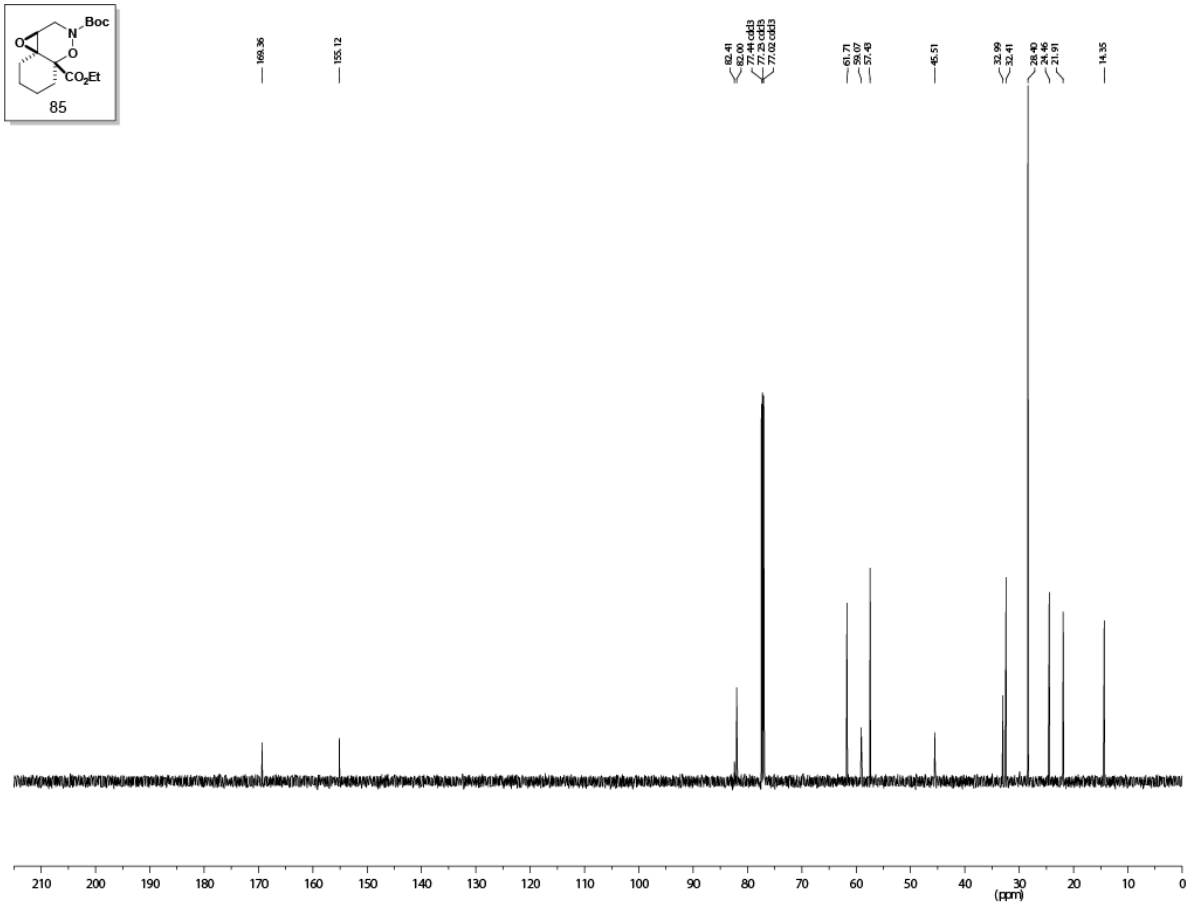


59 **S-33** **85**

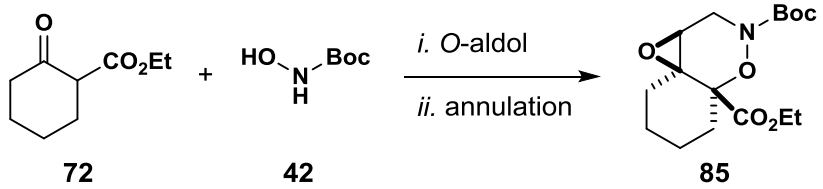
Vinyldiphenylsulfonium triflate **S-33** (81 mg, 0.23 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (56 μL, 0.38 mmol, 2.0 equiv) were added to ethyl 1-(((*tert*-butoxycarbonyl)amino)oxy)-2-oxocyclohexanecarboxylate **59** (57 mg, 0.19 mmol, 1 equiv) in 1 mL of *iso*propyl alcohol at 0˚C. The reaction was warmed to room temperature and stirred for 24 h. The reaction was quenched with a 10% solution of citric acid (10 mL), the phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford annulation product **85** (43 mg, 63%, >20:1 dr) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.29 (q, J = 7.1 Hz, 2H), 3.86 (s, 2H), 3.21 (t, J = 2.3 Hz, 1H), 2.43 (td, J = 13.4, 4.9 Hz, 1H), 2.29 (dq, J = 13.6, 3.4 Hz, 1H), 1.90 – 1.81 (m, 2H), 1.80 – 1.73 (m, 1H), 1.54 (qt, J = 13.3, 3.4 Hz, 1H), 1.47 (s, 9H), 1.43 (dt, J = 12.8, 3.8 Hz, 1H), 1.42 – 1.35 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 155.1, 82.4, 82.0, 61.7, 59.1, 57.4, 45.5, 33.0, 32.4, 28.4, 24.5, 21.9, 14.4 ppm; IR (thin film) 2939, 1737,

1368, 1230, 1162 cm^{-1}; HRMS (ESI) *m/z* 350.1578 (350.1574 calcd for $C_{16}H_{25}NNaO_6^+$ $[MNa]^+$).





(85) 3-(*Tert*-butyl) 4a-ethyl hexahydro-3H,4aH-benzo[e]oxireno[2,3-d][1,2]oxazine-3,4a-dicarboxylate



CuCl (0.9 mg, 0.0094 mmol, 0.05 equiv) and *tert*-butyl hydroxycarbamate **42** (25 mg, 0.19 mmol, 1 equiv) were added to ethyl 2-methyl-3-oxobutanoate **72** (38 mg, 0.23 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.9 mg, 0.0094 mmol, 0.05 equiv), and ethyl oxazoline (0.9 mg, 0.0094 mmol, 0.05 equiv) in 1.3 mL of *iso*propyl alcohol. The reaction was stirred for 16 h, cooled to 0 ˚C, and then vinyldiphenylsulfonium triflate **S-33** (81 mg, 0.23 mmol, 1.2 equiv)

and 1,8-diazabicyclo[5.4.0]undec-7-ene (56 μL, 0.38 mmol, 2.0 equiv) were added to the solution. The reaction was warmed to rt and stirred for an addition 24 h, and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford annulation product **85** (55 mg, 97%) as a colorless solid.

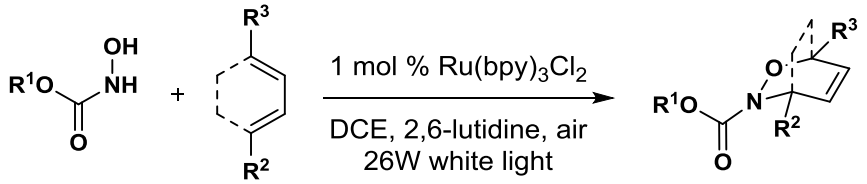
6.3 Chapter 4 Supporting Information

6.3.1 Supporting Information for the Photoredox Oxidation of *N*-Substituted Hydroxylamines

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). ^{1}H NMR spectra were recorded on Varian Spectrometers (at 400, 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Fluorescence experiments were conducted using a Varian Cary Eclipse Fluorimeter by irradiating the sample at 465 nm.

Starting Materials

Starting Hydroxylamines **1** and **S-3** were purchased from commercial vendors and used as received. Starting dienes **2** and **S-1**, **S-2** were purchased from commercial vendors and used as received. Starting olefins **S-3**, **S-4**, **S-5**, **S-6**, and **S-7** were purchased from commercial vendors and used as received. $Ru(bpy)_2Cl_2$ was purchased as the hexahydrate and used as received.

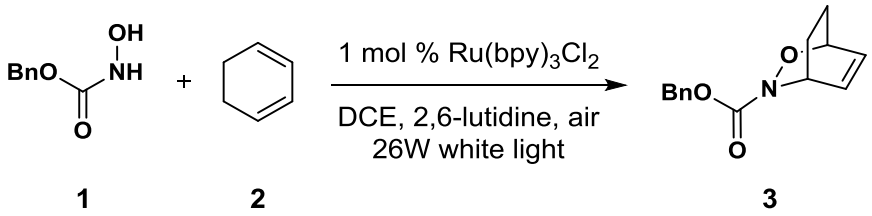


4 **5** **6**

General Procedure for the Photoredox Nitrosocarbonyl Hetero–Diels–Alder Reaction: To a stirred solution of *N*-substituted hydroxylamine **4** and 1,3-diene **5** in 1,2-dichloroethane (DCE) was added $Ru(bpy)_3Cl_2•6H_2O$ (0.01 equiv) and 2,6-lutidine (3 equiv). The reaction was suspended between two 26W white light bulbs which were turned on for the duration of the reaction, and left to stir open to the atmosphere until reaction completion, as determined by TLC analysis of the reaction mixture. During the reaction, the flask was vigorously cooled using compressed air to ensure the reaction temperature remained at rt (approx. 23°C). After completion, the solution was filtered through a plug of basic alumina and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford the desired 1,2-oxazine **6.**

Substrate Scope – Nitrosocarbonyl Hetero–Diels–Alder Reaction

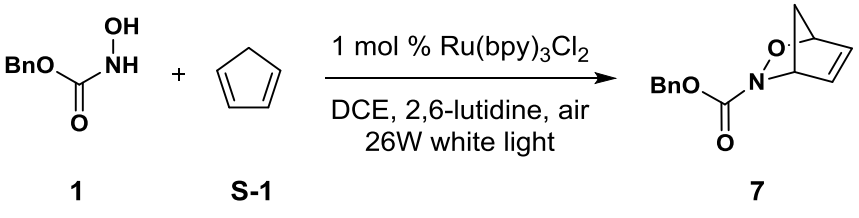
(3) Benzyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



1 **2** **3**

According to the general procedure, $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (1.1 mg, 0.0015 mmol, 0.01 equiv) and 2,6-lutidine (35 μL, 0.30 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (25 mg, 0.15 mmol, 1.0 equiv) and cyclohexa-1,3-diene **2** (45 μL, 0.45 mmol, 3.0 equiv) in 1 mL DCE. The resulting mixture was stirred for 20 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford oxazine **3** (32 mg, 87%) as a colorless solid. Data was consistent with previous literature reports.[16] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.53 (ddd, *J* = 13.7, 7.1, 7.1 Hz, 2H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 2.20 (dddd, *J* = 13.0, 8.2, 3.6, 3.6 Hz, 1H), 2.11 (dddd, *J* = 12.7, 9.3, 3.3, 3.3 Hz, 1H), 1.48 (dddd, *J* = 12.3, 12.3, 2.9, 2.9 Hz 1H), 1.37 (ddd, *J* = 12.5, 12.5, 3.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 136.1, 132.1, 131.8, 128.6, 128.3, 128.2, 71.2, 67.8, 50.3, 23.6, 20.7 ppm.

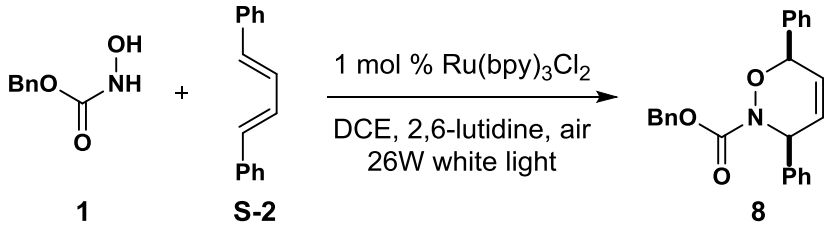
(7) Benzyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate



1 **S-1** **7**

According to the general procedure, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.1 mg, 0.0015 mmol, 0.01 equiv) and 2,6-lutidine (35 µL, 0.30 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (25 mg, 0.15 mmol, 1.0 equiv) and cyclopentadiene **18** (38 µL, 0.45 mmol, 3.0 equiv) in 1 mL DCE. The resulting mixture was stirred for 18 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford oxazine **7** (32 mg, 93%) as a colorless solid. Data was consistent with previous literature reports.[16] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 6.37 (s, 2H), 5.23 (s, 1H), 5.19 (dd, J = 12.3, 1.7 Hz, 1H), 5.12 (dd, J = 12.3, 1.8 Hz, 1H), 5.04 (s, 1H), 2.00 (dd, J = 8.7, 1.7 Hz, 1H), 1.74 (d, J = 8.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 135.8, 134.6, 133.1, 128.6, 128.4, 128.3, 84.0, 67.9, 65.2, 48.3 ppm.

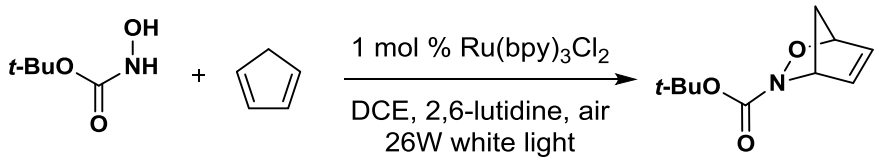
(8) Benzyl 3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate



According to the general procedure, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.1 mg, 0.0015 mmol, 0.01 equiv) and 2,6-lutidine (35 µL, 0.30 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (25 mg, 0.15 mmol, 1.0 equiv) and (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene **S-1** (93 mg, 0.45 mmol, 3.0 equiv) in 1 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford oxazine **8** (30 mg, 54%) as a colorless oil. Data was consistent

with previous literature reports.[16] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.49 – 7.30 (m, 12H), 6.17 (ddd, *J* = 10.1, 4.3, 2.0 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 5.68 (s, 1H), 5.63 (s, 1H), 5.33 (d, *J* = 12.3 Hz, 1H), 5.20 (d, *J* = 12.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0, 138.9, 137.1, 136.3, 129.2, 128.9, 128.8, 128.7, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 126.2, 79.9, 67.8, 29.6 ppm.

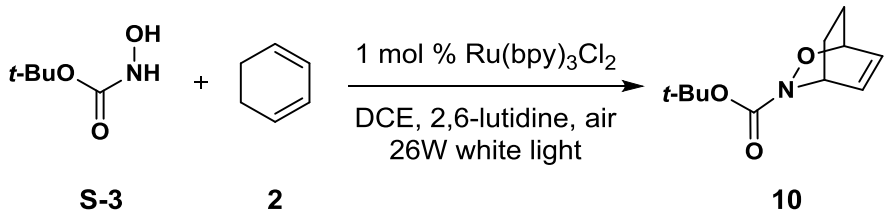
(9) *Tert*-butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate



S-3 **S-1** **9**

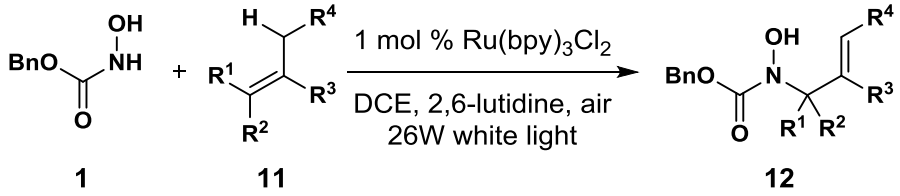
According to the general procedure, $Ru(bpy)_3Cl_2•6H_2O$ (1.1 mg, 0.0015 mmol, 0.01 equiv) and 2,6-lutidine (35 µL, 0.30 mmol, 2.0 equiv) were added to a stirred solution of *tert*-butyl hydroxycarbamate **S-2** (20 mg, 0.15 mmol, 1.0 equiv) and cyclopentadiene **18** (38 µL, 0.45 mmol, 3.0 equiv) in 1 mL DCE. The resulting mixture was stirred for 36 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford oxazine **9** (26 mg, 89%) as a yellow oil. Data was consistent with previous literature reports.[16] ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.42 – 6.38 (m, 2H), 5.20 (s, 1H), 4.97 (s, 1H), 1.98 (dt, *J* = 8.6, 1.8 Hz, 1H), 1.72 (d, *J* = 8.6 Hz, 1H), 1.46 (s, 9H) ppm.

(10) *Tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate



S-3 **2** **10**

According to the general procedure, $Ru(bpy)_3Cl_2•6H_2O$ (1.1 mg, 0.0015 mmol, 0.01 equiv) and 2,6-lutidine (35 μL, 0.30 mmol, 2.0 equiv) were added to a stirred solution of *tert*-butyl hydroxycarbamate **S-2** (20 mg, 0.15 mmol, 1.0 equiv) and cyclohexa-1,3-diene **2** (45 μL, 0.45 mmol, 3.0 equiv) in 1 mL DCE. The resulting mixture was stirred for 36 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford oxazine **10** (28 mg, 77%) as a yellow oil. Data was consistent with previous literature reports.[16] ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 – 6.45 (m, 2H), 4.75 – 4.64 (m, 2H), 2.15 (dddd, J = 12.9, 9.3, 3.7, 3.7 Hz, 1H), 2.06 (dddd, J = 12.9, 9.4, 3.5, 3.5 Hz, 1H), 1.48 – 1.40 (m, 9H), 1.35 – 1.29 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8, 131.9, 131.7, 81.7, 70.8, 50.3, 28.3, 23.7, 20.7 ppm

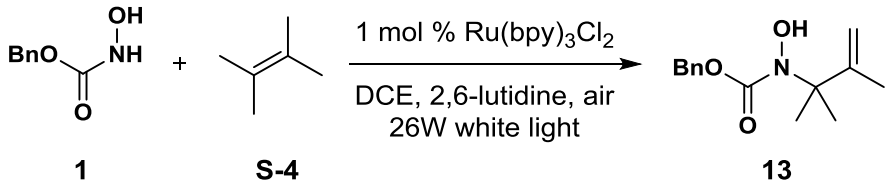


1 **11** **12**

General Procedure for the Photoredox Nitrosocarbonyl Ene Reaction: To a stirred solution of benzyl hydroxylamine **1** (1.0 equiv) and olefin **11** (3.0 equiv) in 1,2-dichloroethane (DCE) was added $Ru(bpy)_3Cl_2•6H_2O$ (0.01 equiv) and 2,6-lutidine (2.0 equiv). The reaction was suspended between two 26W white light bulbs which were turned

on for the duration of the reaction, and left to stir open to the atmosphere until reaction completion, as determined by TLC analysis of the reaction mixture. During the reaction, the flask was vigorously cooled using compressed air to ensure the reaction temperature remained at rt (approx. 23°C). After completion, the solution was filtered through a plug a basic alumina and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford the desired allylic hydroxylamine **12.**

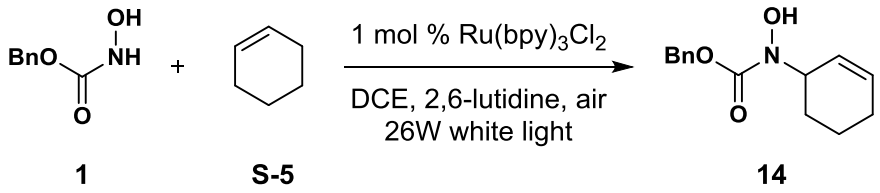
(13) Benzyl (2,3-dimethylbut-3-en-2-yl)(hydroxy)carbamate



1 **S-4** **13**

According to the general procedure, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.2 mg, 0.0030 mmol, 0.01 equiv) and 2,6-lutidine (70 μL, 0.60 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (50 mg, 0.30 mmol, 1.0 equiv) and 2,3-dimethylbutene **S-4** (107 μL , 0.90 mmol, 3.0 equiv) in 2 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford hydroxycarbamate **13** (74 mg, 99%) as a colorless oil. Data was consistent with previous literature reports. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 6.77 (bs, 1H), 5.16 (s, 2H), 4.84 (s, 1H), 4.76 (s, 1H), 1.74 (s, 3H), 1.48 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 149.8, 136.0, 128.6, 128.4, 128.3, 109.5, 68.1, 66.1, 25.7, 19.3 ppm.

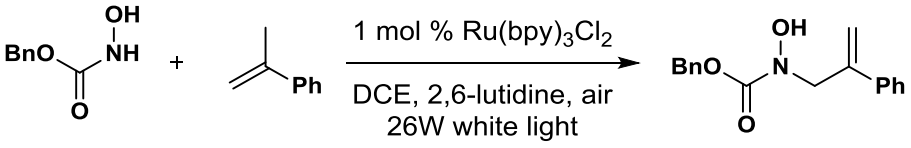
(14) Benzyl cyclohex-2-en-1-yl(hydroxy)carbamate



1 **S-5** **14**

According to the general procedure, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.2 mg, 0.0030 mmol, 0.01 equiv) and 2,6-lutidine (70 μL, 0.60 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (50 mg, 0.30 mmol, 1.0 equiv) and cyclohexene **S-5** (91 μL , 0.90 mmol, 3.0 equiv) in 2 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford hydroxycarbamate **14** (51 mg, 68%) as a colorless solid. Data was consistent with previous literature reports. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 6.48 (bs, 1H), 5.96 – 5.90 (m, 1H), 5.56 (dd, J = 10.2, 1.4 Hz, 1H), 5.20 (s, 2H), 4.70 – 4.64 (m, 1H), 2.09 – 2.02 (m, 1H), 2.00 – 1.80 (m, 4H), 1.66 – 1.56 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.5, 136.2, 132.2, 128.8, 128.5, 128.3, 126.6, 68.2, 55.8, 25.9, 24.6, 21.3 ppm.

(15) Benzyl hydroxy(2-phenylallyl)carbamate

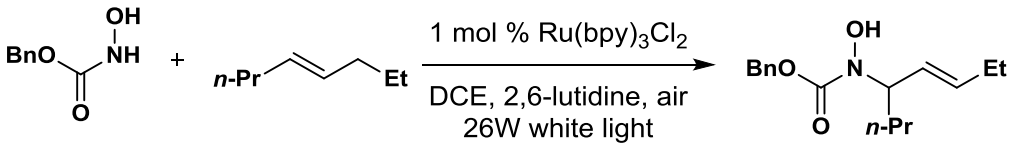


1 **S-6** **15**

According to the general procedure, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.2 mg, 0.0030 mmol, 0.01 equiv) and 2,6-lutidine (70 μL, 0.60 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (50 mg, 0.30 mmol, 1.0 equiv) and cyclohexene **S-6** (117 μL , 0.90

mmol, 3.0 equiv) in 2 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford hydroxycarbamate **15** (63 mg, 85%) as a colorless solid. Data was consistent with previous literature reports. ^{1}H NMR (600 MHz, CDCl3) δ 7.34 – 7.15 (m, 10H), 6.98 (bs, 1H), 5.39 (s, 1H), 5.18 (s, 1H), 5.02 (s, 2H), 4.48 (s, 2H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 157.4, 142.5, 138.8, 136.0, 128.7, 128.6, 128.5, 128.3, 128.1, 126.5, 115.4, 68.3, 54.5 ppm.

(16) Benzyl (*E*)-hydroxy(oct-5-en-4- yl)carbamate

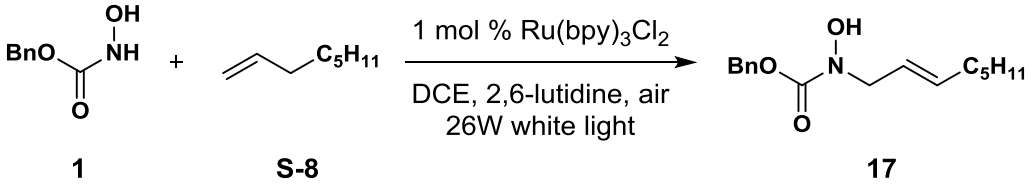


1 **S-7** **16**

According to the general procedure, $Ru(bpy)_3Cl_2$•$6H_2O$ (2.2 mg, 0.0030 mmol, 0.01 equiv) and 2,6-lutidine (70 μL, 0.60 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (50 mg, 0.30 mmol, 1.0 equiv) and (*E*)-oct-4-ene **S-7** (142 μL , 0.90 mmol, 3.0 equiv) in 2 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford hydroxycarbamate **16** (65 mg, 78%) as an inseperable 3:1 *E:Z* mixture as a colorless oil. Data was consistent with previous literature reports. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 7.15 (bs, 1H), 5.65 (dt, *J* = 15.5 Hz, 1H), 5.54 – 5.45 (m, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 4.79 (apt. q, *J* = 8.4 Hz, 1H), 4.45 (apt. q, *J* = 7.2 Hz, 1H), 2.06 – 1.99 (m, 2H), 1.80 – 1.75 (m, 1H), 1.54 – 1.48 (m, 1H), 1.47 – 1.43 (m, 1H), 1.31 – 1.18 (m, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 157.5,

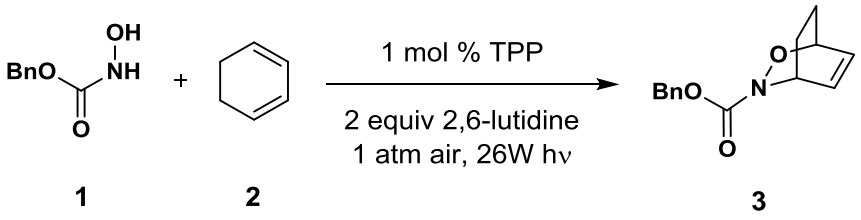
136.3, 136.2, 135.1, 134.4, 128.7, 128.4, 128.4, 128.2, 128.2, 126.6, 126.5, 68.0, 68.0, 61.0, 55.9, 34.5, 33.9, 25.5, 21.3, 19.5, 19.4, 14.3, 14.0, 14.0, 13.6 ppm.

(17) Benzyl (*E*)-hydroxy(oct-2-en-1-yl)carbamate



1 **S-8** **17**

According to the general procedure, $Ru(bpy)_3Cl_2•6H_2O$ (2.2 mg, 0.0030 mmol, 0.01 equiv) and 2,6-lutidine (70 μL, 0.60 mmol, 2.0 equiv) were added to a stirred solution of benzyl hydroxycarbamate **1** (50 mg, 0.30 mmol, 1.0 equiv) and oct-1-ene **S-8** (142 μL , 0.90 mmol, 3.0 equiv) in 2 mL DCE. The resulting mixture was stirred for 24 h at rt. The reaction was filtered through a plug of basic alumina, and the solvent was removed *in vacuo.* The crude residue was purified by flash column chromatography to afford hydroxycarbamate **17** (28 mg, 34%) as an inseperable 3:1 *E:Z* mixture as a colorless oil. Data was consistent with previous literature reports. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 6.98 (bs, 1H), 5.67 (dt, *J* = 15.0, 6.7 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.51 – 5.45 (m, 1H), 5.18 (s, 2H), 4.20 (d, *J* = 5.0 Hz, 1H), 4.18 (d, *J* = 6.9 Hz, 2H), 4.07 (d, *J* = 6.3 Hz, 2H), 2.06 (q, *J* = 7.1 Hz, 2H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.38 – 1.22 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.7, 157.6, 136.1, 136.0, 128.7, 128.7, 128.5, 128.5, 128.3, 128.3, 123.2, 123.0, 68.3, 68.2, 52.9, 47.7, 32.4, 31.6, 31.6, 29.3, 28.9, 27.5, 22.7, 14.2 ppm.



1 2 3

General Procedure for the Nitrosocarbonyl HDA Using TPP: To a stirred solution of benzyl hydroxycarbamate 1 (25 mg, 0.15 mmol, 1.0 equiv) and 1,3-cyclohexadiene 2 (45 μL, 0.45 mmol, 3.0 equiv) in 1,2-dichloroethane (DCE) was added 5,10,15,20-tetraphenylporphyrin (TPP) (0.90 mg, 0.0015 mmol, 0.010 equiv) and 2,6-lutidine (35 μL, 0.30 mmol, 2.0 equiv). An additional 3 equiv of 1,3-cyclohexadiene was added every two hours up to a total of 9 equiv. The reaction was suspended between two 26W white light bulbs which were turned on for the duration of the reaction, and left to stir open to the atmosphere until reaction completion, as determined by TLC analysis of the reaction mixture. During the reaction, the flask was vigorously cooled using compressed air to ensure the reaction temperature remained at rt (approx. 23°C). After completion, the solution was filtered through a plug of basic alumina and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography to afford the desired 1,2-oxazine 3 (14 mg, 37%).

General Procedure for the On-Off Studies on the Photoredox Oxidation

To a stirred solution of benzyl hydroxycarbamate **1** (200 mg, 1.2 mmol, 1.0 equiv) and cyclopentadiene **18** (302 μL, 3.6 mmol, 3.0 equiv) in 1,2-dichloroethane (8 mL) was added $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.012 mmol, 0.01 equiv) and 2,6-lutidine (280 μL, 2.4 mmol, 2.0 equiv). Dimethylterephthalate (58 mg, 0.30 mmol, 0.25 equiv) was added as an internal standard. The reaction was suspended between two 26W white light bulbs which were

iteratively turned on and off for designated periods of time while stirring open to the atmosphere. During the reaction, the flask was vigorously cooled using compressed air to ensure the reaction temperature remained at rt (approx. 23°C). At designated time intervals, 200 μL aliquots were removed, filtered through a plug of basic alumina and concentrated *in vacuo*. Conversion was determined by NMR analysis of the concentrated aliquots.

General Procedure for the Distance Dependence Studies on the Photoredox Oxidation

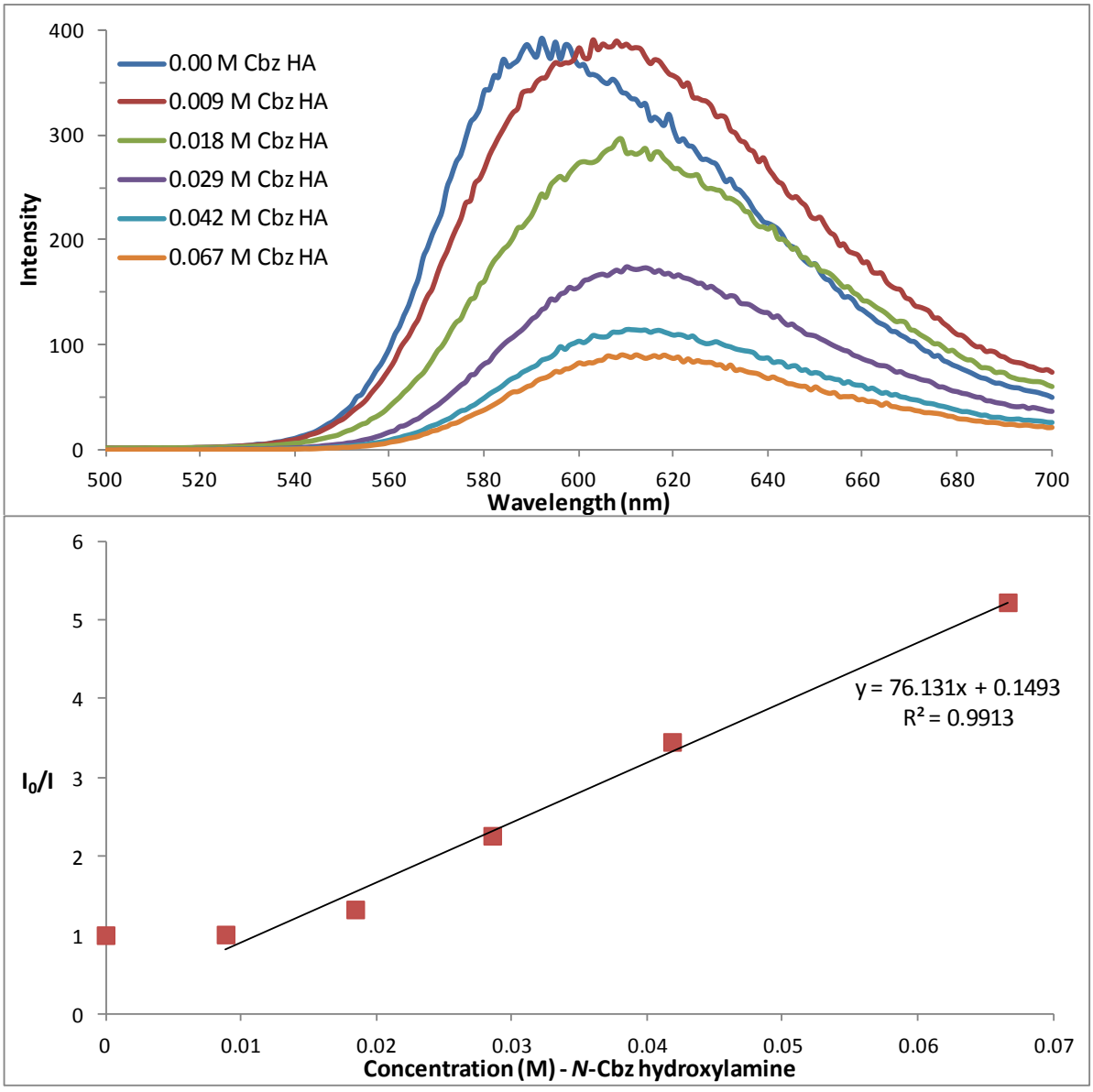
To a stirred solution of benzyl hydroxycarbamate **1** (200 mg, 1.2 mmol, 1.0 equiv) and cyclopentadiene **18** (302 μL, 3.6 mmol, 3.0 equiv) in 1,2-dichloroethane (8 mL) was added $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.012 mmol, 0.01 equiv) and 2,6-lutidine (280 μL, 2.4 mmol, 2.0 equiv). Dimethylterephthalate (58 mg, 0.30 mmol, 0.25 equiv) was added as an internal standard. The reaction was suspended between two 26W white light bulbs which were placed at a designated distance from the sidewall of the flask (0 cm, 1 cm, 2 cm) while stirring open to the atmosphere. During the reaction, the flask was vigorously cooled using compressed air to ensure the reaction temperature remained at rt (approx. 23°C). At designated time intervals, 200 μL aliquots were removed, filtered through a plug of basic alumina and concentrated *in vacuo*. Conversion was determined by NMR analysis of the concentrated aliquots.

General Procedure for the Fluorescence Quenching of the Photocatalyst:

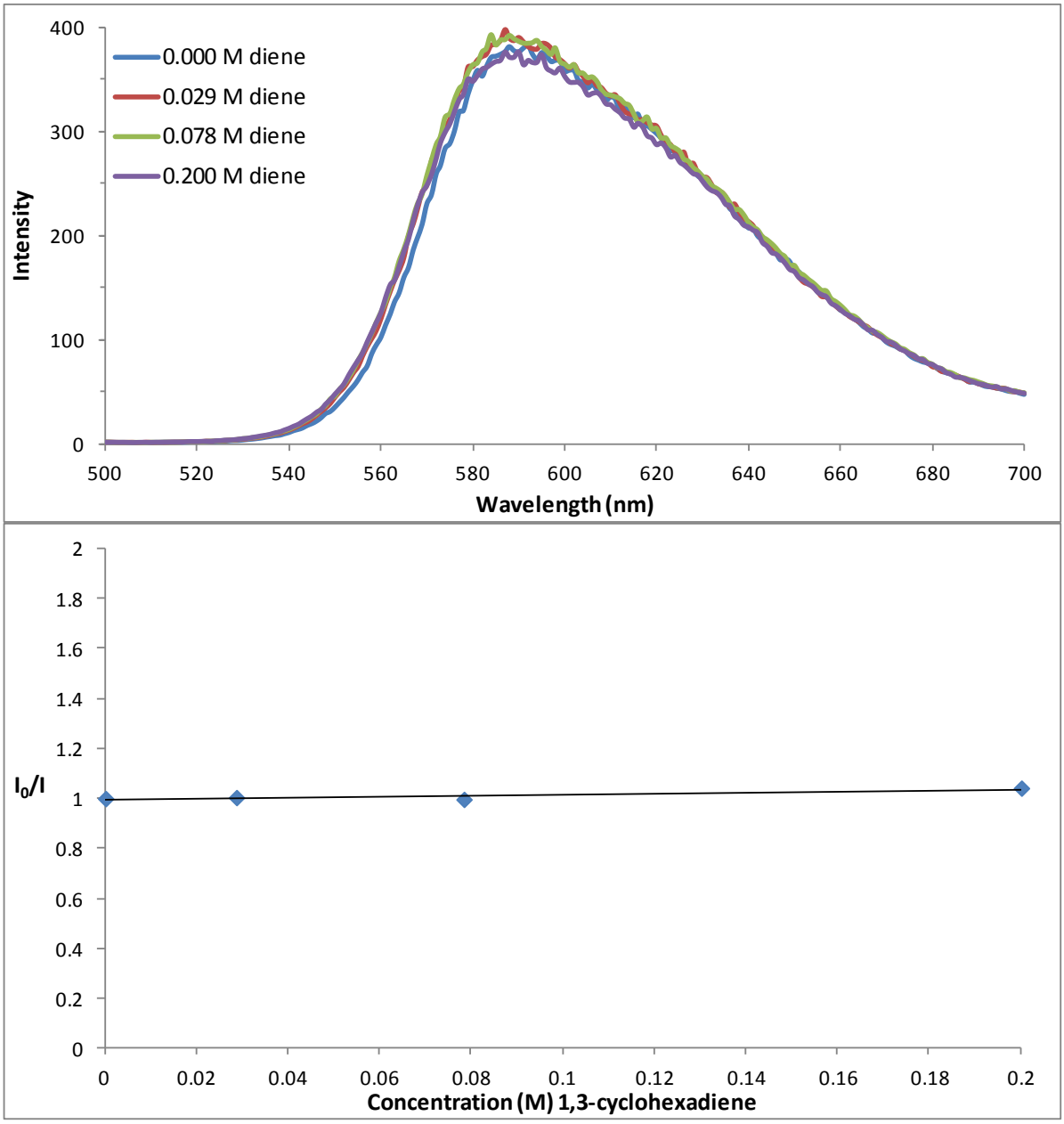
A solution of benzyl hydroxycarbamate **1** in acetonitrile was vigorously degassed *via* freeze-pump-thaw. The solution was added to a sealed cuvette so that an atmosphere of argon was maintained and the cuvette was place in a Varian Cary Eclipse Fluorimeter. The sample was irradiated at 465 nm and the fluorescence was monitored. The experiment was repeated

iteratively at various concentrations of benzyl hydroxycarbamate **1 (Cbz HA)** and cyclohexa-1,3-diene **2 (diene)**.

Fluorescence quenching of $Ru(bpy)_3Cl_2$ by benzyl hydroxycarbamate



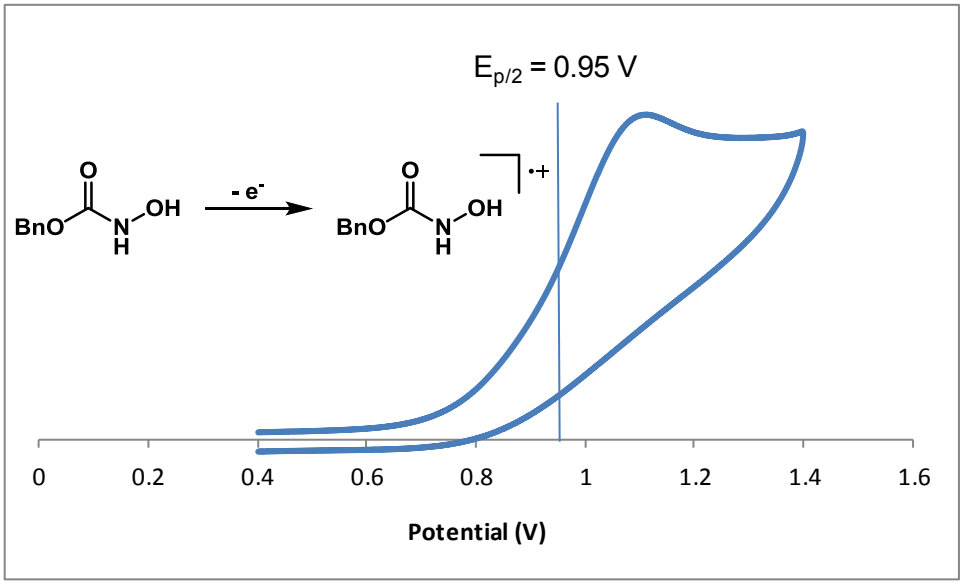
Fluorescence quenching of $Ru(bpy)_3Cl_2$ by 1,3-cyclohexadiene



General Procedure for Cyclic Voltammetry Experiments

The experiments were carried out in a conventional three electrode cell using a Potentiostat 600C (CH Instruments, Austin TX). A glassy carbon disc (diameter: 1 mm) served as a working electrode and a platinum wire as counter electrode. The glassy carbon disc was

polished using polishing alumina (0.05 µm) before each experiment. As reference a $Ag/AgNO_3$ electrode (silver wire in 0.1 M NBu_4BF_4/MeCN solution; $c(AgNO_3)$ = 0.01 M; E_0 = -87 mV vs. ferrocene redox couple) was used and this compartment was separated from the rest of the cell with a Vycor frit. For estimation of the oxidation potentials, the average value of three different measurements was formed (typical deviation within the range of 10 mV). A solution of 1.5 mg of benzyl hydroxycarbamate in 5 ml of electrolyte solution was used.



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