UNIVERSITY OF CALIFORNIA

Santa Barbara

Novel Methods for N- and O- Atom Transfer to Small Molecules

A dissertation submitted in partial satisfaction of the requirements for

the degree Doctor of Philosophy in Chemistry

by

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March 2017

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March 2017

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Acknowledgements

I would first like to acknowledge my mentor, Javier. I am grateful that you allowed me to join the group even though it was bursting at the seams when I got here. Your guidance has led to tremendous personal growth and development as a scientist for me. Thank you for pushing me to always perform to the best of my abilities, it's been awesome working for you.

I wouldn't be in the position I am today without the support system that is my research group. When the going got tough you guys made things better. First, to Chuck, Dave, Don, Leoni and Gesine, you were all senior group members when I arrived, thank you for teaching me the ropes and for your advice and help on the research projects I worked on early in my career. Jimmy, you've been there with me from day one, you know how to keep things entertaining in the lab, thanks for being a great friend. To Andre, my fume hood neighbor, I miss our daily banter buddy, thanks for all the helpful, stimulating chemistry conversations. Jamie and Landon, thank you for playing key roles in the development of the last couple research projects I worked on, you guys are great collaborators.

To my family, you were my earliest support system. Thank you Mom and Dad for instilling in me a strong work ethic, teaching me the importance of education and for your unwavering support and confidence in my ability to successfully accomplish the goals I set for myself. Marilee, your hard work and success is exceptional and constantly a source of inspiration for me.

Finally, to my amazing wife Katie, for believing in me during times when I was unsure of myself, cheering me up at the end of tough days, and for being my biggest advocate. You make me happy and motivate me to succeed. I love you.

Curriculum Vitae

David J. Fisher

March 2017

Research Summary
Development of novel synthetic methods for the incorporation of nitrogen and oxygen into organic molecules. Specifically, this is accomplished through SET processes involving nitrosoarene intermediates.

Education
University of California, Santa Barbara 2012-present
Ph.D. Candidate, Department of Chemistry and Biochemistry
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California Polytechnic State University-San Luis Obispo 2007-2011
Bachelor of Science, Biochemistry

Employment
Gilead Sciences-Medicinal Chemist 2012
Synthesized and characterized nucleoside prodrugs targeting Hepatitis C.

Gilead Sciences-Medicinal Chemistry Intern 2011
Developed an alternate synthesis for the heterobase on a nucleoside prodrug targeting Hepatitis C.

Publications
"Efficient Synthesis of 4-Hydroxycyclopentenones: Dysprosium(III) Triflate Catalyzed Piancatelli Rearrangement" **Fisher, D. J.**; Palmer, L. I.; Cook, J. E.; Davis, J. E.; Read de Alaniz,*J. *Tetrahedron,* **2014**, *70*, 4105-4110.

"A Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds" **Fisher, D. J.**; Burnett, G. L.; Velasco, R.; Read de Alaniz, *J. *J. Am. Chem. Soc.* **2015**, *137*, 11614-11617

"Synthesis of Hindered Anilines: Three-Component Coupling of Arylboronic Acids, tert-Butyl Nitrite, and Alkyl Bromides" **Fisher, D. J.**; Shaum, J. B.; Mills, C. L.; Read de Alaniz, *J. *Org. Lett.* **2016**, *18*, 5074-5077

"Synthesis of Amino Alcohols: An Intramolecular Radical Addition with Nitroso Compounds" **Fisher, D. J.**; Shaum, J. B.; Mills, C. L.; Read de Alaniz, *J. Manuscript in Preparation

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Nitroso Mediated Radical Coupling Reactions: Synthesis of Hindered Anilines

44th ACS National Organic Chemistry Symposium, Bryn Mawr College 2016
Oral Presentation

Alkoxyamines: Molecular Hooks To 'Catch And Release' Carbonyl Substrates

239th ACS National Meeting, San Francisco, CA 2010
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Awards

Mellinchamp Sustainability Fellowship 2015
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Abstract

Novel Methods for N- and O–Atom Transfer to Small Molecules

by

David Fisher

Nitrogen and oxygen are ubiquitous in natural products, pharmaceuticals, polymers, and dyes. As a result, the development of new methods for C–N and C–O bond formation is a major focus for synthetic organic chemists. Several new strategies for the installation of N- and O- atoms in organic molecules are described herein.

4-Hydroxycyclopentenones are important building blocks for the synthesis of prostaglandins and other biologically active molecules and natural products. In 1976, Giovanni Piancatelli discovered that 2-furylcarbinols could be converted to *trans*-4-hydroxycyclopentenones via an acid-catalyzed cascade reaction involving a thermal 4π

electrocyclization. This process is known today as the Piancatelli rearrangement and remains among the most efficient methods for the synthesis of 4-hydroxycyclopentenones. Despite the significance of this approach, it can be limited by high catalyst loadings, harsh reaction conditions, and unavoidable isomerization to the thermodynamic product. We have developed a general, mild, dysprosium (III) trifluoromethanesulfonate-catalyzed rearrangement that provides exclusive access to either 4-hydroxycyclopentenone isomer.

Nitrosoarenes typically serve as 2π synthons in transformations such as the aldol, Diels-Alder, and ene reactions. Despite being efficient spin trapping agents, arylnitrosos have not been utilized in single electron transfer processes as a tool in organic synthesis. In polymer chemistry, alkyl radical additions with nitroso compounds are used in a process known as radical trap-assisted atom transfer radical coupling (RTA-ATRC) to stitch together polymer chains for the synthesis of alkoxyamine-linked diblock copolymers. We have developed this concept as a synthetic tool in small molecule organic chemistry.

Recently, we reported a mild, catalytic method for the synthesis of hindered α-amino carbonyl compounds utilizing radical additions with in situ-generated nitroso compounds. The process is redox neutral, uses catalytic $CuCl_2$ to simultaneously generate the reactive intermediates, occurs at room temperature and has a high degree of functional group compatibility. Additionally, a three component coupling reaction for the synthesis of hindered anilines was developed by merging radical chemistry with nitroso compounds. This process utilizes commercially available starting materials and forms two C–N bonds in one pot. Finally, an intramolecular approach for the synthesis of amino alcohols is reported. This strategy provides spatial control over the N– and O–atom transfer event in the reaction with bis-alkyl halides.

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List of Abbreviations

4Å MS - 4 angstrom molecular sieves

ATRC – atom transfer radical coupling

ATRP – atom transfer radical polymerization

Ar – aromatic

ArNO – arylnitroso

BINAP - 2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl

Bn – benzyl

Boc – *tert*-butyloxycarbonyl

Bz – benzoyl

DCC – *N,N′*-dicyclohexylcarbodiimide

DCM – dichloromethane

DME – dimethoxyethane

DMF – dimethylformamide

DMA – dimethylacetamide

dtbbpy – 4,4′-Di-*tert*-butyl-2,2′-dipyridyl

E – Electrophile

ESR – electron spin resonance

Et – ethyl

EDG - electron donating group

Equiv – equivalent

EWG - electron withdrawing group

FG – functional group

HDA – Hetero–Diels–Alder

HMPA – hexamethylphosphoramide

hr – hours

hν – light

i-Pr – isopropyl

IR – infrared spectroscopy

L – Ligand

LA – Lewis Acid

LDA – lithium diisopropylamide

Me – methyl

MeCN – acetonitrile

min – minutes

MS – mass spectroscopy

Ms – mesyl

n-BuLi – *n*-butyl lithium

NMP – *N*-methyl-2-pyrrolidone

NMP – nitroxide-mediated radical polymerization

NMR – nuclear magnetic resonance

Nu – Nucleophile

O – oxidation

OAc – Acetate

OTf - trifluoromethanesulfonate

PMDETA – N,N,N',N",N"-pentamethyldiethylenetriamine

Ph – phenyl

PhMe – toluene

psi – pounds per square inch

PTSA – para-toluenesulfonic acid

Pyr – pyridine

R – reduction

rt – room temperature

SEGPHOS – 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)

SET – single electron transfer

TBS – *tert*-butyldimethylsilyl

t-BuOH – *tert*-butyl alcohol

t-BuONO – *tert*-butyl nitrite

RONO – Alkyl nitrite

TFA - Trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilyl

TBSCl – *tert*-butyldimethylsilyl chloride

TMSCl – trimethylsilyl chloride

Ts – tosyl

Xantphos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Δ – Heat

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1. Historical Background of the Piancatelli Rearrangement

1.1 Introduction

The Piancatelli rearrangement is a powerful method for the synthesis of 4-hydroxycyclopentenones, valuable precursors to prostaglandins. Starting from easily prepared 2-furylcarbinols, this cascade rearrangement furnishes products with high *trans* selectivity. The observed stereochemistry in the 4-hydroxycyclopentenones is governed by the electrocyclic nature of this transformation.

1.2 Electrocyclic Reactions

Electrocyclic reactions represent a subset of a class of transformations known as pericyclic reactions, which are characterized by their transition states composed of a cyclic array of interacting molecular orbitals.[1] Cycloadditions, sigmatropic rearrangements, and group-transfer reactions are also common examples. An electrocyclic reaction is a process in which a molecule containing a π system is converted to a product where either a π bond is broken and replaced with a newly formed σ bond or a π bond is formed to replace a broken σ bond. The Nazarov cyclization is a classic example in which a divinyl ketone **1** is converted to a cyclopentenone **3** through a 4π electrocyclization (Figure 1.1).[2]

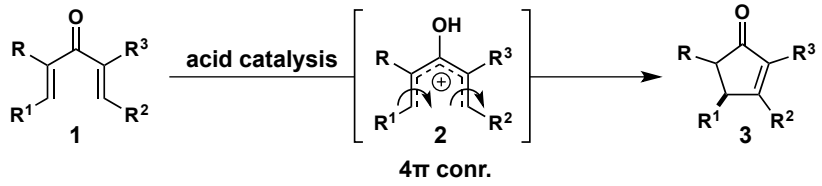

Figure 1.1 The Nazarov Cyclization

The mechanisms of pericyclic reactions are notoriously more difficult to study than classic reactions such Sn1 or E2 reactions because the concerted processes have no discernable intermediates during the course of the transformation. It wasn't until the mid 20th century that

molecular orbit theories were developed to help understand the mechanisms and stereochemical outcomes of these enigmatic transformations. Seminal studies published in 1965 by Woodward and Hoffman postulated that conservation of orbital symmetry in the highest occupied molecular orbital (HOMO) governed the observed stereochemistry in electrocyclic reactions.[3] This work lead to the formation of three critical guidelines for electrocyclic reactions: 1) For thermally promoted processes, in order to maintain orbital symmetry in the HOMO in a system with 4π electrons, cyclization will be conrotatory; 2) In a thermally promoted 4π + 2 system, the cyclization will be disrotatory; 3) In photochemical reactions, an electron from the HOMO of the starting material is promoted to the excited state. This reverses symmetry relationships, leading to disrotation for 4π cyclizations and conrotation for 4π + 2 cyclizations. This set of guidelines, which later became known as the Woodward-Hoffman rules, can be applied to a variety of different pericyclic reactions to rationalize their stereochemical outcomes.[4]

These rules are best illustrated through the use of molecular orbital diagrams. First, we will explore the thermally promoted 4π electrocyclization of *trans,trans*-2,4-hexadiene **4** (Figure 1.2). Examination of the HOMO shows that in order to maintain constructive orbital overlap during the bond forming event, conrotation must occur along the C_2 axis, which also leads to an antiperiplanar relationship between the methyl substituents in the *trans*-butene product **5**. Disrotation causes orbitals of opposite signs to overlap, which is forbidden. The geometry of the olefins in the diene also plays a critical role in the stereochemical outcome of the reaction. For example, *cis,trans*-2,4-hexadiene will cyclize under thermal conditions to form a cyclobutene product where the methyl groups are *syn*.

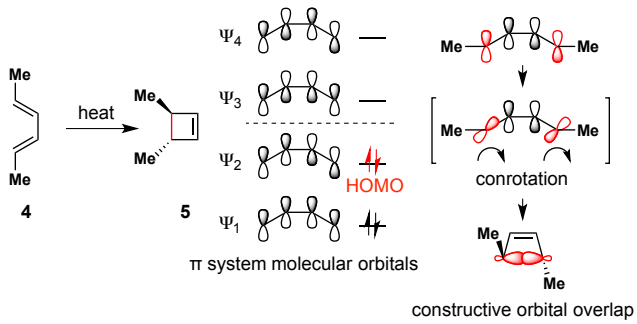

Figure 1.2. Molecular orbital diagram for a thermal 4π conrotatory electrocyclization

Second is a thermally promoted 6π electrocyclization of substituted 1,3,5-hexatriene **6** (Figure 1.3). Inspection of the HOMO illustrates that now disrotation leads to constructive orbital overlap to form the *cis*-cyclohexadiene product **7**. Conrotation leads to forbidden overlap of orbitals with the opposite sign. Photochemically promoted electrocyclizations are governed by an opposite set of rules (Figure 1.4). Photochemical 4π cyclizations are disrotatory in nature and 4π + 2 cyclizations occur in conrotatory fashion.

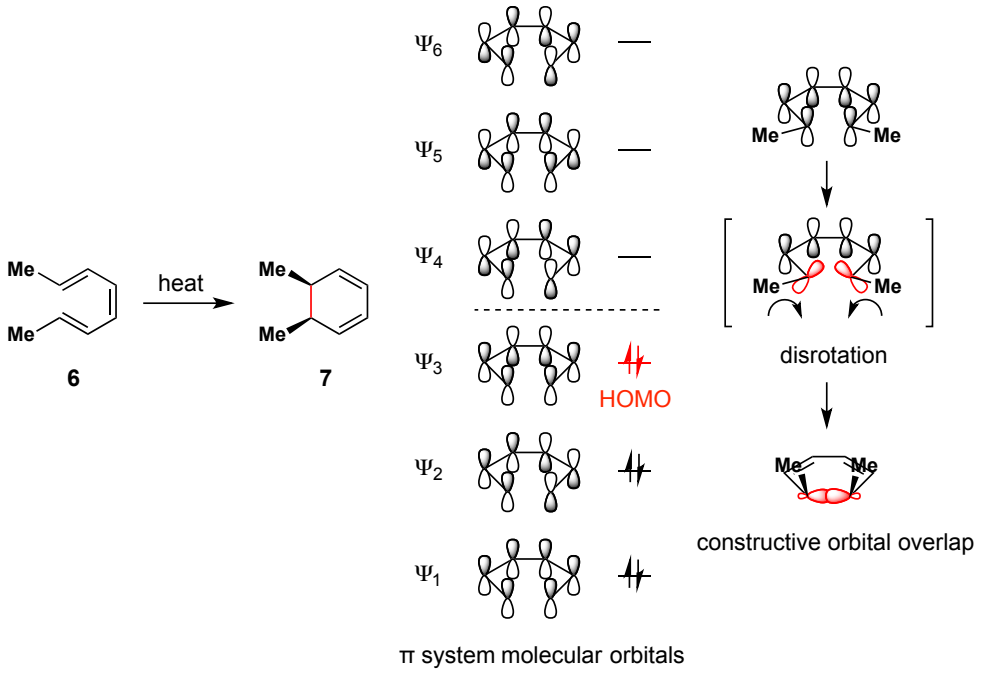

Figure 1.3. Molecular orbital diagram for a thermal 6π conrotatory electrocyclization

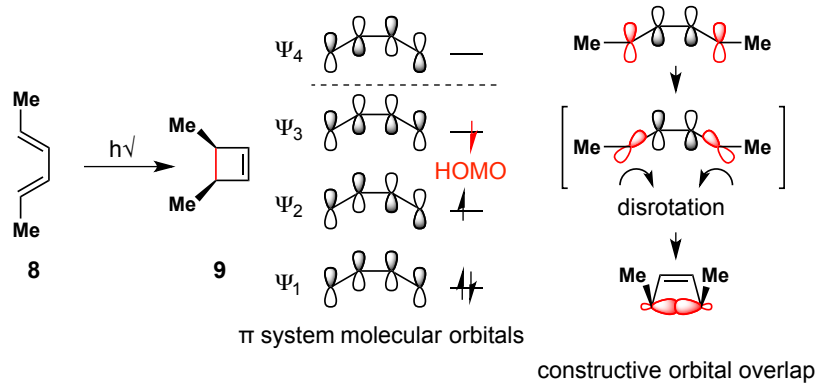

Figure 1.4. Molecular orbital diagram for a light driven 4π conrotatory electrocyclization

In ring opening reactions, the geometry about the resulting olefin is governed by both the stereochemistry of the ring system and the type of rotation that occurs (Figure 1.5). For instance, under thermal conditions *anti*-cyclobutene **10** will open to diene **11** and *syn*-butene **12** to diene **13** with conrotation. *syn*-Diene **14** will undergo a thermally promoted ring opening that is disrotatory to form triene **15.**

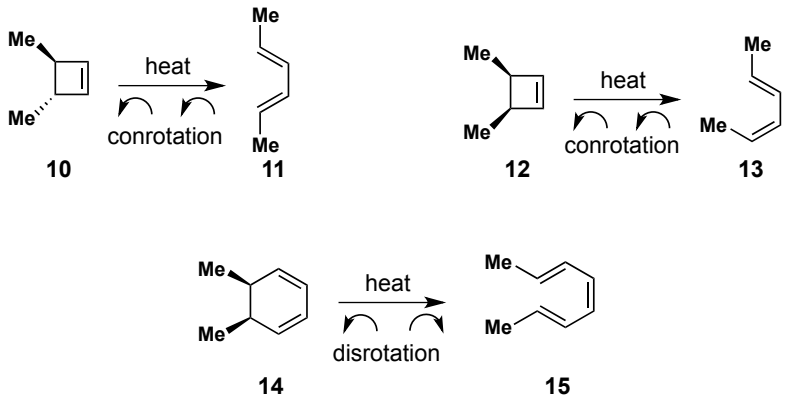

Figure 1.5. Examples of thermally promoted ring opening electrocyclic reactions

1.3 The Piancatelli Rearrangement

In 1976, Giovanni Piancatelli and co-workers reported a novel, stereospecific acid catalyzed cascade rearrangement of 2-furylcarbinols **17** to *trans*-4-hydroxycyclopentenones **18** (Figure 1.6).[5] This method is appealing because a relatively simple starting material is converted to a stereochemically defined, functionalized molecule in a single step. Additionally, the furylcarbinol starting material is easily prepared in one step through a Grignard addition to furfural (**16**), an abundant, renewable feedstock chemical.[6]

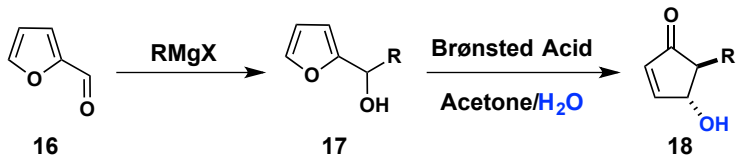

Figure 1.6. The Piancatelli rearrangement of 2-furylcarbinols to 4-hydroxycyclopentenones

The discovery was driven by the need for an efficient method to access the 4-hydroxycyclopentenone core, a valuable precursor to prostaglandins, which at the time were being studied and developed for their biological activity.[7] Today, this process known as the Piancatelli rearrangement continues to be among the most concise for accessing this important scaffold.

The mechanism is proposed to begin with acid activation of the alcohol followed by displacement of water to generate the highly reactive, transient oxocarbenium species **19** (Figure 1.7). Nucleophilic addition by water forms the hemiacetal **20** which undergoes ring-opening to the cyclopentadienyl cation **21**. Bond rotation, followed by a thermal 4π conrotatory electrocyclization furnishes the oxyallyl cation **23**, which upon protonation yields the *trans*-4-hydroxycyclopentenone **18**. Stereochemistry is not transferred from the 2-furylcarbinol to the final product. D'Auria has showed that when (R)-2-phenylfurylcarbinol participates in the rearrangement, a racemic mixture of the *trans*-4-hydroxycyclopentenone is produced.[8] The *trans* stereochemistry is established during the thermal 4π electrocyclization, which following the Woodward-Hoffman rules, must be a conrotatory process.

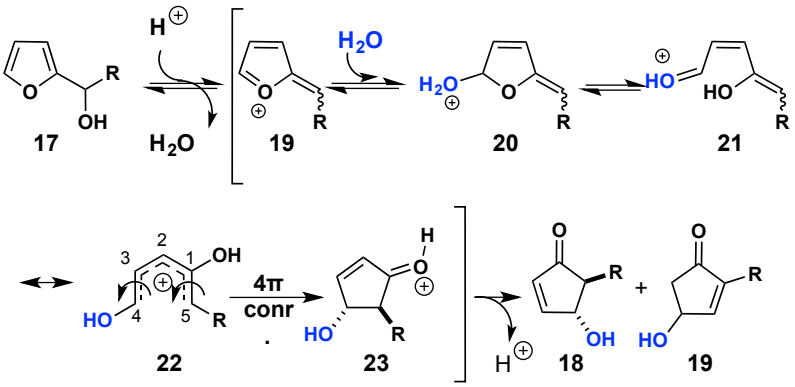

Figure 1.7. Proposed mechanism for the Piancatelli rearrangement

An insightful theoretical study on the electrocyclic ring closure of 1,4-dihydroxycyclo-pentadienyl cations by de Lera and co-workers further supports the thermal 4π-conrotatory electrocyclization mechanistic hypothesis.[9] The various conformers of the cyclopentadienyl cation, the cyclization transition states, and the resulting oxyallyl cations were studied at the 6-311G* DFT level to determine their energetic properties (Figure 1.8). Although out, out-**24** was merely 1.57 kcal mol^{-1} lower in energy than in,out-**30** the

activation energy for the former was only 5.95 kcal mol^{-1} while that of the latter was 15.74 kcal mol^{-1}. Interestingly, out,in-**27** had a slightly lower activation energy (5.29 kcal mol^{-1}) than out,out-**24**, but was less stable by 6.84 kcal mol^{-1}. The instability of in,in-**33** as well as its high activation energy make this isomer and reaction pathway unlikely to exist. The combination of its stability and low energy of activation made out,out-**24** the ideal candidate for cyclization. de Lera's conclusion that the Piancatelli rearrangement progresses through a thermal 4π conrotatory electrocyclization of out, out-**24** coincides with the *trans* selectivity observed in the 4-hydroxycyclopentenone products.

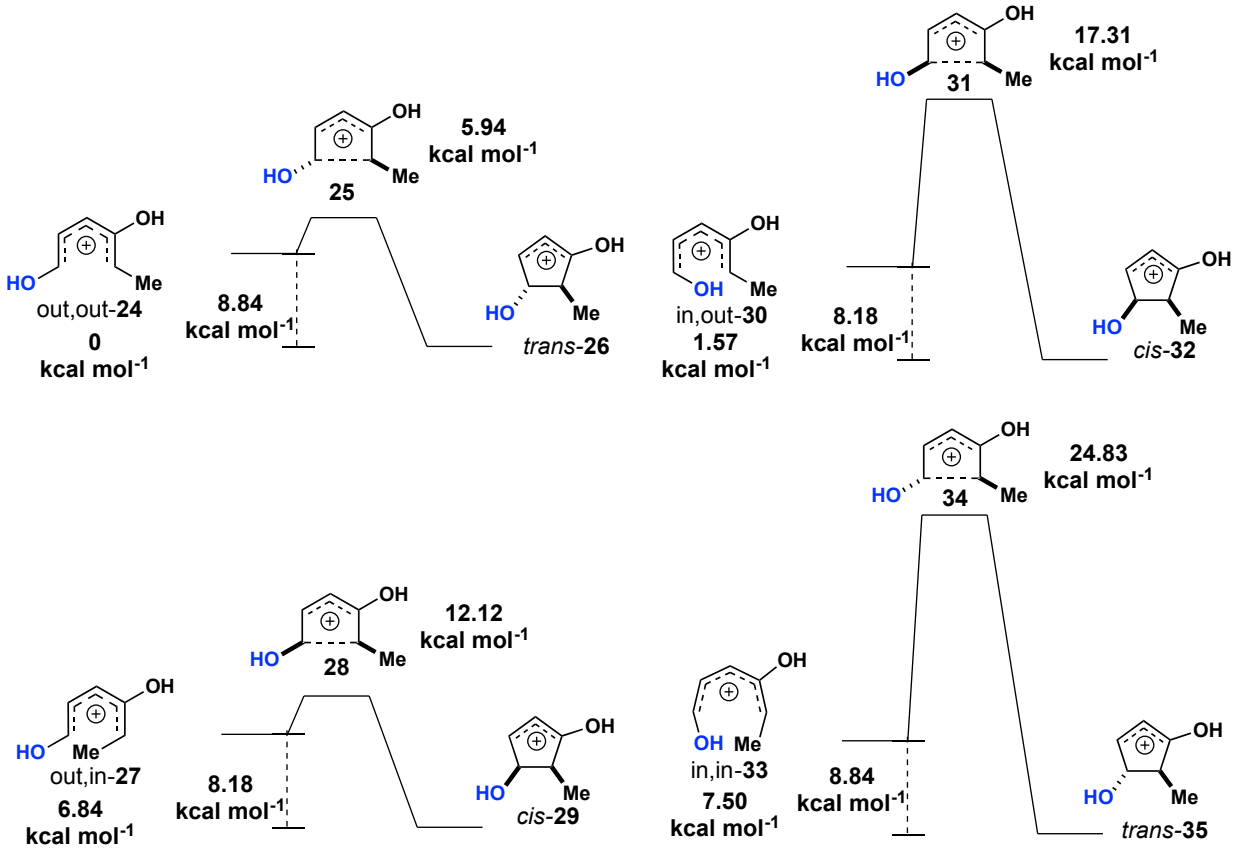

Figure 1.8. Energies of cyclopentadienyl cation conformers

Alternate approaches to the 4-hydroxycyclopentenone core required multi-step syntheses.[10] For example, Nakamura and reported a four step synthesis starting from

2-methylfuran **36** (Figure 1.9). Lithiation of **36** followed by addition of alkyl bromide delivers **37**. The 2,5-dimethoxydihydrofuran **38** was then generated through an anodic methoxylation of the 2,5-disubstituted furan **37**. Hydrolysis of **38** with Amberlite 120B (acidic ion-exchange resin) formed the 1,4 diketone **39**. A base-catalyzed intramolecular aldol reaction affords the 4-hydroxycyclopentenone product **40** which isomerizes to the thermodynamic product **41** spontaneously.

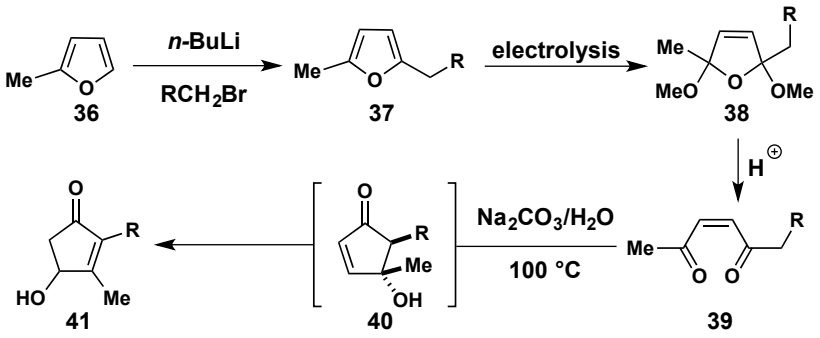

Figure 1.9. Nakamura's multistep synthesis of 4-hydroxycyclopentenones

In Piancatelli's initial report, 2-furylcarbinols were treated with Brønsted acids (formic acid, polyphosphoric acid (PPA) or para-toluenesulfonic acid (p-TSA) in a water/acetone solvent system at 50 °C for 24 hours (Figure 1.10).[5] The best results were achieved with aryl substituted 2-furylcarbinols (**42)**, while the alkyl substituted material (**43-44**) was less prone to dehydration, and the resulting carbocation tended to decompose through elimination reactions during the rearrangement.

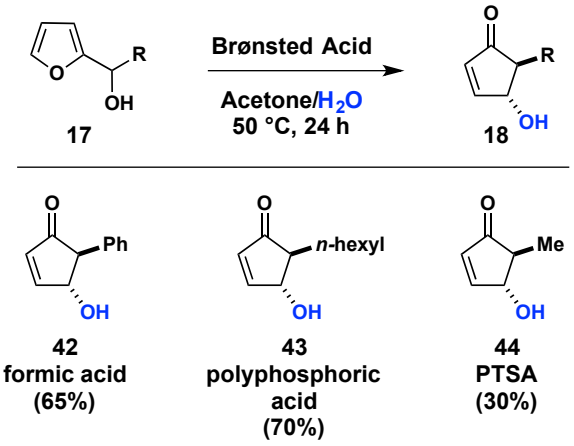

Figure 1.10. Original conditions for the Piancatelli rearrangement

Further studies demonstrated that milder Lewis acids such as $ZnCl_2$ could be employed for more sensitive substrates (Figure 1.11).[11] For example, **44** did not react to give desired products with the Brønsted acids previously mentioned. However, exposure to one equivalent of $ZnCl_2$ for 96 h promoted stereospecific rearrangement to the *trans*-4-hydroxycyclopentenone **45** in 35 % yield.

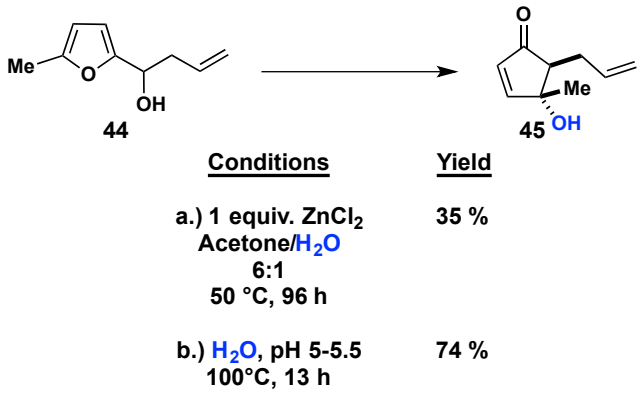

Figure 1.11. Reaction optimization for 5-methyl-2-furylcarbinols

Later, an aqueous-solvent solution buffered to pH 5.5 and heated to 100 °C boosted reactivity to form the desired product **45** in 74 % yield after 13 hrs (Figure 1.11).[12] The 5-methoxy and 5-chloro-2-furylcarbinols **46** did not undergo the desired rearrangement but

instead generated 4-ylidenebutenolides **47** and 4-oxo-2-enoic acid methyl esters **48** (Figure 1.12).[13]

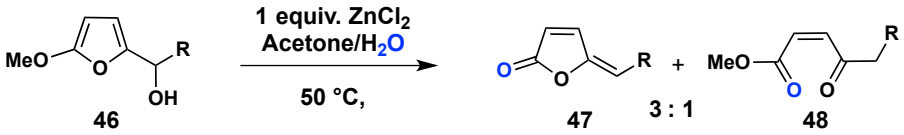

Figure 1.12. Conversion of 5-methoxyfurylcarbinols to 4-ylidenebutenilides

The furan ring could also be substituted with bromine at the 3 and 4 positions (**49**), although heating to 90 °C with H_2SO_4 was required for the reaction to occur (Figure 1.13).[14]

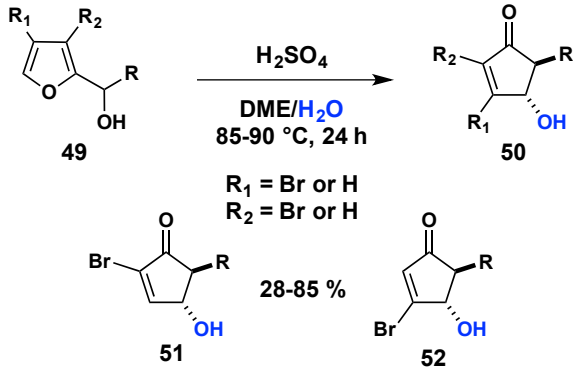

Figure 1.13. Rearrangement of 3- and 4-bromo-2-furylcarbinols with H_2SO_4

Alternative activating groups such as the conjugated 2-furyl-alkenylcarbinols **53** were also developed (Figure 1.14).[15] Increasing conjugation by inserting an additional ethylene unit leads to a highly reactive substrate that does not require acid activation for the rearrangement to occur. 2-Furyl-hydroxymethylphosphonates **55** were suitable precursors but it was discovered that conversion of the alcohol to chlorine was required to access the desired cyclopentenone products **56** (Figure 1.14).[16]

Piancatelli then demonstrates the ability to convert the 4-hydroxyclopentenones **18** to the the more thermodynamically stable isomer **59** through adsorption onto neutral or basic alumina (Figure 1.15).[17]

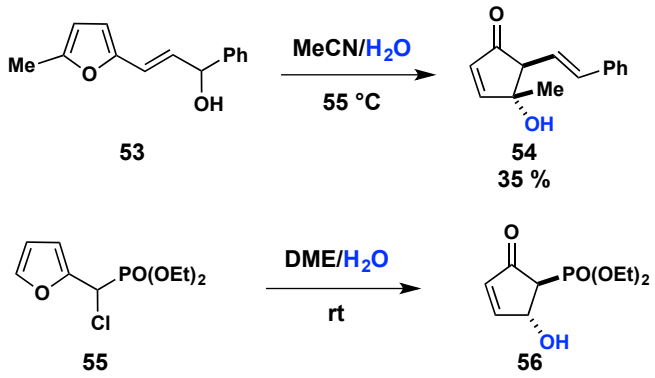

Figure 1.14. New modes of activation for the Piancatelli rearrangement

Mechanistic studies reveal the isomerization occurs through an intramolecular transfer of the hydroxyl rather than elimination followed by 1,4 intermolecular addition of water.[18] Alternatively, chloral can be used to facilitate the isomerization.[19]

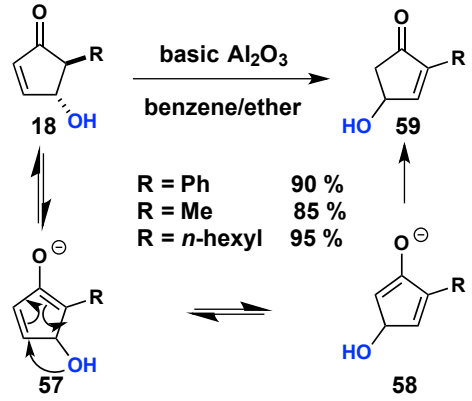

Figure 1.15. Isomerization of 4-hydroxycyclopentenones to the thermodynamic product

These isomers have proven to be valuable synthetic building blocks for a number of prostaglandins and their derivatives. For example, in 1991 Dygos and co-workers utilized the Piancatelli rearrangement and subsequent isomerization to shorten the synthesis of the antisecretory prostaglandin Enisoprost **62** reported by Collins from 13 steps to 10 (Figure 1.16).[20]

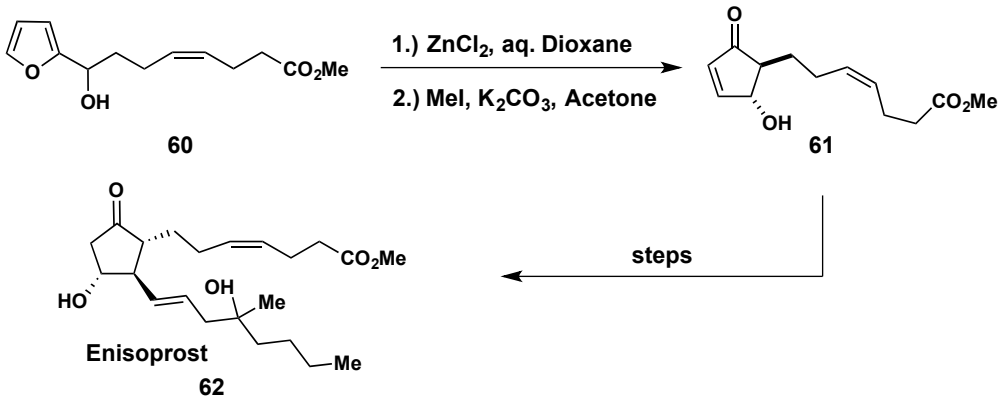

Figure 1.16. Piancatelli rearrangement in the synthesis of Enisoprost

Today the Piancatelli rearrangement continues to be utilized in both academia and industry. Recently, Reiser and co-workers developed a microreactor-assisted process for the conversion of 2-furylcarbinols **17** to 4-hydroxycyclopentenones **18** and **63** (Figure 1.17).[21] This method lowers reaction times from hours to minutes (2-15 min), increases yields (54-96%), and can be run on multi-gram scale. Additionally, no acid catalyst is required, however the elevated temperature (240 °C) and pressure (1000 psi) decrease functional group compatibility and erode the high *trans* selectivity typically observed.

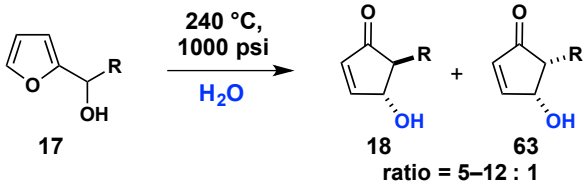

Figure 1.17. A Microwave-assisted Piancatelli rearrangement

Henschke and co-workers showcased the efficacy of the transformation on process scale for the synthesis of several active pharmaceutical ingredients (Figure 1.18).[22] Travoprost and Bimatoprost **68**, prostaglandin analogs used for the treatment of glaucoma, are both accessible in several steps from **67**, which is produced in a tandem Piancatelli rearrangement/chloral isomerization followed by enzymatic resolution. In this case,

superstoichiometric quantities of $ZnCl_2$ are required for the rearrangement, which generates 16 kg of product and 65 kg of $ZnCl_2$ waste. Additionally, an inseparable mixture of the 4-hydroxycyclopentenone **65** and the thermodynamic product **66** are formed during the Piancatelli rearrangement. Although clearly synthetically useful, these examples illustrate the need for a highly stereospecific, catalytic method that employs mild reaction conditions, reduces waste generation and delivers a single isomer as the product. The development of such a process is described in chapter 2.

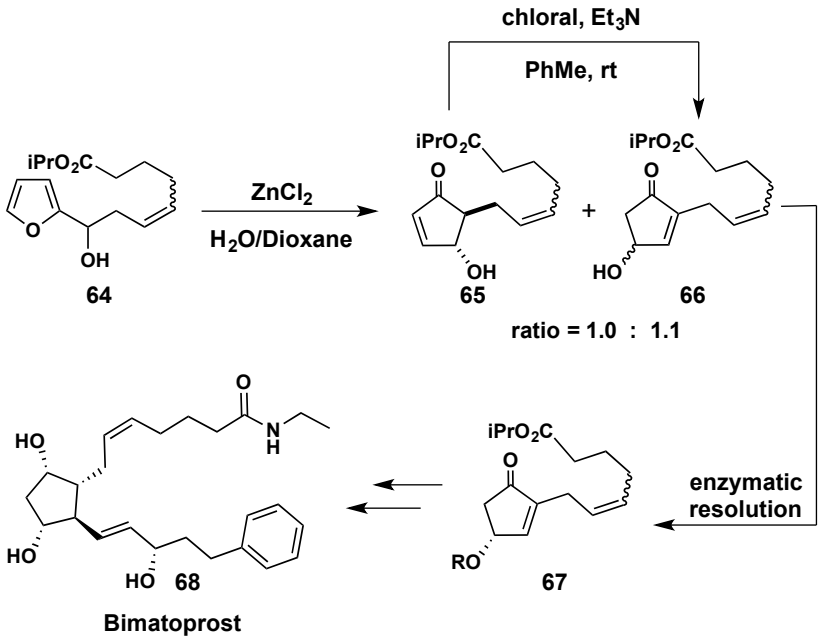

Figure 1.18. Process scale Piancatelli rearrangement for the synthesis of Bimatoprost

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2. A $Dy(OTf)_3$ Catalyzed Piancatelli Rearrangement

2.1 Introduction

The 4-hydroxycyclopentenone scaffold represents an important building block in the synthesis of prostaglandins and other biologically active molecules.[1] Since its discovery in 1976, the Piancatelli rearrangement continues to be among the most efficient methods for the construction of the 4-hydroxycyclopentenone core.[2] In a single acid catalyzed step, a furylcarbinol **1**, generated from a Grignard reaction with furfural, is converted to a *trans*-4-hydroxycyclopentenone **2** (Figure 2.1).

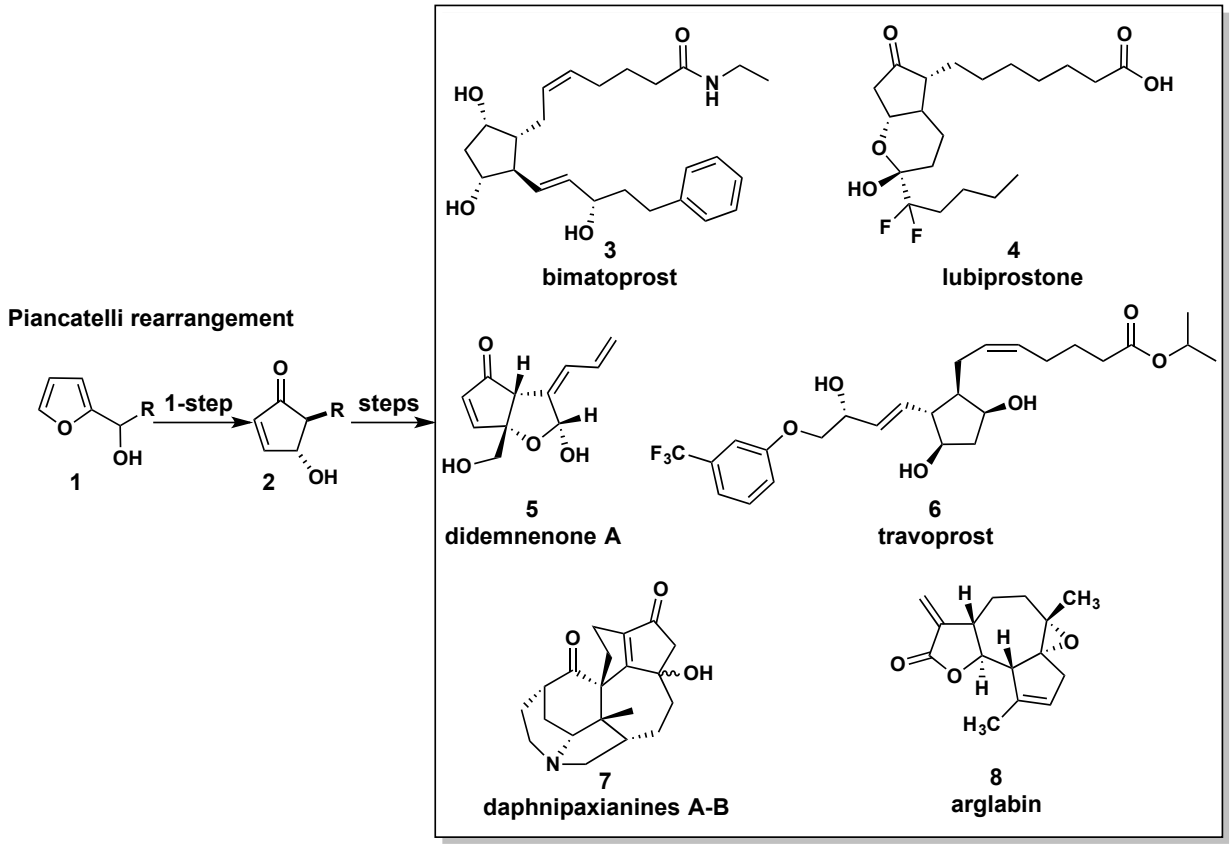


Figure 2.1. Examples of the Piancatelli rearrangement for the synthesis of 4-hydroxycyclopentenones.

The ability to rapidly convert a simple starting material to a complex product with defined stereochemistry has led to extensive development of the Piancatelli rearrangement. Despite many improvements to the method, a number of limitations still exist. One drawback is that stoichiometric amounts of Brønsted or Lewis acid are required, and the products are usually isolated in low yields. Additionally, it is difficult to prevent conversion of the 4-hydroxycyclopentenone to the more thermodynamically stable isomer.[3] As a result, inseparable mixtures of the two isomers are often isolated. Finally, harsh reactions including the use of strong acids or elevated temperatures and pressure decrease the functional group compatibility and the *trans*-selectivity of the process.[4] These limitations were the motivating factor for the development of the mild, catalytic, stereoselective rearrangement described herein.

Soon after the Piancatelli rearrangement was developed, Lewis and co-workers discovered that 4,5-diaminocyclopentenones derived from furfural could be accessed through a related transformation.[5] Recently, Batey and co-workers improved upon this cascade rearrangement by rendering it catalytic in a variety of lanthanide (III) triflates (Figure 2.2).[6] Treatment of furfural **9** with two equivalents of morpholine in acetonitrile (MeCN) with a Lewis acid (typically $Dy(OTf)_3$) or $Sc(Otf)_3$) at room temperature for 16 hours generated the *trans*-4,5-diaminocyclopent-2-en-1-one **17** in quantitative yield. The process is compatible with a variety of acidic secondary amines and primary anilines. Motivated by the lack of direct methods for the synthesis of 4-aminocyclopentenones in the literature, our group sought to develop an aza-Piancatelli rearrangement.[7]

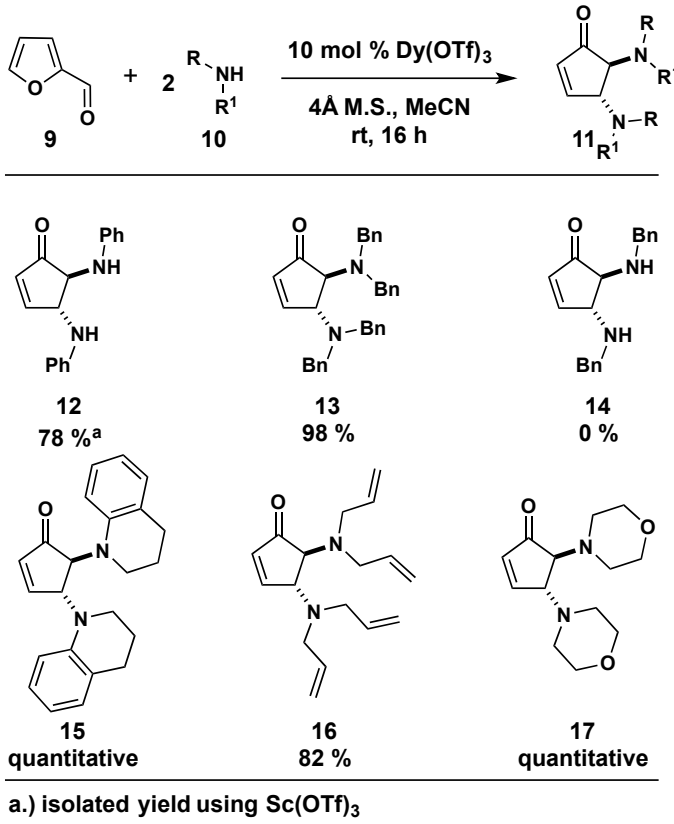


Figure 2.2. Batey's $Dy(OTf)_3$ catalyzed synthesis of 4,5-diaminocyclopentenones

Inspired by Batey's results, our group postulated that $Dy(OTf)_3$ should catalyze the rearrangement of aniline nucleophiles with various 2-furylcarbinols. We were excited to find the transformation was effective and extremely broad in scope. Electron-rich, electron-deficient, sterically hindered and secondary amines all exhibited excellent reactivity when combined with a variety of 2-furylcarbinols and heated to 80 °C in MeCN in the presence of 5 mol % $Dy(OTf)_3$ (Figure 2.3). The synthetic utility of this new method was displayed through the synthesis of hNK1 **34**, used to relieve chemotherapy-induced nausea and vomiting (Figure 2.3).[8] Utilizing the newly developed cascade rearrangement allowed us to

access **34** in five steps with a 19% overall yield; a significant improvement over the Merck route which took more than 15-steps.

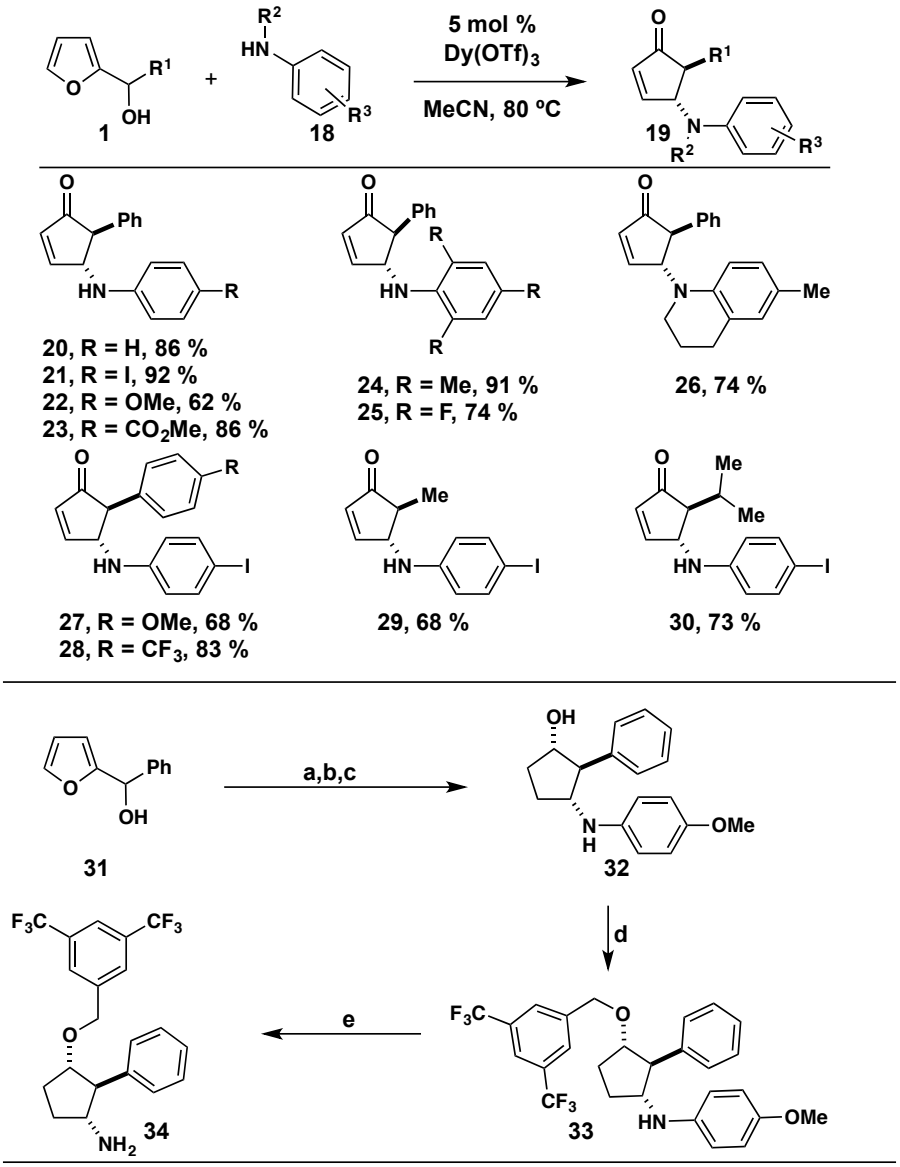


Figure 2.3. The aza-Piancatelli rearrangement and its application in synthesis of hNK1

A logical progression of the aza-Piancatelli rearrangement was to develop an intramolecular variant (Figure 2.4).[9] The intramolecular substrates **35** proved to be just as

effective in the rearrangement. Here, the 3° carbon center bonded to nitrogen and the spirocyclic ring system are formed simultaneously to afford various azaspirocycles **37-46**. Again both the aniline and furylcarbinol portions of the molecule could be modified while remaining compatible with the reaction conditions. Notably, unsubstituted furylcarbinols **45** and **46** were also well tolerated.

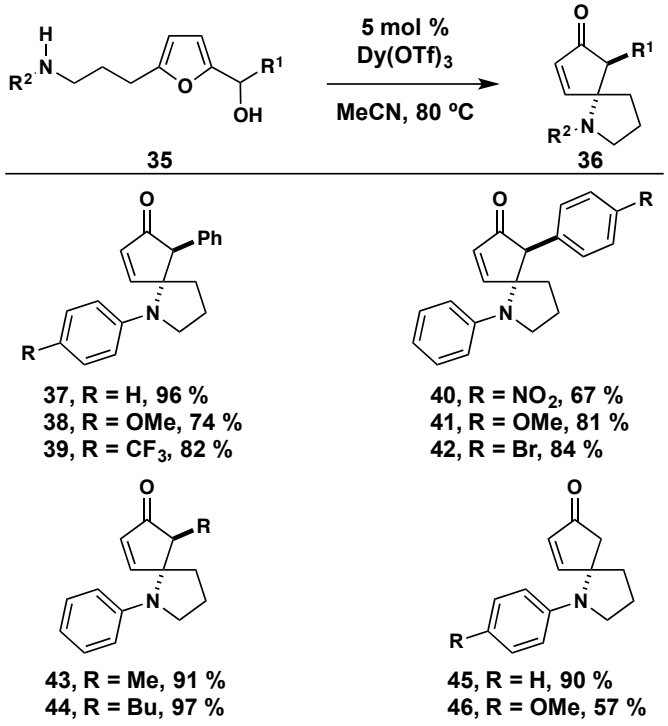


Figure 2.4. The intramolecular aza-Piancatelli rearrangement

Next, alcohols were investigated as nucleophiles in the cascade rearrangement. Although extensive optimization was required, and conversion between intra- and intermolecular variants was not feasible, a $Dy(OTf)_3$ catalyzed intramolecular oxa-Piancatelli rearrangement with alcohol nucleophiles **47** was developed (Figure 2.5).[10] In this case the use of toluene was critical as other solvents led to decomposition.

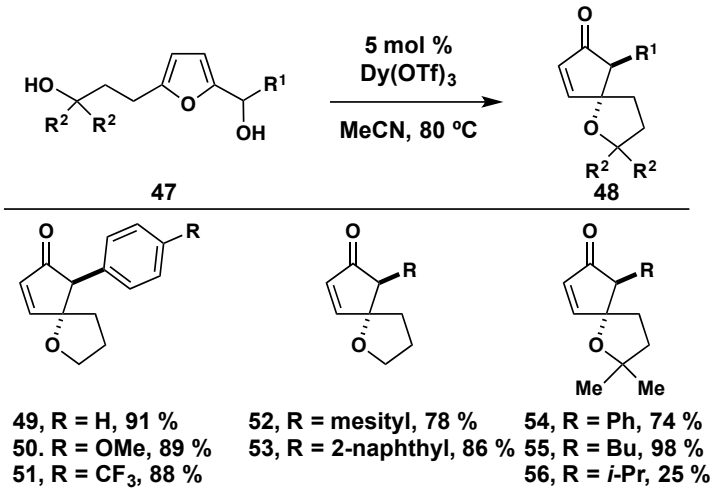


Figure 2.5. The intramolecular oxa-Piancatelli rearrangement

Additional studies revealed that treatment of the oxaspirocycle products **57** with Amberlyst®15 in hot toluene promoted isomerization to the more thermodynamically stable fused oxabicyclic cyclopentenones **58** (Figure 2.6).[11] Having successfully developed both the aza- and oxa-Piancatelli rearrangements, it was our belief that $Dy(OTf)_3$ could also function as an acid catalyst using water as a nucleophile.

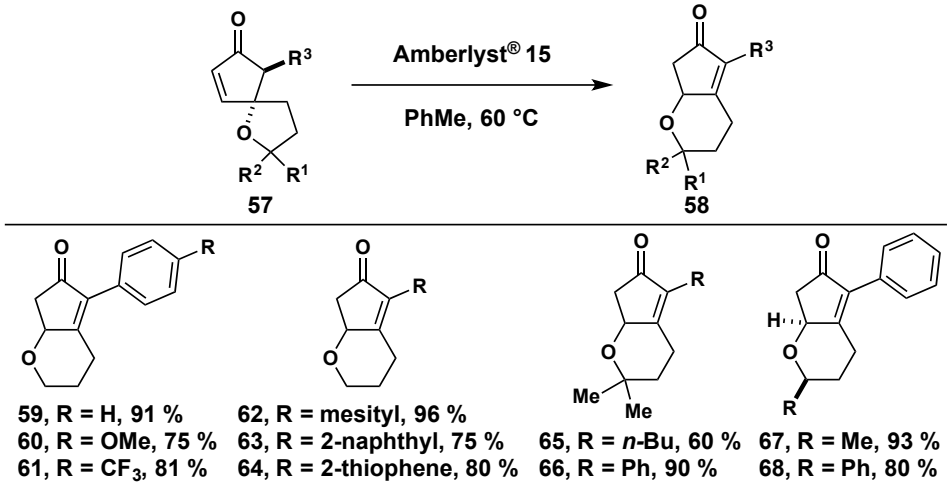


Figure 2.6. Synthesis of fused oxabicyclic cyclopentenones

2.2 Results

Preliminary interest in this process originated from discoveries made during the intermolecular oxa-Piancatelli rearrangement when furylcarbinol **70** was treated with 10 equivalents of isopropanol and 5 mol % $Dy(OTf)_3$ in MeCN at 60 °C (Figure 2.7). In addition to generating the desired product **72**, the 4-hydroxycyclopentenone **71** was unexpectedly isolated in 52% yield.

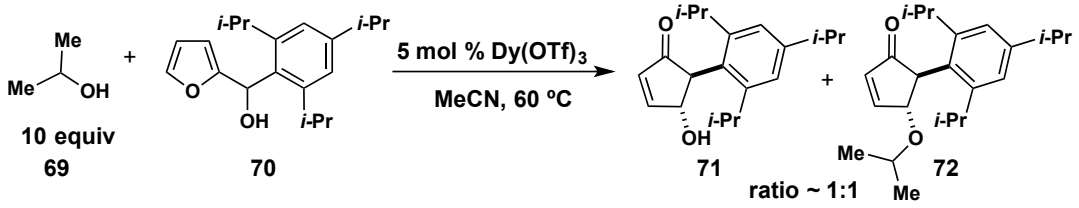


Figure 2.7. Water competes as a nucleophile in the rearrangement with isopropanol

This observation indicated preferential participation in the reaction by water, one equivalent of which is generated during the course of the process by displacement from the furylcarbinol. We were surprised by these findings because water could be used as a co-solvent in the aza-Piancatelli without formation of any 4-hydroxycyclopentenone. Furthermore, acetal **73** generated from addition of isopropanol to furylcarbinol **70**, could be isolated, and treated with water and $Dy(OTf)_3$ to form the 4-hydroxycyclopentenone **71** exclusively (Figure 2.8). Intrigued by the enhanced reactivity of water in the presence of isopropanol and the synthetic utility of the 4-hydroxycyclopentenone products, we sought to develop a mild, $Dy(OTf)_3$ catalyzed Piancatelli rearrangement.[12]

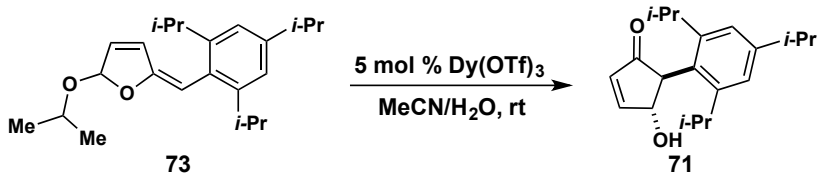
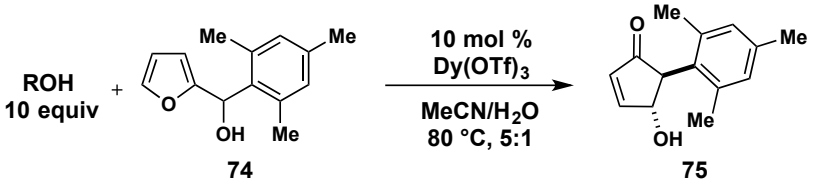


Figure 2.8. Conversion of the isopropyl acetal to the 4-hydroxycyclopentenone

Initial efforts focused on screening different alcohol additives (Table 2.1). With the exception of MeOH (entry 1), every alcohol tested dramatically enhanced reactivity in a 5:1 mixture of MeCN/water with 10 mol % $Dy(OTf)_3$ at 80 °C. Typically, reaction times were accelerated 5x and accompanied by an increase in yield. Although a variety of phenols enhanced efficiency (entries 5-7), we focused on development with *t*-BuOH (entry 3) and *i*-PrOH (entry 2) because they are cheaper and easier to remove from the reaction mixture. Ultimately we found that switching from a 5:1 MeCN/water to a 5:1 alcohol/water solvent system provided the most consistent results across a variety of substrates (entries 8-9). Eventually, *t*-BuOH (entry 8) was identified as the alcohol of choice because *i*-PrOH was found to act as a competing nucleophile in the rearrangement. No similar side products were observed with *t*-BuOH, which is likely too sterically hindered to act as a nucleophile.



Entry	ROH	Time (h)	Yield (%)
1	MeOH	16	76
2	*i*-PrOH	4.5	80
3	*t*-BuOH	3.25	80
4	F_6*i*-PrOH	7	76
5	phenol	4.5	80
6	*p*-nitro phenol	4.5	80
7	*p*-methoxy phenol	3.5	80
8	**5:1 *t*-BuOH/H_2O**	**3.5**	**80**
9	5:1 *i*-PrOH/H_2O	3.5	64
10	–	19	70

Table 2.1. Optimization studies with alcohol additives

The optimized reaction conditions were well suited for variety of aryl substituted 2-furylcarbinols, all of which reacted rapidly to form the corresponding *trans*-4-

hydroxycyclopentenones in high yield (Figure 2.9). Bulky mesityl **75** and triisopropylphenyl **71** substituents did not hinder reactivity. Heteroaromatics such as thiophene **79** were well tolerated. Thiophene does not participate in the rearrangement because of its high resonance stabilization energy (~30 kcal mol^{-1} vs ~16 kcal mol^{-1} for furan).[13] It should be noted that 5 % of the 4-hydroxycyclopentenone derived from the thiophene substituted furylcarbinol was converted to the more thermodynamically stable isomer during the course of the reaction.

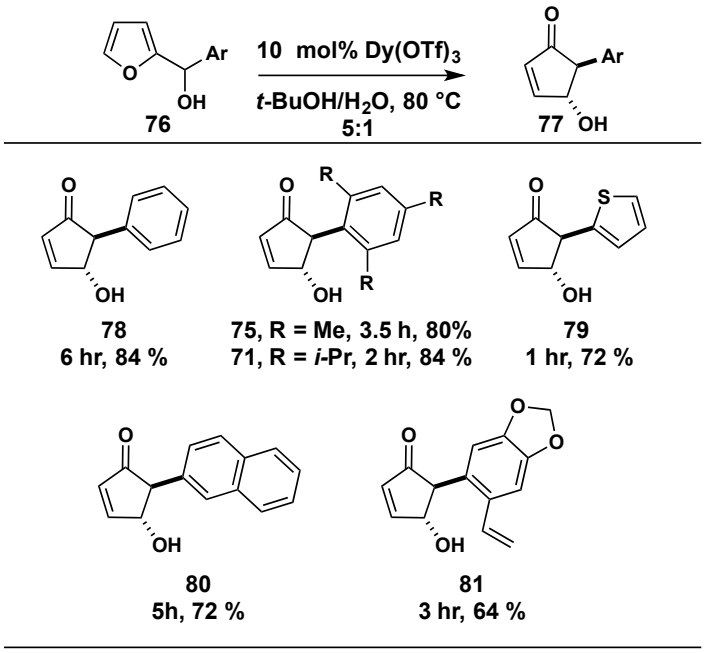
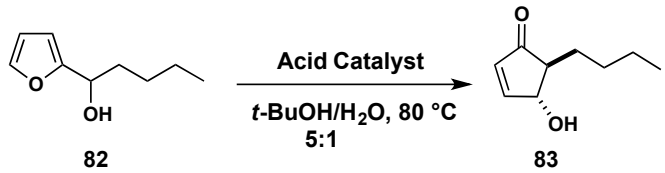


Figure 2.9. Scope with aromatic substituted furylcarbinols

Having showcased the compatibility of the reaction with aryl substituted furylcarbinols, we sought to expand the scope to include alkyl substituted furylcarbinols. 4-Hydroxycyclo-pentenones with aliphatic substituents are important synthetic targets because they serve as prostaglandin precursors. The rearrangement with *n*-butylfurylcarbinol **82** took three days to reach completion in 60 % yield but was also plagued by decomposition (entry 1, Table 2.2). This decrease in reactivity is common with alkyl substituted furylcarbinols, which are initially more stable, but prone to elimination upon oxocarbenium

formation, unlike their aromatic counterparts. In an effort to increase the efficiency of the process, we elected to screen other Lewis and Brønsted acids. Increasing $Dy(OTf)_3$ loading to 30 mol % (entry 2) accelerated decomposition and no product was isolated. Switching the counterion on dysprosium further decreased reactivity. We postulated milder Lewis acids would decrease decomposition but $Dy(Cl)_3$ (entry 3) was lower yielding and $Dy(OAc)_3$ (entry 4) failed to catalyze the reaction after 10 days at 80 °C. More Lewis acidic $Sc(OTf)_3$ accelerated reaction rate but again decomposition was prominent (entry 5). Stoichiometric $ZnCl_2$ was unproductive (entry 6). We were inspired to investigate a dual Lewis-Brønsted acid system based off a similar transformation by Yin and co-workers that involved an intramolecular Friedel-Crafts reaction with furylcarbinols **84** to form spirofurooxindoles **85** (Figure 2.10).[14] Dual catalysis with 10 mol % $Dy(OTf)_3$ and 5 mol % TFA drastically improved the outcome as the 4-hydroxycyclopentenone was isolated in 90% yield after only 16 hrs (entry 9). Both 5 mol % and 10 mol % TFA proved to be ineffective in the absence of $Dy(OTf)_3$ (entries 7-8). A number of other Brønsted acids (acetic acid, phosphoric acid, triflic acid, hydrochloric acid and potassium dihydrogen phosphate) were screened at 5 mol % under dual catalysis conditions with 10 mol % $Dy(OTf)_3$ however TFA gave the best results.



Entry	Acid	Equiv	Time (h)	Yield (%)
1	$Dy(OTf)_3$	0.10	72	60
2	$Dy(OTf)_3$	0.30	-	Decomp.
3	$Dy(Cl)_3$	0.10	146	44
4	$Dy(OAc)_3$	0.10	>240	No reaction
5	$Sc(OTf)_3$	0.10	20	53
6	$ZnCl_2$	1.00	>240	Incomplete
7	TFA	0.05	96	Decomp.
8	TFA	0.20	18	24
9	**$Dy(OTf)_3$ + TFA**	**0.10 + 0.05**	**16**	**90**
10	$Dy(Cl)_3$ + TFA	0.10 + 0.05	24	48
11	$Dy(OAc)_3$ + TFA	0.10 + 0.05	168	28

Table 2.2. Lewis and Brønsted acid screen for rearrangement with aliphatic furylcarbinols

After identifying optimal conditions for the rearrangement with *n*-butylfurylcarbinol **82**, we turned to expanding the scope to include other challenging substrates.

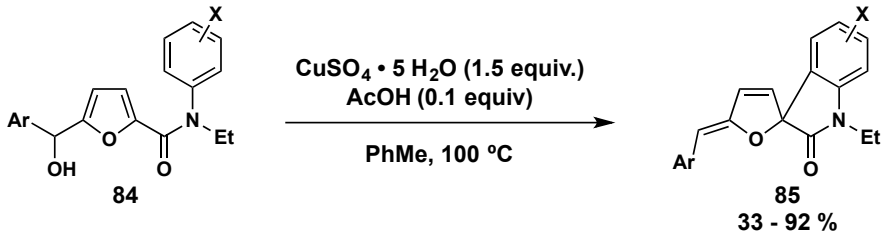


Figure 2.10. Dual Lewis-Brønsted acid catalysis for the synthesis of spirofurooxindoles

To our gratification, a number of other substrates containing aliphatic substituents participated in the rearrangement (Figure 2.11). Terminal alkenes such as **88**, important synthetic handles for the installation of side chains found in prostaglandins could be used. The branched alkane **89** reacted with limited decomposition. Unfortunately, the unsubstituted furylcarbinol did not react to produce the desired cyclopentenone **90**. Instead, extensive decomposition of the starting material was observed, likely cause by the instability

of the oxocarbenium ion formed following displacement of water. A number of other substrates that were problematic with only $Dy(OTf)_3$ responded well to the dual catalytic system. All carbon quaternary centers were prepared efficiently (**91**). Notoriously unreactive 5-methyl substituted furylcarbinols rearranged in a 5:1 d.r. although 5 % was converted to the more thermodynamically stable isomer (**92**). This is not unexpected as a fully substituted olefin is created. Finally, electron-deficient aryl substituted furylcarbinols benefited from the dual catalysis approach (**93**).

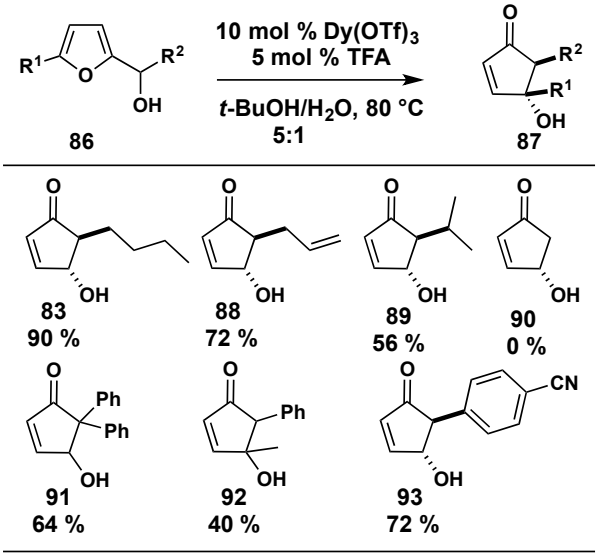


Figure 2.11. Substrate scope utilizing dual acid catalysis

Control over the interconversion of the 4-hydroxycyclopentenone isomers in the synthesis of prostaglandins is critical. We sought to display our ability to exclusively access either isomer. We have demonstrated the ability to form a single cyclopentenone isomer through our mild reaction conditions for the rearrangment, but to promote the isomerization chose to utilize conditions developed by Piancatelli (Figure 2.12).[15] Adsorption of **83** to basic alumina for 16 hrs followed by elution with benzene/diethyl ether afforded the isomerized 4-hydroxycyclo-pentenone **94** quantitatively.

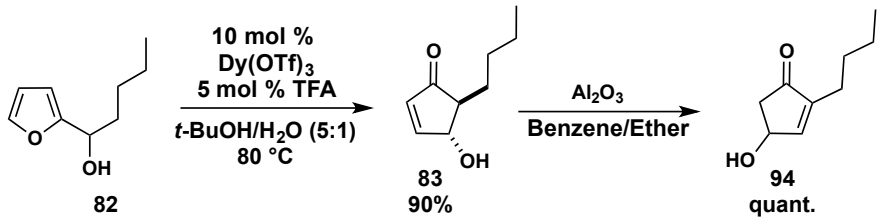


Figure 2.12. Isomerization of the 4-hydroxycyclopentenone to the thermodynamic product

2.3 Conclusion

In conclusion we have successfully developed an acid catalyzed method for the conversion of furylcarbinols to *trans*-4-hydroxycyclopentenones via a cascade rearrangement ending with a thermally promoted 4π conrotatory electrocyclization. 10 mol % $Dy(OTf)_3$ was used to catalyze the reaction with a variety of aryl substituted furylcarbinols and a dual catalyst system comprised of 5 mol % TFA and 10 mol % $Dy(OTf)_3$ was required for more challenging substrates including furylcarbinols with alkyl substituents at the 2-position. This method is robust; all starting materials including $Dy(OTf)_3$ can be weighed out on the benchtop and the reaction run open to air. The mild reaction conditions lead to retention of the *trans*- stereochemistry observed in the products and provide chemists with the ability to access either cyclopentenone isomer exclusively in high yields.

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3. An Introduction to the Chemistry and Reactivity of Nitroso Compounds

3.1 Reactivity of Nitroso Derivatives

Nitroso compounds are versatile building blocks that serve as electrophilic sources of both nitrogen and oxygen in organic synthesis.[1] Of the numerous nitroso compounds that have been synthesized, the N=O functionality is attached to either a carbon atom, or to a heteroatom (N, O, S, P).[2] The stability of these molecules is dictated by the electronic environment in which they exist (Figure 3.1). For example, electron deficient nitrosocarbonyls (**4**) are highly reactive transient species that must be generated in situ. They participate readily in Diels-Alder, aldol, and ene reactions.[3] In contrast nitrosoarenes (**3**) are benchtop stable, as a result Lewis or Brønsted acid activation is often needed for their participation in the previously mentioned transformations.[4] Electron rich nitroso compounds (**1**) such as nitrosamines, alkyl nitrites, and thionitroso compounds are less reactive, and instead typically serve as sources of NO^+.[2] The remainder of this introduction will focus on the synthesis, properties, and synthetic utility of nitrosoarenes.

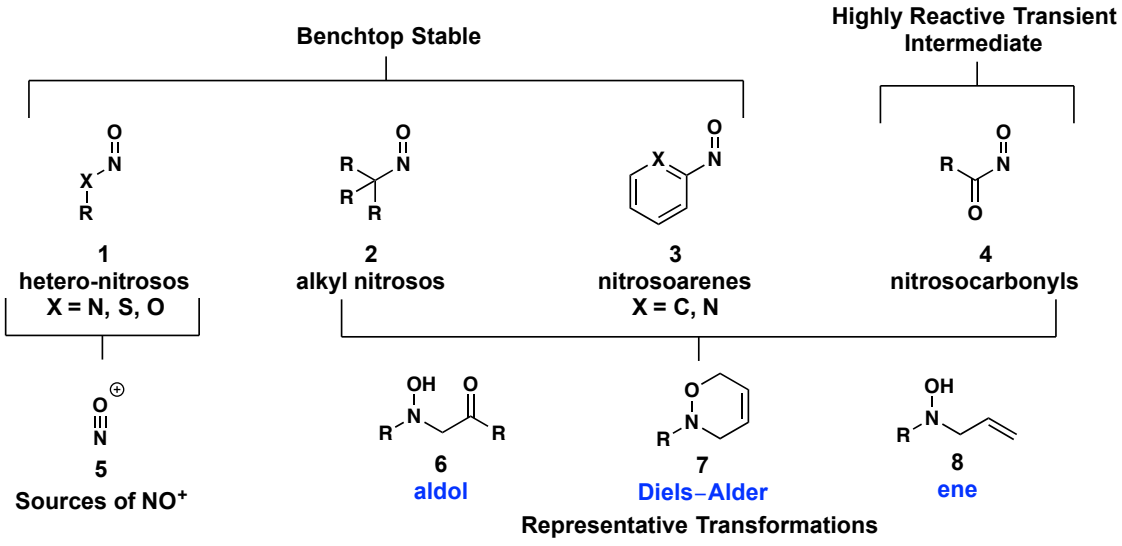

Figure 3.1. Reactivity of Nitroso Compounds

3.2 Synthesis of Nitrosoarenes

Nitrosobenzene was first synthesized in 1874 by Beyer via a reaction between diphenyl mercury and nitrosyl bromide.[5] Since this initial discovery, a number of less hazardous routes have been reported (Figure 3.2). There are two general approaches to the synthesis of nitrosoarenes (**9**), the first utilizes nitrosation reagents, which can either participate in electrophilic aromatic substitution reactions with electron rich arenes (**10**), or react with organometallic species or boronic acid derivatives (**11**).[6] Sodium nitrite can be treated with strong mineral acids to generate nitrous acid, a source of the nitrosonium ion (NO^+) which reacts via substitution reactions with electron rich arenes to generate arylnitroso compounds.[6] Nitrosonium tetrafluoroborate ($NOBF_4$) is a commercially available NO^+ source that was used by Kochi and co-workers for the nitrosation of anisole and its derivatives.[7] More recently Molander and co-workers developed an extremely broad method for the synthesis of aryl- and heteroarylnitroso compounds that involves the *ipso*-nitrosation of aryl- and heteroaryltrifluoroborates with $NOBF_4$.[8] Finally, hetero-nitroso compounds such as alkyl nitrites serve as milder nitrosating reagents. During their development of the nitration of aryl boronic acids with *t*-butyl nitrite Wang and co-workers observed that in some cases when the reaction was run under an atmosphere of N_2 the nitrosoarene could be isolated as the major product.[9]

The second strategy for nitrosoarene synthesis is through oxidation of the corresponding aniline **12** or *N*-arylhydroxylamine **13** (Figure 3.2). The reduction of nitroarenes (**14**) is difficult to control and often results in over reduction. However, due to their widespread availability, nitroarenes are often reduced to produce the requisite *N*-arylhydroxylamine or aniline starting material.[10] A variety of different oxidants can be

utilized for this process. The first to be discovered was Caro's acid (peroxomonosulfuric acid H_2SO_5) in 1898, which was used in the oxidation of many different electron-rich and electron-deficient substituted anilines to generate the corresponding nitrosoarenes.[11] More recently, it was shown that Oxone® could be used in a similar manner for the oxidation of anilines in a biphasic mixture of water and DCM.[12] Other peroxy acids such as MCPBA, which is used for the synthesis of 2-nitrosopyridine, are suitable reagents for these oxidations as well.[13] *N*-Arylhydroxylamines (**13**), generated by partial reduction of their nitro-precursors with Zn/NH_4Cl, are usually then reoxidized with either $FeCl_3$ or acidified sodium dichromate for arylnitroso synthesis.[14]

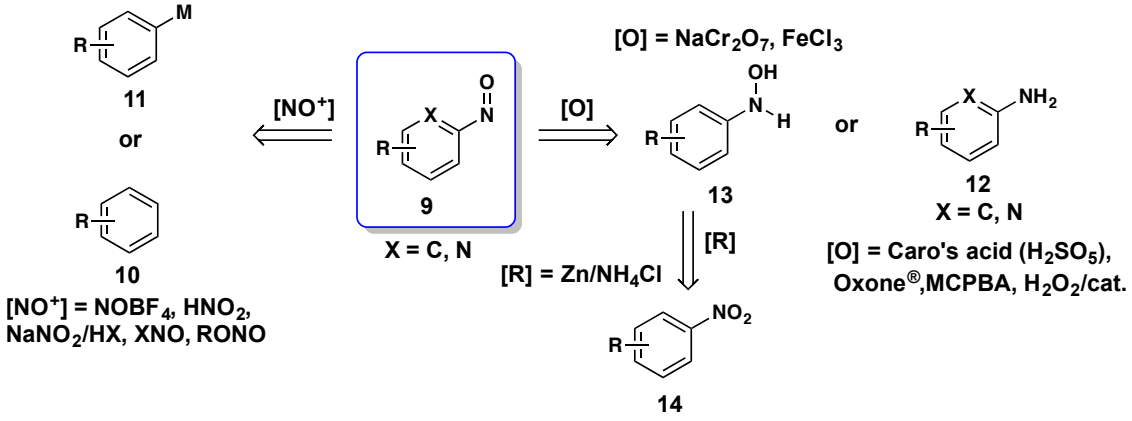

Figure 3.2. Retrosynthetic Analysis of Nitrosoarenes

3.3 Chemical Properties of Nitrosoarenes

During the syntheses reported above, reaction mixtures often adopt a blue hue, which disappears upon concentration after purification to yield a colorless or yellow/brown substance. This phenomenon occurs because C-nitroso compounds exist in a monomeric or dimeric form in equilibrium with one another.[15] The dimeric species is typically colorless or yellow while the monomers are normally blue or green. The dimers, known as azodioxides,

exist in either the *trans*- or *cis*- form (**17** and **18**), and can be chemically inert under certain conditions (Figure 3.3).

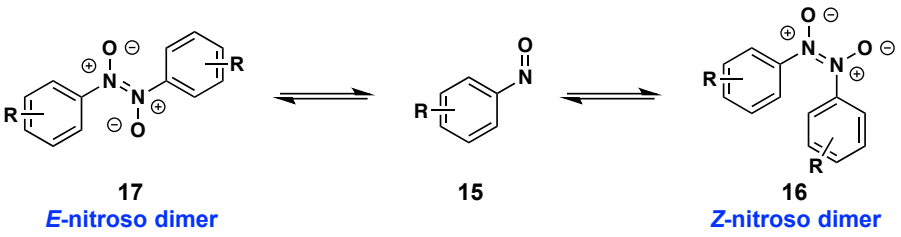

Figure 3.3 Nitrosoarene Monomer-Dimer Equilibrium

As a result, the equilibrium between these two forms is important to consider during reaction design. This equilibrium is most affected by the electronic environment of the aryl ring, and by solvent effects.[15] In general, electron rich arylnitroso compounds are more stable and generally exist as monomers, whereas electron deficient nitrosoarenes are destabilized and tend to reside in their dimeric form. Typically, nitroso compounds exist as monomers in solution, however polar solvents shift the equilibrium towards the dimer.

Due to their inherent reactivity, nitrosoarenes are relatively unstable; they are prone to decomposition and as a result can be difficult to work with (Figure 3.4). Arylnitroso compounds **15** are very redox sensitive; they readily oxidize to nitroarenes **18** in the presence of oxygen, and are easily reduced to *N*-arylhydroxylamines **13** or anilines **19** in the presence of certain reducing reagents. Furthermore, these degradation products can also react with their nitroso precursors. For example, *N*-arylhydroxylamines undergo condensation reactions with nitrosoarenes to form azoxybenzene **20**.[16] The analogous reaction with aniline produces azobenzene **21**.[17] This competing reaction is destructive, and often times difficult to avoid.

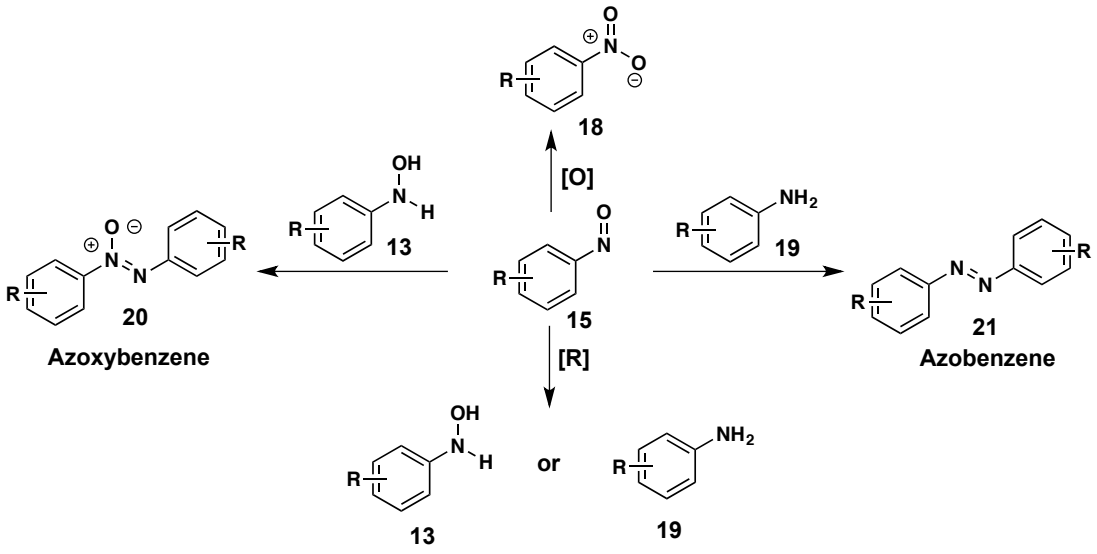

Figure 3.4. Decomposition Reactions of Nitrosoarenes

Despite these restrictions, arylnitroso compounds remain important tools for the delivery of both N and O heteroatoms in synthetic chemistry. The intrinsic instability of nitrosoarenes make the identification of mild yet effective conditions for transformations involving these compounds a challenging, yet critical endeavor.

Nitroso compounds are often compared to carbonyls when discussing the polarization of the N=O bond. The comparison is not entirely accurate because nitroso compounds are ambident electrophiles, meaning that both N and O heteroatoms can act as electrophiles under certain circumstances (Figure 3.5).[18]

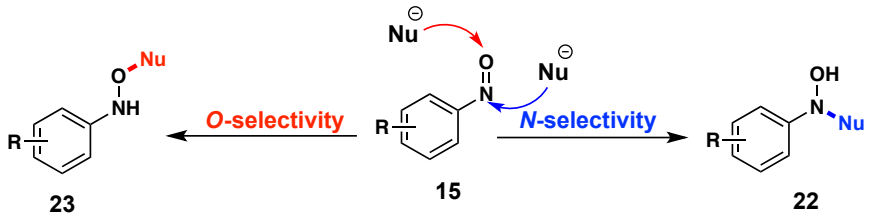

Figure 3.5. Ambident Electrophilicity of Nitrosoarenes

This characteristic can complicate reaction outcomes, but is also extraordinary because it has allowed chemists to develop transformations that involve selective nucleophilic additions at N or O. The ambident reactivity of nitrosoarenes is exemplified in the aldol reaction, where both *N*- and *O*- selective processes have been developed.[19] The chemistry of arylnitroso compounds has predominantly been explored in the context of C–N and C–O bond formation. The most developed relevant transformations are the *N*- and *O*- aldol, Diels–Alder and ene reactions. These processes will be summarized in the remainder of the chapter.

3.4 The Arylnitroso Aldol Reaction

The *N*- and *O*-selective nitroso aldol reactions have been developed extensively with nitrosoarenes. First, the *N*-selective nitroso aldol reaction will be discussed. The earliest example of this transformation was reported by Walker and co-workers in 1924 when diethyl malonate was treated with nitrosobenzene to form what was proposed to be diethylphenyliminomalonate **26 (**Figure 3.6).[20] Mukaiyama and co-workers later showed the product to be diethyl dianilinomalonate **27**, likely formed through hydrolysis of diethylphenyliminomalonate.[21]

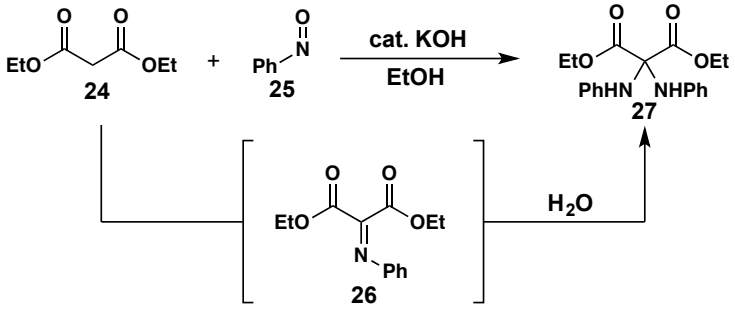

Figure 3.6. The First Nitrosobenzene Aldol Reaction with Diethyl Malonate

In 1972, Lewis and co-workers disclosed the first synthesis of α-hydroxyamino ketones **29** from the addition of morpholine derived enamines **28** to nitrosobenzene **25** (Figure 3.7).[22] However, the α-hydroxyamino ketones are particularly unstable and often dehydrate to form a mixture of imino-ketone isomers **30** and **31**. Further mechanistic investigation revealed the formal *N*-aldol products were actually generated via an ene reaction pathway.

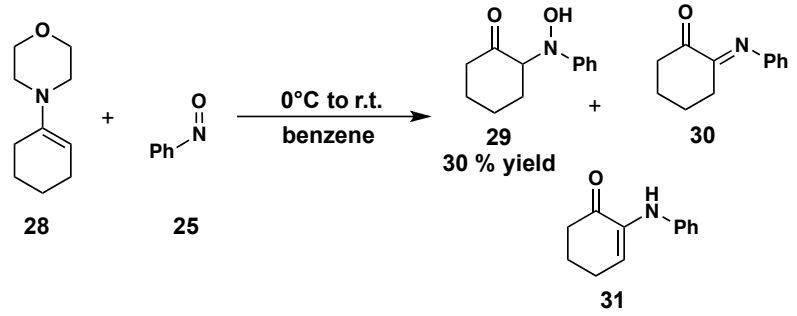

Figure 3.7. Nitroso Aldol Reaction with Morpholine Enamines

Subsequently, Sasaki and Ohno developed a similar strategy utilizing silyl enol ethers (Figure 3.8).[23] The unstable siloxyamino ketones **33** eliminate in the presence of triethylamine and then cyclize in a Diels-Alder reaction promoted by Lewis acid catalysis.

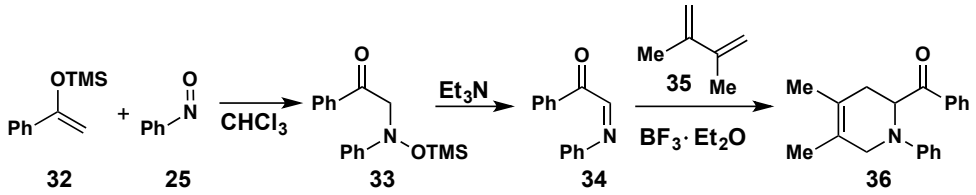

Figure 3.8. Nitroso Aldol Reaction with Silyl Enol Ethers

It wasn't until 2002 that the reaction between nitrosobenzene and metal enolates was developed (Figure 3.9). This discovery revolutionized this area of research. Yamamoto and co-workers demonstrated that metal enolates (**37**) derived from Na, Sn, Mg and Li all participated with high *N*-selectivity.[24] Two year later, the same group would render the

process asymmetric through the use of a chiral silver-BINAL Lewis acid catalyst with stoichiometric Sn enolates.[25]

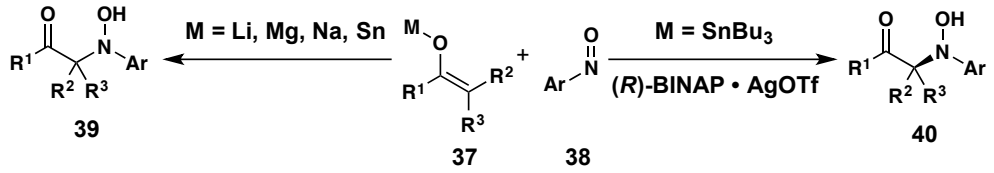

Figure 3.9. Nitroso Aldol Reaction with Metal Enolates

While exploring the use of Lewis acid catalysis in the reaction with nitrosobenzene **25** and silyl enol ethers **41**, Yamamoto and co-workers observed that the isolated products were *O*-selective (Figure 3.10).[25] This breakthrough would lead to the development of the first of many *O*-selective nitroso aldol reactions and represents the initial discovery of the ambident reactivity of nitrosoarenes.

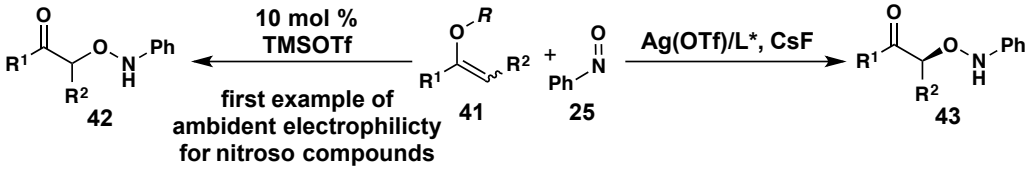

Figure 3.10. The First *O*-selective Nitroso Aldol Reaction

Shortly after these preliminary findings, the same group developed an asymmetric *O*-selective method with a chiral BINAP silver Lewis acid catalyst (Figure 3.10).[26] In 2009 Zhong revealed that chiral Brønsted acids can also be used to activate arylnitrosos **25** for an asymmetric α-hydroxylation with with β-ketoesters **44** (Figure 3.11).[27] Notably, the *N*-aryl moiety is lost in the formation of product **45**.

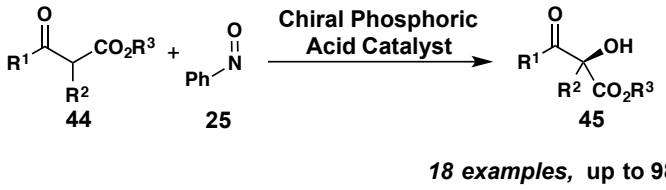

Figure 3.11. Chiral Phosphoric Acid Catalyzed Asymmetric Nitroso Aldol Reaction

The utilization of enamine catalysis as a strategy for the development of enantioselective *O*-aldol reactions is widespread (Figure 3.12). Zhong, MacMillan, and Hayashi simultaneously published their work in 2003 on the asymmetric *O*-aldol reaction with aldehydes and nitrosobenzene utilizing L-proline **48** as an organocatalyst for enamine formation.[28] Yamamoto would subsequently report the identical process using a proline-derived tetrazole organocatalyst **49**.[29]

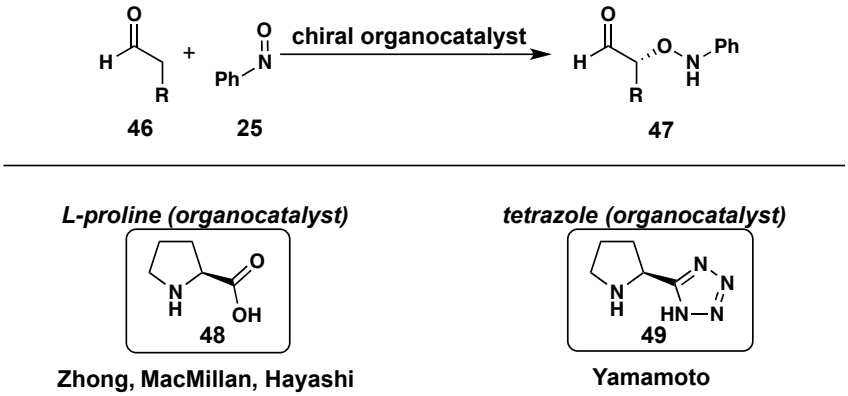

Figure 3.12. *O*-selective Asymmetric Nitroso Aldol Reaction with Enamine Catalysis

3.5 The Arylnitroso Diels-Alder Reaction

The nitrosoarene-Diels-Alder (NDA) reaction is a powerful synthetic tool because it allows for the simultaneous construction of C–N and C–O bonds in a single step.[3b] Wichterle and Arbuzov reported the first example of the important transformation in 1947 with the cycloaddition of nitrosobenzene **25** and 1,3-butadiene **50** to generate the 1,2-oxazine **51** (Figure 3.13).[30]

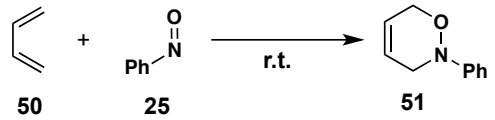

Figure 3.13. The First Nitroso Diels-Alder Reaction

Since this initial discovery, this process has been developed as an important tool for the synthesis of a number of natural products and biologically active molecules. The stereoselectivities of nitroso Diels-Alder reactions are heavily influenced by the use of Lewis acid catalysts. Ukaji and Inomata utilized one equivalent of a Zn Lewis acid in their development of an enantioselective, reagent controlled nitroso Diels-Alder (NDA) (Figure 3.14).[31] The hydroxyl group in the diene **52** was important to chelate the Lewis acid for asymmetric induction.

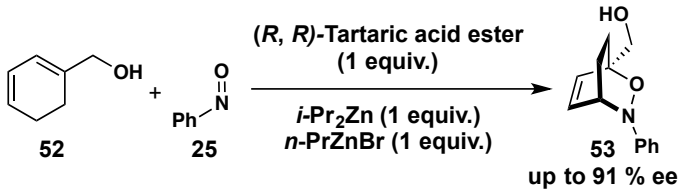

Figure 3.14. An Enantioselecitve Nitroso Diels-Alder Reaction

Alternatively, Lewis acid-nitroso complexes can be implemented catalytically to induce enantioselectivity. This concept was established by Yamamoto and co-workers through the bidentate chelation of 2-nitrosopyridine derivatives **55** with a chiral Cu(PF6)(MeCN)4–
(S)-SEGPHOS catalyst (Figure 3.15).[32] This strategy produced high enantioselectivity with an extensive range of cyclic dienes **54**. The N-O bond in the bridged 1,2-oxazine **57** products can be cleaved with $Mo(CO)_6/NaBH_4$ to generate 1,4-amino alcohol derivatives **58**. The NDA is a valuable tool for the efficient stereoselective construction of C–N and C–O bonds.

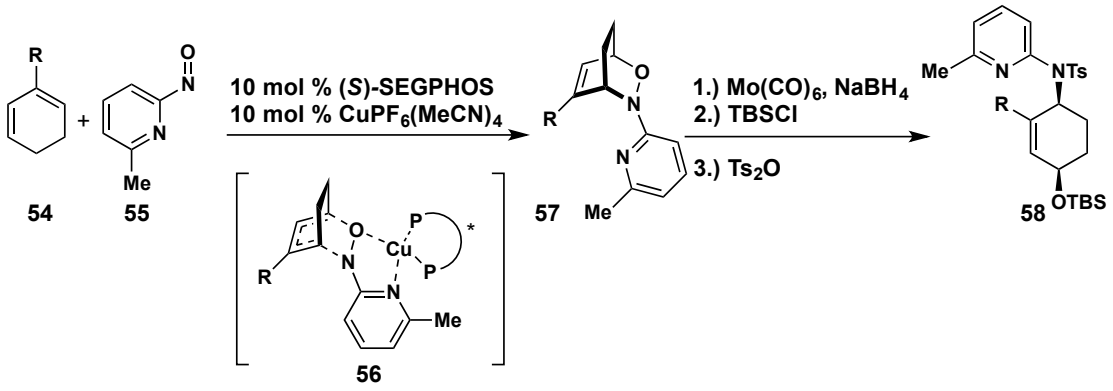

Figure 3.15. A Catalytic Enantioselective Nitroso Diels-Alder Reaction

3.6 The Arylnitroso Ene Reaction

The arylnitroso ene reaction is an important process for the electrophilic amination of unactivated alkenes. However, this transformation is less developed than the nitroso aldol and NDA reactions because the allylic *N*-arylhydroxylamine products are prone to decomposition under typical reaction conditions through pathways including disproportionation, dehydration and oxidation.[16] Nonetheless, allylic amines exist in many natural products and represent an important moiety in synthetic chemistry. In 1910 Allesandri and co-workers reported the first ene reaction, which occurred between safrole **59** and nitrosobenzene **25** (Figure 3.16A).[33] Later, Knight found evidence using electron spin resonance (ESR) that the reaction of nitrosoarenes (**25**) with 2,3-dimethyl-2-butene **61** produced allylic nitroxide radicals **63** but resulted in azoxybenzene formation (**64**) upon isolation (Figure 3.16B).[34]

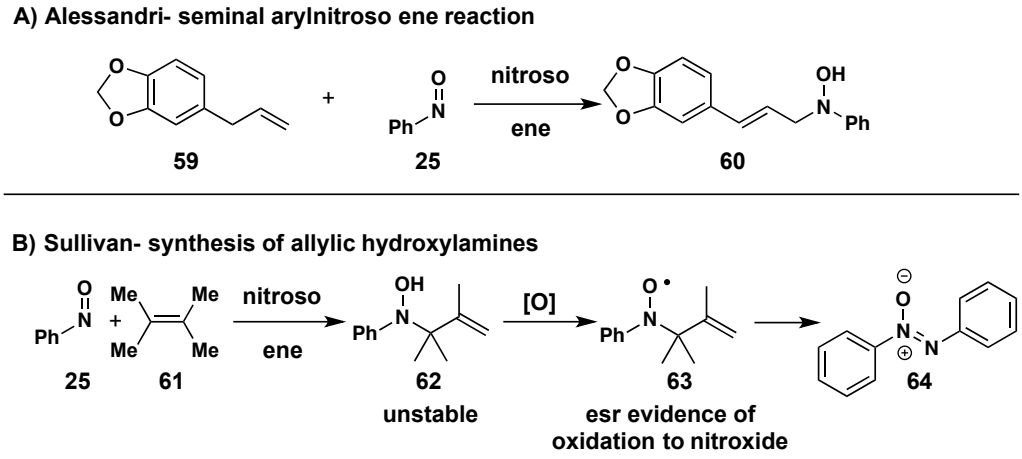

Figure 3.16. The First Arylnitroso Ene Reactions

Subsequently it was shown that immediate purification afforded the desired ene adducts **62**. Adam reported the first stereoselective ene reaction with nitrosoarenes **38** utilizing allylic alcohols **65** to induce stereocontrol through hydrogen bonding (Figure 3.17A).[35] Alternatively, chiral auxillaries such as Oppolzer's sultam **70** can be used with tiglic acid derivatives **67** for highly diastereoselective nitroso ene reactions (Figure 3.17B).[36]

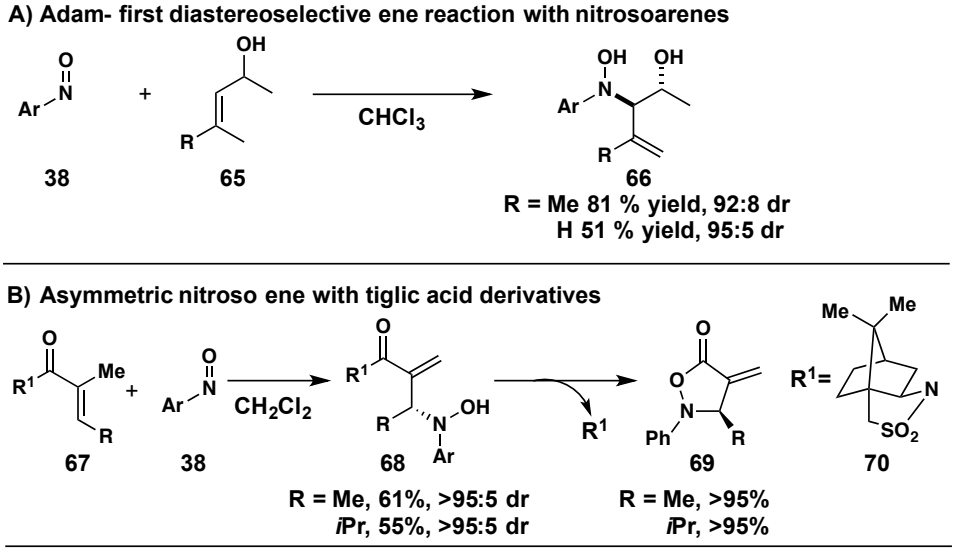

Figure 3.17. Diastereoselective Arylnitroso Ene Reactions

Nitrosoarenes serve primarily as 2π components in two electron transfer processes such as those discussed above. Single electron transfer reactions involving arylnitrosos in organic synthesis remain scarce.

3.7 Single Electron Transfer Reactions with Nitroso Compounds

3.7.1 Spin Trapping with Nitroso Compounds

Nitroso compounds have been used in radical reactions as spin trapping agents since the late 1960's.[37] Free radicals are short lived reactive species that can only be detected by electron spin resonance (ESR) when produced in high enough concentrations. Spin trapping involves an addition of the highly reactive radical with a radical trap to create a more stable, radical capable of reaching concentrations detectable by ESR.[38] Both alkyl and arylnitroso compounds **72** are used for this purpose because they react with carbon centered radicals **71** to produce persistent nitroxide radicals **73** that can be detected using ESR (Figure 3.18).

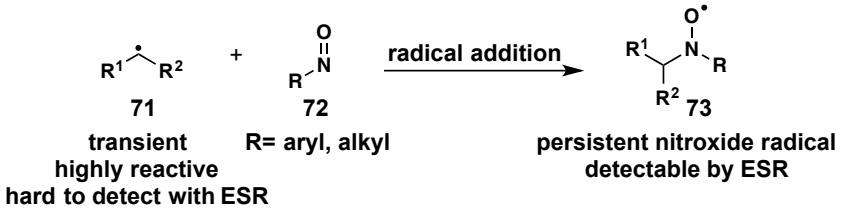

Figure 3.18. Spin Trapping with Nitroso Compounds

Nitroxide formation from radical addition to nitroso compounds was first discovered by Mackor and co-workers in 1966.[39] While studying the photochemical reactions of nitrosobenzene they observed by ESR that photolysis generated nitroxide radicals. These early investigations led to the adaptation of this technique for biological systems which has since become one of its most important applications.[37]

3.7.2 Alkyl Radical Addition with Nitroso Compounds

The addition of carbon centered radicals to nitrosoarenes can be traced back to 1954 in a report by Gingras and Waters studying addition reactions of 2-cyano-2-propyl radicals **75** generated by thermal decomposition of azobisisobutyronitrile **74** (AIBN) (Figure 3.19A).[40] Refluxing nitrosobenzene **72** in toluene with AIBN resulted in formation of alkoxyamine dimer **77.** Heating AIBN liberates the 2-cyano-2-propyl radical **75** which adds to nitrosobenzene **72** to form the nitroxide radical **76**. The nitroxide then reacts with **75** to form **77**. Reduction of **77** with zinc dust and sodium acetate in acetic anhydride generates the secondary hydroxylamine **78** in low yields. In 1958 Inamoto and Simamura showed that the identical alkoxyamine product **80** could be produced when nitrobenzene **79**, instead of nitrosobenzene was refluxed with AIBN **74** (Figure 3.19b).[41] The mechanism of this process is not fully understood, but again it is thought that nitrosobenzene is produced and trapped with the 2-cyano-2-propyl radicals **75**.

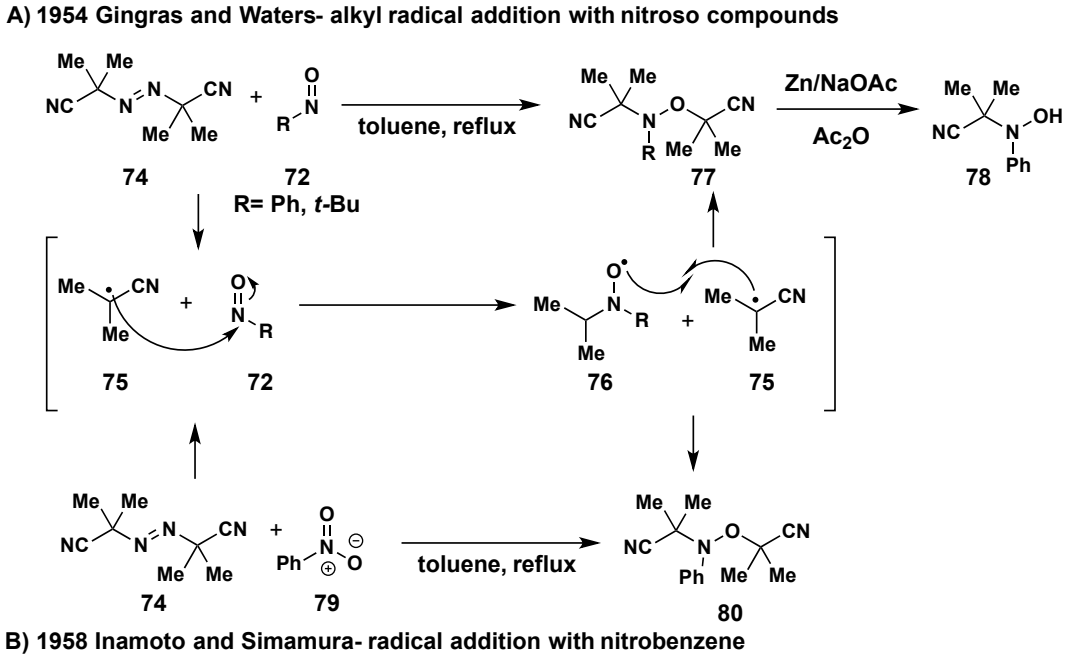

Figure 3.19. Alkyl Radical Addition to Nitroso Compounds

Corey and Gross employed carbon radical additions to α-tertiary alkyl nitroso compounds for the synthesis of hindered α-tertiary amines (Figure 3.20A).[42] Treatment of commercially available *t*-butylhydrazine **81** with lead dioxide generates *t*-butyl radicals **83** which can be efficiently trapped with alkyl nitroso **72** compounds to form alkoxyamines **84** that are reduced directly to di-*tert*-alkyl amines **85**. *t*-Butylhydrazine can be replaced with chiral hydrazines to generate sterically hindered chiral amine products.[43] Although this process utilizes alkyl nitrosos, it is important because it illustrates the potential for this radical based approach to be used for the construction of hindered C–N bonds under mild reaction conditions. Russell and Yao would later show that *t*-butyl radicals **83** generated by photolysis of *t*-BuHgI/KI, would participate in analogous addition reactions with nitrosobenzene **25** (Figure 3.20B).[44]

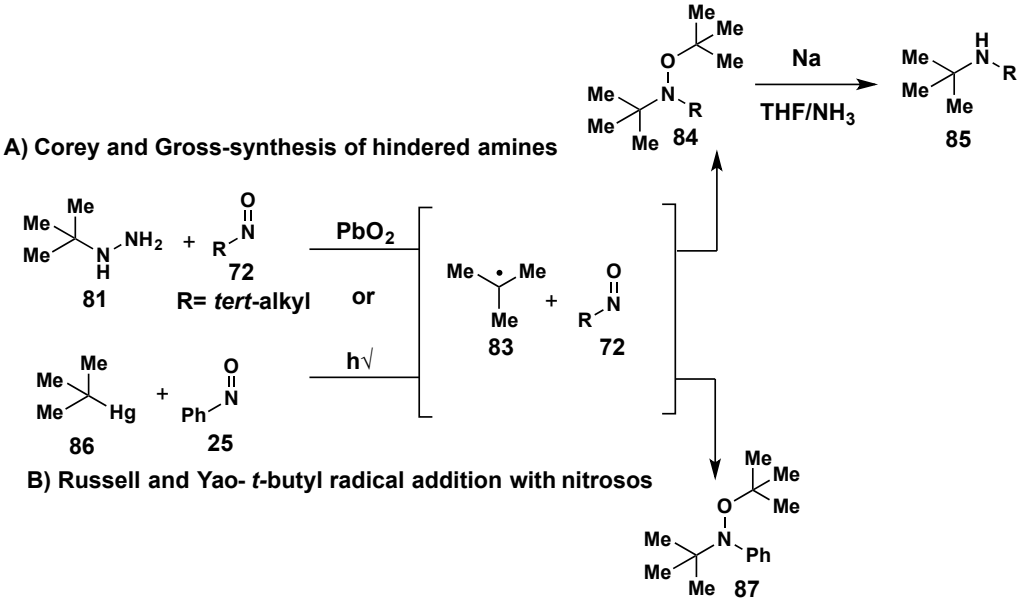

Figure 3.20. Synthesis of Hindered C–N Bonds Through Radical Addition with Nitrosos

More recently, Grubbs merged radical chemistry with nitroso compounds for the synthesis of alkoxyamine initiators for nitroxide-mediated radical polymerization (Figure

3.21).[45] Here, copper bromide (CuBr) is used for single electron reduction of 1-bromoethylbenzene **89** to generate the benzylic radicals **90** that react with 2-methyl-2-nitrosopropane **88** twice to form the alkoxyamine products **92**.

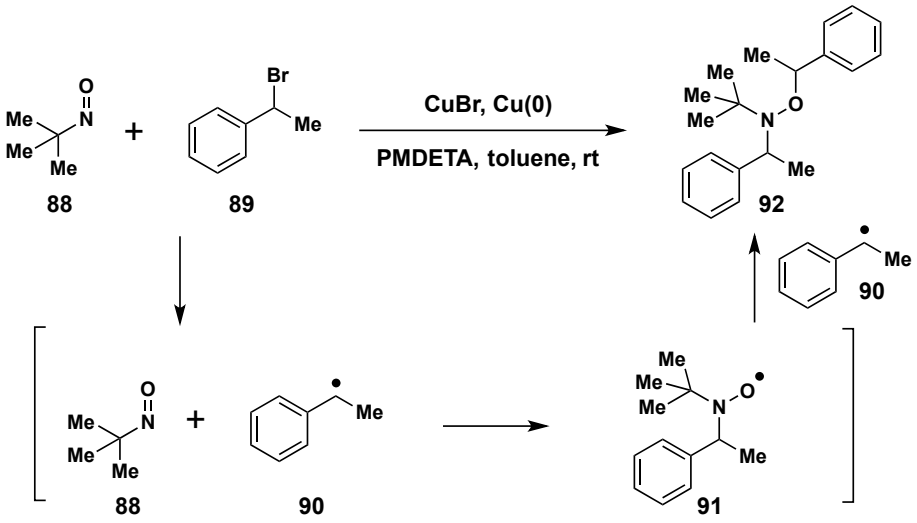

Figure 3.21. Synthesis of Alkoxyamine Initiators for Nitroxide Mediated Radical Polymerization

In 2015 Baran and co-workers disclosed an iron-catalyzed hydroamination of substituted olefins with nitroarenes that involved radical addition with nitrosoarenes (Figure 3.22).[46] In this system they utilized a hydrido iron complex that simultaneously converts an olefin (**93**) to a carbon centered radical (**95**) and reduces a nitroarene (**94**) to the corresponding arylnitroso (**38**). Combination of these intermediates forms the stable nitroxide radical **96**, which is either reduced to the amine product **98** or trapped with another alkyl radical to form alkoxyamine **97**. Zinc mediated reduction of the N–O bond affords amine **98**.

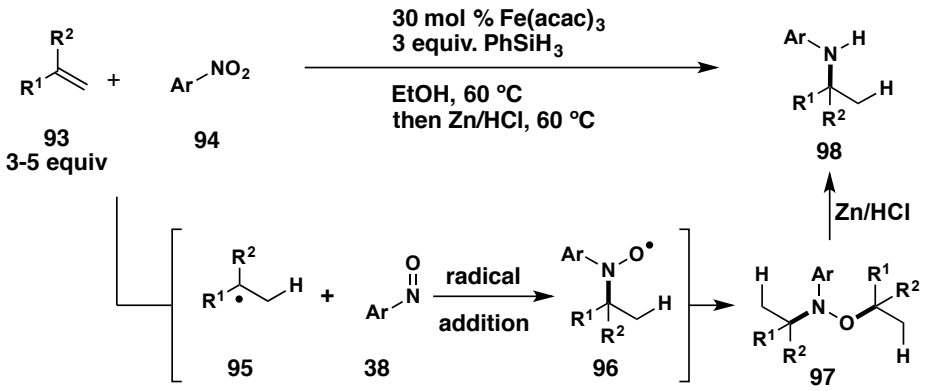

Figure 3.22. Radical Hydroamination Reaction with Nitrosoarenes

Although radical additions with nitroso compounds exist, their development as a synthetic tool in organic synthesis remains extremely limited.[47]

3.7.3 Nitroso Compounds as Tools in Polymer Chemistry

Single electron transfer processes are an important part of polymer chemistry. Controlled radical polymerization techniques such as atom transfer radical polymerization (ATRP) have transformed the field.[48] Since much of the research described in this dissertation was inspired in part by ATRP, a brief description of this process is provided.

Atom transfer radical polymerization is a form of controlled radical polymerization that proceeds through a reversible deactivation mechanism regulated by a transition metal complex (Mt^m/L) (Figure 3.23).[49] This reversible deactivation is governed by an equilibrium (k_{act}/k_{deact}) that exists between a dormant alkyl halide species (P_n–X) and propagating radical chains (P_n•). This equilibrium is shifted towards the dormant alkyl halide, resulting in a controlled growth of the polymer chains. Occasionally, the transition metal complex in its lower oxidation state (Mt^m/L) will reduce the dormant alkyl halide species through a single electron transfer (SET) process to generate the active propagating radical chain (P_n•) and the transition metal complex in its higher oxidation state (Mt^{m+1}/L). The reverse reaction then

occurs between the transition metal complex and the growing radical chains to regenerate the dormant alkyl halide.

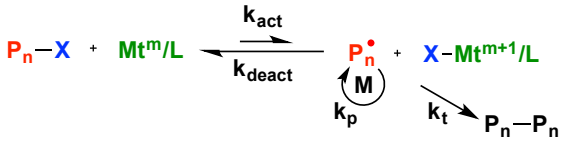

Figure 3.23. The ATRP Mechanism

ATRP is a catalytic process typically controlled by Cu^{I}/L and Cu^{II}/L complexes but other transition metals such as Fe, Ru, Mo, and Os can be used. ATRP rates are determined by the propagation rate constant, concentration of propagating radicals and monomer concentration. The concentration of radicals depends on the ATRP equilibrium constant which is affected mainly by the structures of both ligand and dormant species. Amine ligands are typically used with Cu catalysts. In general, aliphatic amine ligands like PMDETA (N,N,N',N",N"-pentamethyldiethylenetriamine) **103** produce a more active metal complex than arylamines such as BIPY **101** (Figure 3.24). Additionally, the order of Cu complex activity with respect to ligand is: tetradentate > tridentate > bidentate. Ligand effect is dramatic; the range of Cu complex activities spans six orders of magnitude. Akyl halide reactivity depends on the halogen used, degree of substitution, and structure of the radical stabilizing group. Reactivity follows 3° > 2° > 1° and I > Br > Cl (following bond dissociation energy required for homolytic bond cleavage). The α-cyano functionality **100** is more active than the α-ester **99** and the α-aryl group **89** is least active (Figure 3.24). ATRP has revolutionized polymer chemistry. As a result, a number of related processes have been developed.

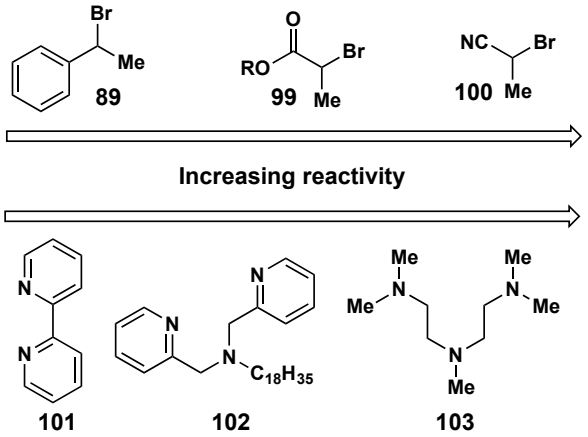

Figure 3.24. Factors Influencing ATRP Equilibrium

Atom transfer radical coupling (ATRC) is conceptually similar to ATRP (Figure 3.25).[50] ATRC utilizes ATRP conditions to create an environment where active polymeric radical (**105**) concentrations are high. Propagation is not possible because monomers aren't present, therefore bimolecular radical radical coupling is promoted. Typically, radical-radical couplings are inefficient and plagued by side reactions with solvent and disproportionation (**106** and **108**). As a result, yields of the desired ATRC products **108** are often low.

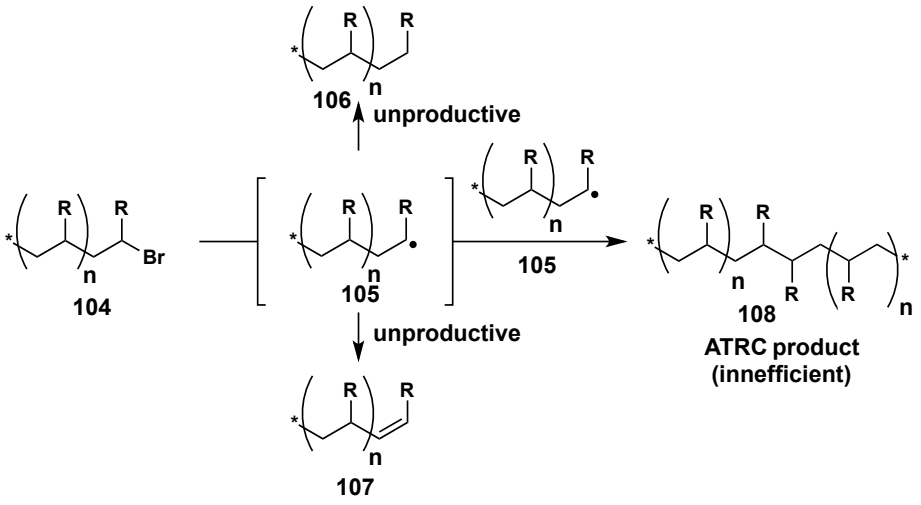

Figure 3.25. Atom Transfer Radical Coupling (ATRC)

Tillman and Wang have both independently shown that radical traps, such as nitroso compounds, can serve as linkers in radical-radical coupling reactions and greatly increase the efficiencies of such processes (Figure 3.26).[51] This process is known as radical trap assisted atom transfer radical coupling (RTA-ATRC). In such a scenario, a SET reaction between a Cu^{I}/L complex and a halide capped polymer would generate the active radical species **105**. Addition of **105** to the nitroso compound **72** (present in much higher concentrations than alkyl radicals) generates a persistent nitroxide radical **109**. This relatively stable species serves as a protecting group for the carbon centered radical and is not in equilibrium with a dormant form. As a result, the nitroxide is able to react with a second alkyl radical, which occurs at near diffusion control rates (10^{7} to 10^{9} M^{-1} s^{-1} at room temperature), to form the alkoxyamine linked product **110**.[52]

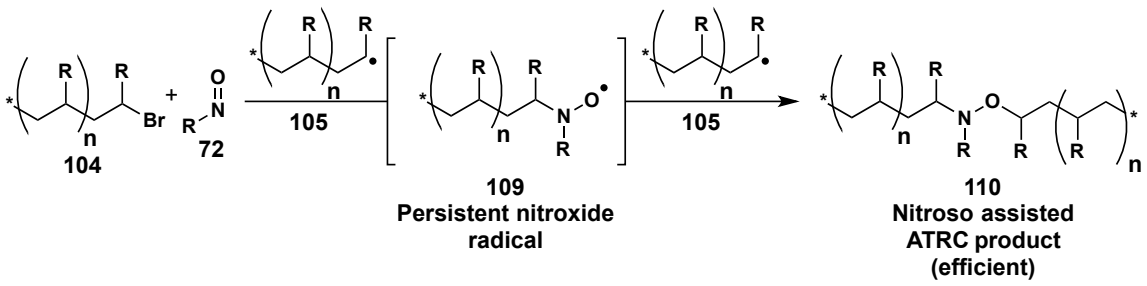

Figure 3.26. Nitroso-Assisted Atom Transfer Radical Coupling

Although this process represents an important advancement in polymer science, it has not yet been developed as a synthetic tool in organic synthesis. This will be the subject of Chapter 4.

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4. Radical Addition with Nitrosoarenes for Hindered α-Amino Carbonyl Synthesis

4.1 Motivation for the Synthesis of Hindered Amines

The construction of C–N bonds using alkylation,[1] reductive amination between amines and carbonyls,[2] C–N cross coupling,[3] and electrophilic amination[4] has been thoroughly investigated over the past several decades. This massive endeavor can be attributed to the prevalence of nitrogen-containing functionality in natural products and pharmaceuticals. In 2014, the Njardarson group published a perspective reporting that 84 % of unique small-molecule FDA approved drugs contained at least one nitrogen atom.[5] More recently, analysis of a data set comprised of 7315 reactions for the synthesis of pharmaceuticals revealed that C–heteroatom bond formation accounts for almost half (45.5 %) of these transformations and that 80 % of all heteroatom arylation and alkylation strategies involve nitrogen derivatizations.[6] Sterically hindered amines represent an important functionality because they increase the metabolic stability and lipophilicity of bioactive molecules.[7] α-Tertiary amines exist in a variety of biologically active natural products and pharmaceuticals including psychotrimine **1**,[8] ketamine **2**,[9] carfentanil **3**,[10] and conagenin **4** (Figure 4.1).[11]

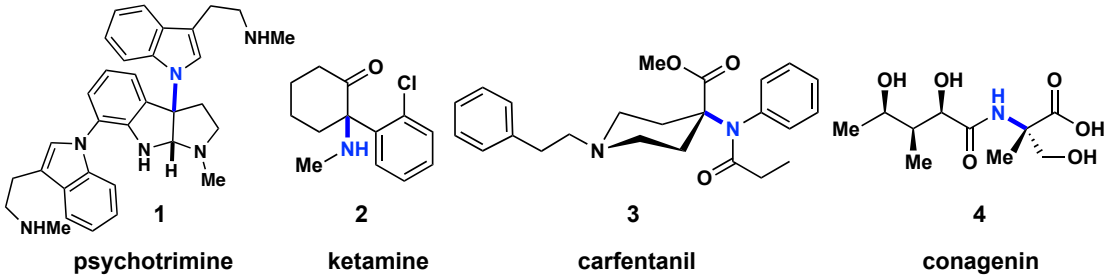


Figure 4.1. α-Tertiary Amines in Biologically Active Molecules

Despite their significance, the synthesis of sterically hindered amines remains challenging, often requiring harsh reaction conditions or protection group strategies.

4.2 Strategies for the Synthesis of Hindered Amines

Sterically hindered anilines can typically be divided into two general categories: 1) anilines bearing α-tertiary alkyl substituted groups[12] (psychotrimine); and 2) α-anilino carbonyls with N-containing quaternary centers (carfentanil).[13] Retrosynthetic analysis reveals two general approaches in accessing these functionalities. The most common method is through construction of the of the *N*-aryl bond with the arylation of hindered amine derivatives **6** (Figure 4.2a). These strategies initially required the use of highly reactive organometallic intermediates **5**. Diorganozinc reagents are commonly used in combination with transition metal catalysts for C–N coupling reactions with electrophilic amine derivatives such as *O*-benzoyl hydroxylamines or dialkyl-*N*-chloroamines.[14] Recently, milder methods have been developed for this *N*-aryl bond formation approach. For example, Buchwald recently demonstrated that his C–N cross coupling could be implemented for the *N*-arylation of hindered primary amines.[15] Additionally, Lalic disclosed a Cu catalyzed coupling of *O*-benzoyl hydroxylamines with arylboronic acid derivatives in a process related to the Chan-Lam coupling reaction.[16]

Alternatively, hindered anilines can be produced through formation of the hindered C–N bond. Regarding the second approach, there are several prominent strategies for hindered C–N bond formation. The first is through electrophilic amination of carbonyls **8** with nitrosoarenes **9** (Figure 4.2b). Although synthetically useful, this approach is limited by *N*- and *O*- regioselectivity issues and nitrosoarene reactivity problems requiring the use of Sn based enolate or activated carbonyl compounds.[17] An alternative strategy for hindered C–N

bond formation is nucleophilic addition to ketimines (Figure 4.2c).[18] Again this process suffers from several limitations. Often highly reactive nucleophiles such as Grignard or organolithium reagents **14** are required due to the limited electrophilicity of ketimines **13**. Additionally, ketimines can be prone to enamine formation and as a result often require a protecting group.[19] This leads to a stepwise protocol that limits the efficiency of the approach.

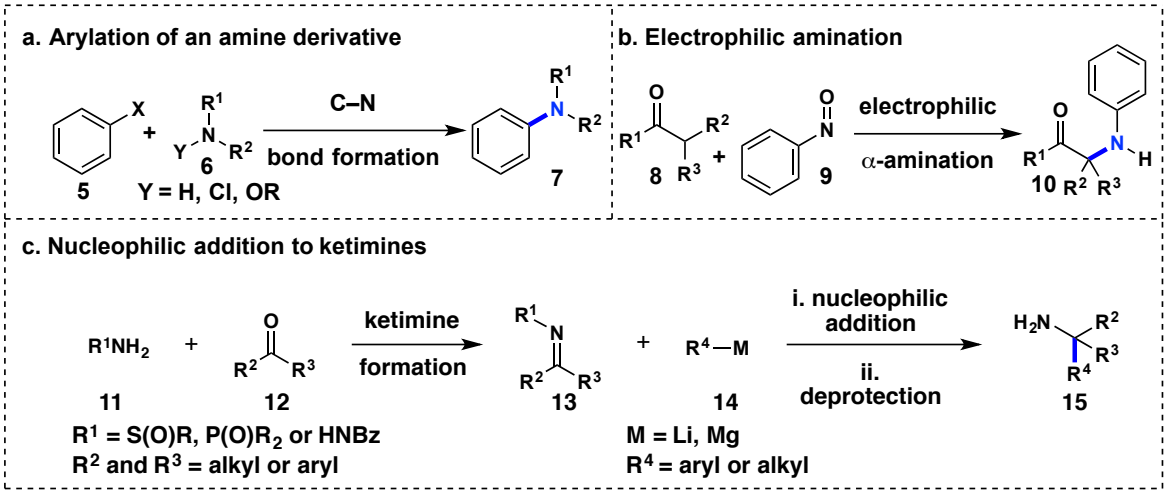


Figure 4.2. Different Approaches to the Synthesis of Hindered Amines

4.3 Radical Additions to Nitroso Compounds for Hindered C–N Bond Formation

Given the drawbacks associated with current methods for the construction of hindered C–N bonds, we sought to develop a mild, general, efficient process for the synthesis of hindered anilines utilizing a new disconnection that merges radical reactions with nitroso chemistry (Figure 4.3).

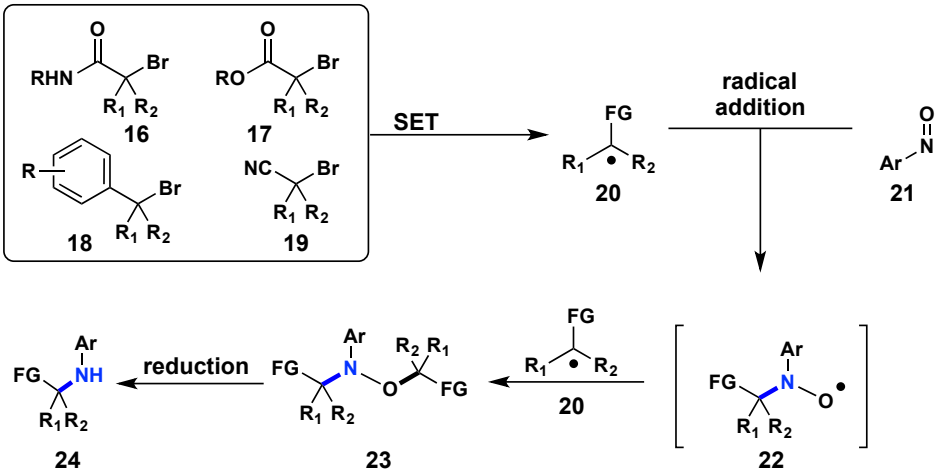


Figure 4.3. A New Disconnection for the Synthesis of Hindered Anilines

Radical transformations involving nitroso compounds had not been developed as synthetic tools in organic chemistry until very recently when Baran's group and our group independently reported related transformations.[20] We will now disclose our results regarding the development of a Cu-catalyzed radical addition with nitroso compounds.

We elected to utilize ATRP conditions (Cu^{I}/L) with alkyl halides as our alkyl radical source (Figure 4.4).[21] We were enticed by Cu based catalysts because they are utilized in ATRC to generate polymer chain end radicals which undergo addition with radical traps, such as nitroso compounds, to form diblock copolymers efficiently.[22] Initially, two equivalents of *tert*-butyl 2-bromopropanoate **25** were treated with one equivalent of nitrosobenzene **26** in the presence of Cu(0) and PMDETA in sparged THF under a N_2 atmosphere. We were excited to isolate the product **27** from this reaction in 76% yield.

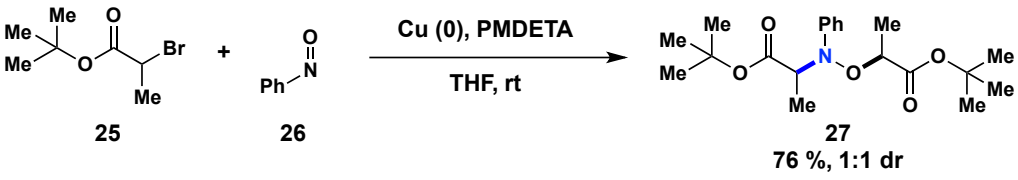


Figure 4.4 Initial Results for the Copper Catalyzed Radical Additions with Nitrosobenzene

Encouraged by this preliminary result, we sought to expand the scope to include other radical precursors (Figure 4.5). This nitroso-assisted radical coupling proved to be efficient for a variety of different α-bromo esters (**30**–**37**). Notably, yields were higher with more hindered substrates. The functional group compatibility of the process was high. Heteroaromatics **34**, olefins **35**, terminal alkynes **36**, TMS protected alcohols **37**, aryl bromides **40** and primary alcohols **39** were all well tolerated. Additionally, tertiary, secondary and primary α-bromo amides (**38-39, 42**) could be utilized as radical precursors. Next, we focused on the conversion of the alkoxyamine dimers to the free aniline.

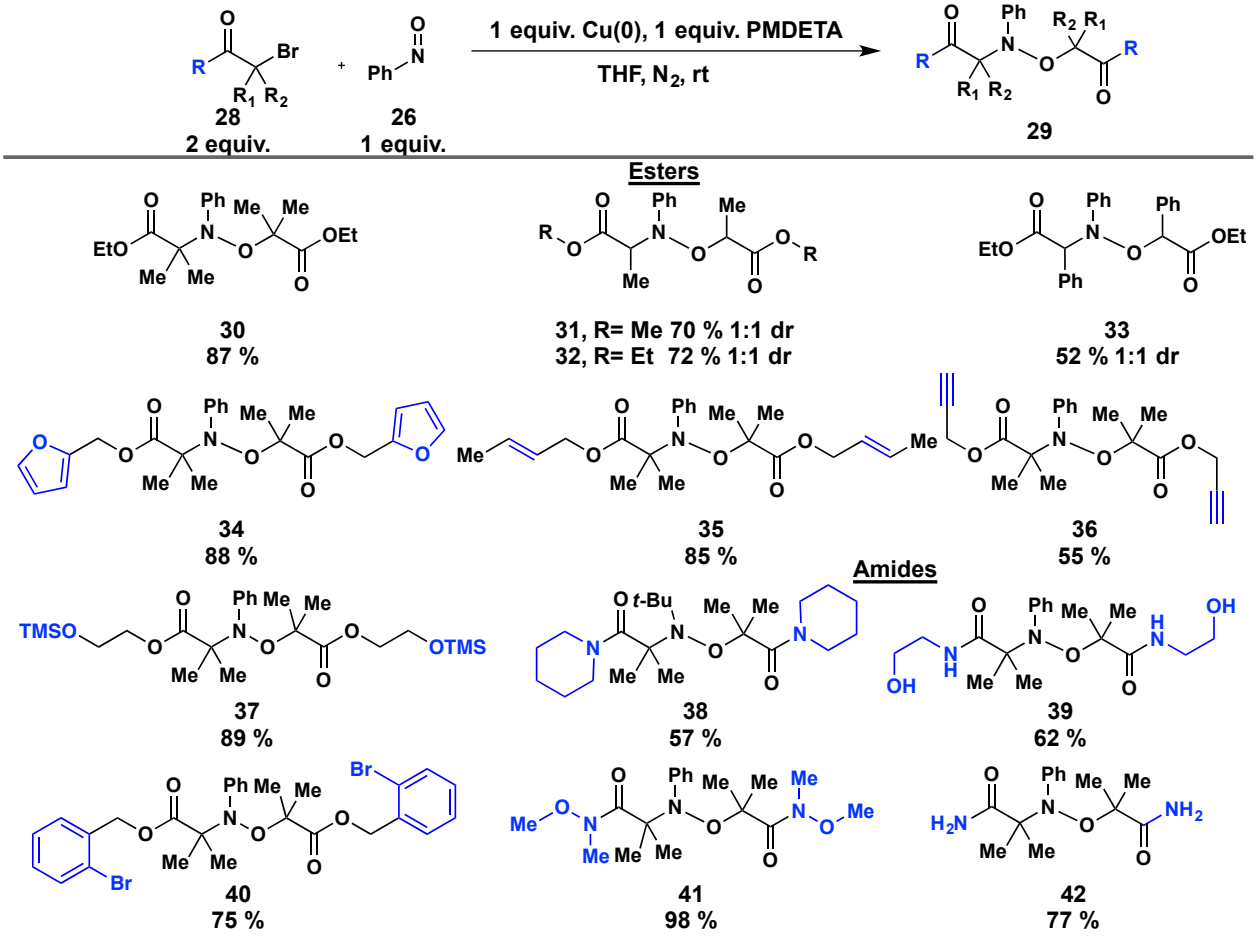
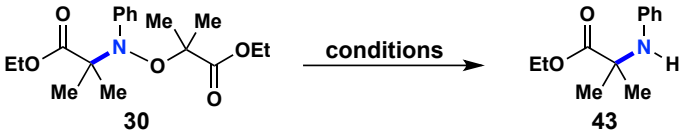


Figure 4.5. Scope of the Stoichiometric Radical Coupling Reaction with α-Bromocarbonyls

The first real challenge was identifying reaction conditions that efficiently reduced the N–O bond in the alkoxyamine **30** to liberate the aniline product (Table 4.1). Typical reducing conditions such as Zn/AcOH (entry 1), Zn/HCl (entry 2) and H_2, Pd/C (entry 5) resulted in only partial conversion to the desired product **43**. Unreacted starting material was recovered from treatment with both $Mo(CO)_6$ (entry 3) and Raney nickel (entry 5). To our delight, we found that treatment of **30** with SmI_2 rapidly facilitated the reduction to afford **43** in 86% yield after only five minutes (entry 7). Eventually we discovered that SmI_2 could be added directly to the crude radical coupling reaction mixture, enabling development of a one pot protocol for the synthesis of α-amino carbonyl compounds.

The proposed mechanism for the reduction involves an initial SET transfer from SmI_2 to **29** to generate ketyl radical **44** (Figure 4.6). Homolytic cleavage of the C–O bond generates the nitroxide radical **45** and enolate **46**. Further reduction of **45** results in the formation of the hindered aniline **47**. **46** is eventually protonated and remove under reduced pressure. This would explain why the alcohol products are not isolable following reduction.



Entry	Conditions	Result
1	Zn/AcOH, 60 °C	Mixture of S.M. and product
2	Zn/HCl, 60 °C	50% yield
3	$Mo(CO)_6$, 60 °C	No reaction
4	Na/naphthalene	Complex mixture of products
5	H_2, Pd/C	48% yield
6	Raney Nickel	No reaction
7	**SmI_2**	**86% yield**

Table 4.1. Conditions for Reductive N–O Bond Cleavage

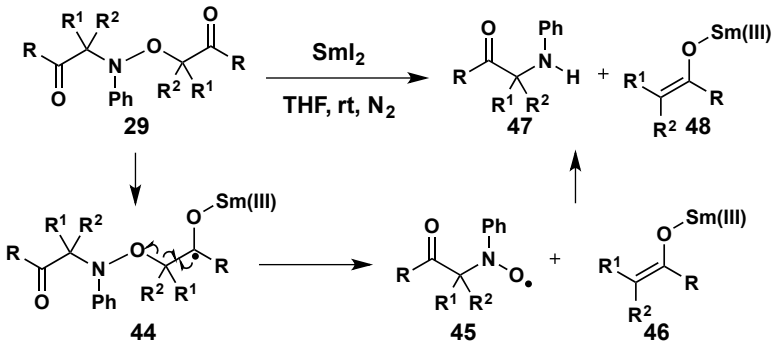


Figure 4.6. Proposed mechanism for the SmI_2-promoted reduction of the alkoxyamines

A constant challenge in synthetic methodology is the minimization of waste produced during a process. One way to do this is through catalytic method development. Although copper is abundant and inexpensive, we sought to lower Cu loading due to the known toxicity of metal salts and high cost for removal from process scale reactions involving the synthesis of pharmaceutical targets required for GMP. It has been shown in the ATRP literature that stoichiometric reductants such as glucose, ascorbic acid,[23] tin (II) 2-ethylhexanoate,[24] and zero-valent metals including Cu, Zn, Mg and Fe can be used to regenerate Cu(I) in situ, allowing for a decrease in catalyst loading.[25] We envisioned that a similar, redox-neutral strategy could be applied to render our process catalytic (Figure 4.7). Replacing the nitrosoarene with an *N*-arylhydroxylamine **50** would allow for regeneration of the Cu(I) needed for radical formation through a Cu(II)-catalyzed oxidation of **50** to the nitrosoarene **21**. This would produce the reactive intermediates needed for the coupling reaction to occur simultaneously in situ.

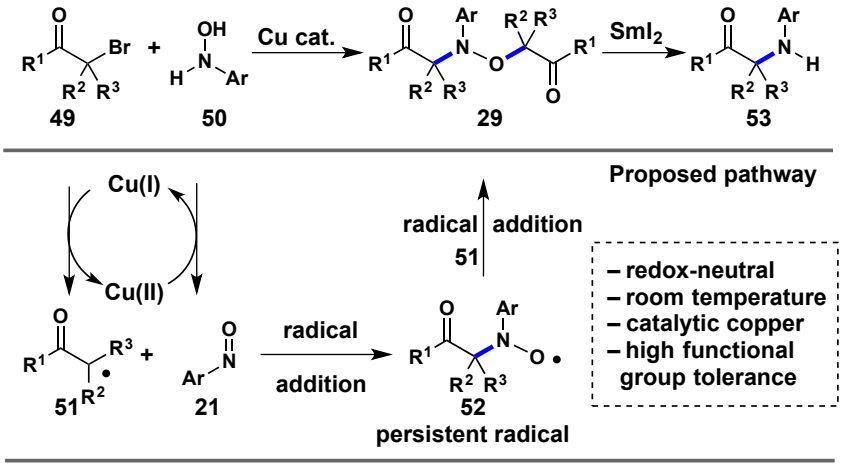
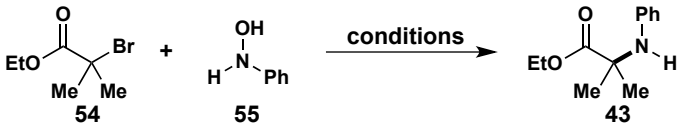


Figure 4.7. Proposed Cu-catalyzed radical addition with in situ generated nitroso compounds

Initial efforts towards developing this catalytic cycle utilized 5 mol % $CuCl_2$ and *N*-phenylhydroxylamine **55** as the nitrosoarene precursor (entry 1, Table 4.2). Disappointingly, only a trace amount of desired product **43** was generated. The major product isolated from this reaction was azoxybenzene, formed from a competing condensation reaction between nitrosobenzene and **55**. To minimize *N*-phenylhydroxylamine concentration in solution, it was added over the course of 5 h which increased reaction yield to 22% (entry 2). Further optimization revealed that increasing PMDETA loading from 0.5 to 1.8 equivalents resulted in the formation of **43** in 73% (entry 3). PMDETA is a tridentate ligand for copper necessary for radical formation but is also believed to act as a proton sponge during the oxidation of *N*-phenylhydroxylamine to nitrosobenzene. Once protonated, PMDETA no longer binds to copper, shutting the reaction down. It should be noted that no reaction occurred in the absence of $CuCl_2$ (entry 4).

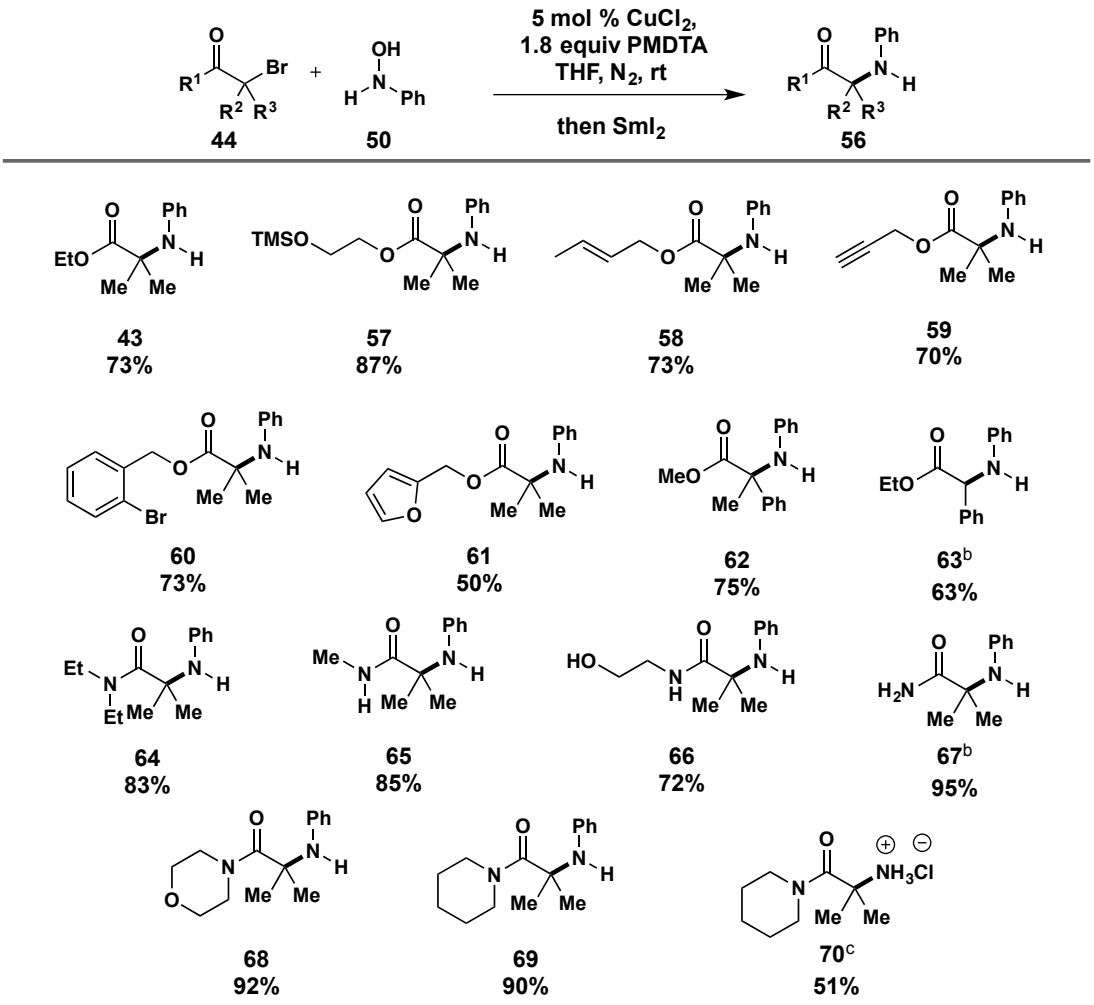


entry	5 mol % catalyst	equiv PMDTA	yield (%)
1	5 mol % $CuCl_2$	0.5	< 5
2[a]	5 mol % $CuCl_2$	0.5	22
3[a]	5 mol % $CuCl_2$	1.8	73
4	—	1.8	0

Table 4.2. Optimization of Catalytic Reaction Conditions

The same remarkable functional group compatibility was observed with the newly developed catalytic conditions (Figure 4.8). For instance, acid labile TMS ethers were well tolerated, leading to isolation of the desired product **57** in 87% yield. Substrates containing alkenes (**58**) and terminal alkynes (**59**) were also compatible. Selective reduction of the α-bromo–carbon occurred in the presence of aryl bromides (**60**), which serve as synthetic handles for further postfunctionalization. Again, yields were highest for the synthesis of α-tertiary anilines. The compatibility of primary alcohols (**66**) and amides (**67**) makes the utilization of protecting group chemistry unnecessary. It should be noted that SmI_2 also reduces the N–O bond in the Weinreb amide to form the methyl amide product **65**. A morphiline amide can be used as a Weinreb amide surrogate, which affords the desired product **68** in 92% yield.[26] Stochiometric copper conditions were required to achieve the desired reactivity with α-bromophenylacetate **63** and the primary α-bromo amide **67**. Under catalytic conditions **63** was isolated in only 38 % yield and the reaction with **67** was prohibitively slow. Additionally, hindered primary amine **70** was isolated in 51% yield over a three step sequence. First, 2-methyl-2-nitrosopropane was used in the radical coupling

reaction. The isolated alkoxyamine was treated with methanesulfonic acid to remove the *t*-butyl group. Subsequent reduction with SmI_2 afforded the desired product **70**.



[a] Isolated yields based on 8 as the limiting reagent are shown. [b] The reaction conducted with stoichiometric amounts of Cu(0) and nitrosobenzene was used. [c] 1) Cu(0), PMDETA, THF, N_2, rt, 2) MsOH, 60 ºC, 3) SmI_2, THF, rt then HCl

Figure 4.8. Scope of the α-Bromocarbonyls in the Catalytic Reaction

After successfully demonstrating the generality of the reaction with a variety of α-bromocarbonyl compounds, we concentrated our efforts on the incorporation of new *N*-arylhydroxylamines **50** (Figure 4.9).[27] Both electron rich and electron deficient aryl

groups could be utilized under standard reaction conditions (**73**, **72**). Substituents at the *meta* and *para* positions were well tolerated (**72-77**).

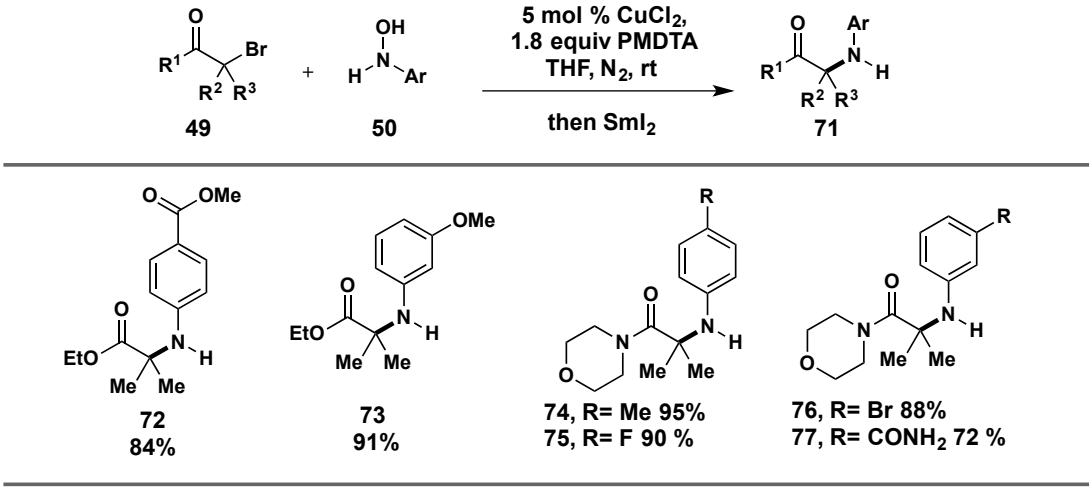


Figure 4.9. Scope of the *N*-arylhydroxylamines

To highlight the synthetic utility of this radical addition process, it was utilized for the synthesis of **82** (Figure 4.10b), a derivative of **80** (Figure 4.10a), an intermediate generated enroute to the 4-anilidopiperidine class of synthetic opioid analgesics which includes carfentanil (**3**), an extremely potent veterinary sedative used for large animals, and remifentanil, a general anesthetic.[10] The most popular route utilizes a Strecker reaction followed by hydrolysis of amide **79** to form the carboxylic acid, which is methylated to furnish **80**.[28] This sequence relies on harsh acidic and basic conditions as well as extremely high temperatures. For example, H_2SO_4 is required for the conversion of the nitrile to **79**. Additionally, KOH and heating to 190 °C are needed for the hydrolysis of **79** to the carboxylic acid. As a result, protecting groups are required, reducing the efficiency of the synthesis. In comparison, our radical based approach starts with α-bromo ester **81**, accessible in a single step from readily available material (Figure 4.10b). The key C–N bond forming event furnishes the hindered amine **82** in 89 % yield under mild conditions

compatible with the Boc protecting group which could easily be removed for efficient derivatization of the piperidine nitrogen.[29] This approach is valuable because it provides synthetic chemists with the ability to construct hindered C–N bonds in the late stages of multistep syntheses. The synthesis of **85** highlights the compatibility of the radical coupling with the aryl bromide functionality, which was used in a Suzuki cross coupling reaction to generate the biaryl found in **86** (Figure 4.10c).[13]

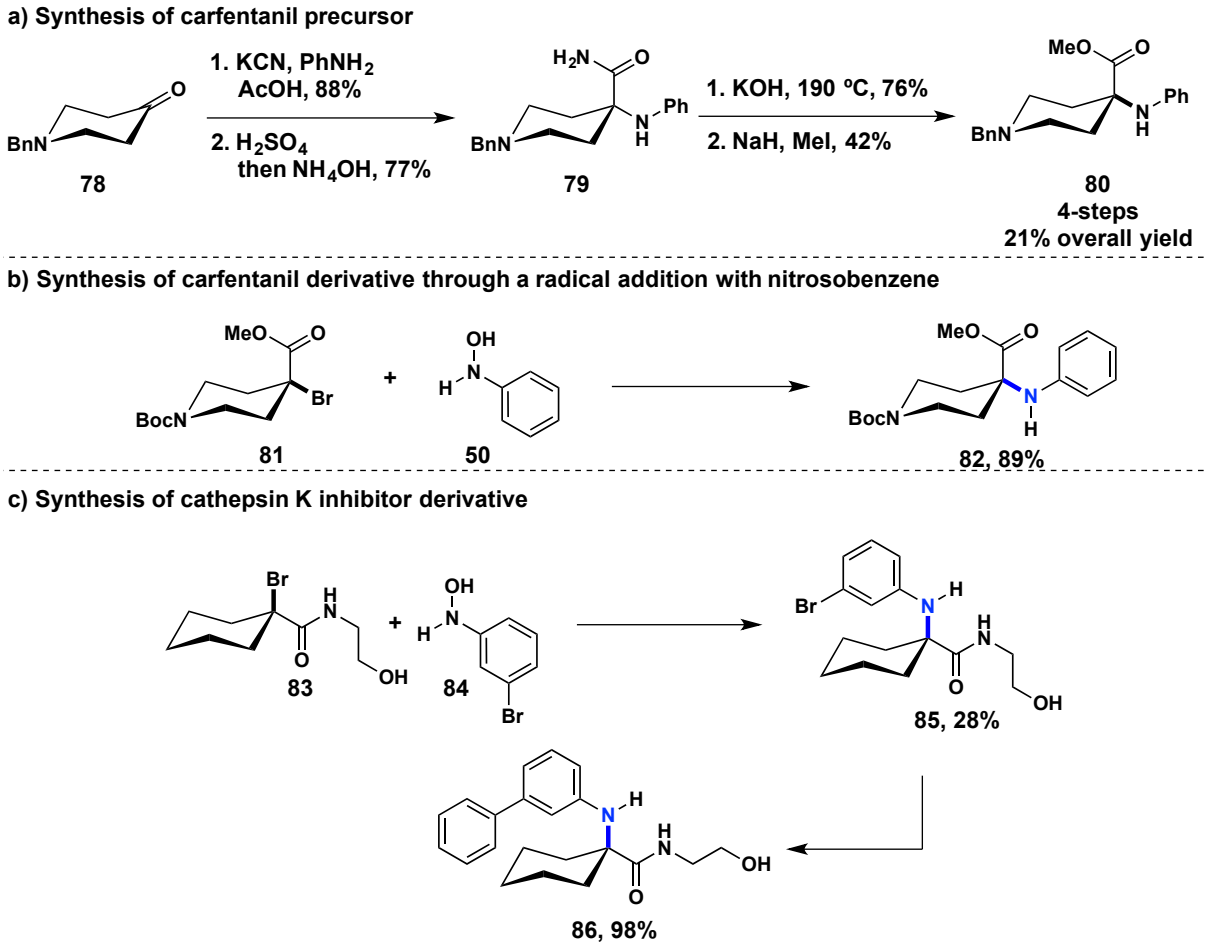


Figure 4.10. Synthetic Applications of the Radical Coupling Reaction with *N*-arylhydroxylamines

4.4 Conclusion

In conclusion, a novel copper catalyzed synthesis of hindered α-aminocarbonyls has been developed. This process utilizes an alkyl radical addition with nitrosoarenes for the C–N bond forming event, representing a new bond disconnection for amine synthesis. Catalytic copper can be used because the transformation is redox neutral. Functional group compatibility is high due to the mild reaction conditions. This strategy provides synthetic chemists with the ability to construct hindered C–N bonds in the late stages of multistep syntheses.

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Chapter 5. A Three Component Coupling of Arylboronic Acids, *t*-Butyl Nitrite and Alkyl Halides for the Synthesis of Hindered Anilines

5.1 Arylboronic Acid Background

Arylboronic acids are versatile synthetic building blocks for increasing molecular complexity in medicinal chemistry and organic synthesis. These valuable compounds participate in a variety of transformations, but are most widely used in C–C bond forming reactions; the most notable is the palladium catalyzed Suzuki-Miyaura cross coupling (Figure 5.1) between arylboronic acids **1** and aryl halides **2**.[1] Suzuki won the 2010 Nobel Prize (shared with Heck and Negishi) for his contributions to palladium-catalyzed cross-coupling reactions through the development of this transformation. It continues to be commonly used for the synthesis of biaryls **3**, styrenes and poly-alkenes, especially in the pharmaceutical industry. Roughley and Jordan showed in their analysis of 7315 reactions used in the pursuit of drug candidates, that Suzuki-Miyaura cross couplings accounted for 40 % of all C–C bond forming reactions.[2] Alternatively, arylboronic acids can react with olefins (**4**, **6)** in oxidative Heck reactions[3] or through conjugate addition[4] for C–C bond formation (**5**, **7**).

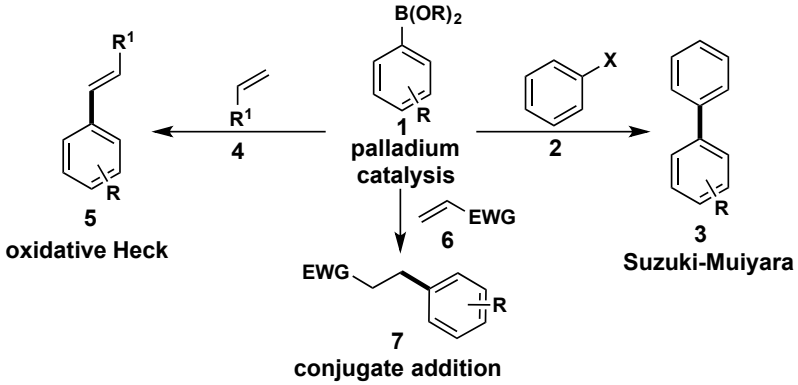


Figure 5.1. Palladium-Catalyzed C–C Bond Forming Reactions with Arylboronic Acids

Finally, boronic acid derivatives participate in homologation reactions with organometallic species.[5] Although less developed, arylboronic acids are also important synthons in C–N bond forming reactions.

In 1998 the groups of Chan and Lam independently disclosed a copper-catalyzed C–N cross coupling reaction with arylboronic acids.[6] This transformation, known today as the Chan-Lam coupling (Figure 5.2), represents a practical alternative to the Buchwald-Hartwig coupling for the synthesis of *N*-arylamines **9**. The coupling is compatible with many different primary and secondary amine derivatives **8** including heteraromatics (imidazole pyrazole, indazole), alkylamines, anilines, ureas, amides, sulfonamides, imides and carbamates. The initial reports utilized stoichiometric amounts of copper (II) acetate and base (triethylamine or pyridine) in dichloromethane at room temperature in the presence of air. These conditions differ considerably from the Buchwald-Hartwig amination with aryl halides **2** (Figure 5.2), which utilizes expensive palladium catalysts, requires a strong base to promote reductive elimination, and frequently must be run under inert atmosphere.[7]

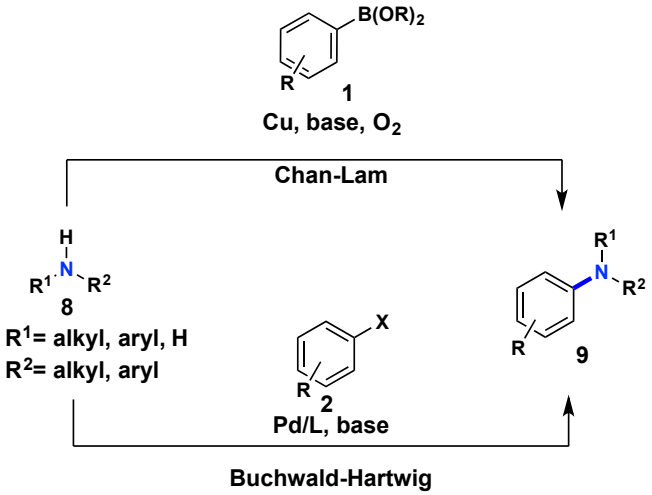


Figure 5.2. Transition Metal-Catalyzed Methods for N–Aryl Bond Formation

One limitation of the Chan-Lam reaction is that it cannot be used to construct hindered anilines. Recently Lalic and co-workers addressed this shortcoming (Figure 5.3) through the development of a copper catalyzed coupling of arylboronic esters **10** with *O*-benzoyl-hydroxylamines **11** with a Xantphos ligand and *t*-butoxide base for the synthesis of hindered anilines **13**.[8] Later he discovered milder, robust conditions that utilized cesium fluoride instead of *t*-butoxide and a more stable copper (I) complex as the catalyst.[9]

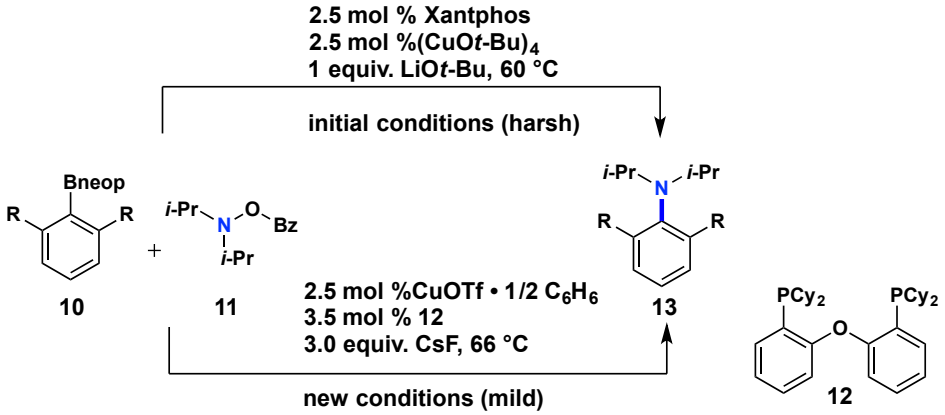


Figure 5.3. Lalic's Methods for Hindered Aniline Synthesis

In the context of C–N bond formation, arylboronic acids and their derivatives are commonly involved in *ipso*-nitration reactions for the metal free synthesis of nitroarenes **16** (Figure 5.4).[10] Conceptually similar, although less common are *ipso*-nitrosations of arylboronic acids and their derivatives to produce nitrosoarenes **15**. In these scenarios, a source of NO^+ participates in a substitution with aryl or heterarylboronic acids/derivatives under inert atmosphere. These transformations are less prominent because overoxidation of **15** to **16** can be difficult to avoid. Typically, electron-rich arylboronic acids **14** participate most readily in these reactions and aren't prone to overoxidation.

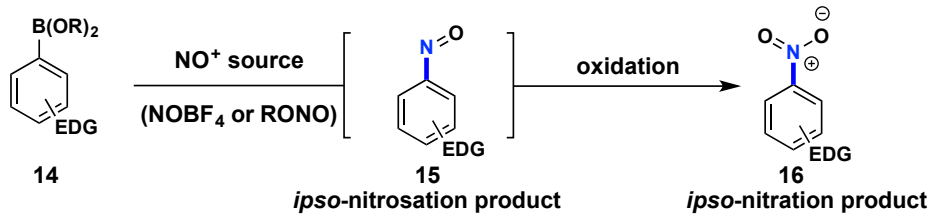


Figure 5.4. Metal Free Nitration of Arylboronic Acids

In 2012 Yan and co-workers reported a metal free *ipso*-nitrosation/nitration of arylboronic acids with *t*-butylnitrite.[11] While developing the *ipso*-nitration process they noticed side products were generated with electron-rich arylboronic acids, which turned out to be the nitrosoarenes (Figure 5.5). Preliminary studies showed that treatment of 4-*t*-butylphenylboronic acid **17** with 1.5 equivalents of *t*-butylnitrite in acetonitrile open to air generated 4-*t*-butyl-nitrosobenzene **20** and 4-*t*-butylnitrobenzene **21** in a 78:22 ratio. Repeating the reaction under an N_2 atmosphere increased the ratio to 93:7.

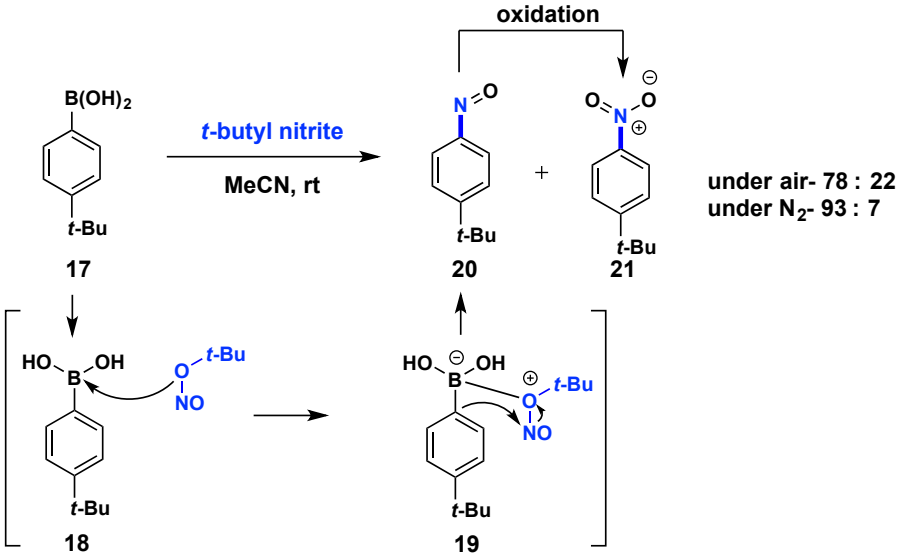


Figure 5.5. Yan's metal free *ipso*-nitrosation/nitration of arylboronic acids

It should be noted that Beller and co-worker simultaneously reported a similar process for the nitration of arylboronic acids.[12] *t*-Butylnitrite was used as the nitrating reagent

in dioxane at 80 °C. Beller postulates that an intermediate nitrosoarene is first generated through *ipso*-nitrosation with *t*-butylnitrite followed by oxidation to the nitroarene. Later Olah and co-workers would show that *t*-butylnitrite could be replaced with a combination of sodium nitrite and trimethylsilyl chloride (TMSCl) to generate an efficient nitrosating reagent in situ (Figure 5.6).[13] This process was effective with *para*-substituted electron-rich arylboronic acids **22** for the synthesis of several nitrosoarenes **24-27**. Yields were low with *ortho*-substituted substrates, and electron-neutral and deficient arylboronic acids were prone to overoxidation to the corresponding nitroarene.

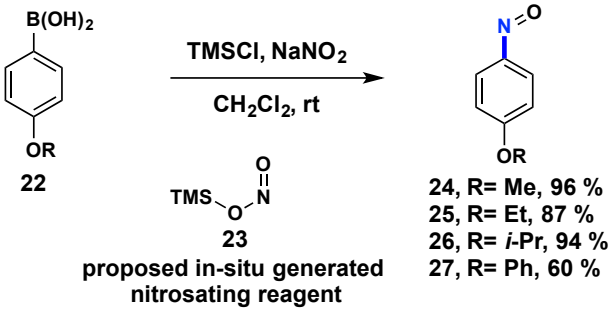


Figure 5.6. Olah's Nitrosation of Arylboronic Acids with TMSCl and $NaNO_2$

In 2012, Molander reported the *ipso*-nitrosation of aryl and heteroaryltrifluoroborates **28** with nitrosonium tetrafluoroborate ($NOBF_4$) (Figure 5.7).[14] This method proved to be extremely general and allowed for the development of a broad substrate scope. Both electron-rich and electron-poor systems were well tolerated and allowed for efficient conversion to the nitroso products **29**. A one pot nitrosation/nitroso Diels-Alder reaction with cyclohexadiene **30** was developed to trap the desired nitroso product with substrates susceptible to overoxidation.

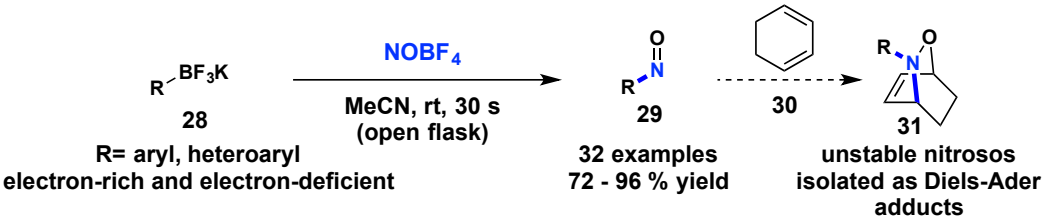


Figure 5.7. Molander's Nitrosation of Aryl and Heteroaryltrifluoroborates with $NOBF_4$

Arylboronic acids are convenient to work with because they are benchtop stable. Additionally, due to their widespread use in organic synthesis, they are inexpensive and commercially available; over 1000 aryl and heteroarylboronic acids can be purchased through Sigma Aldrich. In our efforts to design a general, practical method for C–N bond formation, we thought it was important to utilize commercially available starting materials. Arylboronic acids as nitrosoarene precursors represent an attractive alternative to *N*-arylhydroxylamines (nitroso source in our previous work),[15] which are not commercially available and difficult to work due to their instability. *N*-arylhydroxylamines can be prepared efficiently through a Rh-catalyzed reduction of the corresponding nitroarene, but rhodium is an expensive precious metal and the *N*-arylhydroxylamines are prone to decomposition.[16] We envision the mild metal-free conditions for the *ipso*-nitrosation of arylboronic acids **1** would be compatible with copper catalysis for radical formation **(37)** from alkyl halides **32-35**, enabling the development of a general, highly modular three component coupling approach to the synthesis of hindered anilines **40** from commercially available starting materials (Figure 5.8).

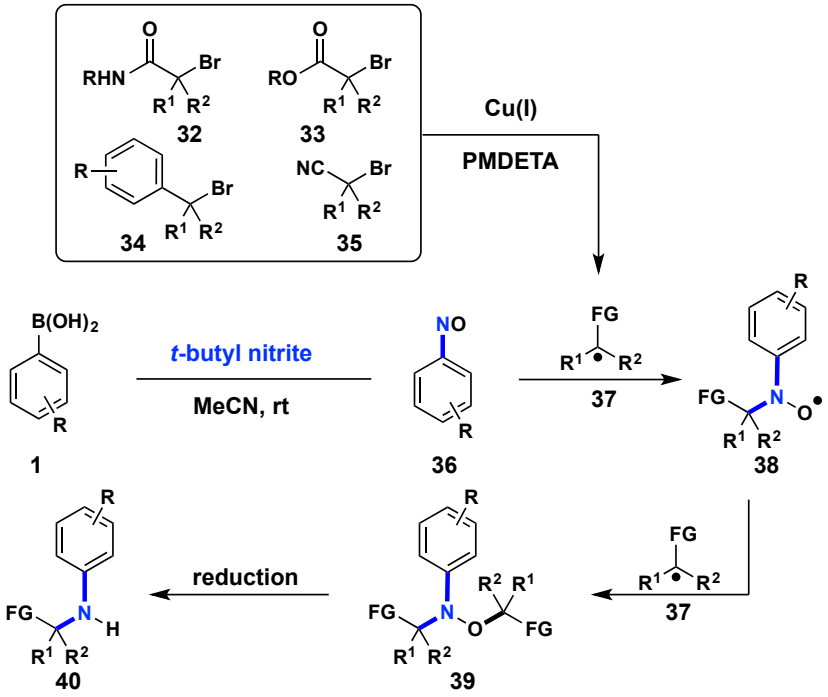


Figure 5.8. Three Component Coupling of Arylboronic Acids, *t*-Butyl Nitrite and Alkyl Halides

5.2 A Three Component Coupling for the Synthesis of Hindered Anilines

The study of metal-catalyzed methods for the construction of C–N bonds is widespread in organic synthesis. This endeavor is important because metal catalysis allows for the formation of C–N bonds that can't be formed through typical substitution reactions, such as N–aryl and hindered C–N bonds. The ubiquity of the amine functionality makes it important that these processes are general, robust and utilize readily available starting materials and earth-abundant metals. Other key features include practicality, scalability and mildness. In the context of N–aryl bond formation the transition metal-catalyzed Buchwald-Hartwig[7a,b,17a,7c,17b,c] (palladium) and Ullman[18] (copper) coupling reactions between aryl halides **41** and amine derivatives **42**, and the copper-catalyzed Chan-Lam coupling[6] between

arylboronic acids **41** and nitrogen nucleophiles **42**, have transformed the field (Figure 5.9a). With respect to the synthesis of hindered anilines **43**, a number of significant advances have been made in the area. For example, in 2015 Lalic reported a mild copper-catalyzed coupling of arylboronic acids with sterically congested *O*-benzoylhydroxylamines.[9] Additionally, Buchwald recently reported new strategies for the palladium-catalyzed addition of hindered amines to aryl halides through the utilization of rational ligand design.[17b] Despite the improvements being made for C_{Sp2}–N bond formation, the use of metal catalysis for the construction of C_{Sp3}–N bonds remains underdeveloped and needs to be addressed.

The use of alkyl halides as electrophiles in substitution reactions with nitrogen nucleophiles is a common strategy for the synthesis of amines.[19] However, N-alkylation reactions can suffer from problems such as overalkylation and diminished product formation with less reactive electrophiles like secondary and tertiary alkyl halides.[20] In 2012, Peters and Fu published the first of several papers documenting their use of metal catalysis to increase the reactivity of more hindered alkyl halides in N-alkylation reactions (Figure 5.9b).[21] Utilizing copper catalysis, they developed a photoinduced coupling reaction between alkyl halides **44** and a variety of nitrogen nucleophiles **45** including carbazoles, indoles and amides. It is believed that light promotes the L_n-Cu-nucleophile complex to the excited state which is involved in a single electron transfer (SET) to the alkyl halide to form a radical anion. Combination of the radical anion with the resulting radical cation forms the coupled product **48** and a L_n-Cu-X species that can react with a nitrogen nucleophile to regenerate the L_n-Cu-nucleophile complex.

Recently, our group[15] and Baran[22] disclosed independent reports of an alternative approach to metal-catalyzed hindered C_{Sp3}–N bond formation utilizing radical chemistry with

nitroso compounds (Figure 5.9c). In contrast to the work of Fu and Peters, our strategy involves the coupling of two electrophiles (alkyl halides **49** and nitrosoarenes **50**), through an alkyl radical (**37**) addition to **50**. Theoretically, this process should be broadly applicable because alkyl halides are abundant and commercially available. However, despite being synthetically useful for the copper-catalyzed synthesis of hindered α-aminocarbonyls, our process was limited because *N*-arylhydroxylamines, the nitrosoarene precursors, are unstable and not commercially available. Now we will disclose our findings on the development of a general, radical based strategy for the synthesis of hindered anilines **54** that utilizes a highly modular three component coupling reaction with arylboronic acids **52**, *t*-butyl nitrite and alkyl halides **49** (Figure 5.9d).[23] The starting materials are all commercially available, two C–N bonds are formed in one pot, and benzyl bromides, α-bromonitriles, and α-bromocarbonyls are included in the substrate scope.

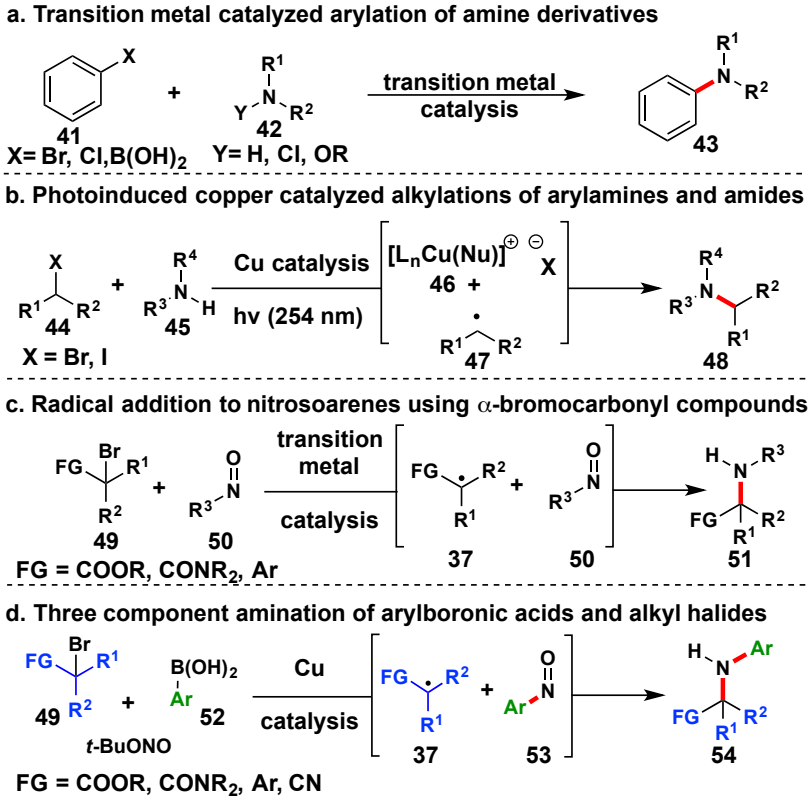


Figure 5.9. Transition Metal-Catalyzed C–N Bond Formation with Alkyl Halides

5.3 Results

Initially, we focused on using Molander's nitrosation method with aryltrifluroborates and $NOBF_4$ for nitroso formation because it seemed most broadly applicable and was compatible with heterocycles (Figure 5.10).[14] The preliminary results were promising; treatment of trifluoroborate **56** with $NOBF_4$ for 30 seconds, quenching with water and then combining with ethyl α-bromoisobutytrate **55** and the Cu/PMDETA complex[24] (ATRP conditions) enabled the three component coupling for the synthesis of α-aminoester **57** in 56% yield.

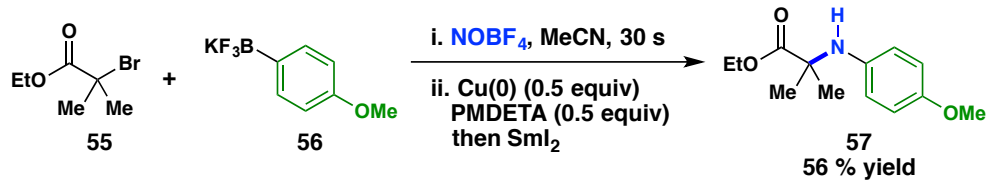


Figure 5.10. Results with Aryltrifluoroborates in the Three Component Coupling

Disappointingly, further investigation revealed these results were not reproducible or applicable to other trifluoroborates. We then began exploring other *ipso*-nitrosation conditions amenable to the three component coupling procedure. The methods developed independently by Yan and Beller for the metal free *ipso*-nitration of arylboronic acids with *t*-butyl nitrite were intriguing to us because the process is believed to proceed through a nitrosoarene intermediate which undergoes oxidation to the corresponding nitroarene (Section 4.1, Figure 4.5).[12,11] This system proved to be more compatible with the radical coupling conditions. Treatment of *p*-methoxyphenylboronic acid **58** with 1.5 equivalents of *t*-butyl nitrite in acetonitrile under N_2 for two hours afforded the corresponding nitrosoarene **59** in 95% yield (Figure 5.11a). Utilizing the three component coupling protocol with *t*-butyl

nitrite produced the desired alkoxyamine dimer **61** in 93% yield (Figure 5.11b). It should be noted that simultaneous addition of reagents is ineffective; only a trace amount of **61** is recovered. Additional exploration demonstrated that the crude reaction mixture containing **61** could be treated directly with SmI_2 to generate the α-aminoester **57** in 81% yield using the three component coupling strategy (Figure 5.11c).

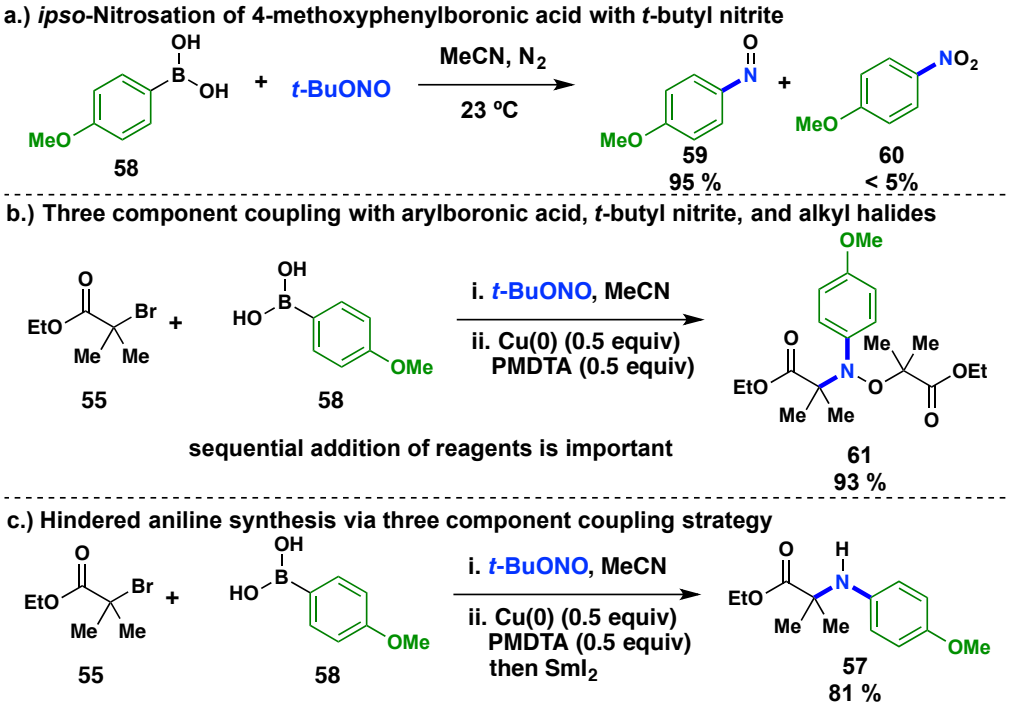


Figure 5.11. Preliminary Results with Arylboronic Acids and *t*-Butyl Nitrite

With optimization of the reaction conditions complete, we sought to expand the substrate scope. Mono- and di-substituted electron-rich arylboronic acids proved to be compatible with both α-bromoamides and α-bromoesters (Figure 5.12). For instance, *O*-alkyl substituents at the 2, 3, and 4 positions afforded products in high yield (**57**-**68**). Ethoxy-3-chlorophenylboronic acid participated in the reaction to form **63**; the aryl chloride serving as a synthetic handle for postfunctionalization. Aromatic thioethers were well tolerated in the process to produce **65**. Excess electron-neutral arylboronic acid must be used

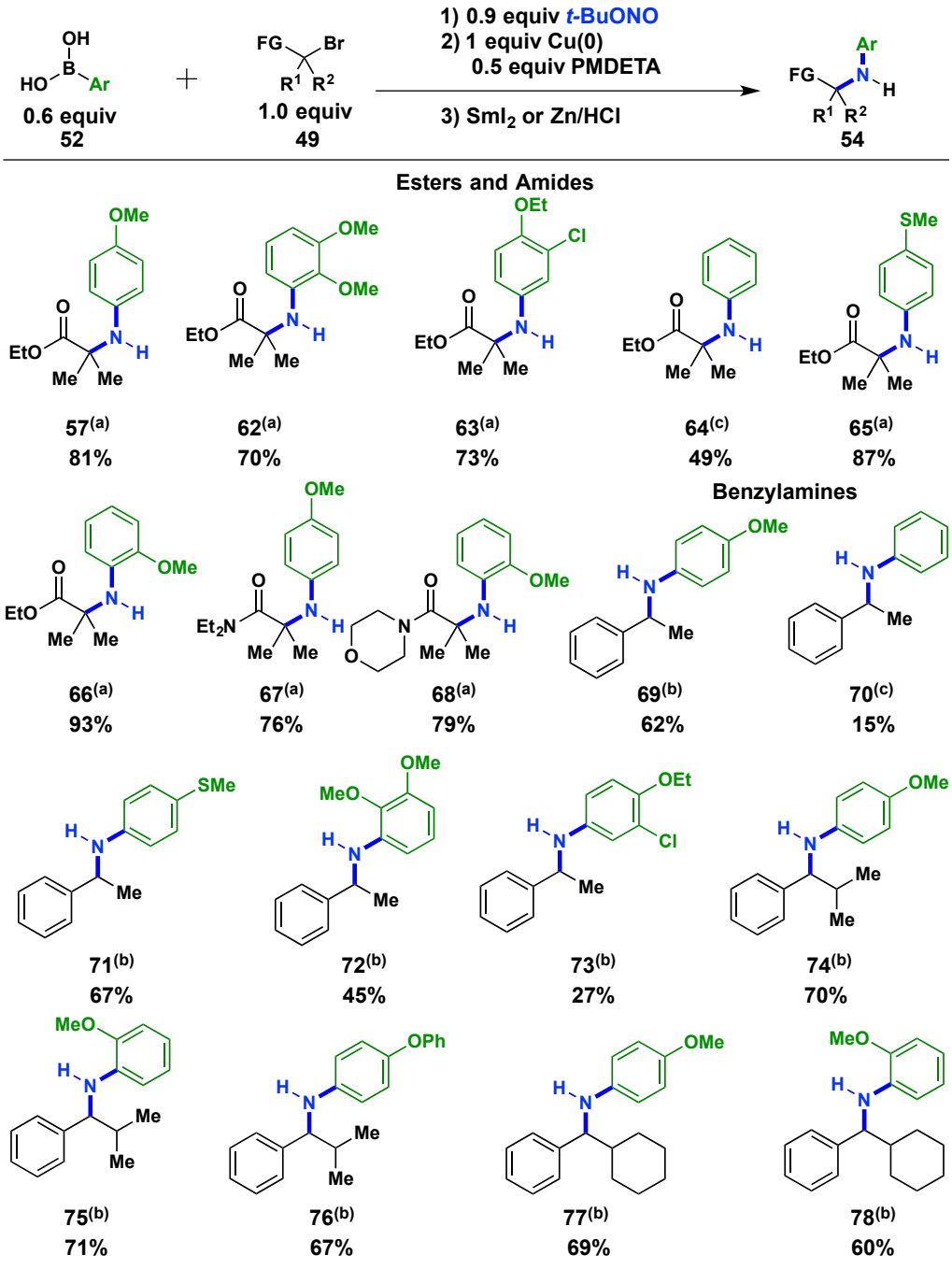
in the reaction, because overoxidation to the corresponding nitroarene could not be avoided using optimized reaction conditions. As a result, three equivalents of phenylboronic acid was required to produce **64** in 49% yield. Electron-deficient arylboronic acids are also prone to overoxidation.

To broaden the generality of the process we sought to demonstrate that a diverse range of alkyl halides could be incorporated as radical precursors for the nitroso mediated C–N bond forming strategy. We envisioned that benzyl bromides, which are commonly used in ATRP as radical initiators would be amenable to the reaction to furnish benzylamines.[24]

N-Alkylation[25] and reductive amination[26] are two commonly employed techniques for the synthesis of benzylamines. Despite their widespread use in academia and industry, N-alkylation reactions between nitrogen nucleophiles and alkyl halides are often plagued by overalkylation and functional group compatibility issues due to the use of stoichiometric base. Reductive amination is a useful alternative because it avoids overalkylation, but requires the presence of a carbonyl group, and is ineffective in sterically hindered environments. We feel these limitations can be overcome using our protocol involving alkyl radical additions to nitrosoarenes.

We were excited to successfully prepare a variety of electron-rich secondary benzylamines (**69**-**78**) derived from the copper-mediated three component coupling process with 1-bromoethylbenzene (Figure 5.12). Standard reaction conditions were utilized for the radical coupling, but the N–O bond reduction with SmI_2 was not successful. It was quickly determined that Zn/HCl reducing conditions produced superior results. Disappointingly, bromomethylbenzene failed to react under standard reaction conditions. Furthermore, tertiary benzyl bromides such as (2-bromopropan-2-yl)benzene proved to be extremely

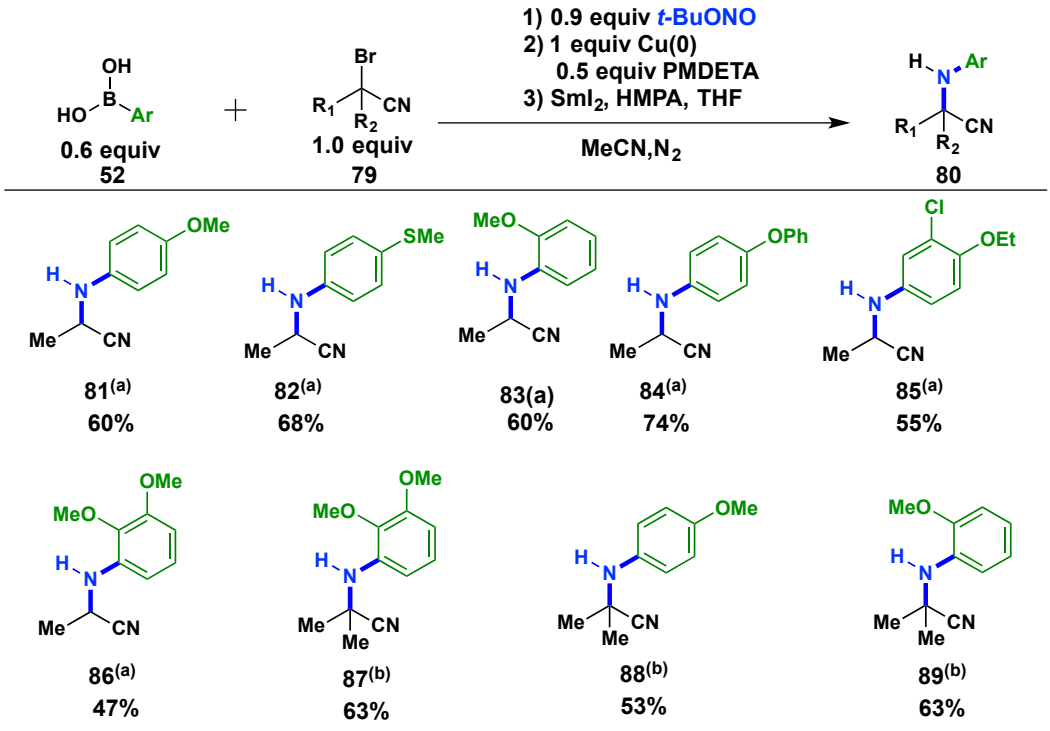
unstable in our hands; elimination to the styrene derivative was unavoidable during purification. Despite these drawbacks, sterically hindered benzyl bromides that are typically poor substrates for alkylations and reductive aminations, including those with α-ispropyl (**74-76**) and α-cyclohexyl (**77-78**) substituents exhibited excellent reactivity under standard reaction conditions (Figure 5.12).[27] Since the C–N bond forming event is a radical process, overalkylation, which is problematic with nitrogen based nucleophilic substitution reactions involving benzyl bromides, is never observed.



[a] N-O bond cleavage with SmI_2/THF at 23 °C. [b] N-O bond cleavage with Zn/HCl in THF at 60 °C. [c] 3 equiv of phenylboronic acid and 4.5 equiv of *t*-BuONO used. PMDETA = N,N,N',-N'',N''-pentamethyldiethylenetriamine

Figure 5.12. Scope with α-Bromocarbonyls and 1-Bromoethylbenzene

To further display the broad generality of the strategy, it was applied to the synthesis of α-aminonitriles **80**,[28] important building blocks for a variety of pharmacologically relevant molecules (Figure 5.13).[29] α-Bromonitriles **79** serve as extremely active radical initiators in ATRP,[30] indicating they should be effective radical sources for the three component coupling. To our satisfaction, both α-bromopropionitrile and α-bromoisobutyronitrile generated the N–O alkylated adducts in 75% and 95% respectively in the reaction with *p*-methoxyphenylboronic acid and *t*-butyl nitrite under standard conditions. N–O bond reduction was not facilitated by either SmI_2 or Zn/HCl. Instead we found the addition of HMPA, which is known to increase the reactivity of SmI_2,[31] efficiently promoted desired product formation. C–N bond formation using both secondary and tertiary α-bromonitriles was successful with a variety of *ortho, meta,* or *para* substituted electron-rich arylboronic to prepare an assortment of α-aminonitriles (**81**-**89**, Figure 5.13).



[a] N-O bond cleavage at 23 °C. [b] N-O bond cleavage at 40 °C. PMDETA = N,N,N',N",N"-pentamethyldiethylenetriamine

Figure 5.13. Scope with α-Bromonitriles

Finally, to display the synthetic utility of the copper-mediated three component coupling reaction it was applied to the synthesis of the 2-thiohydantoin scaffold, present in chemotherapeutic pharmaceutical Enzalutamide **90**,[32] and other molecules with interesting biological activity such as **91**[33] (antimicrobial) and **92**[34] (treatment of diabetes) (Figure 5.14a). As illustrated in Figure 5.14b, 2-thiohydantoin can be generated in two steps from readily available starting materials. First, the copper-mediated three component coupling of *p*-methoxy-phenylboronic acid **58** with *t*-butyl nitrite and α-bromoisobutyronitrile **93** followed by N–O bond reduction furnished α-aminonitrile **88** in 53 % yield. Acid promoted cyclization of **88** with 4-nitrophenyl isothiocyanate generates the 2-phenylthiohydantoin **94**

in 68% yield. Cyclization attempts with α-aminonitrile **81**, derived from α-bromopropionitrile , and 4-nitrophenyl isothiocyanate were unsuccessful.

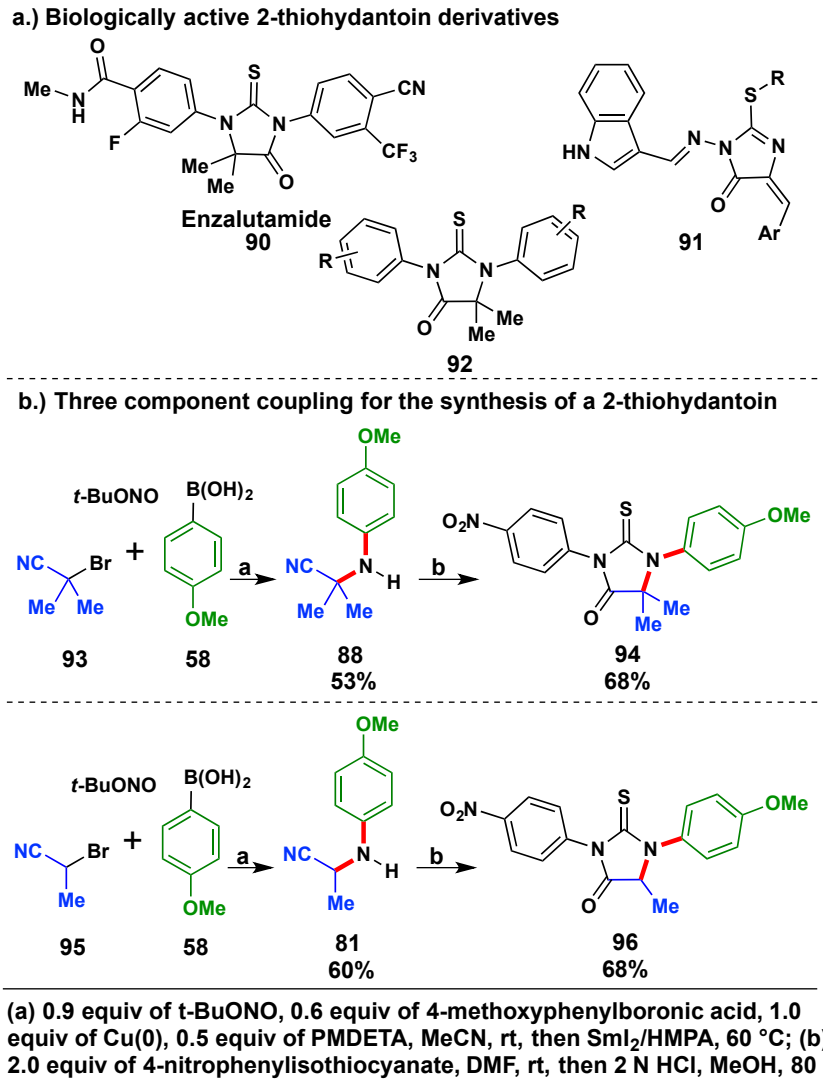


Figure 5.14. Application to the Synthesis of a 2-Thiohydantoin Derivative

5.4 Conclusion

In conclusion, we have developed a general protocol for the synthesis of hindered, electron-rich secondary anilines via a copper-mediated three component coupling of numerous arylboronic acids with *t*-butyl nitrite and various alkyl halides. A variety of α-aminocarbonyls, α-aminonitriles and benzylamines are synthesized, highlighting the

modularity of the process. All starting materials are commercially available, the reaction conditions are mild, and both N–aryl and C_{sp}^3–N bonds are formed in a single pot. The synthetic utility of this method was showcased through its application to the synthesis of biologically active 2-thiohydantoin derivative.

5.5 References

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Chapter 6: An Intramolecular Radical Coupling Reaction with Nitrosoarenes for the Synthesis of Amino Alcohols

6.1 Introduction

Nitroso compounds are important synthons in organic synthesis because they are able to simultaneously deliver both N and O heteroatoms to small molecules. In this context, cycloaddition reactions involving nitroso compounds as 2π components, such as the nitroso Diels–Alder, are powerful tools for the transfer of N and O atoms to hetercyclic products.[1] The inherent value of these heterocycles lies in the synthetically useful amino alcohol products (**1-6**) generated from N–O bond reduction (Figure 6.1).

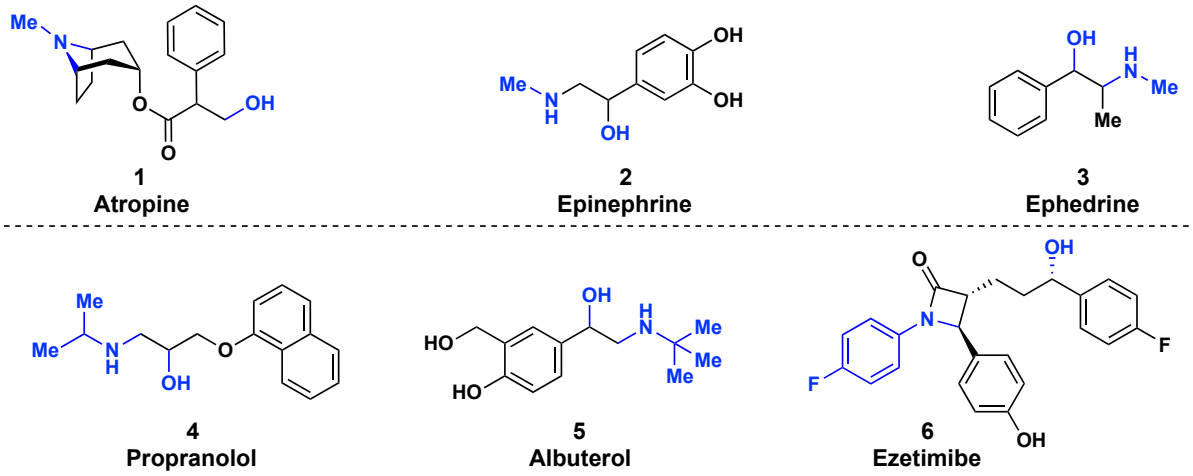


Figure 6.1. Biologically active molecules containing amino alcohols

The 1,4-amino alcohol structural motif **17** is found in many natural products and molecules with interesting biological activity; as a result, the nitroso Diels–Alder reaction has become an important strategy in total synthesis for the efficient incorporation of N and O atoms into target molecules (Figure 6.2c).[2] Despite the significance of the nitroso Diels–Alder reaction, it can only be used to access 1,4-amino alcohols.[3] 1,3-Amino alcohols **13** can be constructed through 1,3-dipolar cycloadditions between olefins **10** and nitrones **11** and

subsequent reduction of the N–O bond in the isoxazolidines **12** (Figure 6.2b).[4] Olefins can also be used to prepare 1,2-amino alcohols **9** through aminohydroxylation with amine derivatives **8** (Figure 6.2a).[5]

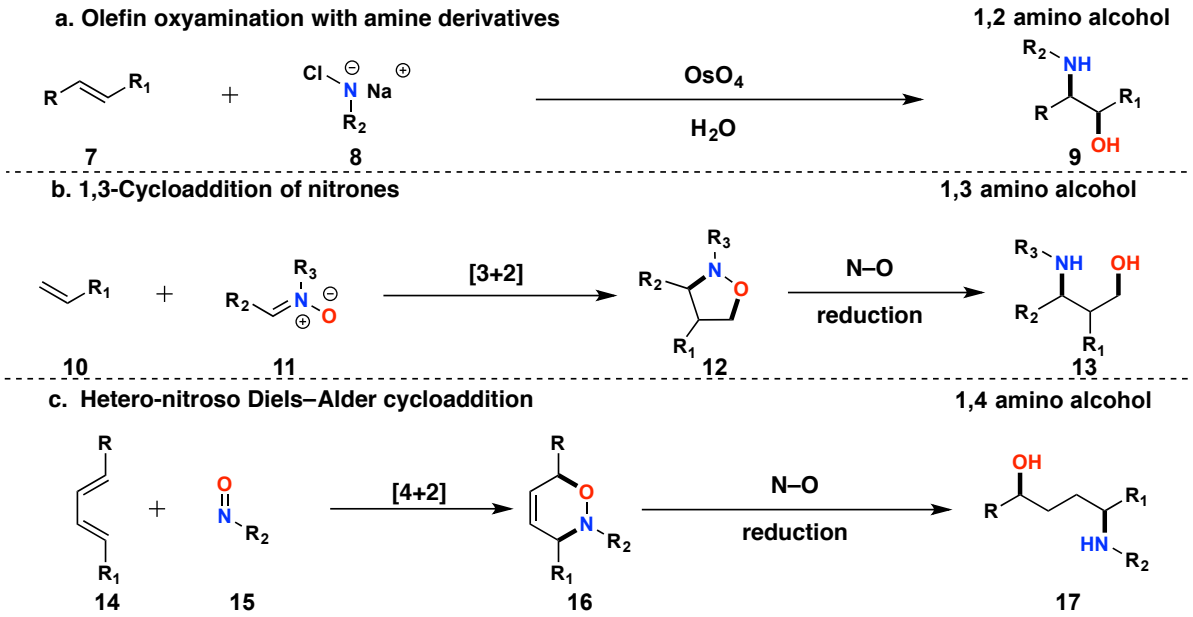


Figure 6.2. Common approaches for N-O transfer

Although N and O-atom transfer reactions have been extensively developed, there is still no general method for the delivery of N and O heteroatoms with spatial control over their connectivities. This limitation exists because the N and O-atom transfer processes depend on additions with olefins/dienes. The development of a new coupling partner could enable installation of N and O atoms with a series of different connectivities. An intramolecular radical coupling reaction with nitroso compounds **15** and bis-alkyl halides **18** would allow for the delivery of N and O atoms with spatial control (Figure 6.3). By using alkyl halides as radical precursors we could synthesize a library of bis-halide compounds with different linker lengths, which would dictate the N and O atom connectivity in the heterocyclic products **22**.

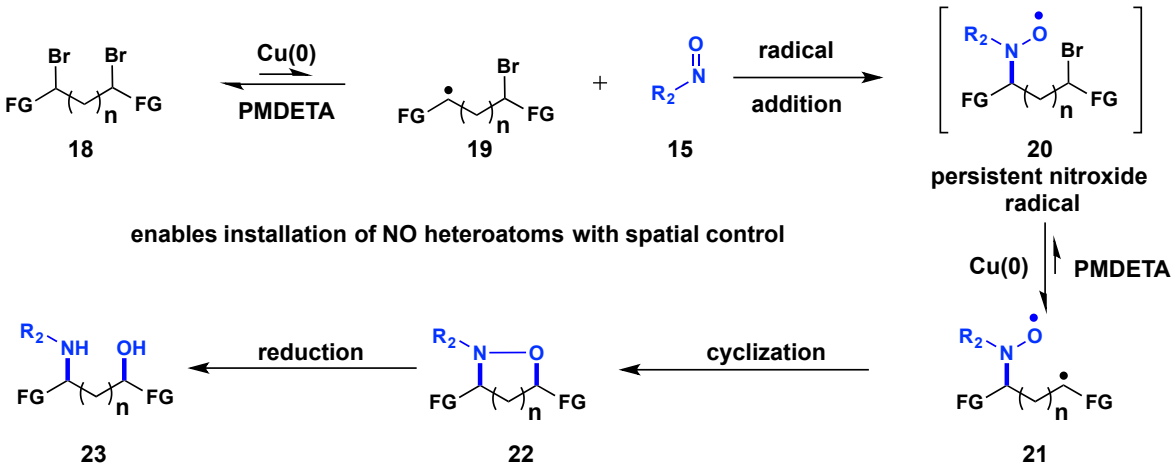


Figure 6.3. An intramolecular radical coupling with nitroso compounds

The concept of an intramolecular radical coupling with nitroso compounds has been developed in polymer chemistry for the synthesis of macrocyclic polymers, whose properties often differ substantially from their linear counterparts and have applications in medicine as drug delivery vehicles. This process, known as intramolecular radical trap assisted atom transfer radical coupling (RTA-ATRC), was first reported by Tillman in 2012 (Figure 6.4).[6] First, the bis-bromide capped telechelic polystyrene precursor **25** was prepared using standard ATRP conditions with a dibrominated initator **24**. Then the RTA-ATRC was performed by adding a solution of **25** and 2-methyl-2-nitrosopropane **27** (MNP) in THF dropwise via syringe pump into a redox active solution of ligand and CuBr to create pseudo-dilute conditions to favor intramolecular radical coupling. Notably, ligands N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA) and tris[2-(dimethylamino)ethyl]amine (Me_6TREN) both furnished the macrocycle **29** in up to 85% yield via GPC analysis. The

addition of a radical trap **27** alters the pathway of the cyclization so that it occurs in a stepwise fashion and simultaneous activation of the chain ends is no longer required. Instead, activation of one chain end generates an alkyl radical **26** capable of reacting with **27** to form a persistent nitroxide radical **28**, which acts as a protecting group for the chain end radical. Under sufficiently dilute conditions **28** subsequently reacts with the radical generated at the other end of the polymer chain to form **29**. As a result, macrocyclizations that were once second order with respect to polymer radicals (traditional ATRC) are now first order, leading to faster cyclization rates and more flexibility in the choice of metal-ligand complex. Using traditional ATRC, cyclization is only seen in the presence of Me_6TREN, but with RTA-ATRC, PMDETA can also be used. Importantly, the same group would later disclose an analogous RTA-ATRC process for the synthesis of cyclic poly(methacrylate) which can't be produced using traditional ATRC.[7]

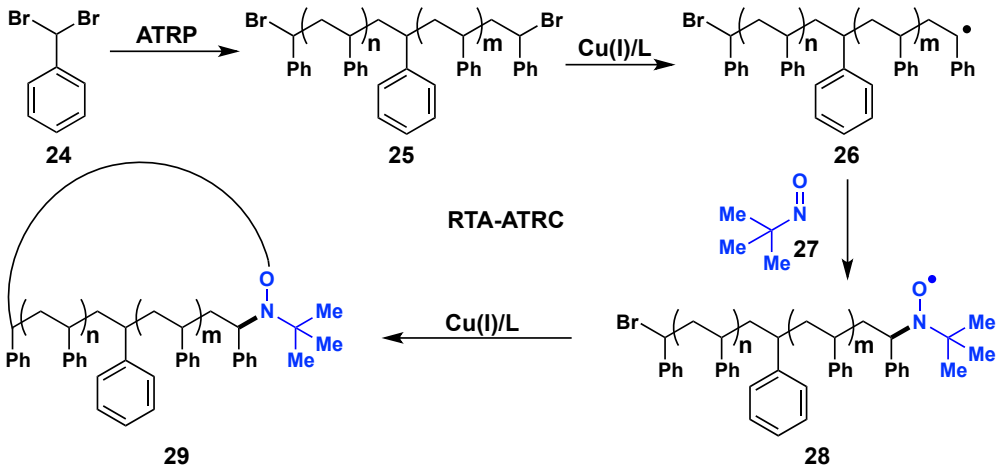


Figure 6.4. Intramolecular radical trap-assisted atom transfer radical coupling

The realization of this process in a small molecule setting would enable the novel synthesis of heterocycles and provide access to the corresponding amino alcohols while maintaining control over the spatial delivery of N and O atoms. Additionally, this approach

would improve the synthetic efficiency of the radical coupling because the nitroso compound would be completely incorporated into the final product (both N and O) and only one equivalent of alkyl halide is required.

6.2 Results

We began by studying the macrocyclization (Figure 6.5) of nitrosobenzene **31** with dibromoester **30**, which was prepared in a single step from ethylene glycol and α-bromoisobutyryl bromide. To our satisfaction, we found that the 10-membered macrocycle **32** could be produced in 64% yield using the approach described previously by Tillman where the **30** and **31** in a THF solution were added dropwise via syringe pump into a redox active solution of PMDETA and CuBr at 40 °C. The N–O bond reduction was unsuccessful with SmI_2 however the addition of HMPA led to complete consumption of the macrocyclic starting material **32**. Unfortunately, instead of isolating the desired 1,8 amino alcohol we isolated the deoxygenated aniline **35**.

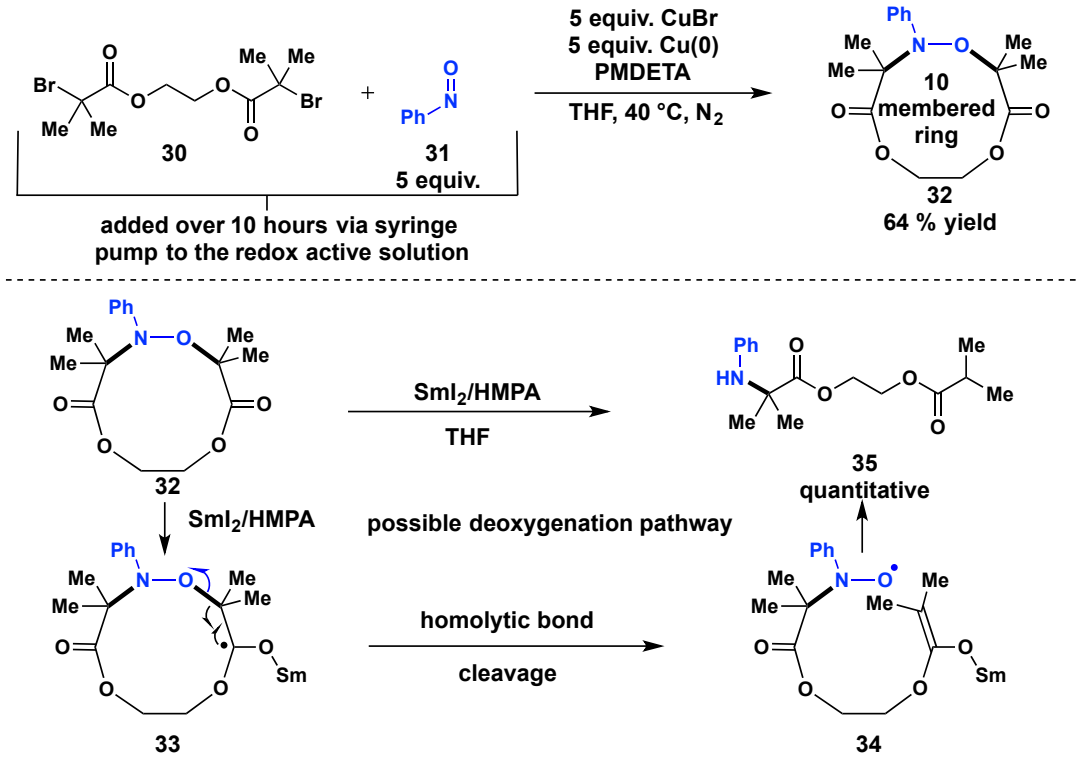


Figure 6.5. Intramolecular radical coupling reaction with nitrosobenzene

This result was interesting because it provided us with mechanistic insight regarding the N–O bond cleaving event and also explained why the alcohol products were never isolated during the synthesis of α-aminocarbonyls (Figure 6.5).[8] We postulate that a SET event from SmI_2 to the ester generates a ketyl radical **33**. Homolytic cleavage of the C–O bond forms the nitroxide-enolate species **34**, which can be further reduced to **35**. This observation prompted us to create to a 1,3 dibromo-1,3 diphenyl-propane intramolecular substrate. The benzyl bromide functionality was selected because Zn/HCl mediated reduction of the N–O alkylated adduct derived from nitrosobenzene and 1-bromoethylbenzene **37** produced both the benzylamine **38** and benzyl alcohol **39** (Figure 6.6).

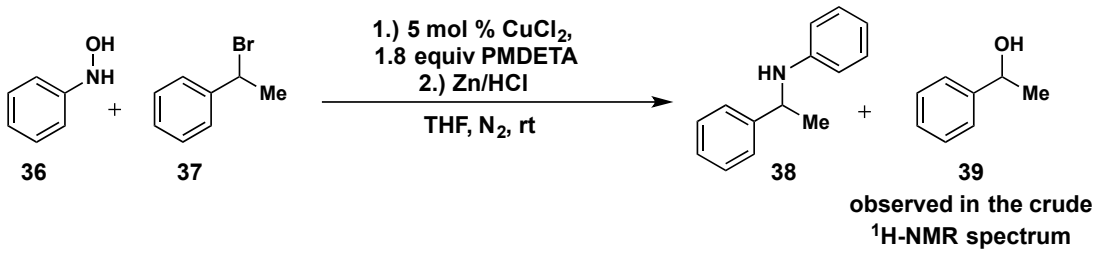


Figure 6.6. The radical coupling reaction with *N*-phenylhydroxylamine and 1-bromoethylbenzene

We postulated the reduction must proceed through a different pathway and that Zn/HCl-mediated reduction of an N–O heterocycle such as **43** would allow us to access the 1,3-amino alcohol **44** (Figure 6.7). The synthesis of **42** was accomplished in two steps from commercially available starting material. First, reduction of dibenzoylmethane **40** with sodium borohydride afforded diol **41**. Subsequent bromination with PBr_3 produced **42**.

To our delight, dropwise syringe pump addition of a solution of **42** with five equivalents of nitrosobenzene **31** in THF to a redox active solution containing five equivalents of both Cu(0) and CuBr in the presence of PMDETA in THF afforded the isoxazolidine **43** in 85% and 2:1 dr. The ensuing Zn/HCl mediated reduction of the N–O bond formed the 1,3 amino alcohol **44** in 75 %. NOESY experiments would show the cis diastereomer was formed predominantly.

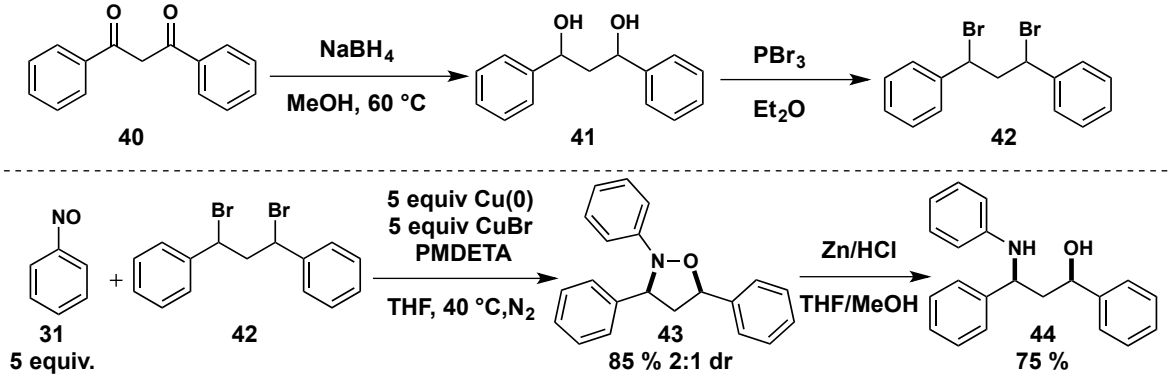
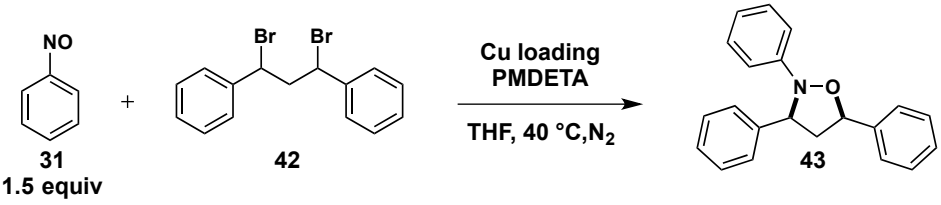


Figure 6.7. 1,3 dibromo-1,3 diphenyl-propane synthesis and subsequent cyclization

Optimization of the reaction conditions revealed that only one copper source was necessary, and that the loading could be significantly reduced (Table 6.1). Five equivalents of CuBr afforded the isoxazolidine **43** in 85% yield (entry 3). Cu(0) wasn't as effective, five equivalents produced **43** in 53% yield (entry 2). Decreasing the CuBr loading to two equivalents promoted cyclization in 83% yield with 1.5 equivalents of nitrosobenzene (entry 5). Further investigation showed that 1.5 equivalents of CuBr led to a decline in yield (entry 4). This is not unexpected; two equivalents of CuBr should be required for the single electron reductions of the two C–Br bonds in the molecule.



Entry	Copper Loading	% Yield
1	5 equiv. Cu(0), 5 equiv. CuBr	82
2	5 equiv. Cu(0)	53
3	5 equiv. CuBr	85
4	1.5 equiv. CuBr	70
5	2 equiv. CuBr	83

Table 6.1. Optimization of Cu loading

PMDETA and Me_6TREN both produced similar results when used as the ligand, so the process was developed using PMDETA because it is inexpensive and readily available. Interestingly, the N–O bond reduction of **43** was found to promoted efficiently by ascorbic acid, a known reducing reagent.[9] However, this strategy proved to be ineffective with larger heterocycles. Direct addition of Zn/HCl to the crude heterocycle was not successful. Instead, removal of copper salts from the crude reaction mixture (extraction with aq. EDTA (0.5 M, pH 7)) was critical to the success of the Zn/HCl promoted reduction. Once completely optimized, the 1,3-amino alcohol could be isolated in 67% over two steps from 1,3 dibromo-1,3 diphenyl-propane and nitrosobenzene (Figure 6.8).

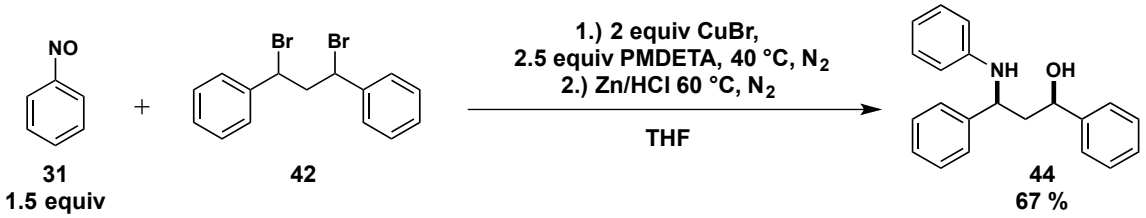


Figure 6.8. Optimized conditions for the synthesis of 1,3 amino alcohols

With optimized conditions in hand, we sought to demonstrate our ability to deliver N and O atoms with spatial control. The requisite dibromo-diphenyl-propanes **47** with various linker lengths could be prepared in three steps from the commercially available linear dicarboxylic acids **45** (Figure 6.9). **45** was first converted to the diacid chloride for a Friedel-Crafts alkylation with benzene. The resulting dibenzyl ketone **46** could be reduced to the diol with sodium borohydride. Bromination with PBr_3 generated **47** in excellent yields.

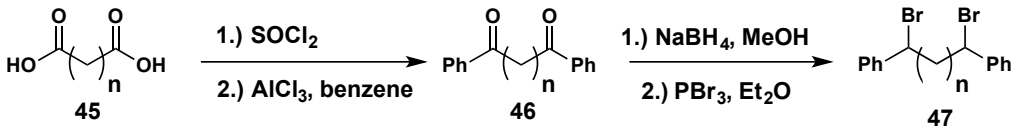


Figure 6.9. Synthesis of bis-bromides with varying linker lengths

Using this radical based approach with nitroso compounds allowed us to generate a range of different sized N–O heterocycles with consistently satisfactory yields. Remarkably, 12-membered macrocycles can be generated through the intramolecular radical coupling reaction with nitrosoarenes, although the yield for cyclization is slightly lower. It should be noted that the sodium naphthalenide promoted reduction proved to be more general than Zn/HCl and afforded the amino alcohols with a variety of connectivities, including up to a 1,10 relationship (Figure 6.10). Such spatial control over N and O atom delivery is unprecedented in organic synthesis.

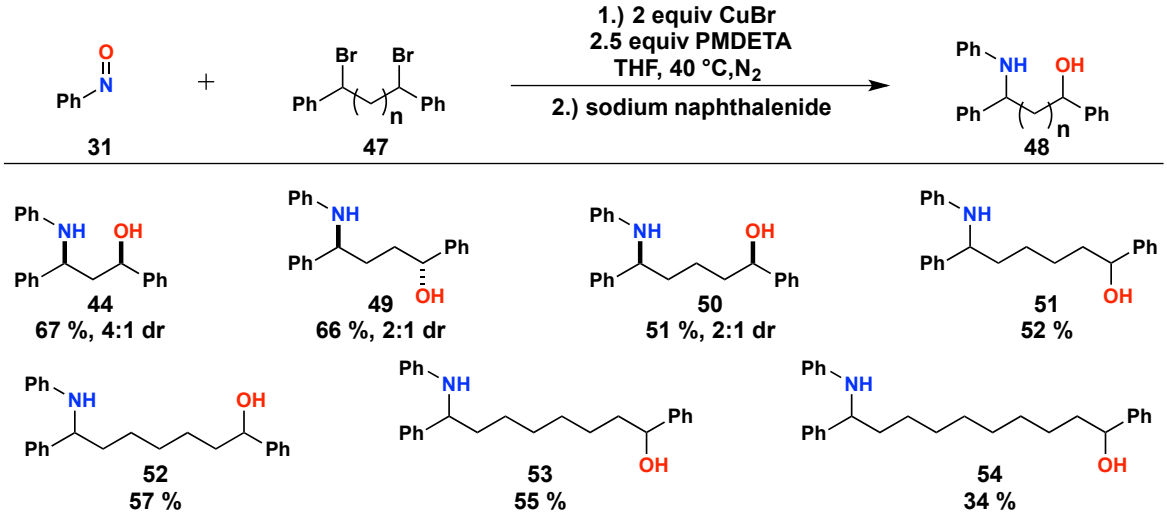


Figure 6.10. N and O atom delivery with spatial control

Disappointingly, attempts at making oxaziridines and 1,2-oxazetidines were unsuccessful (Figure 6.11). α-Bromoester could be brominated to furnish dibromide **53**. Rapid consumption of **53** was observed under standard conditions in the presence of nitrosobenzene. Interestingly, instead of forming desired oxaziridine, nitrone **54** was formed quantitatively. Presumably, radical coupling with nitrosobenene could occur to form an

oxaziridine intermediate, which are known to isomerize to nitrones in the presence of copper. Dibromide **55** was produced through the bromination of stilbene as a precursor in our pursuit of 1,2-oxazetidines. Unfortunately, **55** was rapidly converted back to stilbene **56** quantitatively under standard copper-mediated conditions.

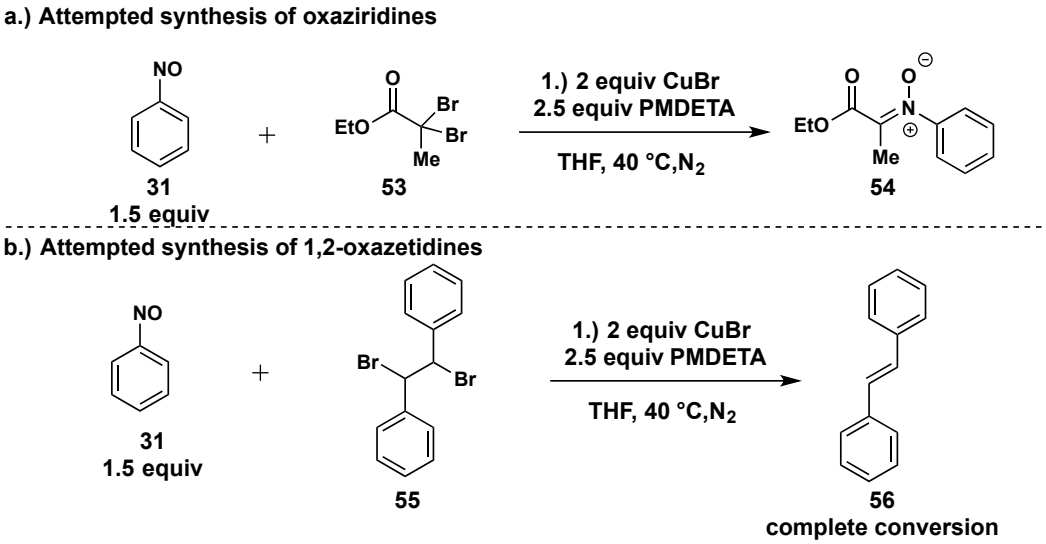


Figure 6.11. Attempts to generate oxaziridines and 1,2-oxazetidines

After highlighting the ability to install N–O bonds with an assortment of connectivities, we pursued the integration of new nitrosoarenes. We found a variety of nitrosoarenes could be efficiently prepared through the oxone-promoted oxidation of the corresponding aniline in a rapidly stirred biphasic mixture of water and dichloromethane.[10] Under standard reaction conditions, both electron-rich and electron-deficient nitrosoarenes could be used for the synthesis of 1,3-amino alcohols (Figure 6.12). Substituents at the *ortho*, *meta* and *para* positions were compatible with the radical coupling reaction (**61**-**66**). There was no discernible correlation between the position/electronics of the substituents, and the diastereselectivity of the cyclization.

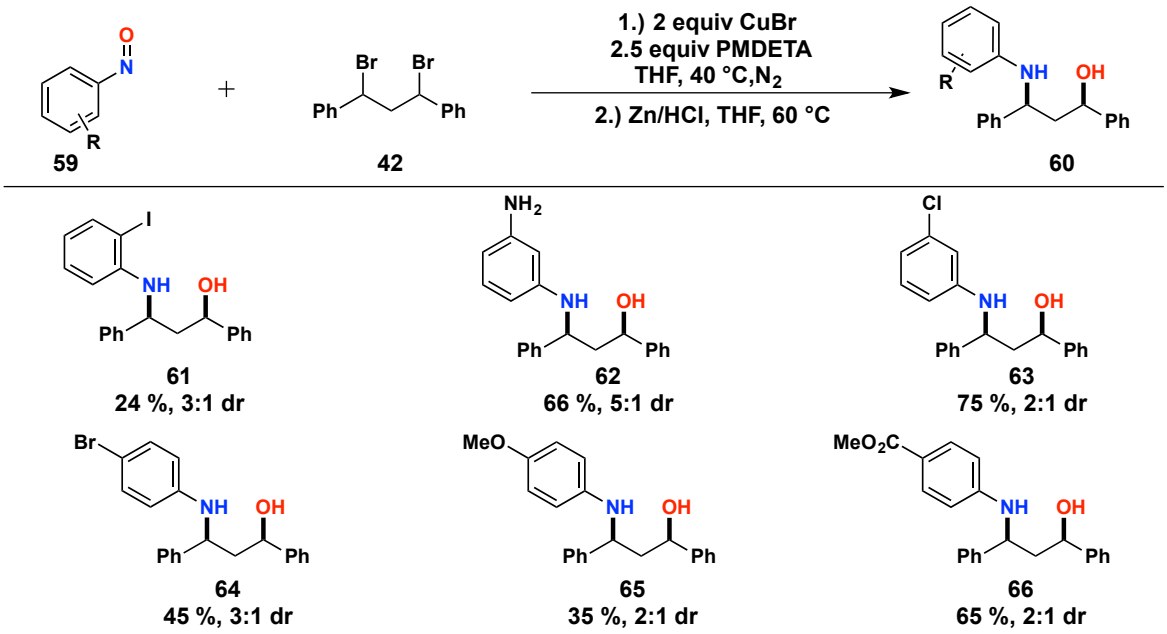


Figure 6.12. Nitrosoarene substrate scope

Finally, substituted 1,3 dibromo-1,3 diphenyl-propanes were well tolerated (Figure 6.13). Substrates with substituted aryl groups could be prepared through a BBr_3 promoted coupling reaction between styrenes and benzaldehydes. Conveniently, the requisite styrene was made through a Wittig reaction with the corresponding benzaldehyde derivative. The positioning of the substituents on the aryl ring had an interesting effect on diastereoselectivity. *Ortho, meta,* and *para* substituted aryl bromides produced products with diastereoselectivities of 2:1, 8:1, and 4:1 respectively. Additionally, bisalkylation of the methylene linker lowered the efficiency of the cyclization; **70** was isolated in 40% yield.

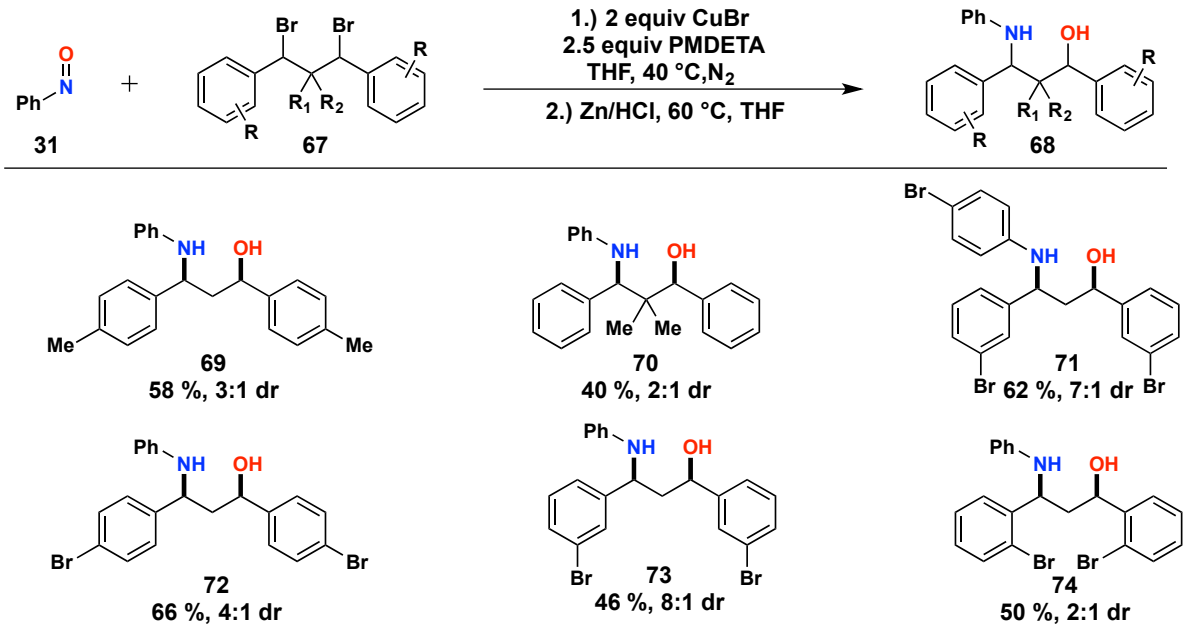


Figure 6.13. Scope with substituted 1,3 dibromo-1,3 diphenyl-propanes

Another aspect of this project currently being explored is the postfunctionalization of the N–O-heterocycles. At elevated temperatures the C–O bond in N–O bis-alkylated adducts is known to undergo thermal homolytic cleavage to generate alkyl and nitroxide radicals, which can recombine, or react in the presence of an added radical trap (Figure 6.14). The equilibrium between the nitroxide radical **21** and the dormant alkoxyamine species **22** has been harnessed for the development of a controlled polymerization process known as nitroxide-mediated radical polymerization (NMP).[11] When heated in the presence of sufficient monomer, such as methacrylate, stepwise propagation controlled by this equilibrium occurs to generate alkoxyamine capped polymer chains with low polydispersities (PDI). Postfunctionalization, typically involving thermal homolytic cleavage of the C–O bond in the presence of a radical trap, can be used to remove the alkoxyamine cap. For example, when heated in the presence of an alkoxyamine dimer, phenylhydrazine can serve

as an H• donor. In 2013, Schmitt and Mahanthappa reported that heating a styrene-methacrylate diblock copolymer capped with an alkoxyamine **22** to 118 °C in toluene with phenylhydrazine reduced the nitroxide radical formed via thermolysis to the hydroxylamine **75**.[12] This process rendered their diblock copolymer more thermally stable. Alternatively, the alkoxyamine chain end functionality can be converted to a ketone. In 2008, Braslau found thermolysis of an alkoxyamine capped polystyrene polymer **22** generated benzylic radical **21** which could add to benzyl enol ethers **76** to install a ketone on the polymer chain end **77**.[13] Additionally, Braslau showed that the analogous process performed with ethylsulfonyl azide as the radical trap formed the azide capped polymer chain **80** which was converted to the triazole **82** through a copper (I) catalyzed cycloaddition with terminal alkyne **81**.[14]

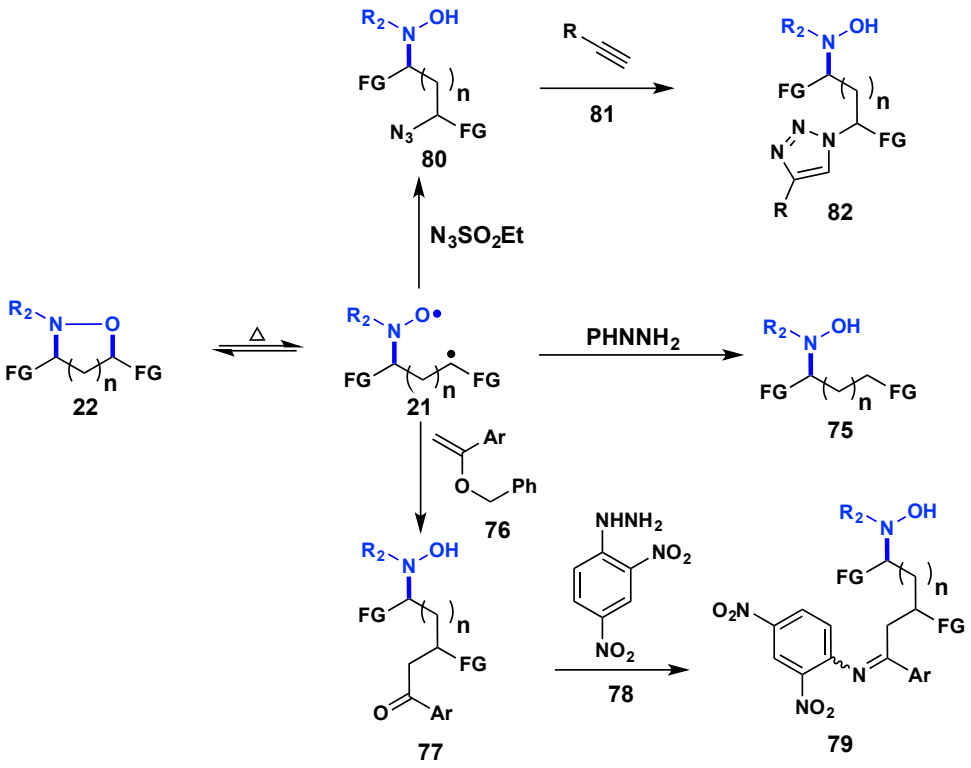


Figure 6.14. Functionalization of alkoxyamines

Finally, to study the regioselectivity of the reaction, unsymmetrical bis-bromoalkane radical precursors were prepared. Initially, 1,3 dibromo-1,3 diphenyl-propanes were prepared through the BBr_3 promoted coupling of styrene and benzaldehyde derivatives.[15] We postulated that differentiating the 1,3 dibromo-1,3 diphenyl-propanes electronically by using different aryl substituents would shift the equilibrium such that one side of the molecule was more biased towards radical formation (Figure 6.15). In such a scenario, regioselective addition of the nitrosoarene should occur. Unfortunately, no selectivity was achieved with **83** and nitrosobenzene. Despite the electronic differences, the equilibrium constants seemed to be too similar to prevent indiscriminate radical addition to nitrosobenzene.

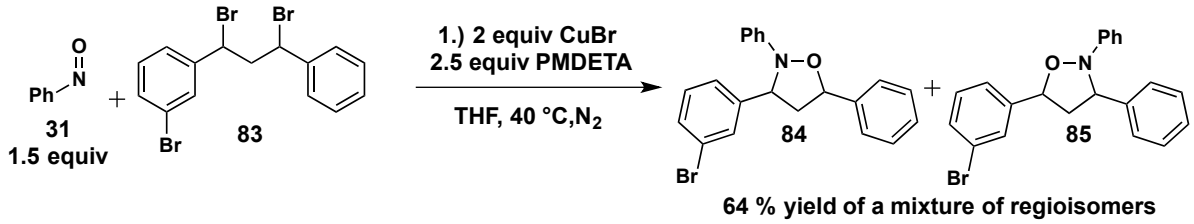


Figure 6.15. Regioselectivity studies with unsymmetrical 1,3 dibromo-1,3 diphenyl-propanes

To fix this problem, we surveyed the ATRP literature to identify radical initiators with distinct equilibrium constants. The decision was made to install an α-bromoester because they are an order of magnitude more active than benzyl bromides (Figure 6.16).[16] The synthesis of **87** was accomplished in a single step through a copper-catalyzed atom transfer radical addition reaction between the di-α-bromoester **55** and styrene **86** (Figure 6.16a). To our satisfaction, the isoxazolidinones **88** and **89** from the copper-mediated radical addition with nitrosobenzene was isolated in 50% yield as a 7 to 1 mixture of regioisomers (Figure 6.16b). Encouraged by the increased regioselectivity, we incorporated an α-

bromonitrile because they are more active radical initiators than α-bromoesters. The substrate **90** was prepared in an analogous atom transfer radical addition reaction between the di-α-bromonitrile and styrene. Currently, the regioselective outcome of the copper-mediated reaction between **90** and nitrosobenzene is being investigated (Figure 6.16c).

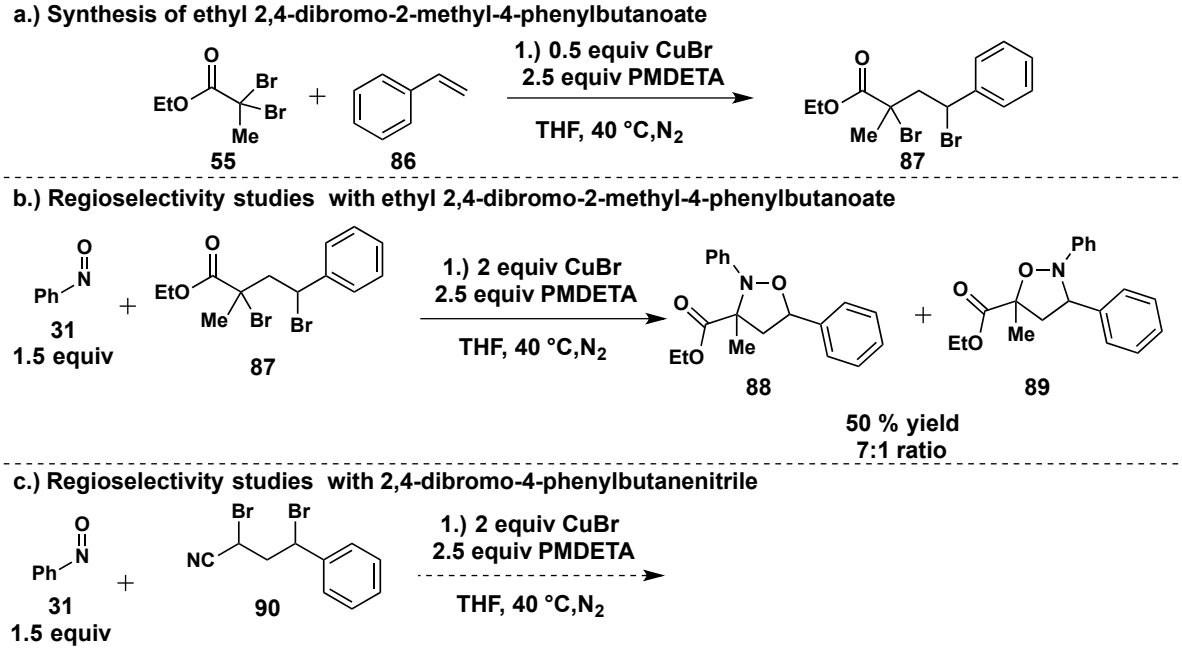


Figure 6.16. Regioselectivity studies in the intramolecular radical coupling with nitrosobenzene

6.3 Conclusion

In conclusion we have developed a copper-mediated intramolecular radical coupling reaction with dibromo diaryl alkanes and nitroso compounds for the synthesis of amino alcohols. This represents the first time a process has been established that allows for the simultaneous installation of N and O atoms with spatial control. Numerous heterocycles, ranging in size from 5 to 12 membered rings were generated. There heterocycles could be reduced to the corresponding amino alcohols with sodium naphthalenide. A variety of

different nitrosoarenes could be utilized with the protocol. Currently the regioselectivity of the method is being studied.

6.4 References

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Chapter 7: Coupling of Redox Active Esters with Nitrones

7.1 Introduction

Alkyl halides are valuable building blocks for the synthesis of amines (Figure 7.1). Classically, they serve as electrophiles in substitution reactions with nitrogen nucleophiles **2** (Figure 7.1a).[1] Transition metal catalysis has emerged as an important method to activate less reactive secondary and tertiary alkyl halides **4** for nucleophilic substitutions with nitrogen **5** (Figure 7.1b).[2] Alternatively, alkyl halides **1** can be converted to highly reactive organometallic nucleophiles for addition to ketimines **10** (Figure 7.1c).[3] Recently, alkyl halides **12** have been developed as radical precursors for SET reactions with electrophilic nitrogen sources such as nitroso compounds **13** (Figure 7.1d).[4]

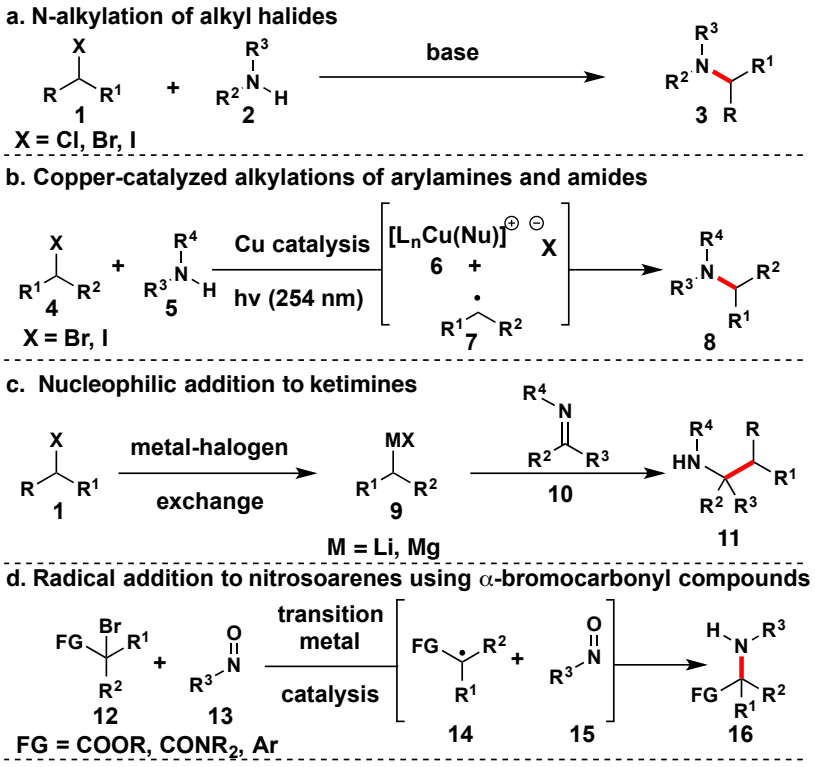


Figure 7.1. Amine synthesis with alkyl halides

Despite the versatility of these approaches for amine synthesis, several drawbacks associated with the use of alkyl halides include their limited availability, potential instability and toxicity. In this context, carboxylic acids represent an excellent alternative, as they are ubiquitous in chemistry, nontoxic, stable, inexpensive and an easily manipulated functional group. As a result, they are readily available from many commercial vendors. For example, Sigma Aldrich sells > 1600 carboxylic acids, not including their derivatives. Importantly, carboxylic acids are valuable alkyl radical precursors.

Alkyl radical formation from carboxylic acids was first reported by Kolbe in 1848 (Figure 7.2a).[5] The Kolbe reaction refers to the dimerization of carbon centered radicals **20** generated through the anodic oxidative decarboxylation of alkyl carboxylic acids **17**. In 1861 Hunsdiecker reported that silver carboxylate salts **22** could be treated with bromine to form alkyl bromides **24** (Figure 7.2b).[6] This process also proceeds through an oxidative decarboxylation to form an alkyl radical **20** which combines with bromine.

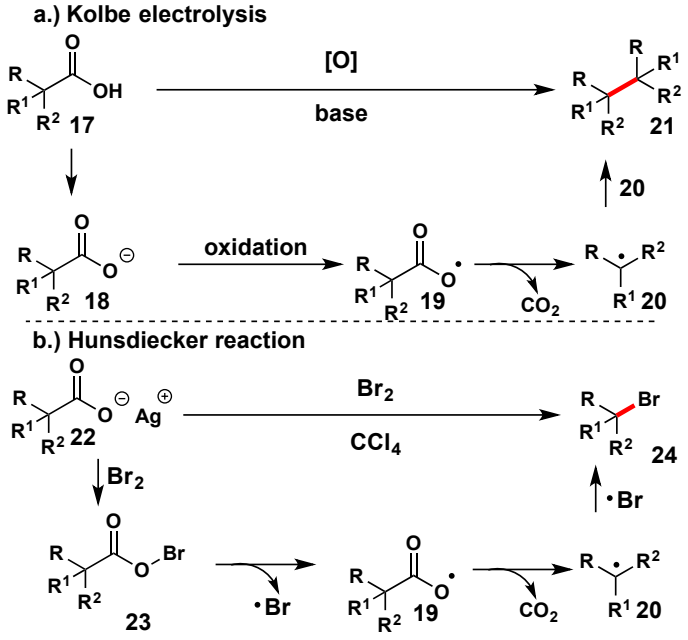


Figure 7.2. Oxidative decarboxylations of carboxylic acids

Since these initial discoveries, a number of different methods utilizing oxidative decarboxylations of carboxylic acids have been developed as synthetic tools. For example, in 1971 Minisci reported a regioselective alkylation of heteroaromatic bases **25** with carboxylic acids involving radical addition (Figure 7.3).[7] The alkyl radicals were generated through a silver-catalyzed oxidative decarboxylation of carboxylic acids **17** with peroxydisulphate. The heteroaromatic radical acceptors included quinolone, 2-methylquinoline, isoquinoline, pyridine, 4-cyano-pyridine and acridine.

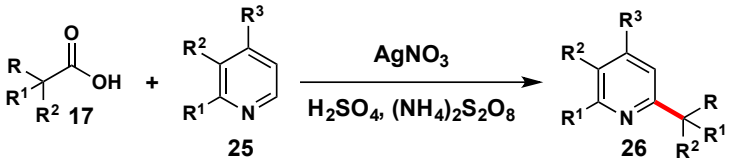


Figure 7.3. The Minisci reaction

More recently, numerous groups have utilized photoredox catalysis for the oxidative decarboxylation of carboxylic acids in the presence of different radical trapping agents. For example, in 2014 MacMillan used an iridium photocatalyst for the oxidative extrusion of CO_2 from carboxylic acids **17** to form alkyl radicals **20** for conjugate additions with electron deficient alkenes **27** (Figure 7.4).[8] This process is effective with secondary and tertiary alkyl carboxylic acids as well as many Boc- and Cbz-protected amino acids. It is proposed that the iridium complex accepts photons from visible light and is promoted to a strongly oxidizing excited state ($E_{1/2}^{*III/II} = +1.21$ V vs saturated calomel electrode (SCE) in acetonitrile). Deprotonation of **17**, followed by SET oxidation of the resulting carboxylate would immediately expel CO_2 and **20**. The highly reactive radical species would undergo conjugate addition with **27** for C–C bond formation.

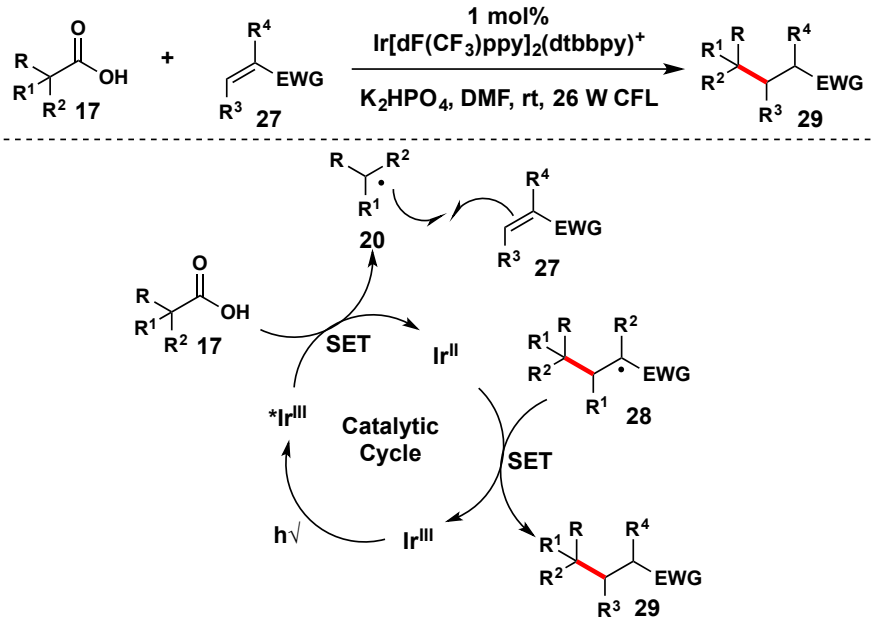


Figure 7.4. Oxidative decarboxylation of carboxylic acids

Additionally, Nicewicz used an acridinium based organophotocatalyst for the hydrodecarboxylation of carboxylic acids **17** and malonic acid derivatives (Figure 7.5a).[9] Primary, secondary, and tertiary alkyl carboxylic acids participate in the oxidative decarboxylation process. The mechanism is similar to MacMillan's in that the organophotocatalyst in its excited state is a strongly oxidizing species responsible for electron abstraction from the carboxylate which triggers the explusion of CO_2. Hydrogen atom abstraction from thiophenol, which is generated in situ from diphenyl disulfide, forms the reduced product **30**. In 2016, using the same organophotocatalyst, Tunge reported the aminodecarboxylation of unactivated alkyl carboxylic acids **17** (Figure 7.5b).[10] The carbon radical intermediates were trapped with electrophilic diazo compounds such as DIAD **32** for C–N bond formation. Although important, oxidative decarboxylations are limited because the strongly oxidizing conditions can lower the functional group compatibility of the transformation in the presence of redox active functionality such as aldehydes or alcohols.

The development of milder reaction conditions for the expulsion of CO_2 to form reactive radical intermediates is a worthwhile endeavor.

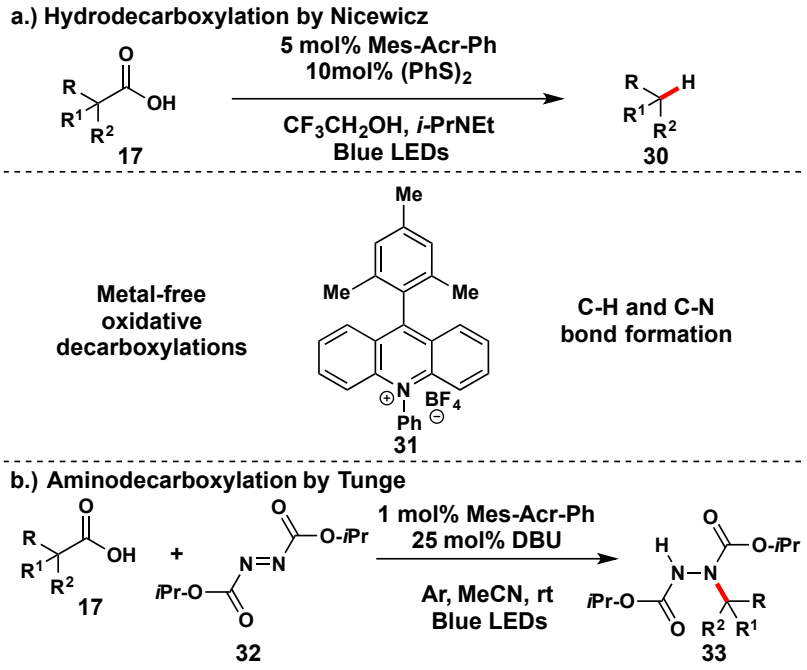


Figure 7.5. Oxidative decarboxylations with acridinium photocatalysts

In 1983, Barton and co-workers showed that esters derived from carboxylic acids and *N*-hydroxypyridine-2-thione underwent hydrodecarboxylation in the presence of tributyltin hydride, heat, and light (Figure 7.6b).[11] Compatibility was observed with primary, secondary and tertiary alkyl carboxylic acids as well as ester, ketone and olefin functionalities. The esters **35** were easily prepared though a DCC coupling reaction with the carboxylic acid **17** and the sodium salt of *N*-hydroxypyridine-2-thione **34**, all of which are commercially available (Figure 7.6a). The esters are believed to be reduced in a radical chain reaction with tributyltin hydride to form the alkyl radical **20**, CO_2, and the organotin species **36** (Figure 7.6b). Hydrogen atom abstraction from tributyltin hydride forms the product **30**. This process, known now as the Barton decarboxylation, helped spawn a new era of radical chemistry. Eventually the process would be developed for C–C bond formation (**38**) through

radical addition to Michael acceptors and electron deficient heteroaromatic bases (Figure 7.6c).[12] Barton also demonstrated his esters could be applied to C–N bond formation utilizing radical additions to electrophilic diazerenes for ketimine synthesis **41**.[13] Additionally, reactions involving C−Cl, C−O, C−I, C−S, C−Se, and C−Br (**37-40**) bond formation via the decarboxylation of Barton esters have been developed.[14] Despite their synthetic utility, Barton esters are notoriously difficult to work with because they decompose readily in the presence of light and/or heat and are moisture sensitive.

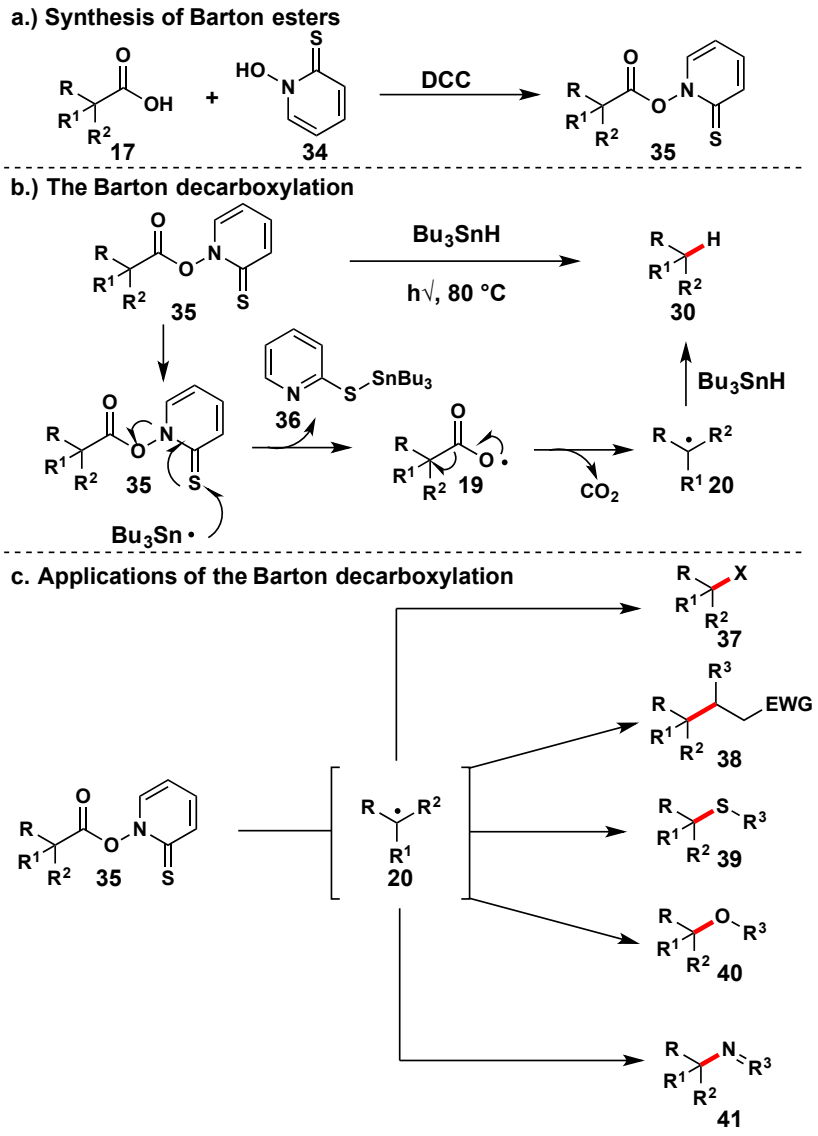


Figure 7.6. The Barton decarboxylation

Motivated by the need for more stable carboxylic acid-derived radical precursors, Okada and co-workers developed a new class of redox-active esters in 1988.[15] The *N*-acyloxyphthalimides **43** are derived from alkyl carboxylic acids **17** through a DCC coupling reaction with *N*-hydroxyphthalimide **42** (Figure 7.7a). These carboxylic acid derivatives are benchtop stable and not moisture sensitive. Initially, *N*-acyloxyphthalimides **43** were developed for a hydrodecarboxylation using organophotoredox catalysis with 1,6-

bis(dimethylamino)-pyrene (BDMAP) as the photosensitizer and *t*-butylthiol as a source of H• (Figure 7.7b). Unlike the decarboxylation of carboxylic acids, the same process with *N*-acyloxyphthalimides is not an oxidation; instead, the redox active esters are reduced before the extrusion of CO_2 occurs. In the presence of light, BDMAP is promoted to its excited singlet state and transfers an electron to the ester to form a radical anion. Fragmentation via homolytic cleavage of the N–O bond produces the carboxy radical **19**. Then decarboxylation followed by hydrogen atom abstraction from *t*-butyl thiol affords the hydrocarbon **30**. This method was also compatible with primary, secondary, and tertiary acids and it was run in aqueous tetrahydrofuran or isopropanol solutions under a 100-W high-pressure mercury lamp and argon. This decarboxylation is efficient, general and widely applicable. The hydrocarbon products are isolated in excellent yields and can be prepared on gram scale. In 1991, the same group developed a similar process that utilized photoredox catalysis, this time with $Ru(bpy)_3Cl_2$, for the reductive decarboxylative alkyl radical conjugate addition to electron-deficient alkenes **27** (Figure 7.7b).[16] Okada developed this process because he recognized that when Barton esters are used for conjugate addition the 2-pyridylthio group is always introduced to the α-position of the electron deficient group due to the high affinity of alkyl radicals for the sulfur atom in the thiocarbonyl; this requires additional steps to remove. Radical conjugate additions utilizing Okada's esters are more efficient because the group transfer event doesn't occur.

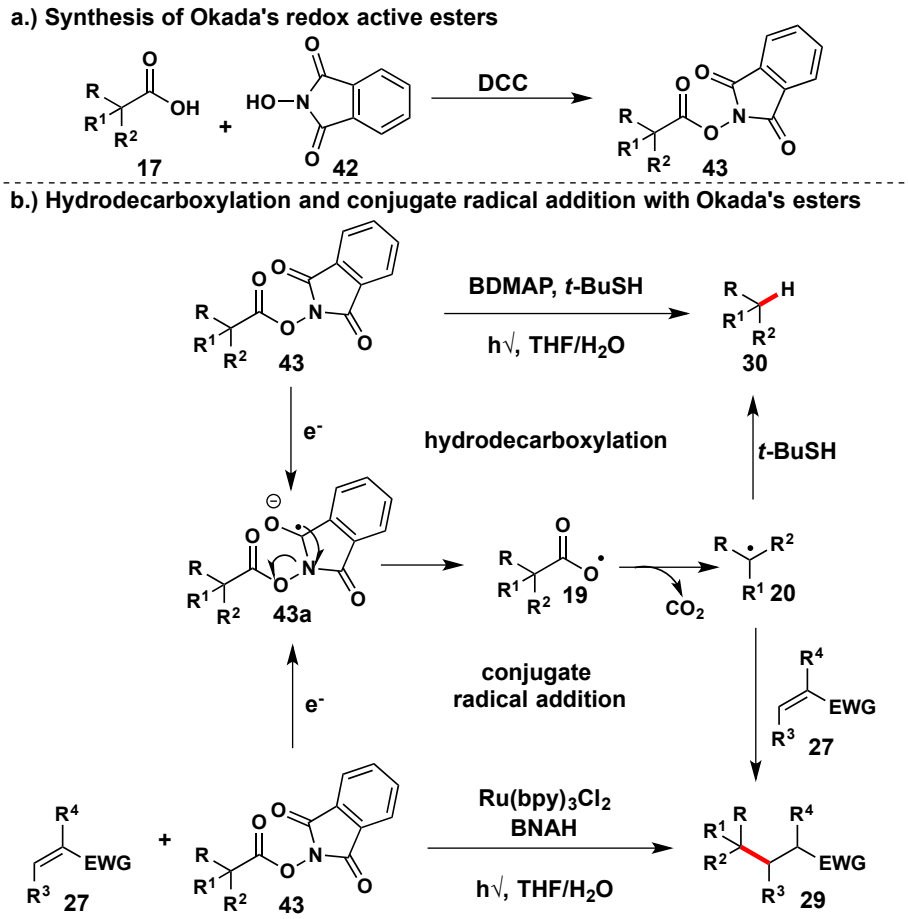


Figure 7.7. *N*-Acyloxyphthalimides as radical precursors

The inherent value of Okada's method stems from its ability to efficiently unite complex carbon fragments. For example, conjugate addition of tertiary radicals **20** can be used to construct new quaternary carbon stereocenters **29**. Overman recognized the synthetic utility of this process for quickly increasing structural complexity and applied it in several total synthesis projects to generate new quaternary carbon stereocenters.[17] Furthermore, Overman recently published a research article exploring Okada's method for generating tertiary radicals and their subsequent conjugate additions for concomitant formation of quaternary carbons (Figure 7.8).[18] The reaction was developed with 1 mol % $Ru(bpy)_3(PF_6)_2$ as the photoredox catalyst and the scope was explored with four tertiary *N*-

acyloxyphthalimides (**50-53**) and numerous alkene radical acceptors (**44-49**). In addition to conjugate radical additions, reductive couplings with electron-deficient alkenes and radical substitution reactions with allylic/vinylic bromides/chlorides were explored.

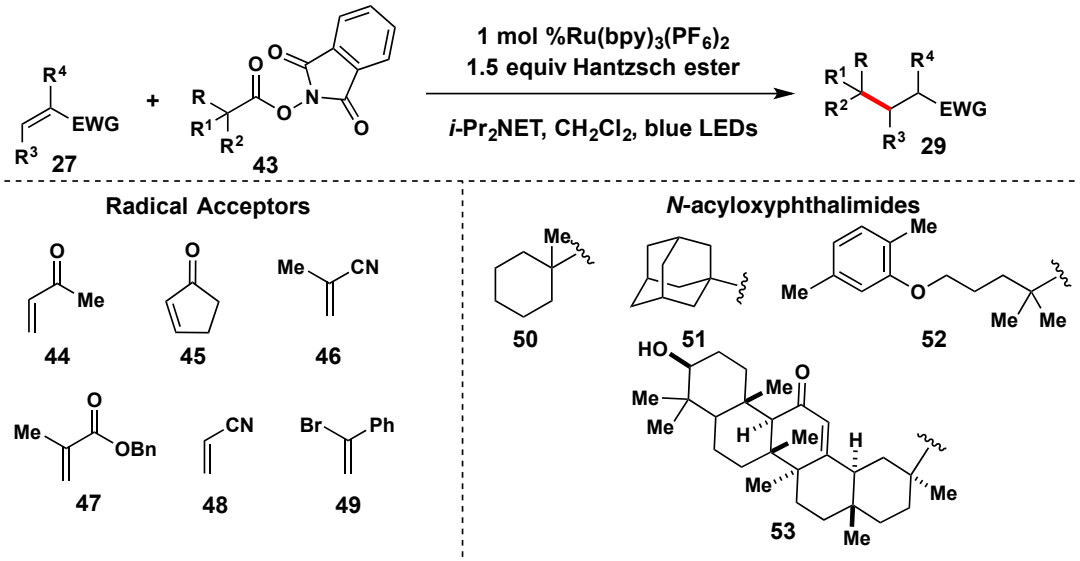


Figure 7.8. Overman's work with *N*-Acyloxyphthalimides

In 2016 Weix and Baran would simultaneously, independently discover that nickel complexes could be used to activate Okada's esters for radical formation.[19] This would lead to the development of numerous transition metal-catalyzed SET based cross coupling reactions for C–C bond formation with Okada's redox active esters replacing alkyl halides. The precedent was based off the observation that aryl-nickel complexes **55** reacted with Barton esters **54** without light at room temperature to form **56** in 54% yield (Figure 7.9a). This discovery led Baran to believe that **55** acts as a single electron reducing agent to the pyridothione functionality (Figure 7.9e). The ensuing radical anion **68** fragments to expel the acyloxy radical which upon decarboxylation forms **20**, recombination with an aryl-Ni complex eventually leads to **71** (Figure 7.9e). Barton esters result in the formation of side products arising from alkyl radical addition to sulfur, and they are difficult to handle and

impractical for scale up due to their inherent instability. This led Baran to screen other redox active esters; Okada's ester proved to be the right fit. The C–C cross coupling proved to be compatible with a variety of secondary alkyl carboxylic acids and a range of aryl and heteroaryl zinc reagents (Figure 7.9b). Even alkyl zinc reagents could be utilized.[20] Again, the key step is the single electron reduction of the ester by the aryl-nickel complex for alkyl radical formation. Baran would go on to display the versatility of this approach; for example, it was discovered that the highly reactive aryl zinc reagents could be replaced with arylboronic acids **63** as the coupling partner for the *N*-acyloxyphthalimides **64** (Figure 7.9c).[21] As a result, the mildness and therefore functional group compatibility of the method increased. Despite being an inexpensive ($9.50/mol), effective catalyst for decarboxylative aryl-alkyl cross coupling reactions, $NiCl_2 \bullet 6H_2O$ was difficult to work with. Extensive optimization was required to identify optimized conditions, and the sensitivity of the catalyst was such that small changes in conditions had dramatic, adverse effects on reaction outcome. A Lewis acid screen revealed that $Fe(acac)_3$ represented a practical alternative to nickel catalysis (Figure 7.9c).[22] In addition to being a much more robust catalyst, $Fe(acac)_3$ accelerated reaction rates, lowered the requisite catalyst loading, and induced reactivity with tertiary carboxylic acids **64**. Finally, Baran repeated with nickel catalysis the transformations Okada originally developed with his redox active esters (Figure 7.9d). The nickel-catalyzed Barton decarboxylation (hydrodecarboxylation) and Giese reactions (conjugate radical addition to a Michael acceptor) with Okada's esters were developed.[23] In the hydrodecarboxylation, phenylsilane was used as an H• source in the production of tertiary, secondary and primary hydrocarbons (**30)**. The nickel-catalyzed Geise reaction was

compatible with a variety of olefins (**27)** with different electron withdrawing groups and could also be run on gram scale.

Weix's concurrent report of a nickel catalyzed decarboxylative cross electrophile coupling of Okada's esters **58** with aryl iodides **60** in the presence of stoichiometric zinc is very similar in concept (Figure 7.9b). These conditions were originally developed for a C–C cross coupling of arylhalides with alkyl bromides.[24] Weix discovered replacement of the alkyl bromides with Okada's esters **64** successfully formed the desired cross-coupled products **59** and required little adjustment of the established reaction conditions. Importantly the redox esters can be used to form products inaccessible with alkyl halides. Again, functional group compatibility is high. Unlike Baran's initial work, methyl, primary and secondary radicals were compatible in the coupling with **60**. Although its exact purpose in the transformation is unknown, zinc is required, along with nickel for activation of the redox esters. Although some uncertainty still remains, the current hypothesis is that zinc helps initiate radical formation through the reduction of the aryl-nickel complex to a nickel (I) species, which serves as a reductant for the redox active esters. The majority of the recent developments with Okada's redox active esters in organic synthesis have focused on the design of new aryl-alkyl C–C cross coupling processes where the alkyl halide is replaced with a carboxylic acid derivative. Synthetic methods for amine formation utilizing Okada's redox active esters do not not exist.

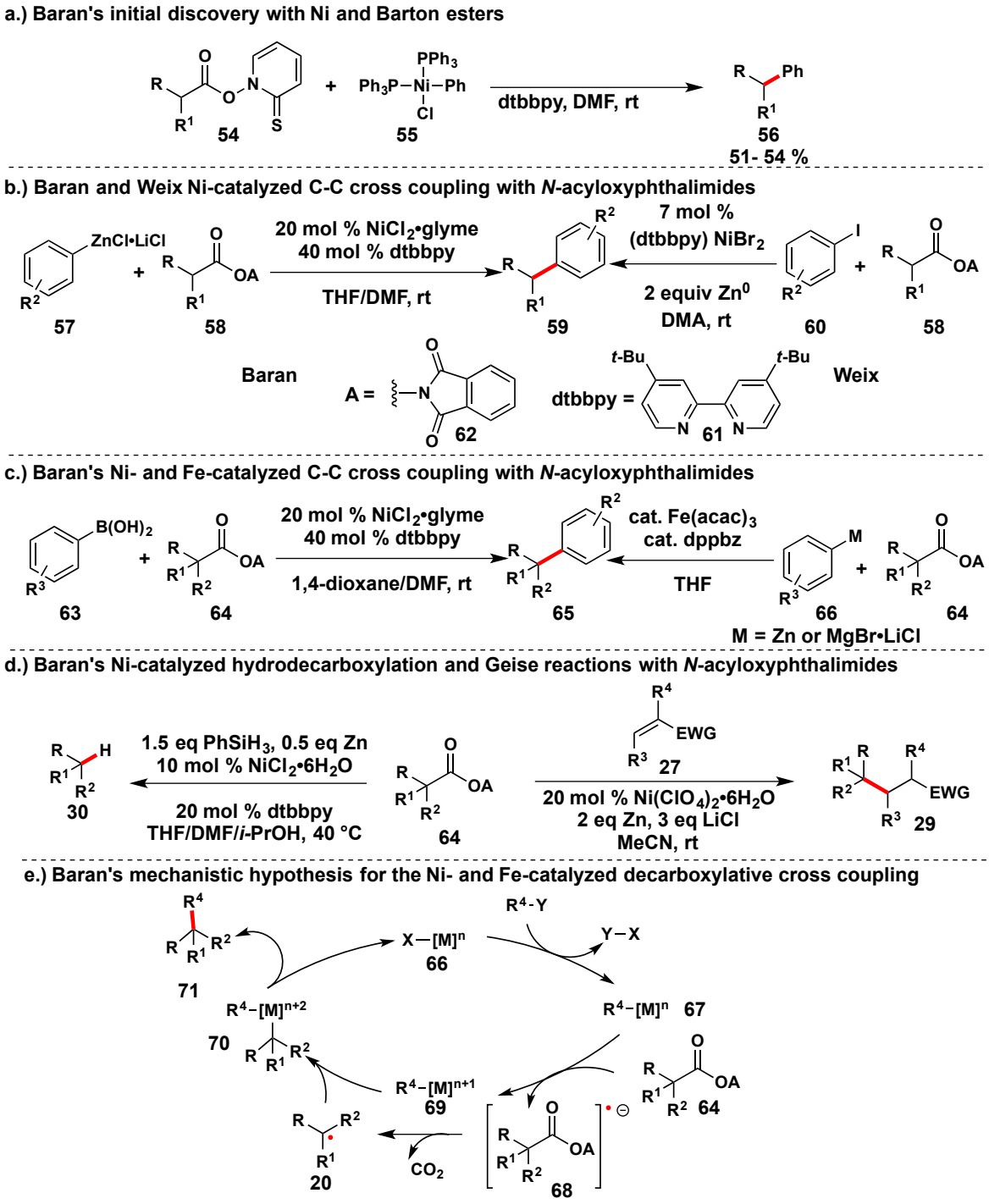


Figure 7.9. Ni- and Fe-catalyzed decarboxylative cross couplings with *N*-acyloxyphthalimides

Amines can be prepared in several different ways from carboxylic acids using conventional two electron pathways (Figure 7.10). The Schmidt reaction is a classic example

of the direct conversion of a carboxylic acid to an amine (Figure 7.10a).[25] In this process, an azide reacts with a carboxylic acid **17** to displace water to form acyl azide **72**. R group migration with concomitant liberation of N_2 generates isocyanate **73**. Hydrolysis of **73** expels CO_2 to afford the primary amine **74**. The Schmidt reaction is an important strategy for the synthesis of primary amines, however, azides represent a safety hazard because they are potentially explosive and extremely toxic. Another prominent approach is the reductive N-alkylation of amine derivatives with carboxylic acids (Figure 7.10b, 10c, 10d). This strategy was discovered in 1974 by Gribble and co-workers; while attempting to develop a general, efficient procedure for the reduction of indoles to the corresponding indoline, they found the simultaneous reduction and alkylation of **75** occurred upon treatment with sodium borohydride ($NaBH_4$) in neat acetic acid to form alkylated indoline **76** (Figure 7.10b).[26] Since this initial discovery, numerous related transformations have been developed. For example, in 2014 Beller and co-workers disclosed a platinum-catalyzed direct reductive *N*-alkylation of amines **77-78** with carboxylic acids **17** (Figure 7.10c).[27] This C–N bond forming protocol proceeds under mild reaction conditions and utilizes Karstedt's catalyst and silanes as the hydride source for the synthesis of a range of secondary and tertiary alkylated amines **79-81**. Recently, Fu and co-workers developed a greener, more practical method by replacing the platinum-based Karstedt's catalyst with a boron catalyst (Figure 7.10d).[28] The synthetic utility of the process was highlighted through the synthesis of three pharmaceuticals using a one pot approach starting from commercially available feedstock carboxylic acids. Until very recently, SET processes for the synthesis of amines from carboxylic acids did not exist.

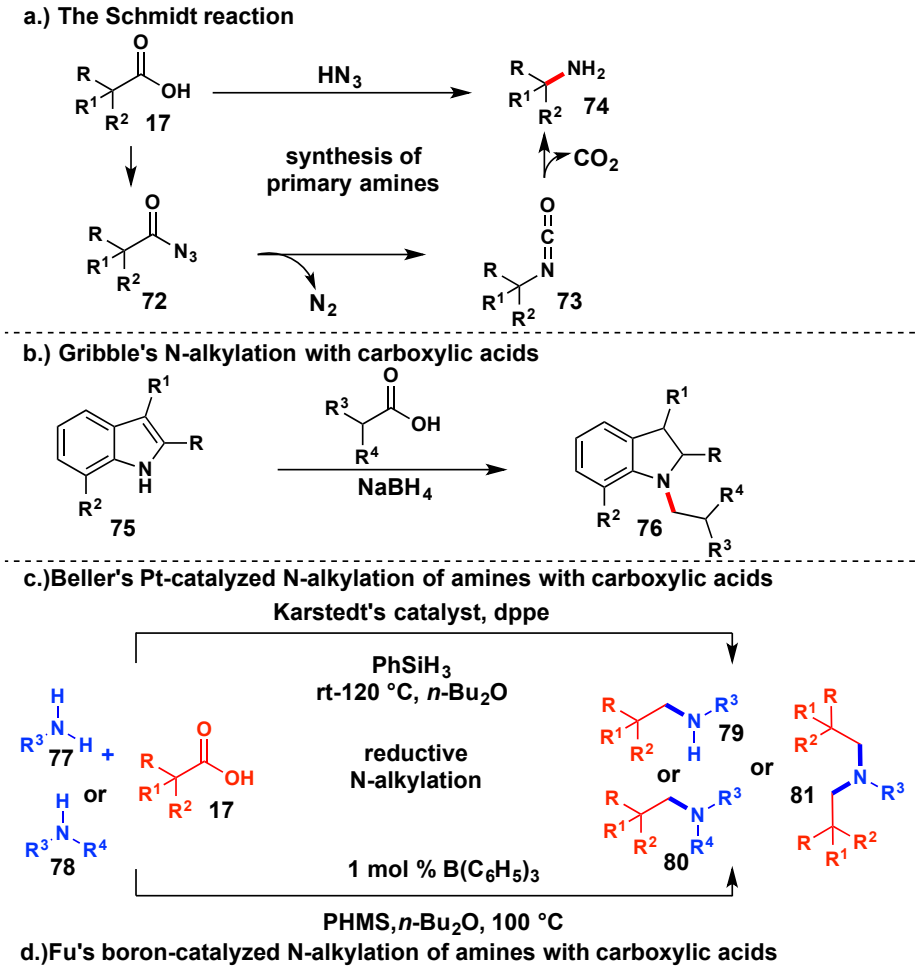


Figure 7.10. Synthesis of amines from carboxylic acids

Alkyl halides are ideal radical precursors for SET reactions with nitroso compounds because the requisite reducing conditions for generation of the SOMO species are sufficiently mild that degradation of the redox sensitive nitroso species does not occur. This exceptional compatibility is part of the reason the projects discussed in the previous three chapters have involved the coupling of radicals derived from alkyl bromides with nitroso compounds. Despite this synergy, alkyl bromides can be unstable, toxic and not readily available. We had been thinking about utilizing alternative radical precursors, such as carboxylic acid derivatives for some time, but our interest was piqued with Baran's report in 2016 that iron

catalysis could be utilized for the single electron reduction of Okada's redox active esters to generate alkyl radicals (Figure 7.9c). This was intriguing because iron is known to be compatible with nitroso chemistry; Baran had recently developed an iron-catalyzed hydroamination that involved radical addition to arylnitrosos[4b] and $FeCl_3$ is used to oxidize *N*-arylhydroxylamines to nitrosoarenes.[29] At this point we began thinking about the development of an iron-catalyzed coupling reaction between Okada's redox active esters and nitrosoarenes for the synthesis of hindered anilines. However, we were concerned because the aryl-Fe complex **55** (Figure 7.9e) seemed to be responsible for the single electron reduction required for radical formation and because we weren't using aryl zinc reagents, we would form no such complex. Around this time we came across a fascinating paper by Hu and co-workers regarding the synthesis of secondary anilines through the iron-catalyzed reductive coupling of nitroarenes with alkyl halides (Figure 7.11).[30] Treatment of the nitroarene **82** with three equivalents of alkyl halide **83**, three equivalents of zinc, and two equivalents of trimethylsilylchloride (TMSCl) using 20 mol% $FeCl_2 \bullet 4H_2O$ in *N*-methyl-2-pyrrolidone (NMP) at 90 °C for 16 h generated a broad range of secondary alkylated anilines **88** in moderate to high yields. The proposed reaction mechanism was intriguing. Zinc was believed to reduce both **82** to the corresponding nitrosoarene **84** and Fe(II) to Fe(I). The Fe(I) reduces **83** to form an alkyl radical **85** which undergoes addition with nitroso to form the nitroxide radical **86**. **86** is trapped with **85** and the resulting N–O alkylated adduct **87** is reduced by zinc in the presence of the oxophilic Lewis acid TMSCl to afford **88**.

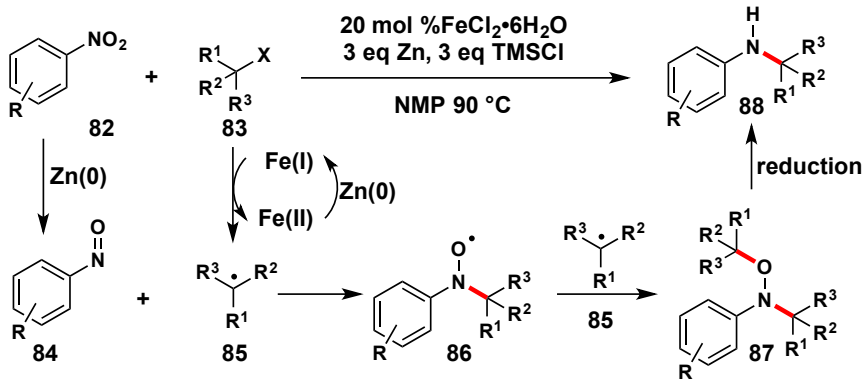


Figure 7.11. Hu's Fe-catalyzed reductive coupling of nitroarenes with alkyl halides

7.2 Preliminary Results

Citing the work of Weix and Baran, we decided to run a reductive coupling reaction using Hu's conditions with nitrobenzene **90** but replaced the alkyl halide with *N*-acyloxyphthalimide **89** (Figure 7.12). We found Okada's esters could easily be prepared through the coupling of the carboxylic acid with *N*-hydroxyphthalimide with EDCI. This reaction worked for the synthesis of primary, secondary and tertiary esters, which could be purified using column chromatography. Notably, some primary esters were prone to hydrolysis on silica. Unfortunately, no alkylated secondary aniline **91** or N–O adduct was isolated in the reaction with nitrobenzene. However, replacing nitrobenzene with nitrosobenzene **92** led to formation of the **91** in 20% yield.

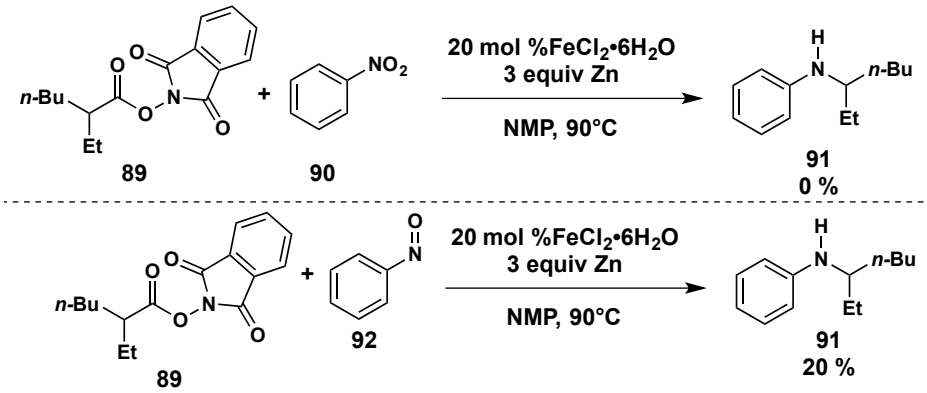
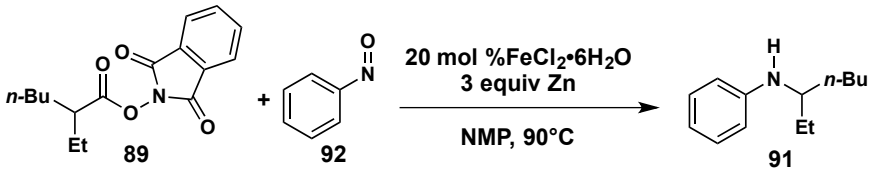


Figure 7.12. Initial results for decarboxylative coupling with nitrosoarenes

Unfortunately, additional optimization attempts were unsuccessful because the nitrosobenzene starting material was always rapidly consumed without significant product formation, indicating that the reducing conditions weren't compatible with nitroso compounds (Table 7.1). Increasing catalyst loading did not have a positive effect on the outcome (entry 1). There was no reaction in the absence of Zn (entry 3) or Fe (entry 4). Using three equivalents of ester did not improve the conversion (entry 5). Presumably, zinc is involved in the reduction of the nitrosobenzene to *N*-phenylhydroxylamine or aniline, both of which can react with nitroso compounds to form azoxybenzene and azobenzene respectively.

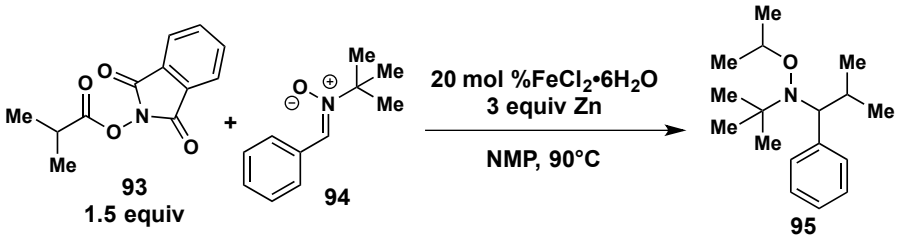


Entry	Deviation from Conditions	% Yield
1	40 mol % $FeCl_2$•$6H_2O$	18 %
2	20 mol % $FeCl_3$	15 %
3	no Zn	0 %
4	no Fe	0 %
5	3 equiv of redox ester	20 %

Table 7.1. Optimization attempts for the decarboxylative coupling with nitrosobenzene

Although disappointed with the initial results with nitroso compounds, we sought to identify other nitrogen-based radical traps compatible with the employed reaction conditions. Looking back at the RTA-ATRC literature, nitrones proved to be effective radical traps in the

synthesis of alkoxyamine linked diblock copolymers.[31] In fact, a survey of the literature reveals that nitrones were developed as spin trapping agents before nitroso compounds.[32] Importantly, nitrones are more stable than nitroso compounds; specifically they aren't prone to reduction/oxidation processes. However, they can easily be prepared through the reductive condensation of nitro compounds with aldehydes. We decided to replace nitrosobenzene with nitrone **94** in the radical coupling reaction with Okada's ester **93** (Table 7.2). Nitrone **94** was easily prepared through a reductive condensation between benzaldehyde and 2-methyl-2-nitropropane with zinc and acetic acid in ethanol. The zinc reduces the nitro group to the hydroxylamine which condenses with benzaldehyde to form the nitrone. To our delight, treatment of **94** with 1.5 equivalents of redox ester **93** with 20 mol % $FeCl_3$ and three equivalents of zinc in NMP at 90 °C led to formation of the N–O alkylated adduct **95** in 20 % yield (Table 7.2, entry 1). We noticed that **93** was consumed within five minutes at 90 °C. This led us to believe activation of the **93** to generate the alkyl radical was occurring too rapidly. If the concentration of the carbon centered radical is too high in solution, side reactions like homodimerization and disproportionation will prevail. In an attempt to slow the activation of **93**, to decrease radical concentration in solution, we repeated the reaction at room temperature. Encouragingly, the yield of **95** increased to 45% at room temperature (entry 2). Still concerned about a competing homodimerization reaction, we decided to add **93** to the reaction mixture via syringe pump over five hours which boosted the yield to 56% (entry 3). Finally, doubling the loading of **93** to three equivalents afforded **95** in 76% yield (entry 4).



Entry	Deviation from Conditions	% Yield
1	none	20 %
2	room temperature	45 %
3	addition of **93** over 5 h	56 %
4	three equivalents of **93**	76 %

Table 7.2. Optimization of the Fe-catalyzed decarboxylative coupling with nitrones

Importantly, this protocol was compatible with tertiary acid derivatives (Figure 7.13). For example, 1.5 equivalents of the ester derived from pivalic acid reacted efficiently with nitrone **94** to form the alkoxyamine product **97** in 56% yield. Additionally, primary esters successfully participated in the reaction to form **98** in 20% yield. This is significant because we never were able to develop a nitroso coupling reaction with primary alkyl radicals derived from alkyl halides. *N*-Aryl nitrones were also incorporated into the process.

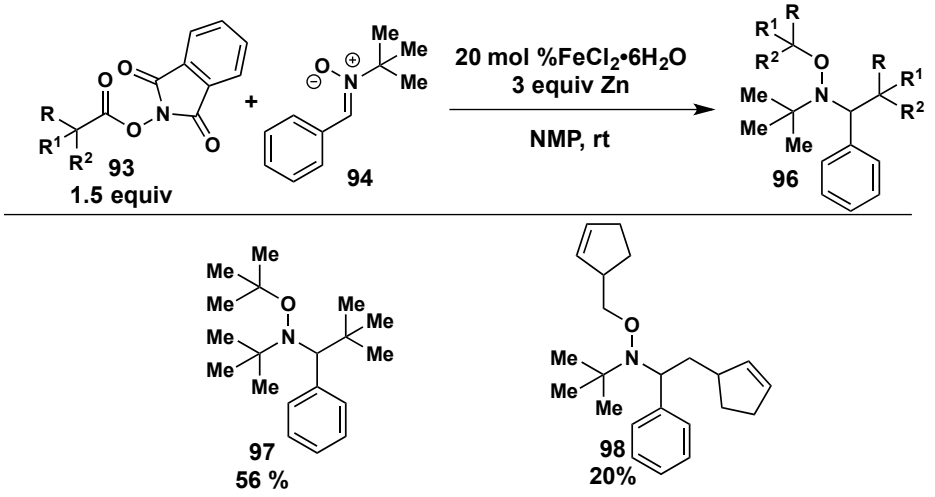


Figure 7.13. Decarboxylative coupling with primary and tertiary carboxylic acid derivatives

Interestingly, phenyl nitrone **99**, derived from nitrobenzene and benzaldehyde, reacted with **93** under standard conditions to form an inseparable 4:1 mixture of the benzylamine **100** and the N–O alkylated adduct **101** (Figure 7.14). Subjection of the purified mixture to Zn/HCl in an attempt to reduce the N–O was unsuccessful, the 4:1 ratio remained unchanged. Currently, efforts are being made to complete the N–O reduction in situ so **100** is isolated exclusively from the radical coupling reaction.

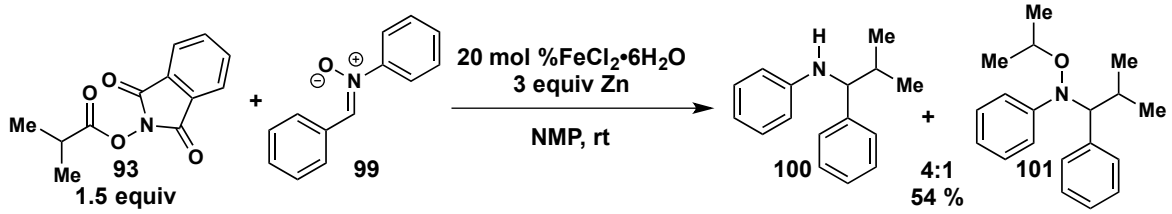


Figure 7.14. Decarboxylative coupling with *N*-phenyl nitrone

7.3 Conclusion

Currently, a reductive, decarboxylative coupling reaction between *N*-acyloxy-phthalimides and nitrones is being developed for the synthesis of anilines. This process utilizes a cheap, commercially available Fe catalyst and occurs at room temperature.

Preliminary results suggest that primary, secondary and tertiary carboxylic acid derivatives can be used as radical precursors. Additionally, a variety of nitrones are utilized as radical traps.

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8. Supporting Information

8.1 Supporting Information for Chapter 2: The $Dy(OTf)_3$ Catalyzed Piancatelli Rearrangement

Materials and general experimental details

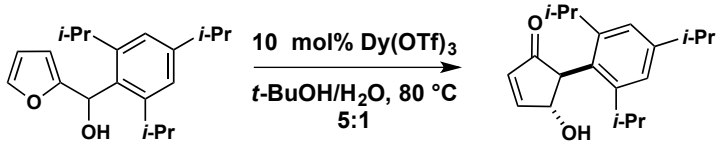
Unless stated otherwise, reactions were conducted in air dried glassware under an atmosphere of air using reagent grade solvents. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 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 anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Merck KGA).

^{1}H NMR spectra were recorded on Varian spectrometers (at 400, 500 or 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 or 150 MHz). Data for ^{13}C NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source.

Furylcarbinols were prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent.

4.2 General experimental procedure A:

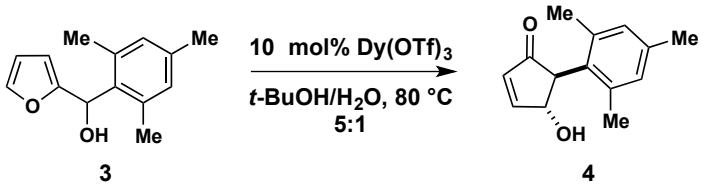
Furylcarbinol was dissolved in a solution of *t*-BuOH/H_2O. To the reaction mixture at rt was added 10 mol % of $Dy(OTf)_3$. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H_2O and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography.



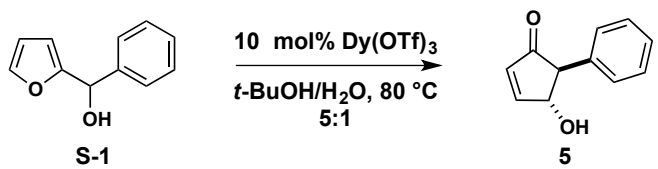
1 2

4-Hydroxy-5-(2,4,6-triisopropylphenyl)cyclopent-2-en-1-one (2): According to general procedure **A** $Dy(OTf)_3$ (5 mg, 0.008 mmol, 0.1 equiv) was added to furan-2-yl(2,4,6-triisopropyl)methanol (25 mg, 0.08 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 2 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **2** (21 mg, 84%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.8, 1.9 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 6.39 (dd, J = 5.8, 1.3 Hz, 1H), 4.94 (dt, J = 5.9, 1.8 Hz, 1H), 3.99 (d, J = 3.1 Hz, 1H), 3.26-3.16 (m, 1H),

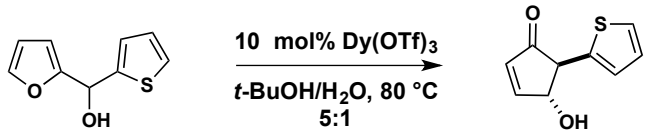
2.92-2.82 (m, 1H), 2.41 (d, J = 5.9 Hz, 1H), 2.02-1.92 (m, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.29 – 1.13 (m, 12H), 1.05 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.1, 159.7, 148.4, 148.2, 147.5, 134.6, 128.3, 122.8, 121.3, 79.6, 57.4, 34.3, 30.9, 30.6, 25.2, 24.1, 24.1, 23.9, 23.5; IR (thin film, cm^{-1}) 3501, 3075, 2959, 2869, 1699, 1102, 765; HRMS (ESI) *m/z* 323.1973 (323.1987 calcd for $C_{20}H_{28}NaO_2^+$[MNa]$^+$).



4-Hydroxy-5-mesitylcyclopent-2-en-1-one (4): According to general procedure **A** $Dy(OTf)_3$ (7 mg, 0.0115 mmol, 0.1 equiv) was added to furan-2-yl(mesityl)methanol (25 mg, 0.115 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 2 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **4** (20 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.9, 2.0 Hz, 1H), 6.79 (m, 2H), 6.32 (m, 1H), 5.07-5.04 (m, 1H), 3.89 (d, J = 3.1 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 4H), 1.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 160.3, 138.4, 137.0, 136.1, 134.4, 130.3, 130.1, 129.2, 78.2, 58.3, 21.2, 20.8, 20.3; IR (thin film, cm^{-1}) 3419, 3062, 2963, 2921, 1701, 852; HRMS (ESI) *m/z* 239.1055 (239.1055 calcd for $C_{14}H_{16}NaO_2^+$[MNa]$^+$).



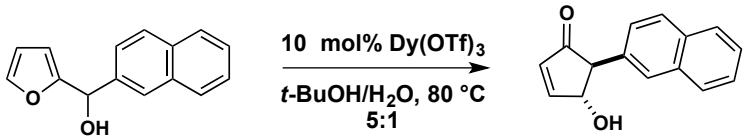
4-Hydroxy-5-phenylcyclopent-2-en-1-one (5): According to general procedure **A** $Dy(OTf)_3$ (8.7 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(phenyl)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 6.5 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **5** (21 mg, 84%) as brown oil. Spectral data for **5** were consistent with those previously reported.[1]



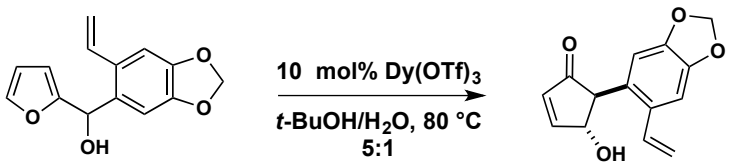
S-2 6

4-Hydroxy-5-(thiophen-2-yl)cyclopent-2-en-1-one (6): According to general procedure **A** $Dy(OTf)_3$ (8.5 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(thiophen)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 1 hour. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **6** (18 mg, 72%) as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (dd, J = 5.9, 2.1 Hz, 1H), 7.25 (dd, J = 5.2, 1.3 Hz, 1H), 7.03 – 7.00 (m, 1H), 7.00 – 6.97 (m, 1H), 6.31 (dd, J = 5.9, 1.5 Hz, 1H), 5.09 – 5.03 (m, 1H), 3.74 (d, J = 3.0 Hz, 1H), 2.63 (d, J = 6.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1, 161.3, 137.7, 133.8, 127.3, 126.1, 125.0, 79.0, 57.1; IR (thin film, cm$^-$

[1]) 3397, 3106, 2889, 1696, 1027, 697; HRMS (ESI) *m/z* 203.0130 (203.0143 calcd for $C_9H_8NaO_2S^+[MNa]^+$).



4-Hydroxy-5-(naphthalen-2-yl)cyclopent-2-en-1-one (7): According to general procedure **A** $Dy(OTf)_3$ (6.8 mg, 0.012 mmol, 0.1 equiv) was added to furan-2-yl(naphthalen)methanol (25 mg, 0.12 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 5 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **7** (22 mg, 86%) as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.79 – 7.76 (m, 1H), 7.64 – 7.61 (m, 1H), 7.60 (dd, *J* = 5.8, 2.1 Hz, 1H), 7.48 (qd, *J* = 7.0, 3.4 Hz, 2H), 7.14 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.33 (dd, *J* = 5.8, 1.4 Hz, 1H), 5.01 (s, 1H), 3.57 (d, *J* = 2.8 Hz, 1H), 2.66 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.5, 162.0, 134.6, 134.2, 133.6, 132.7, 129.0, 127.8, 127.8, 126.5, 126.2, 125.8, 79.0, 62.4; IR (thin film, cm^{-1}) 3397, 3054, 2902, 1697, 1035, 745; HRMS (ESI) *m/z* 247.0724 (247.0735 calcd for $C_{15}H_{12}NaO_2^+[MNa]^+$).



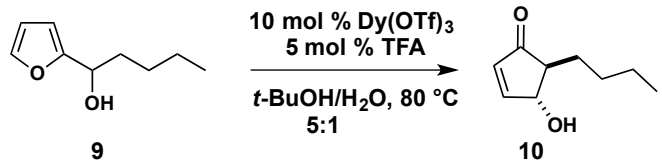
S-4 8

4-Hydroxy-5-(6-vinylbenzo[*d*][1,3]dioxol-5-yl)cyclopent-2-en-1-one (8): According to the general procedure **A** $Dy(OTf)_3$ (6 mg, 0.010 mmol, 0.1 equiv) was added to furan-2-yl(6-vinylbenzo[d][1,3]dioxol)methanol (25 mg, 0.102 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 ºC for 3 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 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 cyclopentenone **8** (16 mg, 64%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.00 (s, 1H), 6.73 (dd, *J* = 17.1, 10.9 Hz, 1H), 6.39 (s, 1H), 6.37 (dd, *J* =5.87, 1.39, 1H), 5.94 (dd, *J* = 6.84, 1.5, 2H), 5.54 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.24 (dd, *J* = 10.9, 1.2 Hz, 1H), 4.99 – 4.86 (m, 1H), 3.69 (d, *J* = 2.9 Hz, 1H), 2.43 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.6, 161.4, 147.9, 147.5, 134.8, 134.1, 132.1, 128.2, 116.2, 108.6, 106.6, 101.4, 79.4, 59.6; IR (thin film, cm^{-1}) 3406, 3084, 2902, 1698, 1483, 1036, 733; HRMS (ESI) *m/z* 267.0615 (267.0633 calcd for $C_{14}H_{12}NaO_4^+[MNa]^+$).

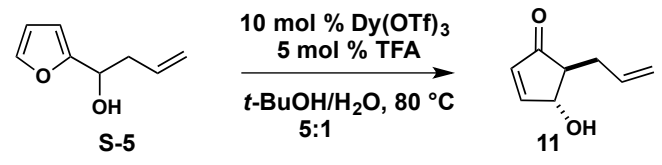
General experimental procedure B:

Furylcarbinol was dissolved in a solution of *t*-BuOH/H_2O. To the reaction mixture at rt was added 10 mol % of $Dy(OTf)_3$ and 5 mol % TFA. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H_2O and extracted with diethyl ether. The combined organic

layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography.

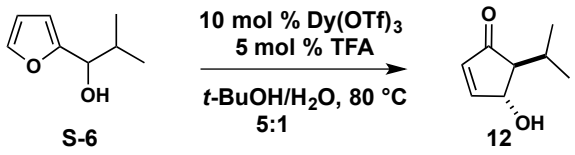


5-Butyl-4-hydroxycyclopent-2-en-1-one (10): According to general procedure **B** $Dy(OTf)_3$ (10 mg, 0.016 mmol, 0.1 equiv) was added to (furan-2-yl)pentan-1-ol (25 mg, 0.16 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.6 µL, 0.008 mmol, 0.05 equiv) and heated to 80 ºC for 16 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **10** (22 mg, 90 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.20 (d, *J* = 5.7 Hz, 1H), 4.70 (t, *J* = 2.7 Hz, 1H), 2.32 – 2.17 (m, 1H), 2.00 (s, 1H), 1.92 – 1.81 (m, 1H), 1.51 – 1.31 (m, 5H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 161.6, 134.5, 76.8, 55.6, 29.6, 28.5, 22.9, 14.1; IR (thin film, cm^{-1}) 3407, 2957, 2860, 1694, 1098; HRMS (FI) *m/z* 154.0991 (154.0994 calcd for $C_9H_{14}NaO_2^+[MNa]^+$).

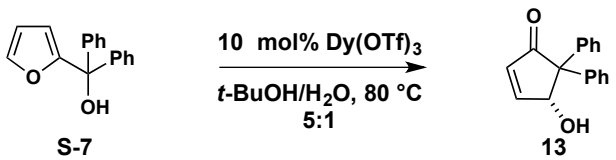


5-Allyl-4-hydroxycyclopent-2-en-1-one (11): According to general procedure **B** $Dy(OTf)_3$ (11 mg, 0.018 mmol, 0.1 equiv) was added to (furan-2-yl)but-3-en-1-ol (25 mg, 0.18 mmol, 1

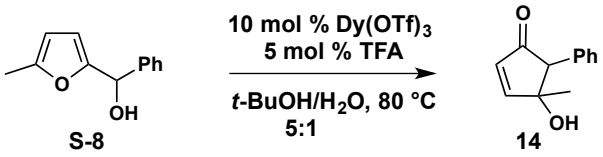
equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.7 µL, 0.009 mmol, 0.05 equiv) and heated to 80 ºC for 15 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **11** (18 mg, 72%) as a brown oil. Spectral data for **11** were consistent with those previously reported.[2]



4-Hydroxy-5-isopropylcyclopent-2-en-1-one (12): According to the general procedure **B** $Dy(OTf)_3$ (11 mg, 0.018 mmol, 0.1 equiv) was added to (furan-2-yl)-2-methyl-propanol (25 mg, 0.178 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.7 µL, 0.009 mmol, 0.05 equiv) and heated to 80 ºC for 34 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **12** (14 mg, 56%) as an oil. Spectral data for **12** were consistent with those previously reported.[3]

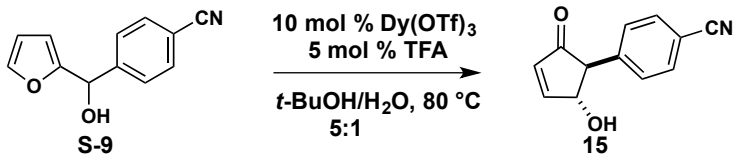


4-Hydroxy-5,5-diphenylcyclopent-2-en-1-one (13): According to general procedure **B** $Dy(OTf)_3$ (6 mg, 0.010 mmol, 0.1 equiv) was added to furan-2,2-yl(diphenyl)methanol (25 mg, 0.10 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.4 µL, 0.005 mmol, 0.05 equiv) and heated to 80 ºC for 43 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **13** (16 mg, 64%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.8, 2.5 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.40 – 7.27 (m, 6H), 7.16 – 7.07 (m, 2H), 6.43 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.54 (dt, *J* = 7.9, 1.9 Hz, 1H), 1.59 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.9, 161.7, 140.5, 139.6, 134.7, 129.9, 128.8, 128.6, 128.5, 127.7, 127.5, 78.8, 65.7; IR (thin film, cm^{-1}) 3418, 3059, 2983, 1705, 1044, 697; HRMS (ESI) *m/z* 273.0881 (273.0891 calcd for $C_{17}H_{14}NaO_2^+$ $[MNa]^+$).

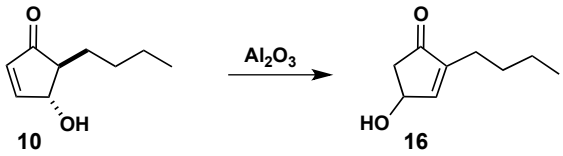


4-Hydroxy-4-methyl-5-phenylcyclopent-2-en-1-one (14): According to general procedure **B** $Dy(OTf)_3$ (8.1 mg, 0.013 mmol, 0.1 equiv) was added to 5-methylfuran-2-yl(phenyl)methanol (25 mg, 0.132 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.6 µL, 0.007 mmol, 0.05 equiv) and heated to 80 ºC for 15.5 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined

organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **14** (10 mg, 40%) as an oil. Spectral data for **14** were consistent with those previously reported.[4]



4-(2-Hydroxy-5-oxocyclopent-3-en-1-yl)benzonitrile (15): According to the general procedure **B** $Dy(OTf)_3$ (7.6 mg, 0.013 mmol, 0.1 equiv) was added to 4-(furan-2-yl(hydroxy)methyl)benzonitrile (25 mg, 0.125 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.5 µL, 0.006 mmol, 0.05 equiv) and heated to 80 ºC for 18 hours. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **15** (18 mg, 72%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 5.8, 2.1 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.36 (dd, J = 5.8, 1.3 Hz, 1H), 5.01 (s, 1H), 3.55 (d, J = 3.0 Hz, 1H), 2.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 203.5, 161.8, 142.2, 134.3, 132.6, 129.2, 128.1, 118.5, 111.3, 105.0, 61.8 IR (thin film, cm^{-1}) 3537, 3057, 2917, 2849, 2228, 1693, 1104; HRMS (ESI) *m/z* 222.0523 (222.0531 calcd for $C_{12}H_9NNaO_2^+[MNa]^+$).



2-Butyl-4-hydroxycyclopent-2-en-1-one (16): 4-Hydroxy-5-butylcyclopent-2-enone (25 mg, 0.162 mmol) was adsorbed on alumina (850 mg, Brockman grade III) for 23 hours and eluted with 4:1 benzene/diethyl ether which was concentrated *in vacuo* to afford cyclopentenone **16** (25 mg, 100 %) as an oil. Spectral data matched literature precedent.[5]

Acknowledgements

This work was supported by UCSB and the National Science Foundation (Career Award CHE-1057180).

References

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8.2 Supporting Information for Chapter 4: Radical Addition with Nitrosoarenes for Hindered α-Amino Carbonyl Synthesis

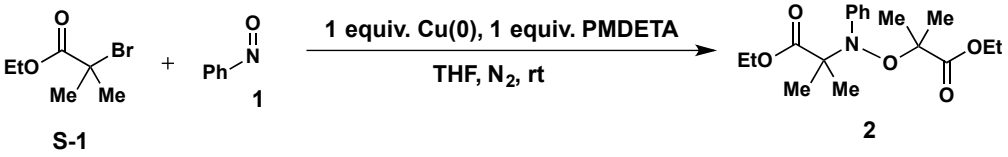
8.2.1 Supporting Information for Alkoxyamine Synthesis

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of N_2 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 or anisaldehyde. 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 (at 100, 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 100 FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility.

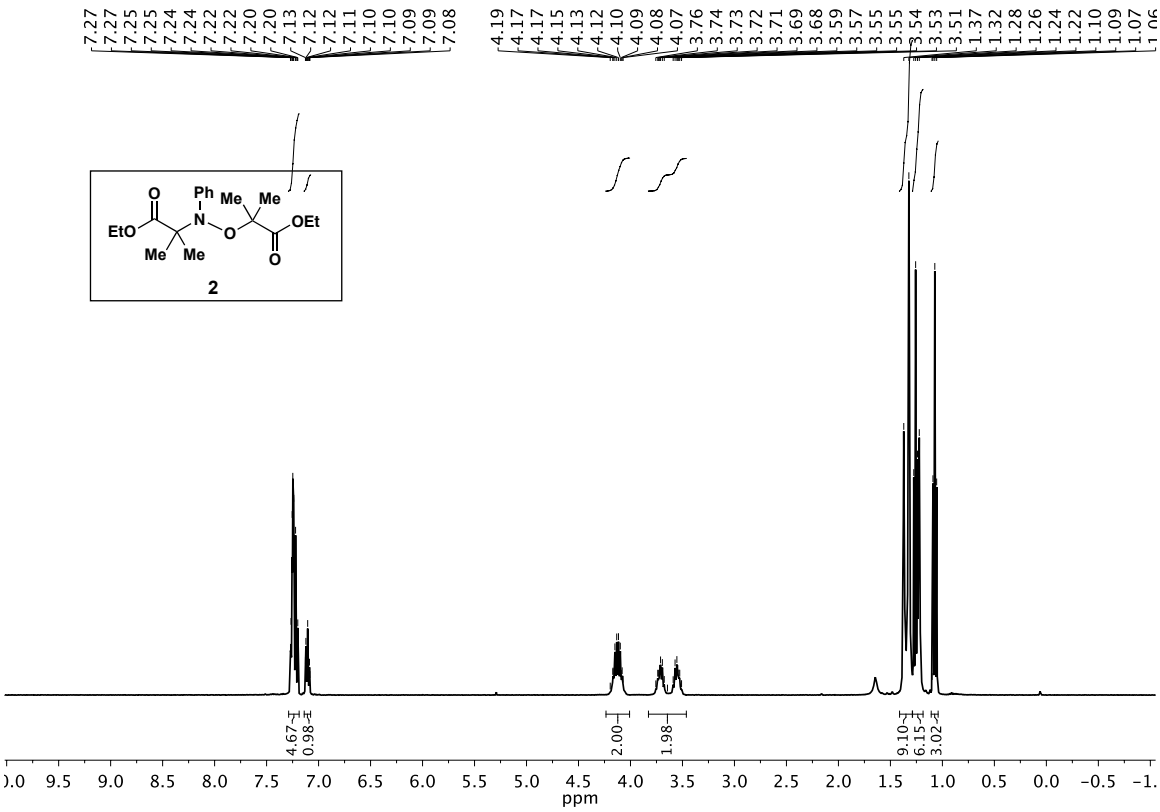
General procedure for the synthesis of alkoxyamines:

A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged

PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography.



ethyl 2-(((1-ethoxy-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanoate (2): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **2** (35 mg, 87%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 4H), 7.14 – 7.08 (m, 1H), 4.24 – 4.01 (m, 2H), 3.83 – 3.46 (m, 2H), 1.35 (d, J = 19.6 Hz, 9H), 1.25 (dd, J = 14.1, 7.0 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.56, 172.84, 148.12, 127.38, 125.81, 125.77, 81.01, 68.01, 60.63, 60.38, 24.40, 24.01, 23.41, 21.04, 14.02, 13.77.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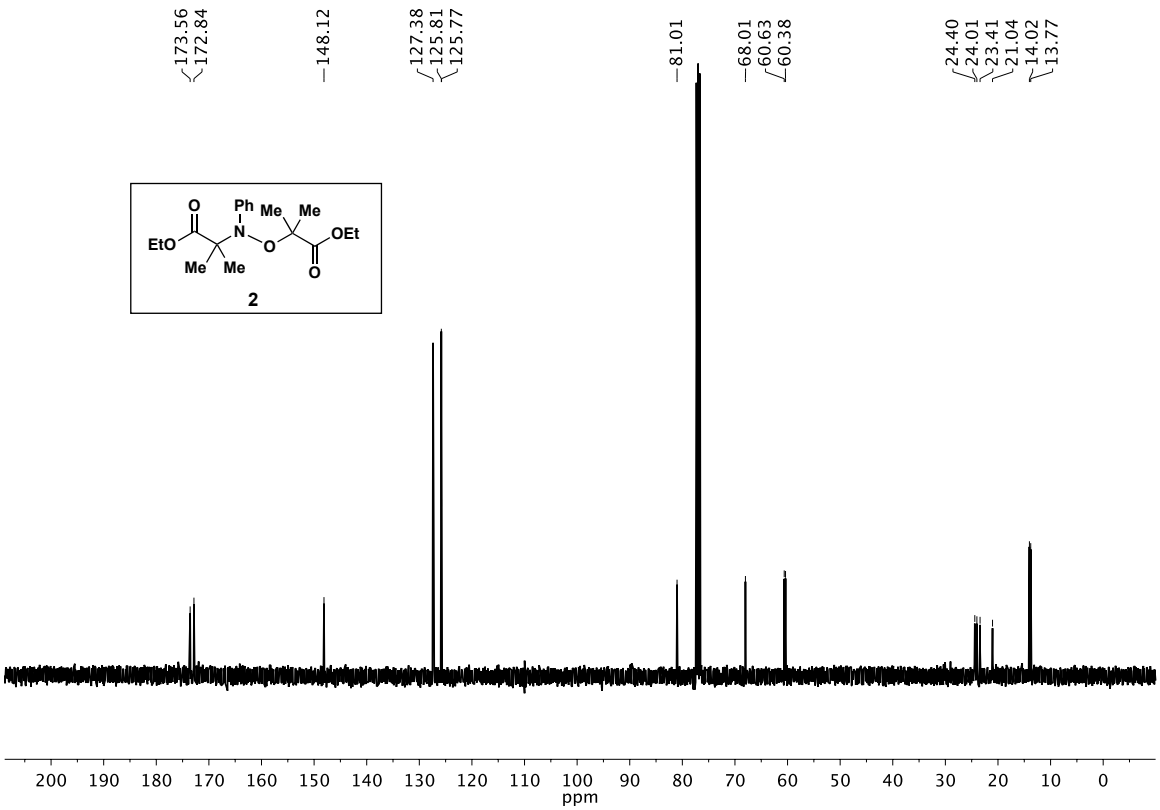
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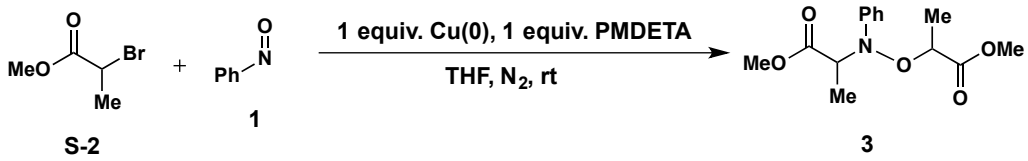
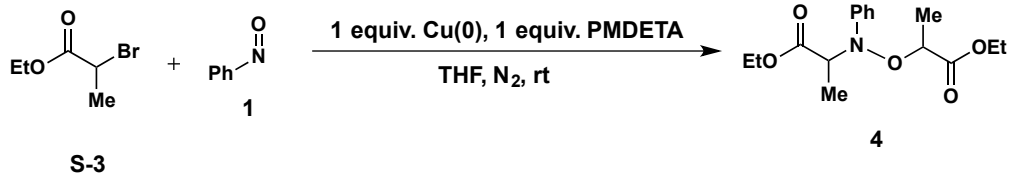
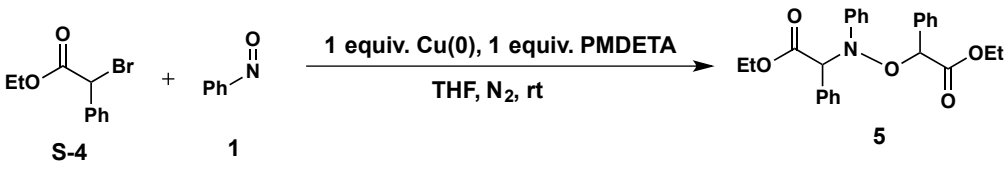


methyl 2-(((1-methoxy-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanoate (3): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **3** (24 mg, 70%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (ddd, *J* = 8.2, 7.2, 2.5 Hz, 2H), 7.20 (td, *J* = 8.7, 1.3 Hz, 2H), 7.10 (dt, *J* = 8.5, 7.2 Hz, 1H), 4.43 (dq, *J* = 9.3, 6.9 Hz, 1H), 4.06 (dq, *J* = 21.1, 7.0 Hz, 1H), 3.73 (d, *J* = 6.4 Hz, 3H), 3.60 (s, 2H), 3.52 (s, 1H), 1.32 (dd, *J* = 6.9, 4.7 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H).

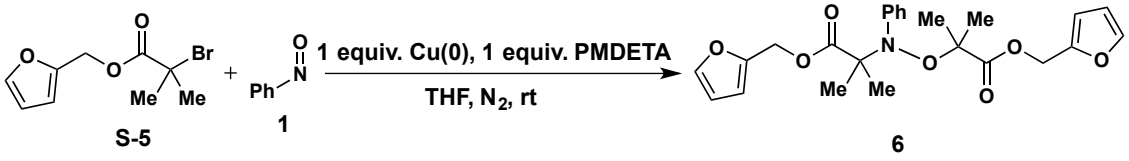


ethyl 2-(((1-ethoxy-1-oxopropan-2-yl)(phenyl)amino)oxy)propanoate (4): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **4** (27 mg, 72%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 4H), 7.09 (m, 1H), 4.45 (dq, *J* = 14.9, 6.9 Hz, 1H), 4.24

– 3.88 (m, 5H), 1.33 (dd, *J* = 6.9, 2.0 Hz, 3H), 1.29 – 1.20 (m, 6H), 1.09 (dt, *J* = 23.1, 7.1 Hz, 3H).

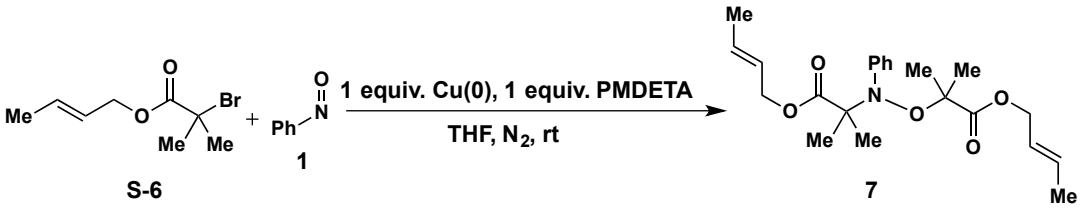


ethyl 2-((2-ethoxy-2-oxo-1-phenylethoxy)(phenyl)amino)-2-phenylacetate (5): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **5** (27 mg, 52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 7.25 – 6.99 (m, 10H), 5.56 (s, 1H), 5.38 (s, 1H), 5.01 (s, 1H), 4.20 – 3.87 (m, 2H), 3.73 (dq, J = 10.8, 7.1 Hz, 1H), 1.17 (t, J = 7.1 Hz, 1H), 1.12 – 1.03 (m, 3H), 0.92 (t, J = 7.1 Hz, 2H);

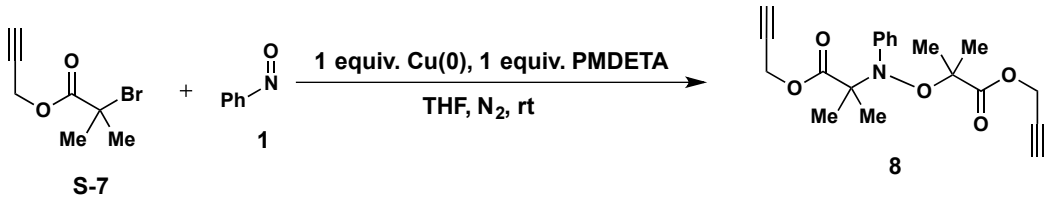


furan-2-ylmethyl 2-(((1-(furan-2-ylmethoxy)-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanoate (6): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the

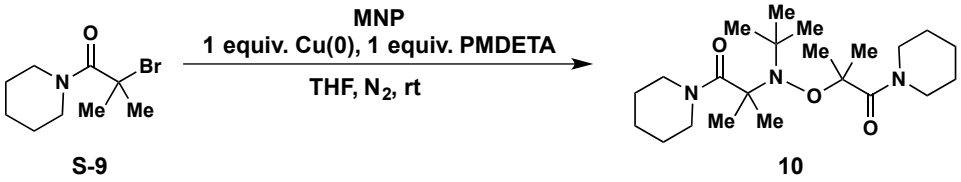
starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **6** (47 mg, 88%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 10.2, 1.9, 0.8 Hz, 2H), 7.24 – 7.17 (m, 4H), 7.11 (ddt, *J* = 8.4, 5.4, 3.1 Hz, 1H), 6.42 – 6.26 (m, 4H), 5.16 – 4.96 (m, 2H), 4.69 – 4.38 (m, 2H), 1.29 (dd, *J* = 37.5, 19.9 Hz, 12H)



(E)-but-2-en-1-yl 2-(((1-(((E)-but-2-en-1-yl)oxy)-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanoate (7): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **7** (40 mg, 85%) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 4H), 7.12 – 7.08 (m, 1H), 5.82 – 5.73 (m, 1H), 5.67 – 5.52 (m, 2H), 5.41 – 5.34 (m, 1H), 4.56 – 4.43 (m, 2H), 4.08 (dd, *J* = 12.6, 6.4 Hz, 1H), 3.91 (dd, *J* = 12.6, 6.3 Hz, 1H), 1.69 (ddd, *J* = 24.4, 6.6, 1.5 Hz, 6H), 1.40 – 1.19 (m, 12H).



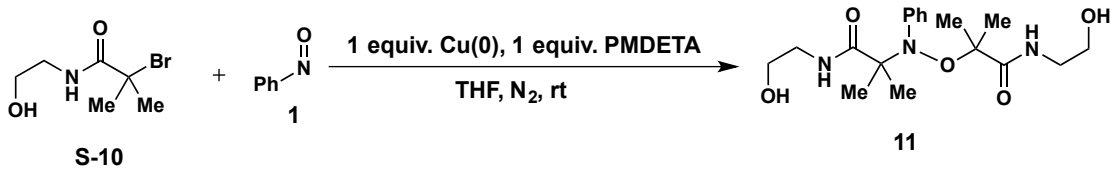
prop-2-yn-1-yl 2-methyl-2-(((2-methyl-1-oxo-1-(prop-2-yn-1-yloxy)propan-2-yl)(phenyl)amino)oxy)propanoate (8): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **8** (26 mg, 55%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 4H), 7.17 – 7.10 (m, 1H), 4.79 – 4.62 (m, 2H), 4.29 – 3.96 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H), 2.41 (t, J = 2.5 Hz, 1H), 1.49 – 1.17 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.77, 171.91, 147.38, 127.63, 126.17, 126.03, 81.02, 74.89, 74.75, 68.09, 52.23, 51.98, 24.32, 23.41, 20.40.



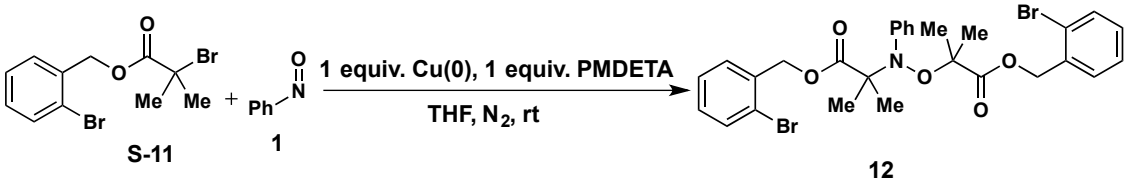
2-(*tert*-butyl((2-methyl-1-oxo-1-(piperidin-1-yl)propan-2-yl)oxy)amino)-2-methyl-1-(piperidin-1-yl)propan-1-one (10): A mixture of α-bromocarbonyl (1 mmol), 2-methyl-2-nitrosopropane dimer (52 mg, 0.3 mmol, 0.6 equiv) and Cu(0) (32 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (100 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 36 hr under N_2. Upon consumption of the

starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **10** (160 mg, 81%)

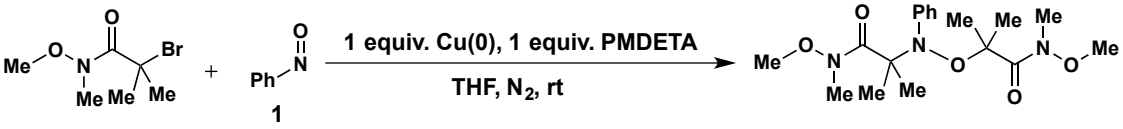
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 – 2.99 (m, 8H), 1.77 – 1.43 (m, 18H), 1.41 (s, 3H), 1.22 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.41, 172.31, 85.05, 70.84, 62.53, 47.45, 46.76, 44.24, 28.89, 27.99, 27.57, 26.68, 25.82, 25.71, 25.64, 24.82, 24.70, 23.28.



N-(2-hydroxyethyl)-2-(((1-((2-hydroxyethyl)amino)-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanamide (11): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **11** (27 mg, 62%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 4.3 Hz, 4H), 7.18 (m 2H), 3.72 (q, J = 6.3, 4.9 Hz, 4H), 3.41 (q, J = 5.2 Hz, 2H), 3.20 (s, 4H), 1.69 – 0.92 (bs, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.81, 175.68, 148.05, 128.19, 126.68, 125.42, 83.98, 68.24, 61.45, 61.00, 42.19, 42.05.



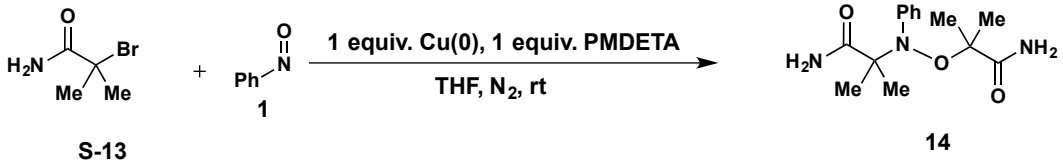
2-bromobenzyl 2-(((1-((2-bromobenzyl)oxy)-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanoate (12): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **13** (56 mg, 75%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 14.6, 7.9 Hz, 2H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 – 7.22 (m, 5H), 7.22 – 7.07 (m, 5H), 5.20 (d, *J* = 4.7 Hz, 2H), 4.85 – 4.50 (m, 2H), 1.39 (t, *J* = 25.7, 22.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.96, 172.13, 147.83, 135.29, 132.69, 132.60, 129.61, 129.48, 129.33, 129.21, 127.60, 127.41, 127.32, 126.05, 125.86, 123.10, 122.81, 81.33, 68.20, 65.97, 65.54, 24.46, 24.36, 23.61, 21.31.



S-12 13

N-methoxy-2-(((1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-N,2-dimethylpropanamide (13): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **13** (43 mg, 98%) ^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.21 (d, *J* = 5.1 Hz, 4H), 7.12 – 7.04 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.43 (s, 3H), 3.14 (s, 3H), 1.55 – 1.06 (m, 12H).

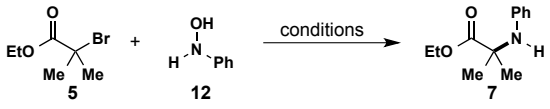


S-13 1 14

2-(((1-amino-2-methyl-1-oxopropan-2-yl)(phenyl)amino)oxy)-2-methylpropanamide (14): A mixture of α-bromocarbonyl (0.24 mmol), nitrosobenzene (16mg, 0.14 mmol, 0.6 equiv) and Cu(0) (15 mg, 0.24 mmol) in dry THF was sparged with N_2 for 5 min. Sparged PMDETA (25 μL, 0.5 equiv) was then added to the mixture which was stirred at rt for about 12 hr under N_2. Upon consumption of the starting material as indicated by TLC, the mixture was dry-loaded onto celite and purified via column chromatography to afford product **14** (26 mg, 77%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.02 (m, 5H), 6.89 (d, *J* = 26.4 Hz, 1H), 6.51 (d, *J* = 9.9 Hz, 2H), 2.10 – 0.90 (m, 12H).

8.2.2 Supporting Information for the Synthesis of α-Amino Carbonyls

Table S1. Identification of catalytic reaction conditions



5 12 7

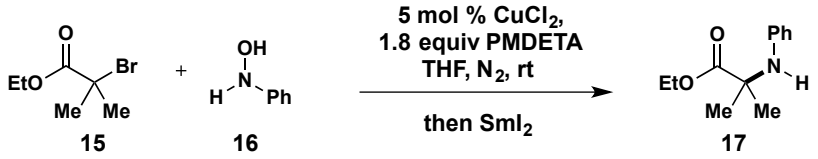
entry	5 mol % catalyst	equiv PMDTA	yield (%)
1	5 mol % $CuCl_2$	0.5	< 5
2[a]	5 mol % $CuCl_2$	**0.5**	22
3[a]	5 mol % $CuCl_2$	1.8	73
4	—	1.8	0

[a] Syringe pump addition over the course of 5 hr.

The reaction was conducted using 5 mol % $CuCl_2$ as the catalyst and phenylhydroxylamine as the nitroso precursor (Table S1). Unfortunately, using this redox-neutral protocol only a trace amount of amine **7** was isolated (Entry 1). However, the low yield was due to a competitive condensation reaction between the in situ generated nitrosobenzene and excess phenylhydroxylamine, a good nucleophile. Slow addition of phenylhydroxylamine showed modest improvement (Entry 2). To our gratification, further optimization revealed that slow addition and increasing the equivalents of the ligand pentamethyldiethylenetriamine (PMDTA) resulted in the formation of **7** in comparable yield to the stoichiometric conditions (Entry 4). No reaction was observed in the absence of the copper catalyst (Entry 5).

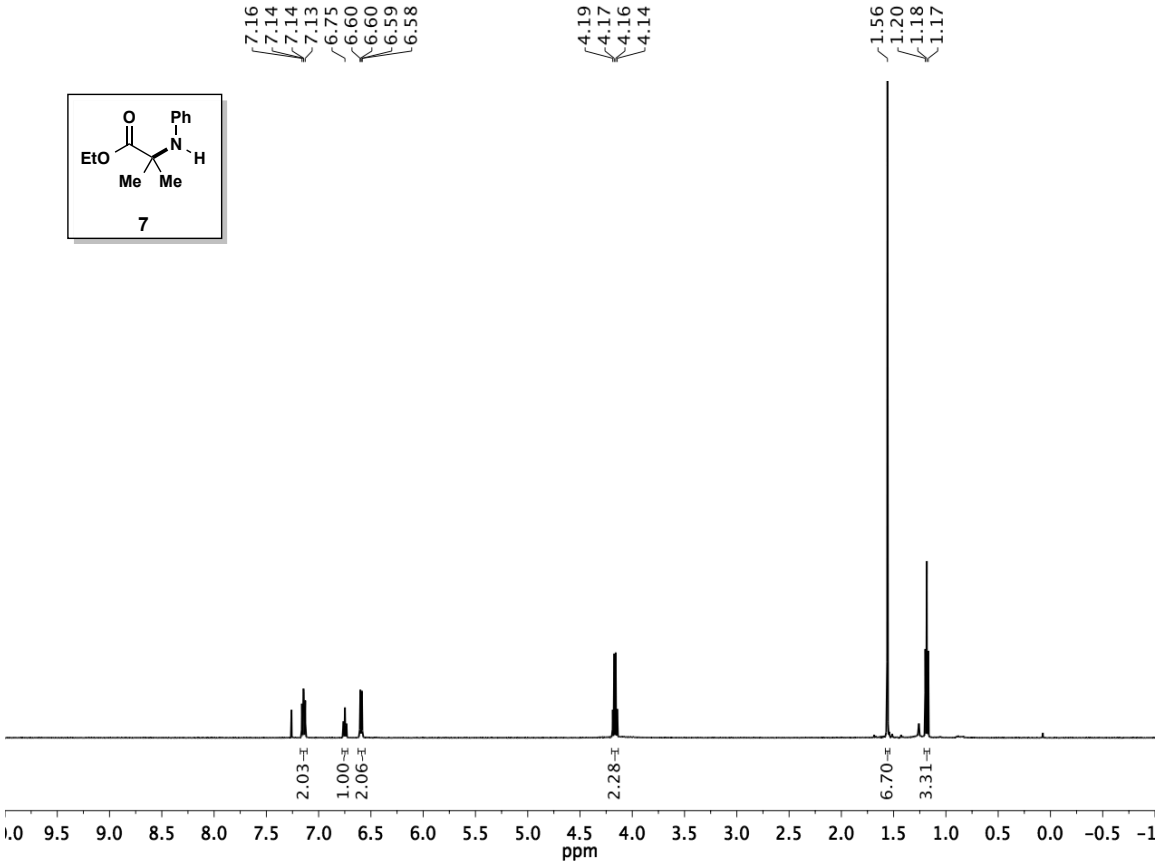
General Procedure A for the Arylnitroso Radical Coupling Reaction: A round bottom flask containing a solution of α-bromocarbonyl (0.250 mmol, 1.0 equiv), $CuCl_2$ (1.6 mg, 0.0125 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) in THF (3.0 mL) was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine (0.150 mmol, 0.6 equiv)[1] in sparged THF (1 mL) was then added via syringe pump over 5 or 10 hours to the stirred round bottom flask at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl compound as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M)[2] was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford the corresponding α-aminated adducts.

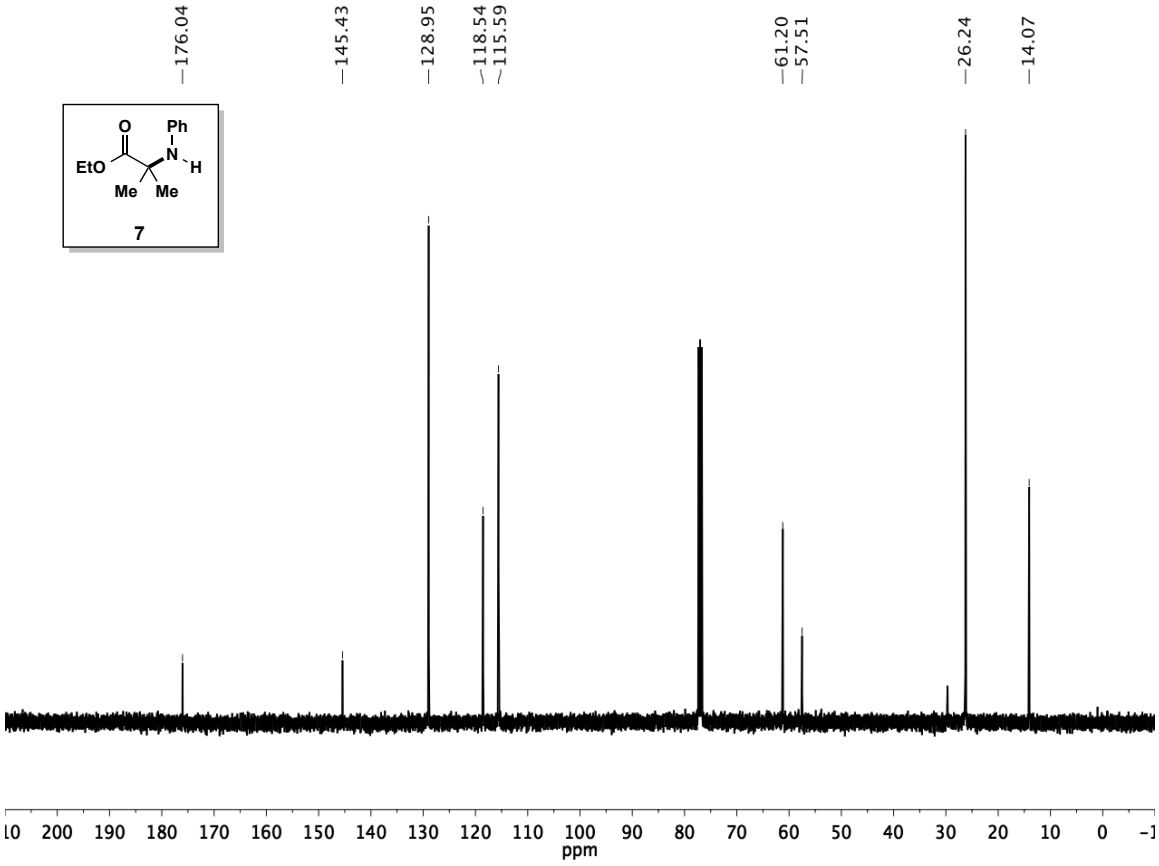
General Procedure B for the Arylnitroso Radical Coupling Reaction: A round bottom flask containing a suspension of α-bromocarbonyl (0.250 mmol, 1.0 equiv), Cu(0) (15.8 mg, 0.149 mmol, 1.0 equiv) and nitrosobenzene (16.1 mg, 0.150 mmol, 0.6 equiv) in THF (3.0 mL) was sparged with N_2 for 15 minutes. Sparged PMDETA (26.0 μL, 0.125 mmol, 0.5 equiv) was added to the suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M)[2] was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford the corresponding α-aminated adducts.

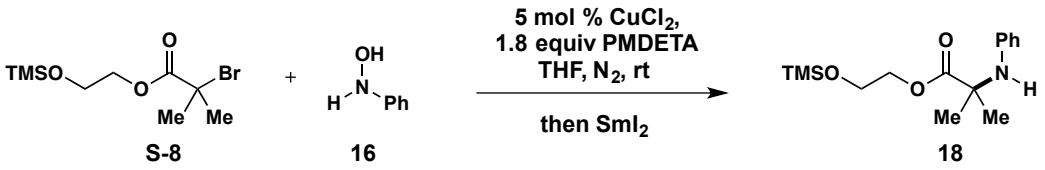


Ethyl 2-methyl-2-(phenylamino)propanoate (17): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.45 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **15** (49.2 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 3.0 mL, 0.3 mmol, 1.2 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford

17 (19 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 2H), 6.75 (tt, J = 7.4, 1.1 Hz, 1H), 6.63 – 6.56 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 1.56 (s, 6H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 145.4, 129.0, 118.5, 115.6, 61.2, 57.5, 26.2, 14.1; IR (ATR) 3399, 2982, 2935, 1726, 1602, 1499, 1274, 1141, 1023, 748, 694 cm^{-1}; HRMS (ESI) *m/z* 230.1143 (230.1157 calcd for $C_{12}H_{17}NO_2Na$ $[M+Na]^+$).

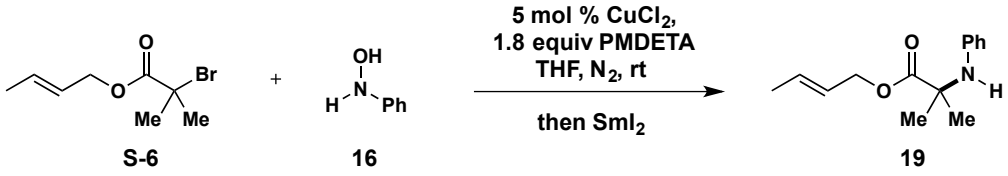






2-((Trimethylsilyl)oxy)ethyl 2-methyl-2-(phenylamino)propanoate (18): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (78.0 μL, 0.374 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **S-8** (70.6 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.5 mL, 1.05 mmol, 4.2 equiv)

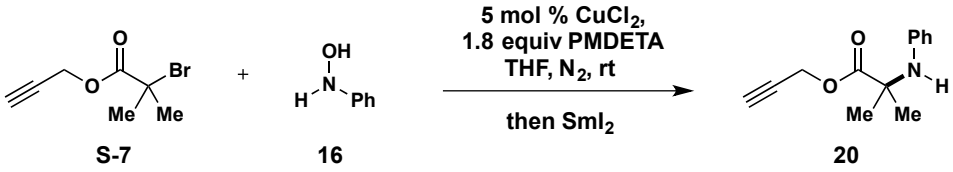
was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **18** (32 mg, 87%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 2H), 6.75 – 6.70 (m, 1H), 6.60 – 6.55 (m, 2H), 4.18 – 4.11 (m, 2H), 3.69 – 3.61 (m, 2H), 1.55 (s, 6H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 145.5, 129.2, 118.9, 116.0, 66.3, 60.5, 57.9, 26.5, -0.4; IR (ATR) 3403, 3055, 2986, 2956, 2872, 1731, 1603, 1500, 1251, 1152, 1126, 1103, 957, 841, 748 cm^{-1}; HRMS (ESI) *m/z* 318.1488 (318.1501 calcd for $C_{15}H_{25}NO_3NaSi$ $[M+Na]^+$).



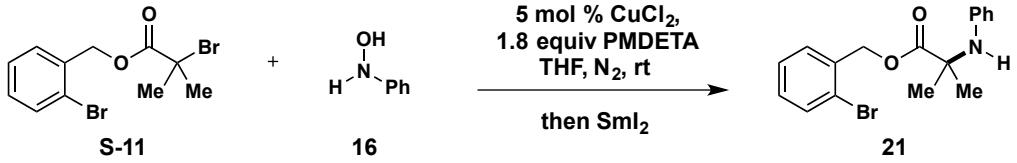
S-6 16 19

(*E*)-But-2-en-1-yl 2-methyl-2-(phenylamino)propanoate (19): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-6** (55.0 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 3.0 mL, 0.3 mmol, 2.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **19** (21 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.10 (m, 2H), 6.75 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.56 (m, 2H), 5.72 (dddd, *J* = 15.3, 7.7, 6.5, 5.3 Hz, 1H), 5.53 – 5.42 (m, 1H), 4.53 (dq, *J* = 6.5, 1.2 Hz, 2H), 1.67 (dq, *J*

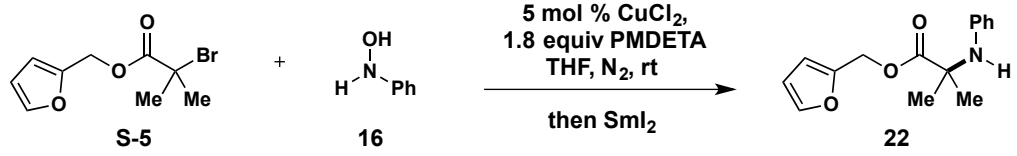
= 6.5, 1.2 Hz, 3H), 1.56 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 145.6, 131.7, 129.1, 124.9, 118.8, 115.9, 66.0, 57.8, 26.4, 17.9; IR (ATR) 3401, 2985, 2941, 1725, 1601, 1499, 1271, 1141, 965, 748, 694 cm^{-1}; HRMS (ESI) *m/z* 256.1296 (256.1313 calcd for $C_{14}H_{19}NO_2Na$ $[M+Na]^+$).



Prop-2-yn-1-yl 2-methyl-2-(phenylamino)propanoate (20): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-7** (51.3 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 3.0 mL, 0.3 mmol, 2.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **20** (19 mg, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 2H), 4.70 (d, *J* = 2.3 Hz, 2H), 2.44 (t, *J* = 2.3 Hz, 1H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 145.1, 129.0, 118.8, 115.7, 74.9, 74.9, 57.5, 52.6, 26.2; IR (ATR) 3407, 3277, 2920, 2851, 2126, 1734, 1602, 1499, 1270, 1137 cm^{-1}; HRMS (CI) *m/z* 218.1184 (218.1181 calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$).

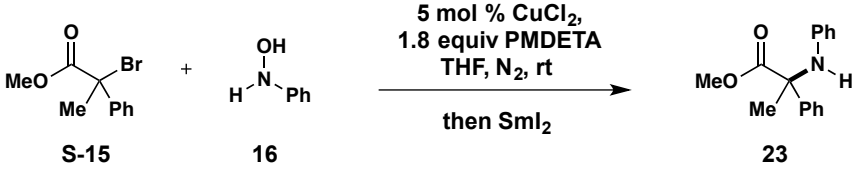


2-Bromobenzyl 2-methyl-2-(phenylamino)propanoate (21): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-11** (83.5 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 6.5 mL, 0.65 mmol, 5.2 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **21** (31 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 1H), 7.23 – 7.08 (m, 5H), 6.75 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.7 Hz, 2H), 5.21 (s, 2H), 1.61 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 145.6, 135.1, 132.9, 130.2, 129.8, 129.2, 127.6, 123.6, 118.9, 115.8, 66.7, 57.9, 26.6. IR (ATR) 3401, 3055, 2985, 2925, 1730, 1601, 1499, 1270, 1139, 748, 694 cm^{-1}; HRMS (ESI) *m/z* 370.0419 (370.0419 calcd for $C_{17}H_{18}BrNNaO_2$ $[M+Na]^+$).



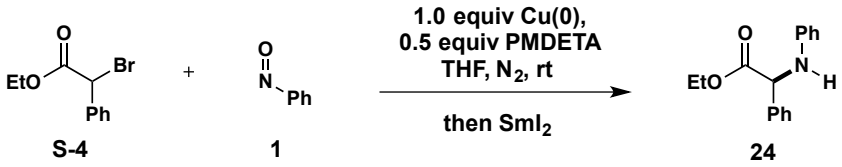
Furan-2-ylmethyl 2-methyl-2-(phenylamino)propanoate (22): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol,

1.8 equiv) were added to a solution of α-bromocarbonyl **S-5** (61.7 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 5.0 mL, 0.5 mmol, 4.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **22** (15 mg, 50%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.10 (t, *J* = 7.9 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 2H), 6.32 (d, *J* = 1.1 Hz, 2H), 5.10 (s, 2H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 149.4, 145.4, 143.3, 129.1, 118.9, 115.9, 110.9, 110.6, 58.8, 57.8, 26.4; IR (ATR) 3402, 2986, 2926, 1728, 1601, 1499, 1151, 1133, 746, 694 cm^{-1}; HRMS (CI) *m/z* 260.1292 (260.1287 calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$).



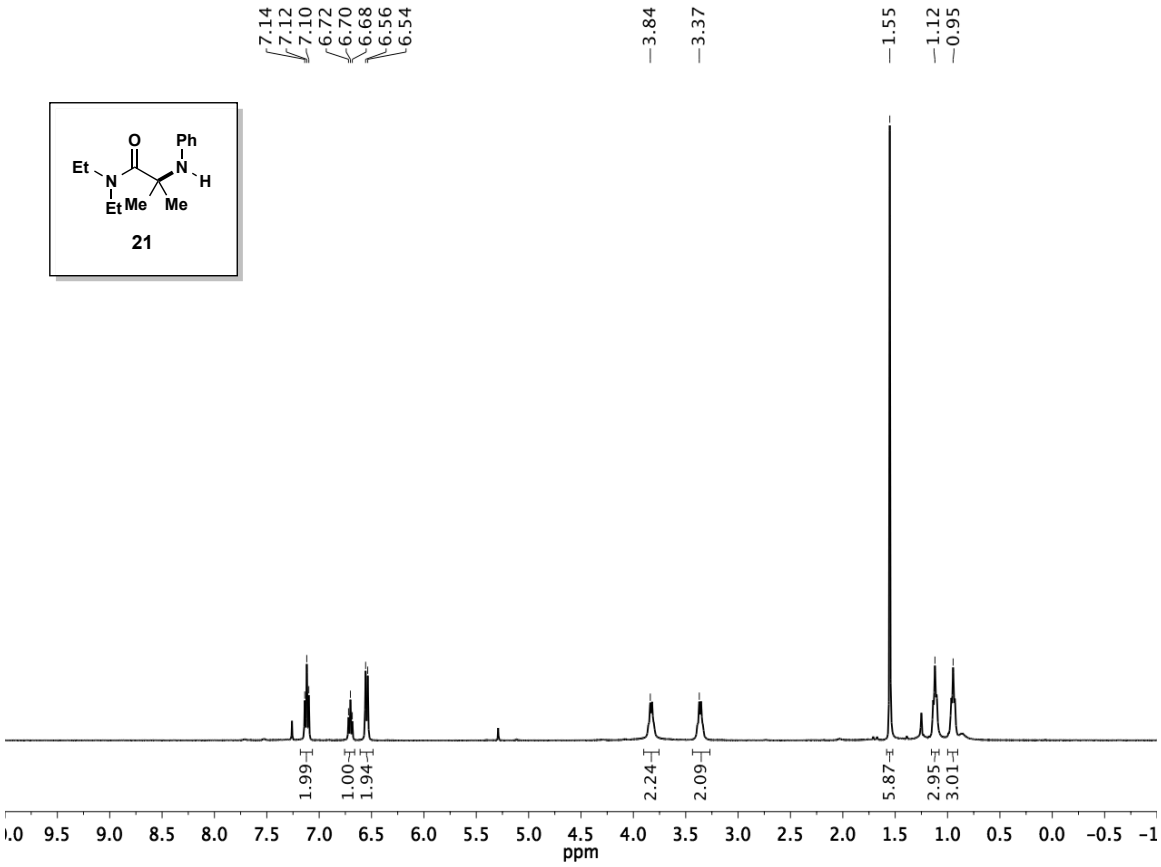
Methyl 2-phenyl-2-(phenylamino)propanoate (23): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-15** (53.0 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 6.0 mL, 0.6 mmol, 4.8 equiv) was added slowly until a deep

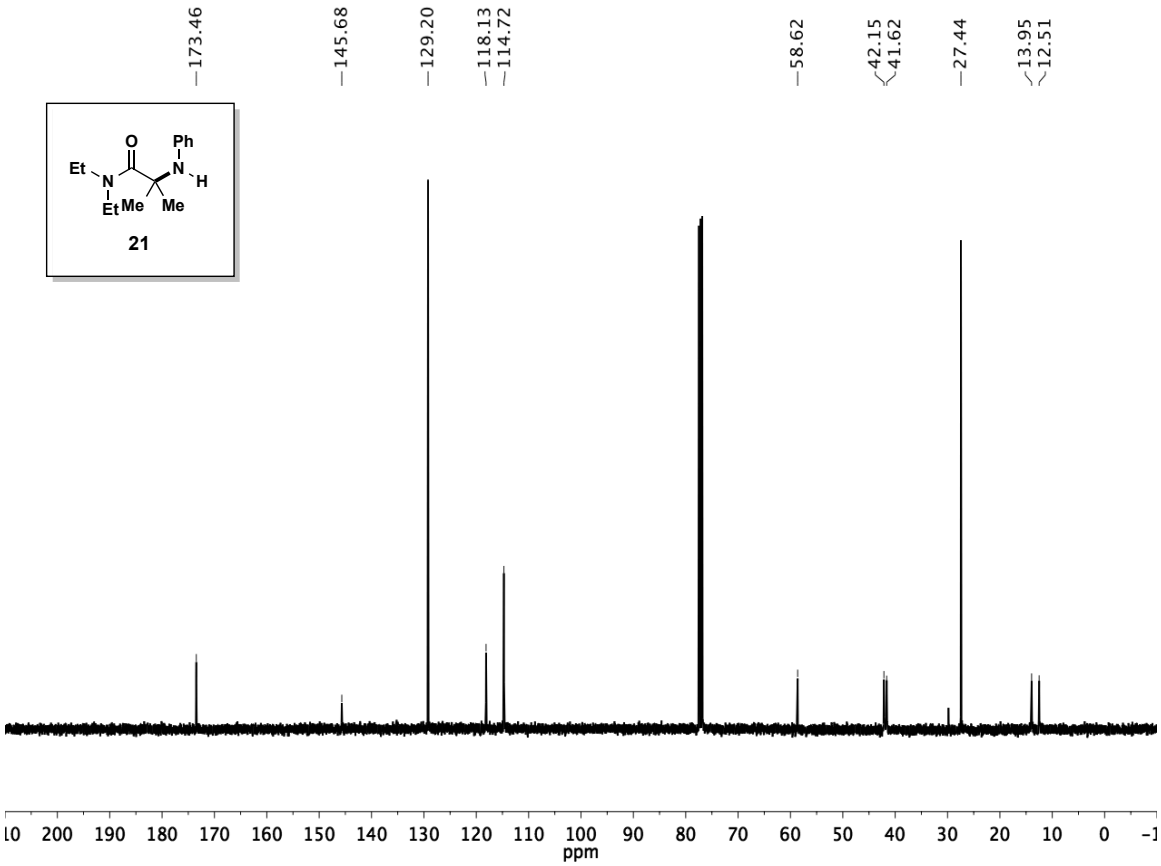
blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **23** (24 mg, 75 %) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.9 Hz, 2H), 6.64 (t, J = 7.3 Hz, 1H), 6.39 (d, J = 7.8 Hz, 2H), 5.23 (s, 1H), 3.67 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 144.5, 141.1, 128.8, 128.6, 127.6, 126.8, 117.6, 115.3, 63.0, 53.1, 22.9; IR (ATR) 3401, 3053, 3003, 2951, 1728, 1601, 1500, 1257, 749, 696 cm^{-1}; HRMS (CI) *m/z* 255.1269 (255.1259 calcd for $C_{16}H_{17}NO_2$ $[M]^+$).

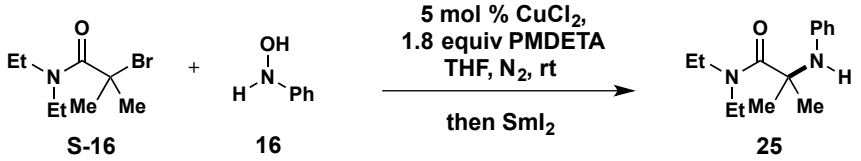


Ethyl 2-phenyl-2-(phenylamino)acetate (24): According to the general procedure B, a round bottom flask containing a suspension of α-bromocarbonyl **S-4** (61.1 mg, 0.250 mmol, 1.0 equiv), Cu(0) (15.8 mg, 0.250 mmol, 1.0 equiv) and nitrosobenzene **6** (16.1 mg, 0.150 mmol, 0.6 equiv) in THF (3.0 mL) was sparged with N_2 for 15 minutes. Sparged PMDETA (26.0 µL, 0.125 mmol, 0.5 equiv) was added to the stirred suspension at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 9.0 mL, 0.9 mmol, 3.6 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **24** (26 mg, 82%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.1 Hz, 2H), 7.38 – 7.26 (m, 3H), 7.11 (t, J = 7.9 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 7.8 Hz, 2H), 5.05 (s, 1H), 4.28 – 4.05 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 171.8, 145.9, 137.7, 129.2, 128.8, 128.2, 127.2, 118.1, 113.5, 61.8, 60.9, 14.0; IR (ATR) 3402, 3054, 2924, 1729, 1602, 1505, 1311, 1176, 748, 691 cm^{-1}; HRMS (CI) *m/z* 256.1348 (256.1338 calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$).

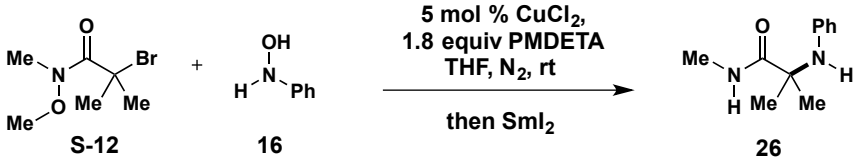






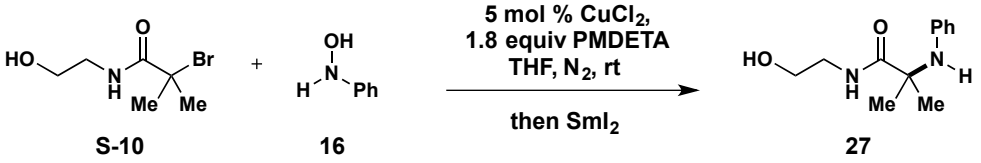
***N*,*N*-Diethyl-2-methyl-2-(phenylamino)propanamide (25):** According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-16** (48.5 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 6.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60

minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **25** (24 mg, 83%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 3.83 (q, *J* = 6.2 Hz, 2H), 3.36 (q, *J* = 6.5 Hz, 2H), 1.55 (s, 6H), 1.12 (t, *J* = 6.6 Hz, 2H), 0.95 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 145.7, 129.2, 118.1, 114.7, 58.6, 42.2, 41.6, 27.4, 14.0, 12.5; IR (ATR) 3335, 2976, 2933, 1603, 1501, 1190, 750, 697 cm^{-1}; HRMS (CI) *m/z* 235.1821 (235.1810 calcd for $C_{14}H_{23}N_2O$ $[M+H]^+$).



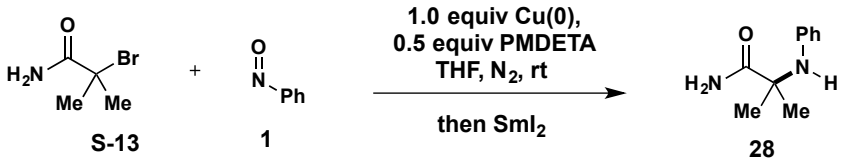
***N*,2-Dimethyl-2-(phenylamino)propanamide (26):** According to the general procedure A, $CuCl_2$ (1.8 mg, 0.013 mmol, 0.05 equiv) and PMDETA (80.0 μL, 0.383 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **S-12** (53.6 mg, 0.255 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (17.1 mg, 0.157 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 13.0 mL, 1.3 mmol, 5.1 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **26** (17 mg, 85%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H), 7.06 (s, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 2H), 2.81 (d, *J* = 4.9 Hz, 3H), 1.50 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 144.8, 129.2, 119.2, 116.0, 58.2, 26.5, 26.1; IR

(ATR) 3385, 3333, 3054, 2983, 2935, 2873, 1652, 1602, 1498, 1314, 1260 cm^{-1}; HRMS (EI) *m/z* 192.1264 (192.1263 calcd for $C_{11}H_{16}N_2O$ $[M]^+$).

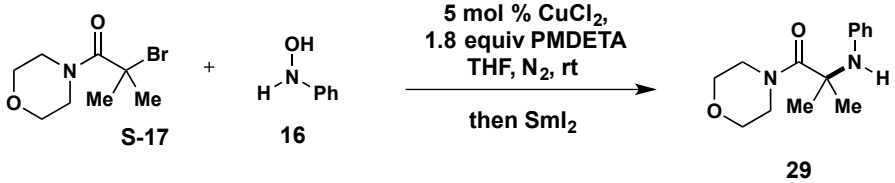


S-10 16 27

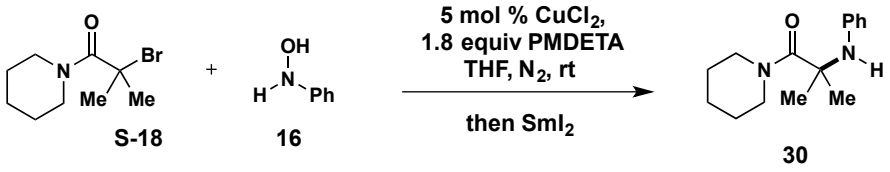
***N*-(2-Hydroxyethyl)-2-methyl-2-(phenylamino)propanamide (27):** According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.45 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-10** (52.2 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.2 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes. The solution was then rinsed with 10% aqueous $Na_2S_2O_3$ (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified via column chromatography to afford **27** (20 mg, 72%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.17 (t, *J* = 7.7 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 2H), 3.67 (t, *J* = 4.8 Hz, 2H), 3.39 (q, *J* = 5.1 Hz, 2H), 1.49 (s, 6H), 1.31 – 1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 144.5 129.2, 119.2, 115.8, 62.6, 58.03, 42.7, 26.0; IR (ATR) 3328, 2982, 2933, 2872, 1647, 1602, 1519, 1498, 754, 697 cm^{-1}; HRMS (CI) *m/z* 223.1457 (223.1447 calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$).



2-Methyl-2-(phenylamino)propanamide (28): According to the general procedure B, a round bottom flask containing a suspension of α-bromocarbonyl **S-13** (41.0 mg, 0.250 mmol, 1.0 equiv), Cu(0) (15.8 mg, 0.150 mmol, 1.0 equiv) and nitrosobenzene **1** (16.1 mg, 0.150 mmol, 0.60 equiv) in THF (3.0 mL) was sparged with N_2 for 15 minutes. Sparged PMDETA (26.0 μL, 0.125 mmol, 0.50 equiv) was added to the suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 6.0 mL, 0.6 mmol, 4.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes. The solution was then rinsed with 10% aqueous $Na_2S_2O_3$ (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified via column chromatography to afford **28** (21 mg, 95%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 7.9 Hz, 2H), 6.86 (s, 1H), 6.79 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.9 Hz, 2H), 5.50 (s, 1H), 3.88 (s, 1H), 1.50 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 144.6, 129.1, 119.1, 115.8, 57.8, 25.9; IR (ATR) 3455, 3335, 2984, 2927, 2854, 1666, 1603, 1498, 752, 695 cm^{-1}; HRMS (CI) *m/z* 179.1191 (179.1184 calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$).

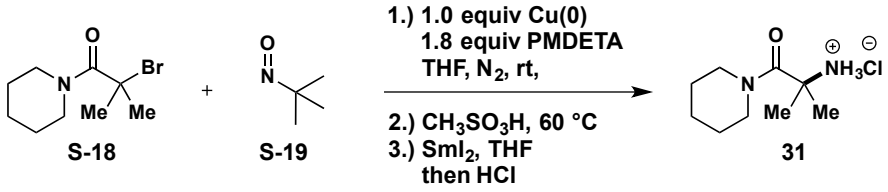


2-Methyl-1-morpholino-2-(phenylamino)propan-1-one (29): According to the general procedure A, $CuCl_2$ (1.8 mg, 0.013 mmol, 0.05 equiv) and PMDETA (80.0 μL, 0.383 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **S-17** (60.5 mg, 0.256 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (17.0 mg, 0.156 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 8.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **29** (29 mg, 92%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 2H), 4.20 – 3.14 (m, 8H), 1.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 144.9, 129.3, 118.5, 114.5, 66.8, 58.5, 47.3 (N-CH_2), 43.9 (N-CH_2), 27.04; IR (ATR) 3342, 2995, 2847, 1605, 1524, 1424, 1112, 1037 cm^{-1}; HRMS (CI) *m/z* 249.1615 (249.1603 calcd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$).



2-Methyl-2-(phenylamino)-1-(piperidin-1-yl)propan-1-one (30): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.45 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-18** (58.2 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of

phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.2 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **30** (28 mg, 90%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.0 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 2H), 3.65 (s, 5H), 1.54 (s, 6H), 1.51 – 1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 145.8, 129.4, 118.1, 114.6, 58.7, 27.6, 26.4, 25.0, 19.8; IR (ATR) 3352, 3332, 3032, 2998, 2938, 2857, 1603, 1428, 1320, 745, 693 cm^{-1}; HRMS (CI) *m/z* 247.1802 (247.1810 calcd for $C_{15}H_{23}N_2O$ $[M+H]^+$).

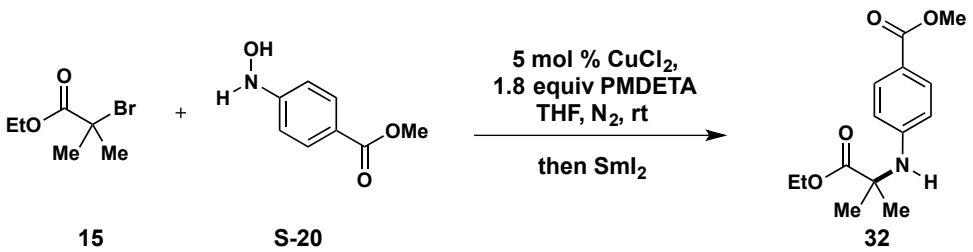


2-Methyl-1-oxo-1-(piperidin-1-yl)propan-2-aminium chloride (31): Step 1: A round bottom flask containing a suspension of α-bromocarbonyl **S-18** (174.6 mg, 0.740 mmol, 1.0 equiv), Cu(0) (47.0 mg, 0.740 mmol, 1.0 equiv) and 2-methyl-2-nitrosopropane dimer **S-19** (38.8 mg, 0.220 mmol, 0.3 equiv) in THF (9.0 mL) was sparged with N_2 for 15 minutes. Sparged PMDETA (75.0 μL, 0.370 mmol, 0.5 equiv) was added to the suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC (40 hr), the crude reaction mixture was dry loaded onto

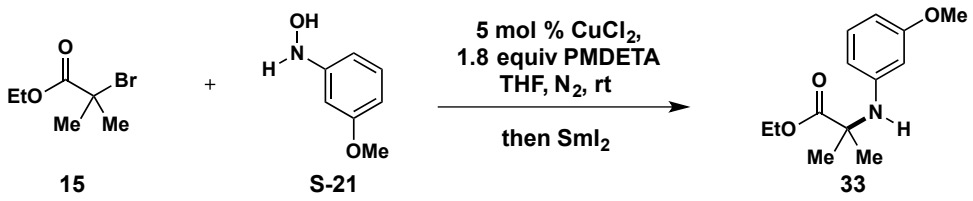
Celite and purified via column chromatography to afford the alkoxyamine dimer (131 mg, 89%).

Step 2: A flask was charged with the alkoxyamine dimer (131 mg, 0.330 mmol) and methanesulfonic acid (5 mL), and the solution was stirred at 60 °C for 14 h. The reaction mixture was cooled to room temperature and then diluted with CH_2Cl_2. The solution was washed with saturated aqueous Na_2CO_3, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the deprotected dimer (85 mg, 76%).

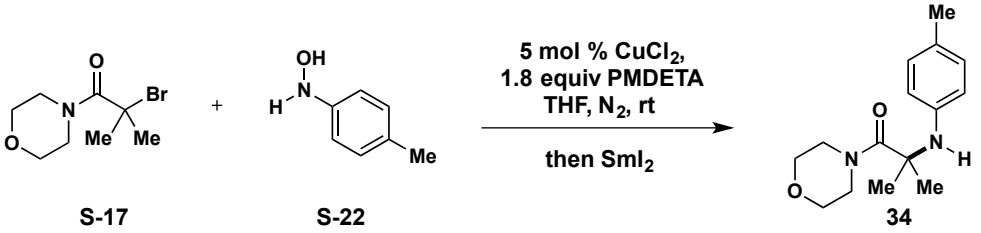
Step 3: A solution of the deprotected dimer (60 mg, 0.177 mmol) in THF (1.5 mL) was sparged with N_2 for 15 minutes. A solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 8.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (10 mL), extracted with 1 N HCl (10 mL). The acidic aqueous solution was made basic (pH 11) with 4 M NaOH, resulting in the formation of a precipitate. The basic aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The material was dissolved in Et_2O (10 mL), and 1 N HCl in Et_2O was added until the solution was acidic (pH 1) and a precipitate formed. The Et_2O was decanted to afford the hydrochloride salt **31** (27 mg, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.64 – 3.57 (m, 4H), 1.76 – 1.69 (m, 2H), 1.67 (s, 6H), 1.64 – 1.57 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.66, 57.94, 45.78, 25.73, 23.86, 22.26; IR (ATR) 3399, 2939, 1634, 151, 1233, 1187, 465 cm^{-1}; HRMS (ESI) *m/z* 193.1296 (193.1317 calcd for $C_9H_{18}N_2ONa$ $[M+Na]^+$).



Methyl 4-((1-ethoxy-2-methyl-1-oxopropan-2-yl)amino)benzoate (32): According to the general procedure A, $CuCl_2$ (1.9 mg, 0.014 mmol, 0.05 equiv) and PMDETA (82.0 µL, 0.393 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **15** (51.4 mg, 0.264 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **S-20** (27.0 mg, 0.162 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 9.0 mL, 0.90 mmol, 3.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **32** (29 mg, 84%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 8.7 Hz, 2H), 4.77 – 4.40 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.59 (s, 6H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 167.3, 149.7, 131.35, 119.1, 113.3, 61.7, 57.3, 51.7, 26.1, 14.2; IR (ATR) 3378, 2985, 2949, 1728, 1709, 1605, 1278, 1179, 1147, 1110 cm^{-1}; HRMS (EI) *m/z* 265.1309 (265.1314 calcd for $C_{14}H_{19}NO_4$ $[M]^+$).



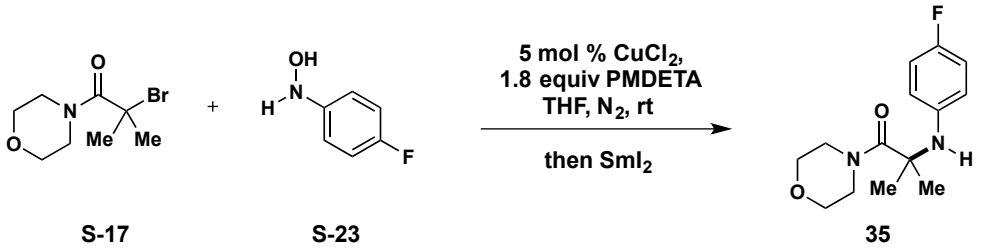
Ethyl 2-((3-methoxyphenyl)amino)-2-methylpropanoate (33): According to the general procedure A, $CuCl_2$ (1.8 mg, 0.013 mmol, 0.05 equiv) and PMDETA (80.0 μL, 0.383 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **15** (49.8 mg, 0.255 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **S-21** (21.9 mg, 0.157 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 5 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 9.0 mL, 0.90 mmol, 3.5 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **33** (28 mg, 91%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 7.7 Hz, 1H), 6.19 (d, *J* = 7.9 Hz, 1H), 6.16 (s, 1H), 4.17 (q, *J* = 6.9 Hz, 2H), 3.74 (s, 3H), 1.56 (s, 6H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 160.6, 146.9, 129.9, 108.4, 103.9, 101.6, 61.4, 57.7, 55.2, 26.4, 14.3; IR (ATR) 3398, 2984, 2937, 2836, 1726, 1598, 1260, 1212, 1143 cm^{-1}; HRMS (EI) *m/z* 237.1363 (237.1365 calcd for $C_{13}H_{19}NO_3$ $[M]^+$).



S-17 **S-22** **34**

2-Methyl-1-morpholino-2-(*p*-tolylamino)propan-1-one (34): According to the general procedure A, $CuCl_2$ (1.8 mg, 0.013 mmol, 0.05 equiv) and PMDETA (80.0 μL, 0.383 mmol,

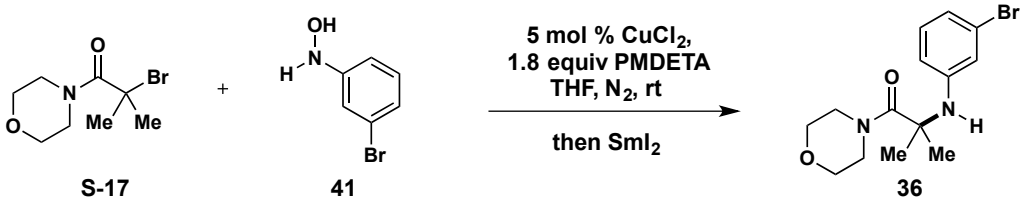
1.5 equiv) were added to a solution of α-bromocarbonyl **S-22** (60.3 mg, 0.255 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **S-17** (19.2 mg, 0.156 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 3.9 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **34** (32 mg, 95%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 7.3 Hz, 2H), 6.49 (s, 2H), 4.22 – 3.26 (m, 9H), 2.21 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 142.5, 129.9, 127.9, 114.9, 66.9, 58.8, 47.2 (N-CH_2), 44.0 (N-CH_2), 27.2, 20.5; IR (ATR) 3334, 3009, 2949, 2920, 2855, 1625, 1516, 1430, 1260, 1107 cm^{-1}; HRMS (CI) *m/z* 262.1675 (262.1681 calcd for $C_{15}H_{22}N_2O_2$ $[M]^+$).



S-17 **S-23** **35**

2-((4-Fluorophenyl)amino)-2-methyl-1-morpholinopropan-1-one (35): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-17** (58.7 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution

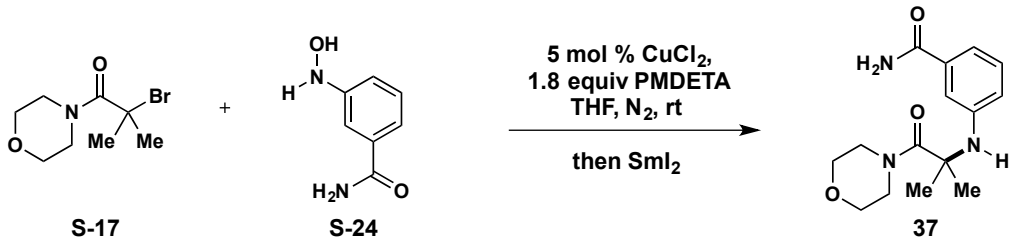
of *N*-aryl hydroxylamine **S-23** (19.0 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 4.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **35** (30 mg, 90%) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (t, *J* = 8.7 Hz, 2H), 6.47 (dd, *J* = 8.7, 4.2 Hz, 2H), 4.34 – 3.17 (m, 9H), 1.51 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 156.2 (d, *J* = 236.9 Hz), 141.32, 115.77 (d, *J* = 22.4 Hz), 115.30 (d, *J* = 6.9 Hz), 66.81, 58.69, 43.8, 27.0; IR (ATR) 3337, 2921, 2853, 1614, 1510, 1423, 1207, 114, 824 cm^{-1}; HRMS (CI) *m/z* 266.1433 (266.1431 calcd for $C_{14}H_{19}FN_2O_2$ $[M]^+$).



S-17 41 36

2-((3-Bromophenyl)amino)-2-methyl-1-morpholinopropan-1-one (36): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 μL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-17** (58.7 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **41** (28.0 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl

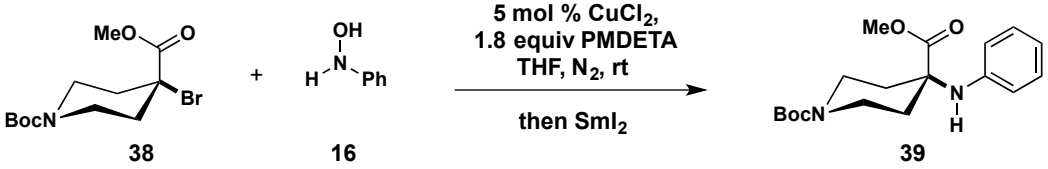
as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 4.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **36** (36 mg, 88%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.44 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.62 (s, 9H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 146.3, 130.6, 123.1, 121.2, 117.2, 112.5, 66.8, 58.4, 47.7 (N-CH_2), 43.9 (N-CH_2), 27.0; IR (ATR) 3333, 2980, 2920, 2856, 1612, 1480, 1112, 764, 686 cm^{-1}; HRMS (CI) *m/z* 327.0703 (327.0708 calcd for $C_{14}H_{20}N_2O_2Br$ $[M+H]^+$).



S-17 S-24 37

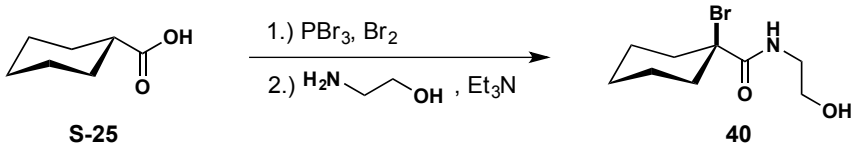
3-((2-Methyl-1-morpholino-1-oxopropan-2-yl)amino)benzamide (37): According to general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 µL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **S-17** (72.8 mg, 0.249 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **S-24** (22.8 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 8.0 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60

minutes. The solution was then rinsed with 10% aqueous $Na_2S_2O_3$ (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via column chromatography to afford **37** (26 mg, 72%) as a light yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.16 (t, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.03 (t, *J* = 2.0 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.01 (s, 2H), 3.64 (t, *J* = 4.5 Hz, 2H), 3.58 (s, 2H), 3.53 – 3.49 (m, 2H), 3.22 (s, 2H), 1.51 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 173.8, 171.5, 146.1, 134.6, 128.7, 116.0, 115.50, 112.9, 66.6, 57.5, 43.6, 25.5; IR (ATR) 3344, 2925, 1606, 1436, 1114, 479 cm^{-1}; HRMS (ESI) *m/z* 314.1468 (314.1481 calcd for $C_{15}H_{21}N_3O_3Na$ $[M+Na]^+$).



1-(*tert*-Butyl) 4-methyl 4-(phenylamino)piperidine-1,4-dicarboxylate (39): According to the general procedure A, $CuCl_2$ (1.7 mg, 0.013 mmol, 0.05 equiv) and PMDETA (94.0 µL, 0.450 mmol, 1.8 equiv) were added to a solution of α-bromocarbonyl **38** (80.3 mg, 0.249 mmol, 1.0 equiv) in THF (3.0 mL) and the solution was sparged with N_2 for 15 minutes. A solution of phenylhydroxylamine **16** (16.4 mg, 0.150 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 6.0 mL, 0.6 mmol, 2.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **39** (37 mg, 89%) as a light brown oil. ^{1}H NMR (400 MHz,

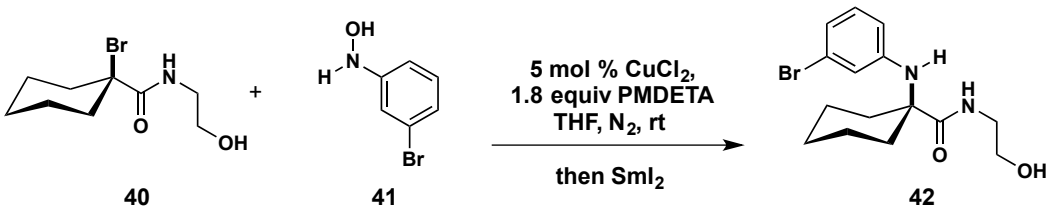
$CDCl_3$) δ 7.14 (t, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 3.66 (s, 5H), 3.32 (ddd, *J* = 13.5, 9.9, 3.3 Hz, 2H), 2.11 (ddd, *J* = 14.0, 9.9, 4.1 Hz, 2H), 1.96 (dt, *J* = 13.6, 4.1 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 154.7, 144.7, 129.1, 119.2, 115.8, 79.7, 58.6, 52.3, 39.2, 32.8, 28.4; IR (ATR) 3358, 2974, 2929, 1730, 1673, 1422, 1153, 1061, 748, 694 cm^{-1}; HRMS (CI) *m/z* 334.1889 (334.1893 calcd for $C_{18}H_{26}N_2O_4$ $[M]^+$).



S-25 **40**

1-Bromo-*N*-(2-hydroxyethyl)cyclohexane-1-carboxamide (40): To a flask fitted with a reflux condenser containing cyclohexanecarboxylic acid **S-25** (3.0128 g, 23.5063 mmol, 1.0 equiv) was added PBr_3 (0.670 mL, 7.059 mmol, 0.3 equiv). The solution was heated to 110 °C and after 1 hour Br_2 (3.0 mL, 58.6 mmol, 2.5 equiv) was added, dropwise over 4 hours. The reaction was then stirred for 13 hours at 110 °C. The reaction was cooled to room temperature and the solution was vigorously sparged with N_2 into a saturated solution of sodium thiosulfate. After sparging for 3 hours the crude residue was dissolved in CH_2Cl_2 (47 mL) and cooled to 0 °C. To the solution was then added Et_3N (13.1 mL, 94.0 mmol, 4.0 equiv) followed by ethanolamine (2.9 mL, 48.0 mmol, 2.0 equiv). The solution was allowed to warm to room temperature and stirred for 5 hours. The solvent was then removed and the crude residue was purified via column chromatography to afford **40** (3.1 g, 52%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 3.73 (t, *J* = 5.1 Hz, 2H), 3.44 (q, *J* = 5.3 Hz, 2H), 2.56 (s, 1H), 2.15 – 1.99 (m, 4H), 1.80 – 1.57 (m, 5H), 1.36 – 1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 71.4, 62.0, 43.0, 38.2, 24.8, 22.9; IR (ATR) 3339, 2934, 2861, 1645, 1529,

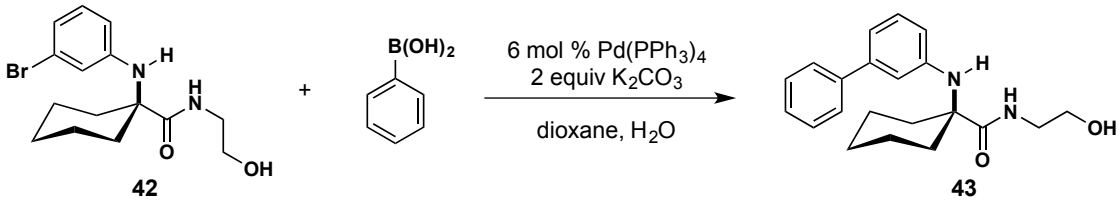
1446, 1061, 877 cm^{-1}; HRMS (ESI) *m/z* 272.0253 (272.0262 calcd for $C_9H_{16}NO_2NaBr$ $[M+Na]^+$).



40 41 42

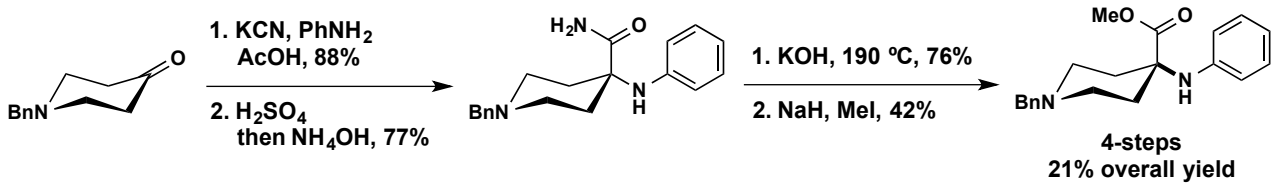
1-((3-Bromophenyl)amino)-*N*-(2-hydroxyethyl)cyclohexane-1-carboxamide (42): According to the general procedure, $CuCl_2$ (1.8 mg, 0.013 mmol, 0.05 equiv) and PMDETA (82.0 μL, 0.393 mmol, 1.5 equiv) were added to a solution of α-bromocarbonyl **40** (65.5 mg, 0.262 mmol, 1.0 equiv) in THF (2.5 mL) and the solution was sparged with N_2 for 15 minutes. A solution of *N*-aryl hydroxylamine **41** (29.8 mg, 0.158 mmol, 0.6 equiv) in sparged THF (1 mL) was then added via syringe pump over 10 hours. Following consumption of the α-bromo carbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 13.0 mL, 1.3 mmol, 10.4 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes. The solution was then rinsed with 10% aqueous $Na_2S_2O_3$ (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via column chromatography to afford **42** (13 mg, 28%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.76 (s, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.08 (s, 1H), 3.65 (t, *J* = 5.0 Hz, 2H), 3.38 (q, *J* = 5.4 Hz, 2H), 2.66 (s, 1H), 2.02 – 1.87 (m, 4H), 1.69 – 1.52 (m, 3H), 1.35 – 1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 145.5, 130.5, 123.0, 122.1, 118.9, 114.5, 62.5, 60.5, 42.5, 31.3, 25.1, 21.1; IR (ATR) 3356,

2930, 2857, 1646, 1594, 1515, 1477, 1286, 1167, 1071 cm^{-1}; HRMS (ESI) *m/z* 363.0688 (363.0684 calcd for $C_{15}H_{21}N_2O_2NaBr$ $[M]^+$).



1-([1,1'-Biphenyl]-3-ylamino)-*N*-(2-hydroxyethyl)cyclohexane-1-carboxamide (43): To a solution of42**8** (19.4 mg, 0.057 mmol, 1.0 equiv) in dioxane (0.225 mL) and H_2O (0.060 mL) was added phenylboronic acid (10.8 mg, 0.089 mmol, 1.6 equiv) followed by tetrakis(triphenylphosphine)palladium (4.0 mg, 0.0035 mmol, 0.06 equiv) and potassium carbonate (15.9 mg, 0.115 mmol, 2.0 equiv). The solution was stirred at 110 °C for 12 hours. The reaction was then cooled to room temperature and quenched with saturated sodium bicarbonate (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford **43** (19 mg, 98%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 1H), 7.54 – 7.48 (m, 3H), 7.47 – 7.37 (m, 3H), 7.34 – 7.28 (m, 1H), 7.26 – 7.20 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 3.69 – 3.62 (m, 2H), 3.41 (q, *J* = 5.4 Hz, 2H), 2.71 (s, 1H), 1.99 (s, 4H), 1.65 – 1.56 (m, 3H), 1.37 – 1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 144.4, 142.4, 141.1, 132.2, 129.6, 128.9, 127.5, 127.2, 118.4, 115.1, 62.8, 60.6, 42.8, 31.4, 25.2, 21.3; IR (ATR) 3362, 2927, 2856, 1652, 1599, 1574, 1516, 1480, 1168, 1073 cm^{-1}; HRMS (ESI) *m/z* 361.1891 (361.1892 calcd for $C_{21}H_{26}N_2O_2Na$ $[M]^+$).

Scheme S1. Standard Synthesis of Carfentanil Precursor[3]



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8.3 Supporting Information for Chapter 5: A Three Component Coupling of Arylboronic Acids, *t*-Buty Nitrite and Alkyl Halides for the Synthesis of Hindered Anilines

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of N_2 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 or anisaldehyde. 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 (at 100, 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 100 FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility.

General Procedure A for the Three Component Coupling Reaction: A round bottom flask containing a solution of arylboronic acid (0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 μL, 0.375 mmol, 0.90 equiv) and heated to

40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 μL, 0.21 mmol, 0.5 equiv) and α-bromo carbonyl (0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromo carbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M)[1] was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford the corresponding α-aminated adducts.

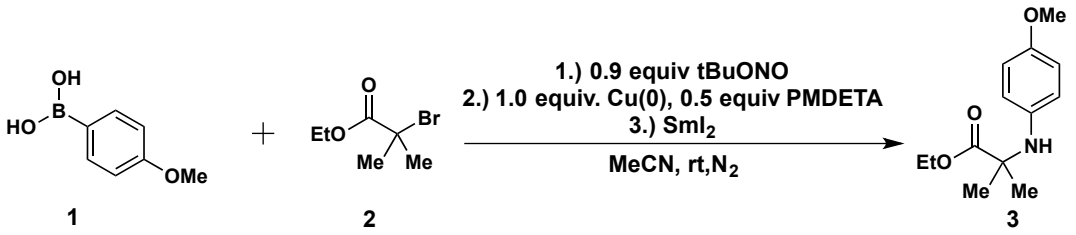
General Procedure B for the Three Component Coupling Reaction: A round bottom flask containing a solution of arylboronic acid (0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 μL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 μL, 0.21 mmol, 0.5 equiv) and α-bromo nitrile (0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromo nitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography.

A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (4.0 equiv relative to SmI_2) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M)[1] was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature or 40 ºC until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford the corresponding α-aminated adducts.

General Procedure C for the Three Component Coupling Reaction: A round bottom flask containing a solution of arylboronic acid (0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was sparged with N_2 for 10 minutes, after which, the solution was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (usually 1-2 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and benzyl bromide (0.51 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and then brine (1x 15 mL) and dried over Na_2SO_4.

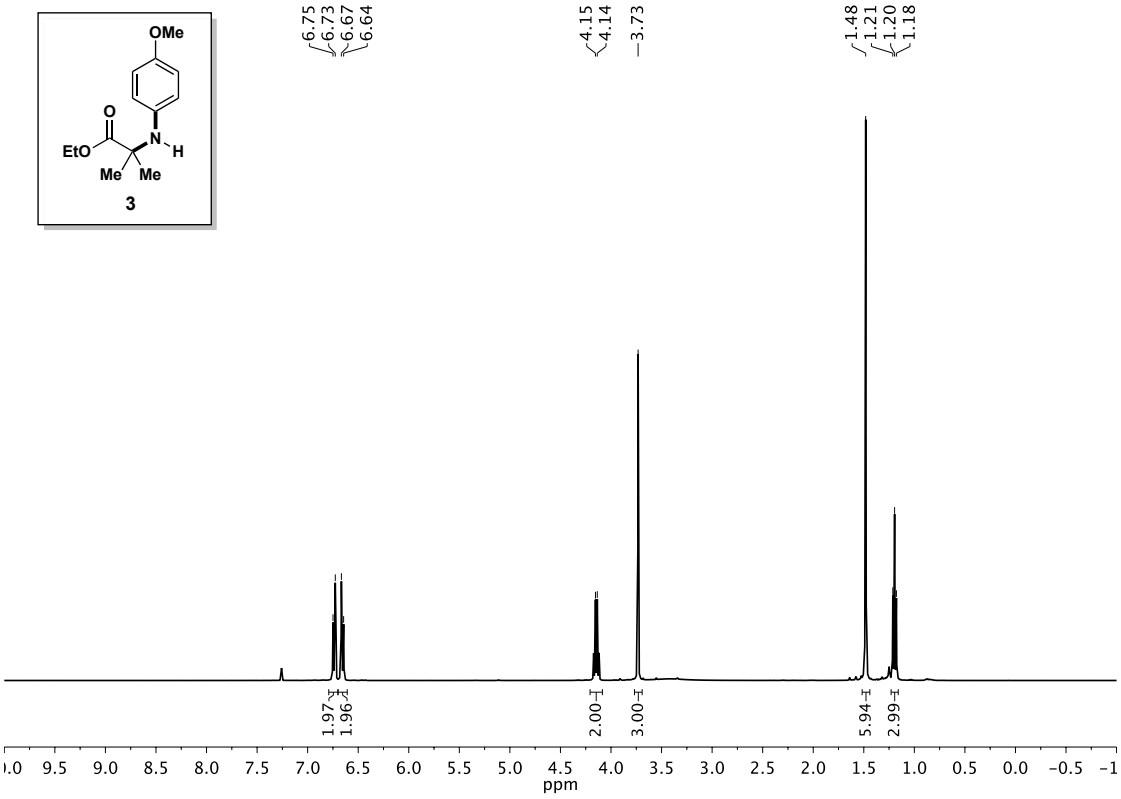
A 1 dram vial containing the resulting crude N-O alkylated adduct and a stir bar was charged with activated Zn (0) (335 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the

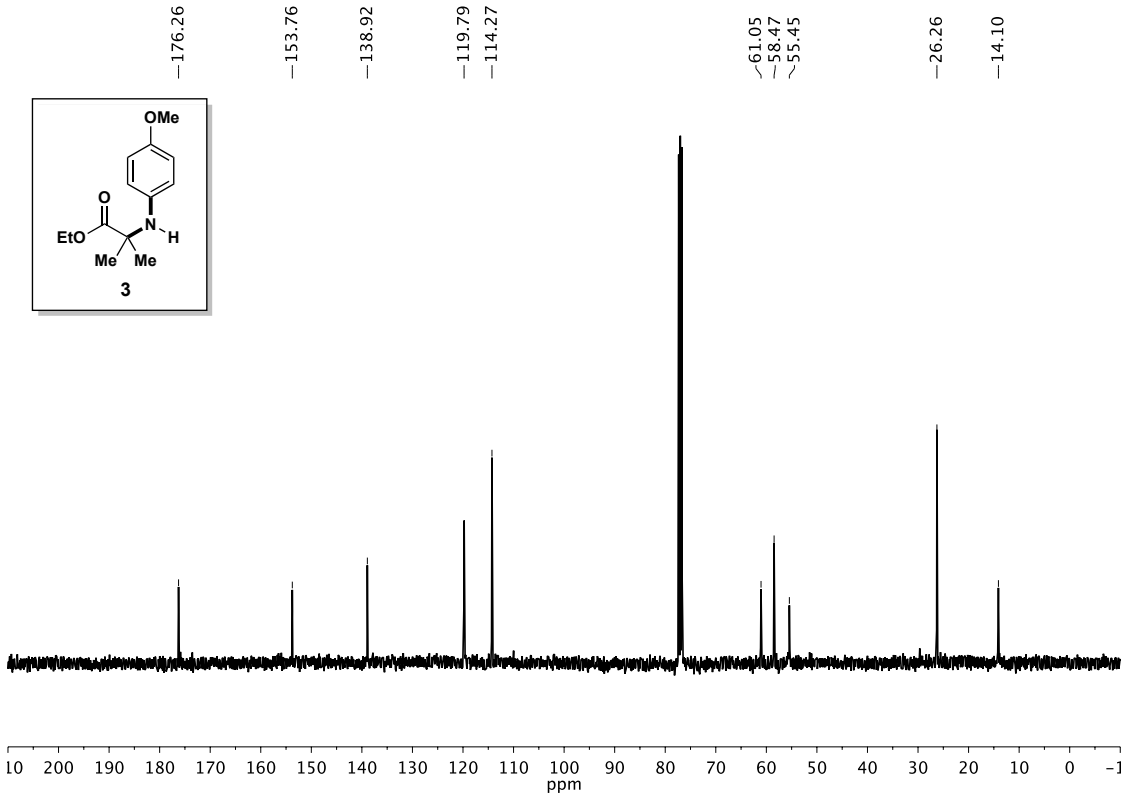
starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford the corresponding aminated adducts.

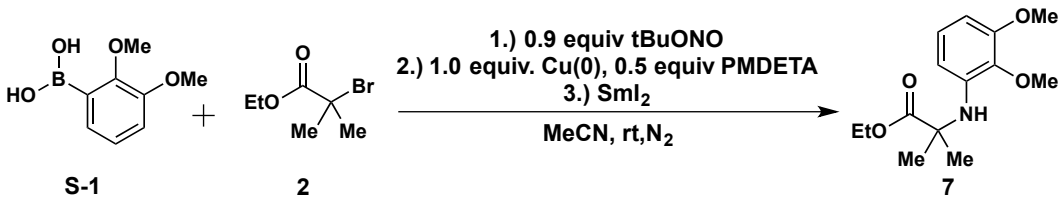


Ethyl 2-((4-methoxyphenyl)amino)-2-methylpropanoate (3): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **1** (38 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and ethyl α-bromoisobutyrate (64 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **3** (40 mg, 81%) as an

orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.70 (m, 2H), 6.70 – 6.62 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.48 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 153.8, 138.9, 119.8, 114.3, 61.0, 58.5, 55.4, 26.3, 14.1; IR (ATR) 3386, 2982, 2934, 2833, 1724, 1510, 1237, 1141,1035, 820 cm^{-1}; HRMS (ESI) *m/z* 260.1237 (260.1263 calcd for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$).

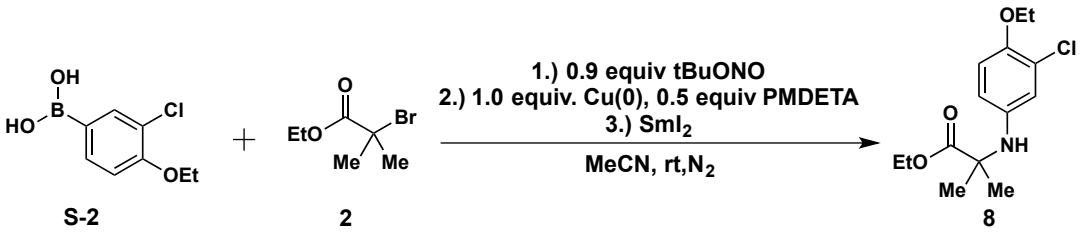






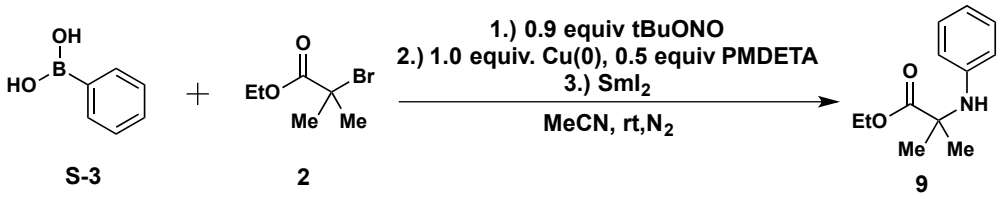
Ethyl 2-((2,3-dimethoxyphenyl)amino)-2-methylpropanoate (7): According to the general procedure A, A round bottom flask containing a solution of arylboronic acid **S-1** (46 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the

arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and ethyl α-bromoisobutyrate (64 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **7** (39 mg, 70%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (t, *J* = 8.3 Hz, 1H), 6.32 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.19 (dd, *J* = 8.2, 1.3 Hz, 1H), 4.72 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 1.57 (s, 6H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 152.4, 140.1, 136.0, 123.8, 106.1, 101.7, 61.1, 59.9, 57.2, 55.6, 26.6, 14.1; IR (ATR) 3398, 2981, 2936, 2838, 1727, 1601, 1479, 1141, 771 cm^{-1}; HRMS (ESI) *m/z* 290.1370 (290.1368 calcd for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$).



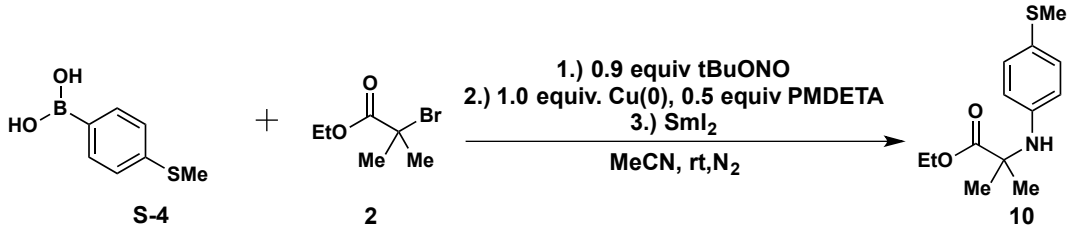
Ethyl 2-((3-chloro-4-ethoxyphenyl)amino)-2-methylpropanoate (8): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-2** (50 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via

cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 μL, 0.21 mmol, 0.5 equiv) and ethyl α-bromoisobutyrate (64 μL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **8** (44 mg, 73%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.51 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.49 (s, 6H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 148.1, 139.9, 123.5, 119.6, 116.6, 115.3, 65.6, 61.2, 58.2, 26.2, 14.9, 14.1; IR (ATR) 3395, 2980, 2935, 1726, 1498, 1476, 1276, 1232, 1143, 1058 cm^{-1}; HRMS (ESI) *m/z* 308.1027 (308.1029 calcd for $C_{14}H_{20}NO_3NaCl$ $[M+Na]^+$).



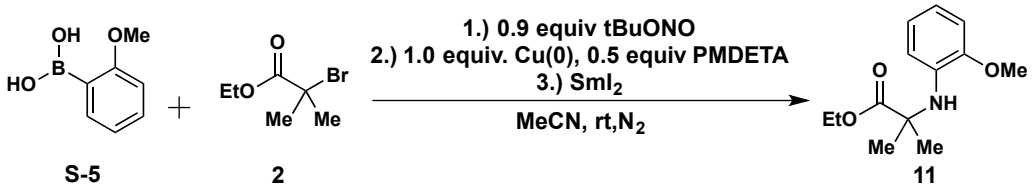
Ethyl 2-methyl-2-(phenylamino)propanoate (9): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-3** (154 mg, 1.26 mmol, 3.0 equiv) in MeCN (5.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (225 μL, 1.875 mmol, 4.5 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round

bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (1 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and ethyl α-bromoisobutyrate (64 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 10.0 mL, 1.0 mmol, 4.75 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **9** (20 mg, 49%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 2H), 6.75 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.63 – 6.56 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.56 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 145.4, 129.0, 118.5, 115.6, 61.2, 57.5, 26.2, 14.1;



Ethyl 2-methyl-2-((4-(methylthio)phenyl)amino)propanoate (10): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-4** (42 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and

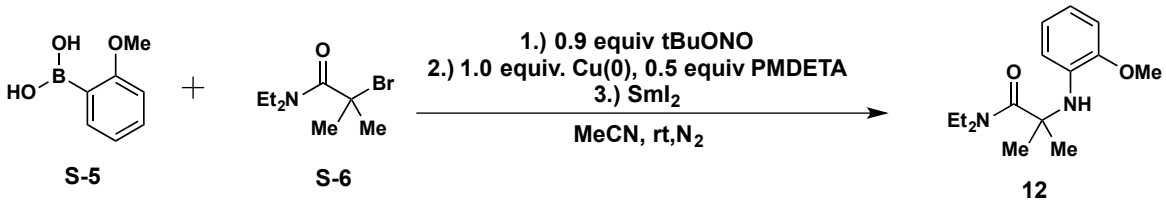
ethyl α-bromoisobutyrate (64 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **10** (46 mg, 87%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 2H), 6.56 – 6.48 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.53 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 144.1, 130.5, 125.8, 116.1, 61.3, 57.5, 26.2, 18.5, 14.1; IR (ATR) 3397, 2981, 2919, 1726, 1598, 1500, 1272, 1023, 816 cm^{-1}; HRMS (ESI) *m/z* 276.1024 (276.1034 calcd for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$).



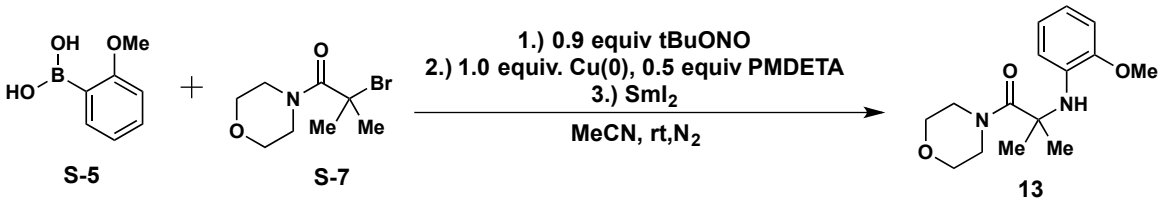
S-5 2 11

Ethyl 2-((2-methoxyphenyl)amino)-2-methylpropanoate (11): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and ethyl α-bromoisobutyrate (64 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged

suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromo carbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **11** (46 mg, 93%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.74 (m, 2H), 6.72 – 6.64 (m, 1H), 6.52 – 6.43 (m, 1H), 4.61 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.59 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 147.3, 135.3, 120.7, 117.2, 112.1, 109.5, 61.1, 56.9, 55.3, 26.2, 14.1; IR (ATR) 3423, 2950, 2936, 1728, 1602, 1512, 1144, 1027 cm^{-1}; HRMS (ESI) *m/z* 260.1254 (260.1263 calcd for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$).



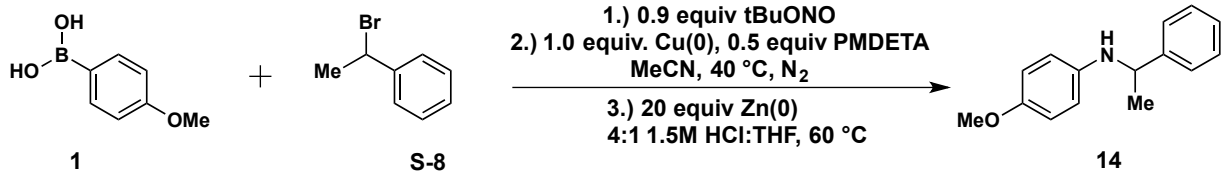
***N*,*N*-diethyl-2-((2-methoxyphenyl)amino)-2-methylpropanamide (12):** According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of 2-bromo-*N*,*N*-diethyl-2-methylpropanamide (93 mg, 0.42 mmol, 1.0 equiv) and Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) was then added to the sparged suspension, which was stirred at room



temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **12** (42 mg, 76%) as a burgundy oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 – 6.67 (m, 2H), 6.52 – 6.45 (m, 2H), 3.88 (q, 2H), 3.71 (s, 3H), 3.36 (q, J = 7.4 Hz, 2H), 1.50 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 152.3, 139.8, 115.9, 114.6, 58.8, 55.6, 42.0, 41.4, 27.4, 13.9, 12.4; IR (ATR) 3337, 2973, 2933, 2832, 1608, 1512, 1464, 1423, 1237, 1123, 1038, 821 cm^{-1}; HRMS (EI) *m/z* 264.1834 (264.1838 calcd for $C_{15}H_{24}N_2O_2$ $[M]^+$).

2-((2-methoxyphenyl)amino)-2-methyl-1-morpholinopropan-1-one (13): According to the general procedure A, a round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.250 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of 2-bromo-2-methyl-1-morpholinopropan-1-one (98 mg, 0.42 mmol, 1.0 equiv) and Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL,

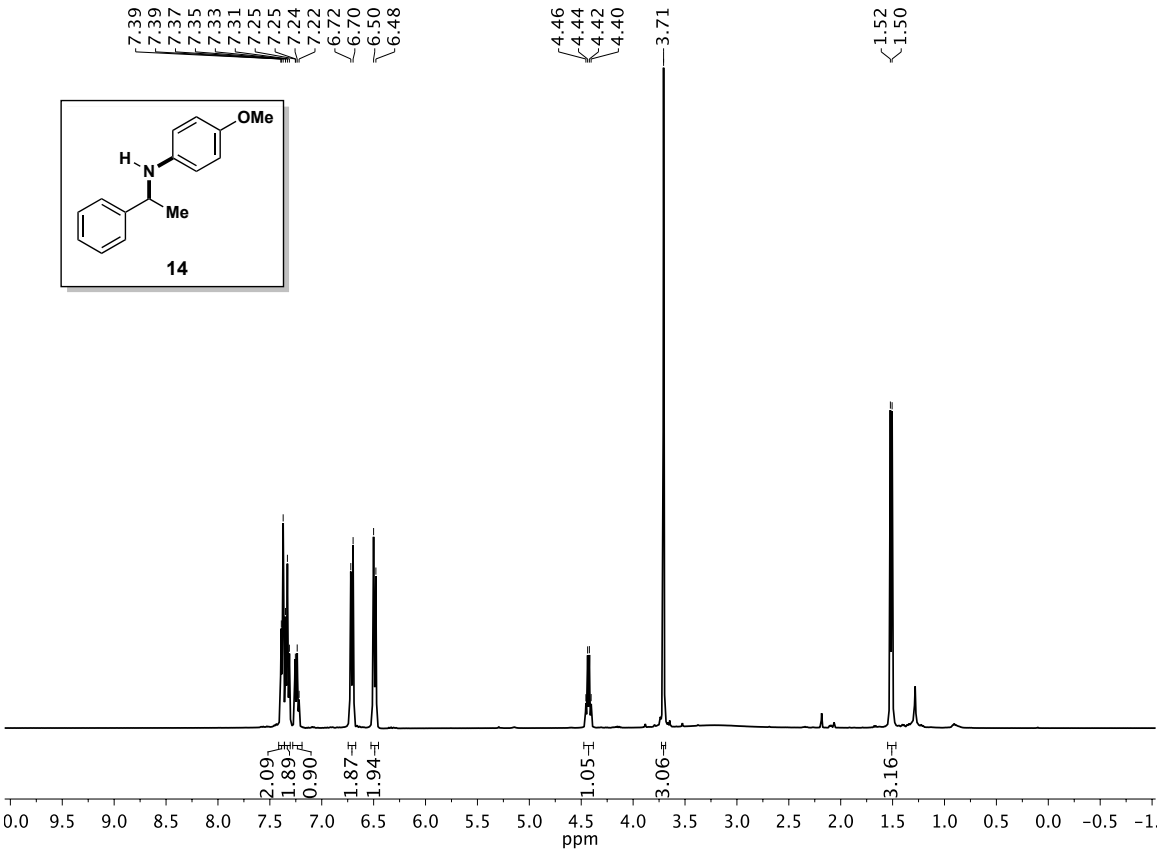
0.21 mmol, 0.5 equiv) was then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of the α-bromocarbonyl as indicated by TLC, a solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was added slowly until a deep blue color persisted. The deep blue solution was stirred for 60 minutes, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **13** (46 mg, 79 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.74 (m, 2H), 6.78 – 6.62 (m, 1H), 6.52 (dd, J = 7.8, 1.5 Hz, 1H), 4.31 (s, 1H), 4.03 (s, 2H), 3.82 (s, 3H), 3.67 (s, 2H), 3.58 (s, 2H), 3.31 (s, 2H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 146.8, 134.7, 121.0, 117.2, 111.9, 109.5, 66.9, 57.9, 55.4, 47.2, 43.6, 27.0; IR (ATR) 3392, 2921, 2854, 1629, 1509, 1416, 1223, 1111, 1027, 737 cm^{-1}; HRMS (EI) *m/z* 278.1629 (278.1630 calcd for $C_{15}H_{22}N_2O_3$ $[M]^+$).



4-methoxy-*N*-(1-phenylethyl)aniline (14): According to the general procedure C, a round bottom flask containing a solution of arylboronic acid **1** (45 mg, 0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and (1-bromoethyl)benzene (69 µL, 0.51 mmol, 1.0 equiv). The resulting suspension was sparged

for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (334 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **14** (35 mg, 62 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 – 7.19 (m, 1H), 6.71 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.8 Hz, 2H), 4.43 (q, J = 6.7 Hz, 1H), 3.71 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.5, 141.5, 128.6, 126.8, 125.9, 114.7, 114.5, 55.8, 55.6, 54.2, 25.1.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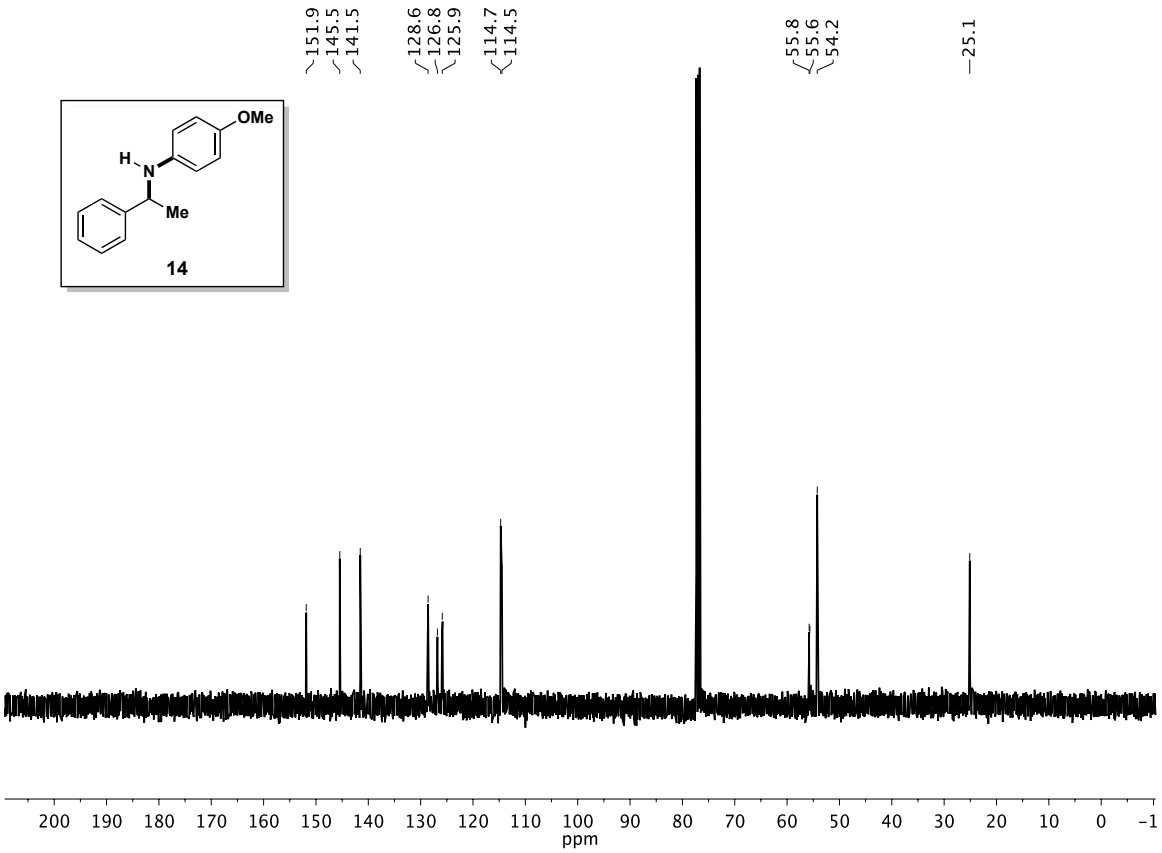
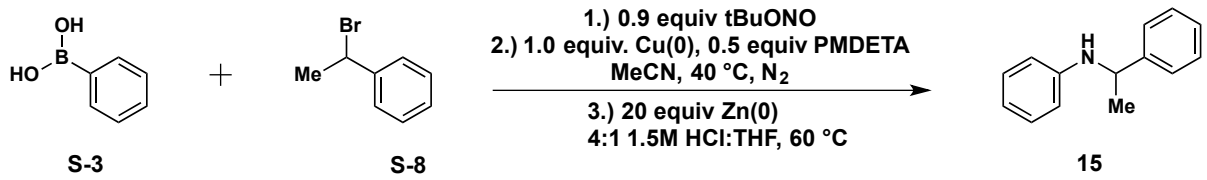
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm



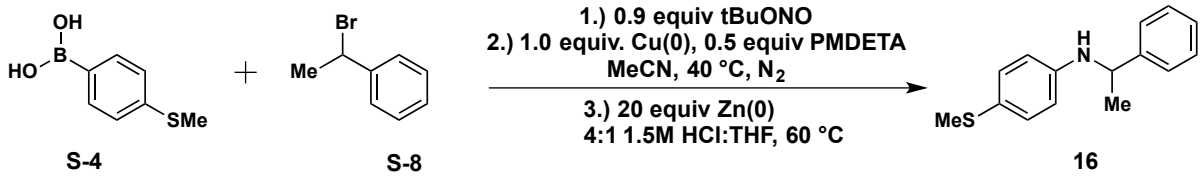


S-3 S-8 15

***N*-(1-phenylethyl)aniline (15):** According to the general procedure C, a round bottom flask containing a solution of arylboronic acid **S-3** (30 mg, 0.250 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv), PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and (1-

bromoethyl)benzene (58 μL, 0.42 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

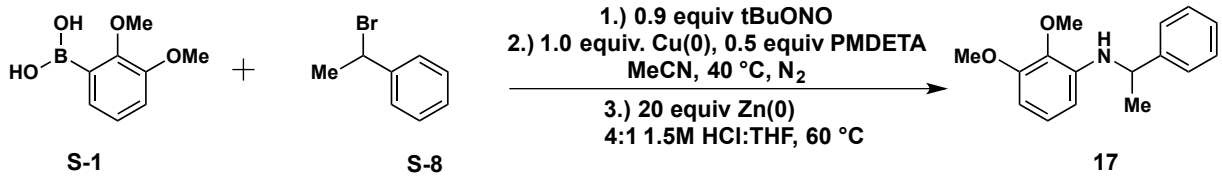
A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (275 mg, 4.2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **15** (6 mg, 14 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 4H), 7.34 – 7.19 (m, 2H), 7.16 – 7.06 (m, 2H), 6.70 (t, 1H), 6.59 (d, 2H), 4.50 (q, J = 6.8 Hz, 1H), 1.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 145.1, 129.1, 128.6, 126.8, 125.8, 117.2, 113.3, 53.5, 25.0.



4-(methylthio)-*N*-(1-phenylethyl)aniline (16): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **S-4** (42 mg, 0.25 mmol, 0.6

equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (45 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.4 mmol, 1.0 equiv), PMDETA (43 µL, 0.2 mmol, 0.5 equiv) and (1-bromoethyl)benzene (58 µL, 0.4 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (327 mg, 5 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **16** (36 mg, 75 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 7.25 (d, *J* = 9.2 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.3 Hz, 2H), 4.47 (q, *J* = 6.7 Hz, 1H), 2.37 (s, 3H), 1.53 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 144.9, 131.3, 128.7, 127.0, 125.8, 124.1, 113.9, 53.5, 25.0, 19.1.

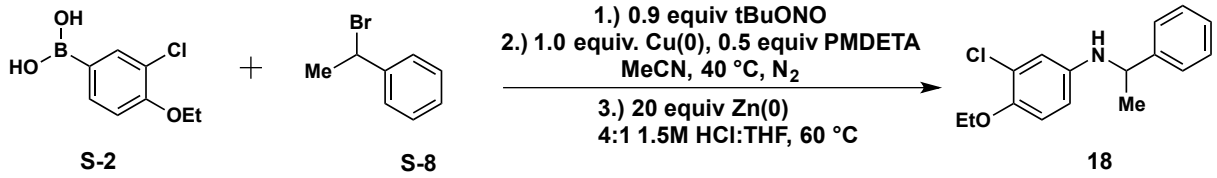


S-1 S-8 17

2,3-dimethoxy-*N*-(1-phenylethyl)aniline (17): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid (54.6 mg, 0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and (1-bromoethyl)benzene (69 µL, 0.51 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (335 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **XX** (29 mg, 45%) as a light yellow oil. ^1H

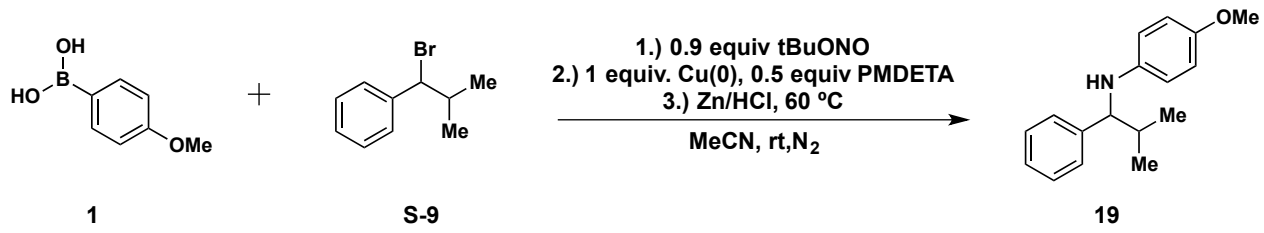
NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 4H), 7.14 (t, *J* = 7.0 Hz, 1H), 6.68 (t, *J* = 8.2 Hz, 1H), 6.18 (d, *J* = 8.3 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 4.61 (s, 1H), 4.40 (q, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 145.4, 141.4, 135.1, 128.6, 126.8, 125.8, 124.2, 105.5, 101.1, 59.9, 55.7, 53.3, 25.1.



3-chloro-4-ethoxy-*N*-(1-phenylethyl)aniline (18): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **S-2** (60.1 mg, 0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and (1-bromoethyl)benzene (69 µL, 0.51 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (334 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of

the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **18** (18 mg, 27 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.27 – 7.20 (m, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 8.7, Hz, 1H), 4.40 (q, *J* = 6.7 Hz, 1H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 1H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 144.9, 142.4, 128.7, 127.0, 125.8, 124.2, 116.4, 115.3, 112.3, 66.0, 54.0, 25.0, 15.0.

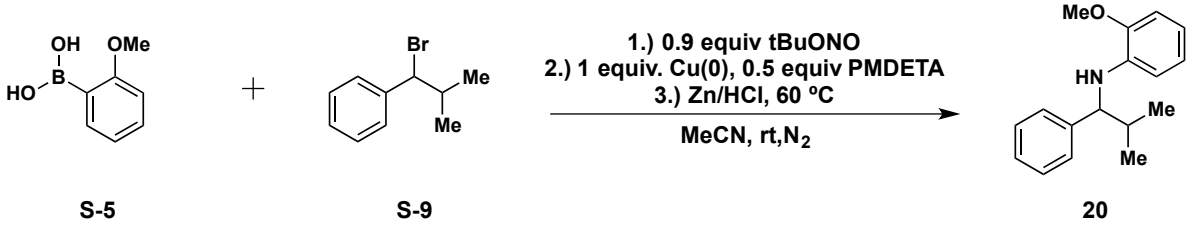


1 S-9 19

4-methoxy-*N*-(2-methyl-1-phenylpropyl)aniline (19): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **1** (38 mg, 0.25 mmol, 1 equiv) in MeCN (1.0 mL) was treated with *t*-BuONO (45 µL, 0.375 mmol, 1.5 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (usually 1-2 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv), PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and (1-bromo-2-methylpropyl)benzene (89 mg, 0.42 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the

reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (275 mg, 4.2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **19** (33 mg, 62 %) as a light pink oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 4.4 Hz, 4H), 7.23 (dt, J = 8.7, 4.3 Hz, 1H), 6.69 (d, J = 8.6 Hz, 2H), 6.48 (s, 2H), 4.07 (bs, 1H), 3.69 (s, 3H), 2.04 (h, J = 6.7 Hz, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 142.7, 141.9, 128.1, 127.2, 126.7, 114.7, 114.0, 64.6, 55.7, 34.9, 19.7, 18.7; IR (ATR) 3404, 2956, 1724, 1618, 1508, 1452, 1231, 1038, 816, 760, 702 cm^{-1}; HRMS (EI) *m/z* 255.1616 (255.1623 calcd for $C_{17}H_{21}NO$ $[M]^+$).

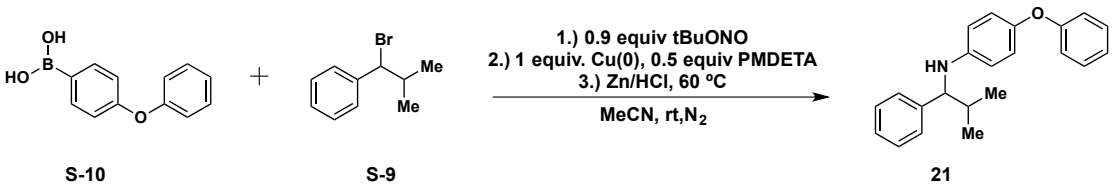


S-5 **S-9** **20**

2-methoxy-*N*-(2-methyl-1-phenylpropyl)aniline (20): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.25 mmol, 1 equiv) in MeCN (1.0 mL) was treated with *t*-BuONO (45 µL, 0.375 mmol, 1.5 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (usually 1-2 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv), PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and (1-bromo-2-methylpropyl)benzene (89 mg, 0.42 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (275 mg, 4.2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **20** (38 mg, 71 %) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H), 7.26 – 7.17 (m, 1H), 6.77 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.69 (td, *J* = 7.7, 1.5 Hz, 1H), 6.59 (td, *J* = 7.7, 1.6 Hz, 1H), 6.33 (dd, *J* = 7.8, 1.6

Hz, 1H), 4.81 (s, 1H), 4.13 (d, J = 5.9 Hz, 1H), 3.91 (s, 3H), 2.10 (dq, J = 13.4, 6.7 Hz, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 142.8, 137.6, 128.1, 127.2, 126.7, 121.1, 115.9, 110.7, 109.2, 63.7, 55.5, 34.9, 19.8, 18.7; IR (ATR) 3437, 2957, 1601, 1508, 1453, 1242, 1229, 1027, 734, 701 cm^{-1}; HRMS (EI) *m/z* 255.1618 (255.1623 calcd for $C_{17}H_{21}NO$ $[M]^+$).

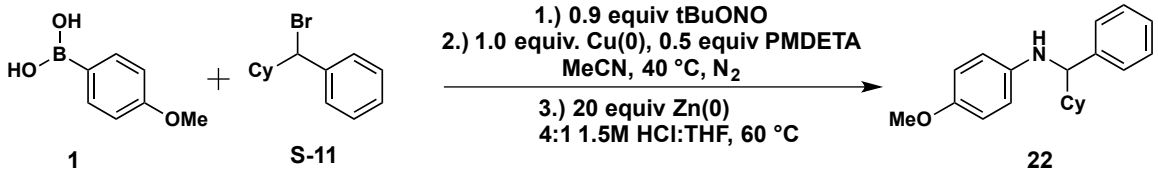


S-10 S-9 21

4-phenoxy-*N*-(1-phenylethyl)aniline (21): According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **S-10** (64.2 mg, 0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and (1-bromoethyl)benzene (69 µL, 0.51 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (334 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of

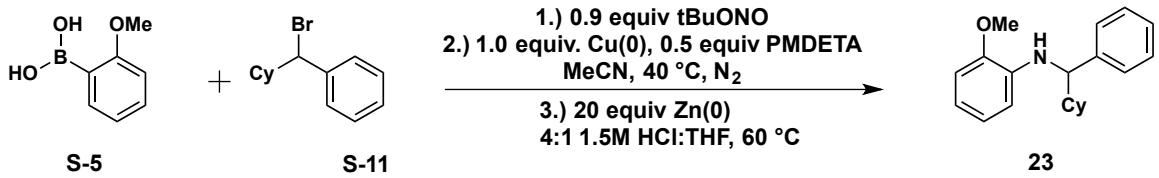
the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **21** (28 mg, 38 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.23 (m, 3H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.46 (q, *J* = 6.7 Hz, 1H), 3.98 (s, 1H), 1.53 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 147.5, 145.2, 143.9, 129.4, 128.7, 126.9, 125.9, 121.9, 121.0, 117.2, 114.2, 54.0, 25.1.



***N*-(cyclohexyl(phenyl)methyl)-4-methoxyaniline (22):** According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **1** (64 mg, 0.3 mmol, 0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (53 µL, 0.45 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (32 mg, 0.51 mmol, 1.0 equiv), PMDETA (50 µL, 0.24 mmol, 0.5 equiv) and (bromo(cyclohexyl)methyl)benzene (129 mg, 0.51 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the

reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (334 mg, 5.1 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **22** (51 mg, 68 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.6 Hz, 4H), 7.25 – 7.18 (m, 1H), 6.71 – 6.64 (m, 2H), 6.52 – 6.44 (m, 2H), 4.06 (d, *J* = 6.2 Hz, 1H), 3.69 (s, 3H), 1.95 – 1.51 (m, 6H), 1.32 – 0.98 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 142.9, 142.1, 128.1, 127.3, 126.7, 114.8, 114.3, 64.3, 55.8, 45.0, 30.2, 29.5, 26.4.

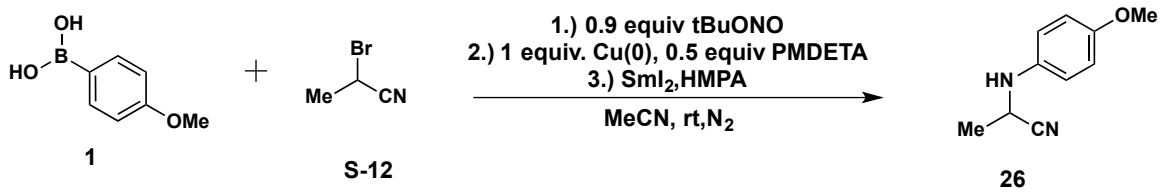


***N*-(cyclohexyl(phenyl)methyl)-2-methoxyaniline (23):** According to the general procedure C, A round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.25 mmol,

0.6 equiv) in MeCN (2.0 mL) was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.9 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC (1 hr), the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.4 mmol, 1.0 equiv), PMDETA (43 µL, 0.24 mmol, 0.5 equiv) and (bromo(cyclohexyl)methyl)benzene (101 mg, 0.4 mmol, 1.0 equiv). The resulting suspension was sparged for 15 minutes with N_2 and heated to 40 °C under an atmosphere of N_2. Following consumption of the benzyl bromide as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (30 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (3x 15 mL). The organic layers were combined, and dried over Na_2SO_4.

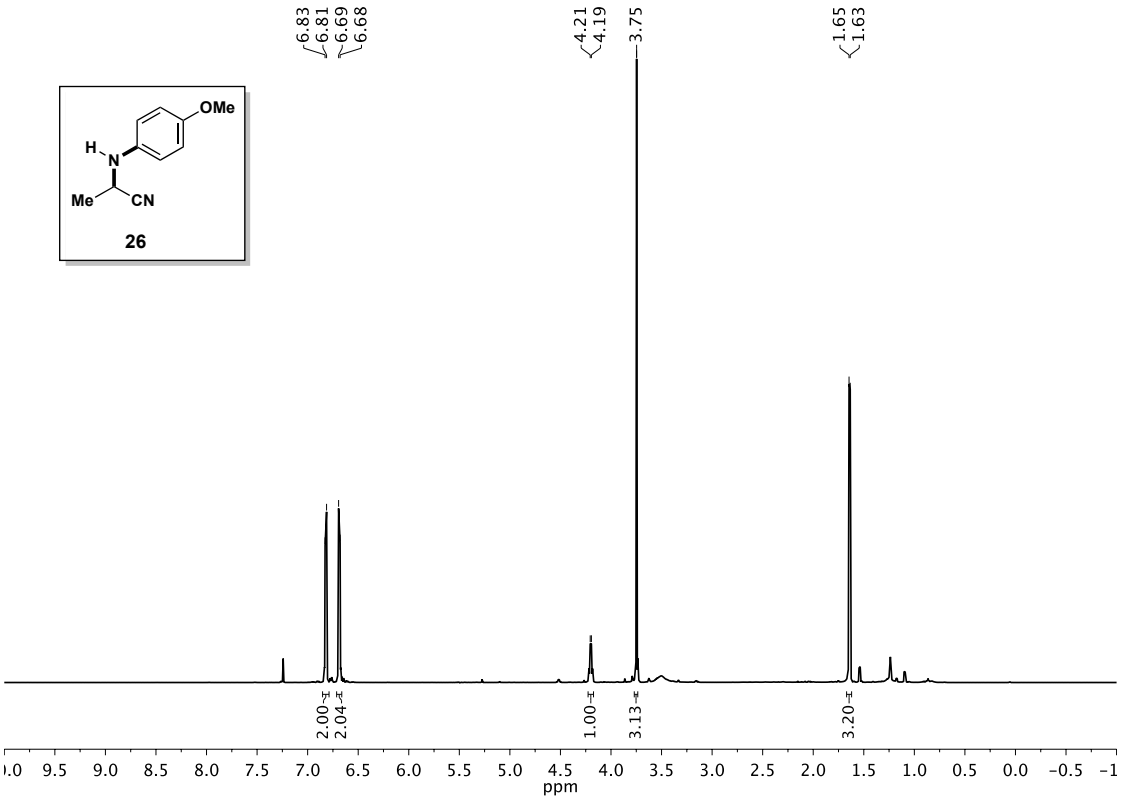
A 1 dram vial containing the resulting purified N-O alkylated adduct and a stir bar was charged with activated Zn(0) (327 mg, 5.0 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over Na_2SO_4. The crude product was dry loaded onto Celite and purified via column chromatography to afford **23** (35 mg, 60 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 4H), 7.13 – 7.08 (m, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.58 (t, *J* = 7.7, 1.4 Hz, 1H), 6.47 (t, *J* = 7.7, 1.6 Hz, 1H), 6.23 (d, *J* = 7.9 Hz, 1H), 4.71 (s, 1H), 4.02 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 1.89 – 1.41 (m, 4H), 1.27 – 0.90 (m, 5H); ^{13}C NMR (100

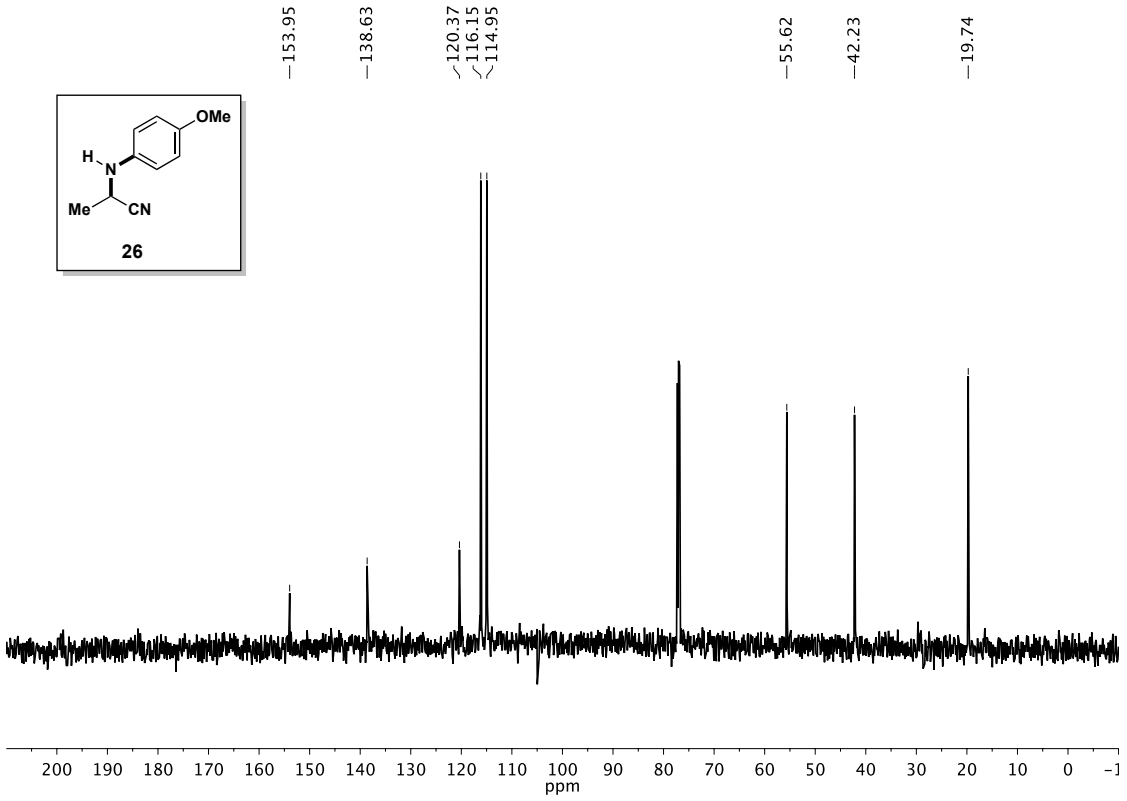
MHz, $CDCl_3$) δ 146.6, 142.9, 137.6, 128.1, 127.2, 126.6, 121.1, 115.8, 110.6, 109.1, 63.2, 55.5, 44.9, 30.3, 29.5, 26.4.

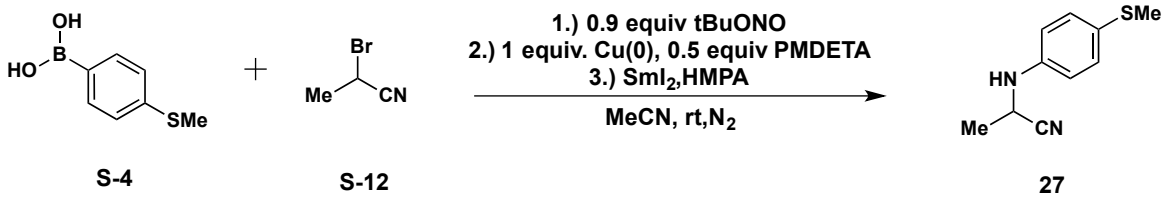


2-((4-methoxyphenyl)amino)propanenitrile (26): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **1** (38 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature until consumption of the starting material was observed

by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **26** (22 mg, 60%) as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 – 6.80 (m, 2H), 6.71 – 6.66 (m, 2H), 4.20 (q, J = 7.0 Hz, 1H), 3.75 (s, 3H), 3.60 – 3.40 (m, 1H), 1.64 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 138.6, 120.4, 116.1, 114.9, 55.6, 42.2, 19.7; IR (ATR) 3343, 2935, 2834, 1512, 1453, 1235, 1033, 823 cm^{-1}; HRMS (EI) *m/z* 176.0948 (176.0950 calcd for $C_{10}H_{12}N_2O$ $[M]^+$).



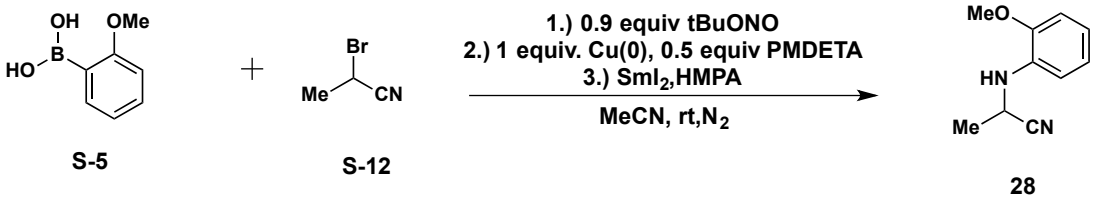




S-4 S-12 27

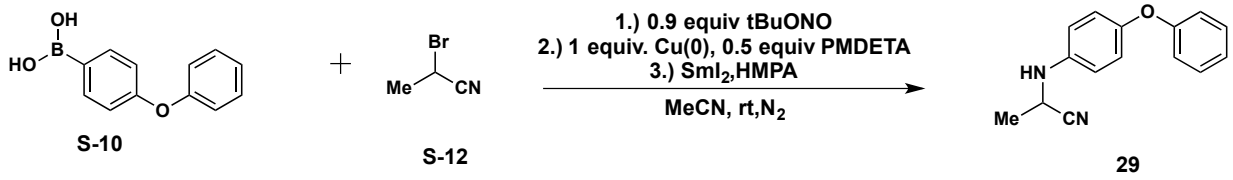
2-((4-(methylthio)phenyl)amino)propanenitrile (27): According to the general procedure B, a round bottom flask containing a solution of arylboronic acid **S-4** (42 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension,

which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **27** (27 mg, 68%) as a red-brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 6.72 – 6.62 (m, 2H), 4.27 (p, J = 7.3 Hz, 1H), 3.79 (d, J = 8.5 Hz, 1H), 2.43 (d, J = 1.3 Hz, 3H), 1.66 (dd, J = 7.0, 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 130.5, 128.0, 120.0, 114.8, 41.0, 19.6, 18.1; IR (ATR) 3352, 2986, 2919, 1599, 1498, 1287, 1162, 816; HRMS (EI) *m/z* 192.0720 (192.0721 calcd for $C_{10}H_{12}N_2S$ $[M]^+$)



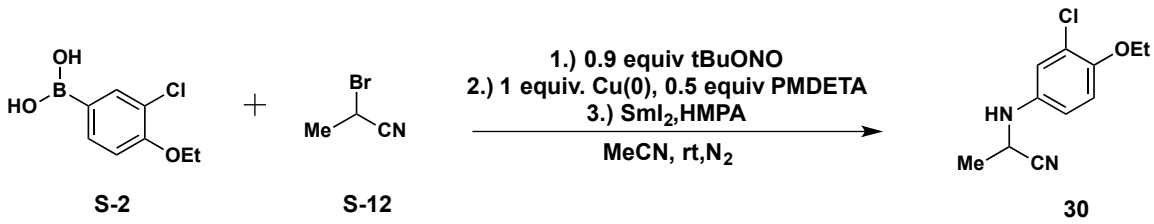
2-((2-methoxyphenyl)amino)propanenitrile (28): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.25 mmol, 0.60

equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **28** (22 mg, 60%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dq, *J* = 8.7, 4.4 Hz, 1H), 6.83 (d, *J* = 4.4 Hz, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 4.41 – 4.26 (m, 2H), 3.86 (s, 3H), 1.73 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 134.6, 121.3, 120.1, 119.3, 111.5, 110.0, 55.5, 55.4, 40.5, 19.7; IR (ATR) 3378, 2939, 2836, 1601, 1508, 1455, 1249, 1222, 1024, 738 cm^{-1}; HRMS (EI) *m/z* 176.0948 (176.0950 calcd for $C_{10}H_{12}N_2O$ $[M]^+$).



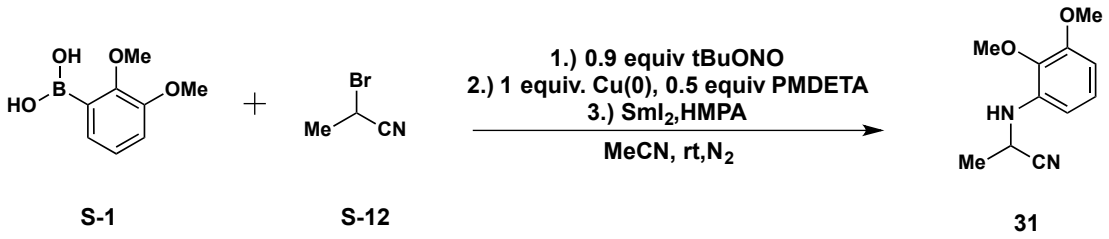
2-((4-phenoxyphenyl)amino)propanenitrile(29): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-10** (54 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 μL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 μL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 μL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature

until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **29** (37 mg, 74 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 2H), 7.05 (td, *J* = 7.4, 1.1 Hz, 1H), 7.05 – 6.83 (m, 4H), 6.76 – 6.65 (m, 2H), 4.27 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 1H), 1.70 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.1, 141.0, 129.6, 122.5, 121.0, 120.1, 117.7, 115.6, 41.6, 19.8; IR (ATR) 3355, 3037, 1588, 1508, 1488, 1229, 1162, 871, 838, 752, 692 cm^{-1}; HRMS (EI) *m/z* 238.1106 (238.1111 calcd for $C_{15}H_{14}N_2O$ $[M]^+$).



2-((3-chloro-4-ethoxyphenyl)amino)propanenitrile (30): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-2** (50 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with

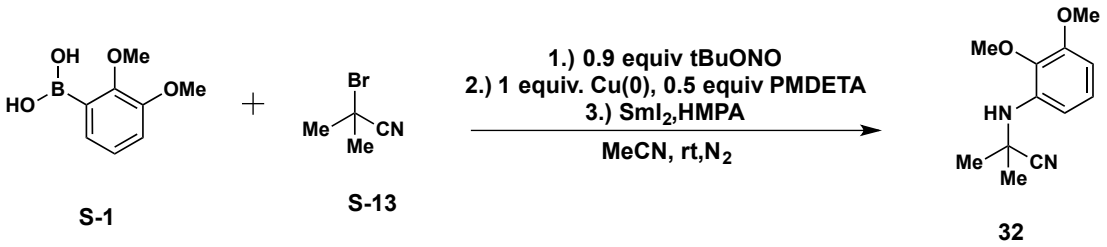
EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **30** (28 mg, 55%) as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.19 (s, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.59 (s, 1H), 1.65 (d, *J* = 7.0 Hz, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 139.3, 124.2, 120.0, 116.9, 115.6, 113.5, 65.6, 41.7, 19.6, 14.8; IR (ATR) 3348, 2982, 2931, 1613, 1502, 1475, 1280, 1227, 1057, 799 cm^{-1}; HRMS (EI) *m/z* 224.0718 (224.0716 calcd for $C_{11}H_{13}N_2OCl$ $[M]^+$).



S-1 **S-12** **31**

2-((2,3-dimethoxyphenyl)amino)propanenitrile (31): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-1** (46 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask

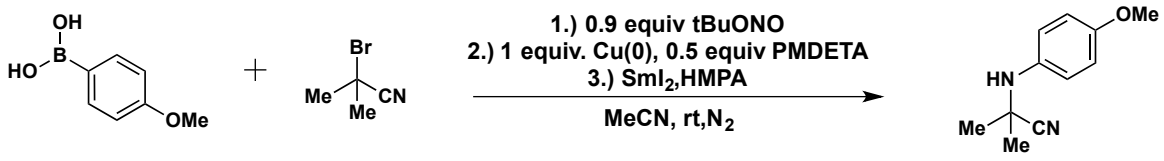
containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 μL, 0.21 mmol, 0.5 equiv) and 2-bromopropionitrile (36 μL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromopropionitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (0.56 mL, 3.2 mmol, 15.2 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 8.0 mL, 0.8 mmol, 3.8 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at room temperature until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **31** (20 mg, 47%) as a red-orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (t, J = 8.3 Hz, 1H), 6.47 (d, J = 8.4, 1.2 Hz, 1H), 6.42 (d, J = 8.2, 1.2 Hz, 1H), 4.43 (d, J = 9.1 Hz, 1H), 4.37 – 4.24 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.59, 139.08, 136.2, 124.5, 120.1, 105.4, 103.8, 60.3, 60.2, 55.8, 55.7, 40.9, 19.8; IR (ATR) 3361, 2938, 2838, 1601, 1478, 1264, 1168, 1088, 1001, 773 cm^{-1}; HRMS (EI) *m/z* 206.1061 (206.1055 calcd for $C_{11}H_{14}N_2O_2$ $[M]^+$).



S-1 S-13 32

2-((2,3-dimethoxyphenyl)amino)-2-methylpropanenitrile (32): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-1** (46 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromoisobutyronitrile (45 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromoisobutyronitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (1.9 mL, 6 mmol, 28.4 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 15.0 mL, 1.5 mmol, 7.1 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at 40 ºC until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **32** (29 mg, 63%) as a red-orange solid. ^{1}H NMR

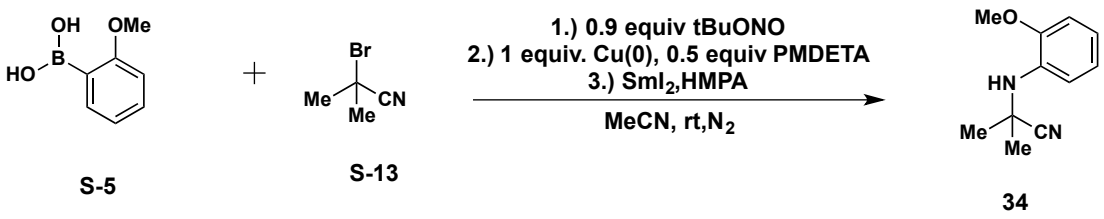
(400 MHz, $CDCl_3$) δ 6.98 (t, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 4.47 – 4.42 (m, 1H), 3.83 (d, *J* = 14.0 Hz, 6H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 138.2, 136.8, 124.1, 122.0, 107.7, 103.8, 103.7, 60.2, 60.1, 55.8, 55.6, 48.5, 28.5; IR (ATR) 3374, 2936, 2838, 1603, 1480, 1264, 1218, 1089, 998, 774, 732 cm^{-1}; HRMS (EI) *m/z* 220.1213 (220.1212 calcd for $C_{12}H_{16}N_2O_2$ $[M]^+$).



1 **S-13** **33**

2-((4-methoxyphenyl)amino)-2-methylpropanenitrile (33): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **1** (38 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromoisobutyronitrile (45 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following consumption of 2-bromoisobutyronitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under

high vacuum and backfilled with N_2 three times. HMPA (1.9 mL, 6 mmol, 28.4 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 15.0 mL, 1.5 mmol, 7.1 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at 40 ºC until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **33** (21 mg, 53%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, 2H), 6.84 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 136.5, 123.4, 122.6, 114.4, 55.5, 55.4, 51.0, 28.1; IR (ATR) 3320, 2931, 2835, 1609, 1512, 1464, 1238, 1035, 824 cm^{-1}; HRMS (EI) *m/z* 190.1108 (190.1106 calcd for $C_{11}H_{14}N_2O$ $[M]^+$).



2-((2-methoxyphenyl)amino)-2-methylpropanenitrile (34): According to the general procedure B, A round bottom flask containing a solution of arylboronic acid **S-5** (38 mg, 0.25 mmol, 0.60 equiv) in MeCN (1.0 mL) under an atmosphere of N_2 was treated with *t*-BuONO (45 µL, 0.375 mmol, 0.90 equiv) and heated to 40 ºC. Following complete consumption of the arylboronic acid as indicated by TLC, the solution was transferred via cannula to a round bottom flask containing a suspension of Cu(0) (27 mg, 0.42 mmol, 1.0 equiv) in MeCN (5 mL) which was then sparged with N_2 for 15 minutes. PMDETA (45 µL, 0.21 mmol, 0.5 equiv) and 2-bromoisobutyronitrile (45 µL, 0.42 mmol, 1.0 equiv) were then added to the sparged suspension, which was stirred at room temperature under an atmosphere of N_2. Following

consumption of 2-bromoisobutyronitrile as indicated by TLC, the reaction mixture was quenched with an aqueous EDTA solution (20 mL, 0.5 M, pH 7). The aqueous phase was extracted with EtOAc (4x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite and purified via column chromatography. A round bottom flask containing the resulting purified N-O alkylated adduct and a stir bar was evacuated under high vacuum and backfilled with N_2 three times. HMPA (1.9 mL, 6 mmol, 28.4 equiv) which had been sparged for 15 minutes with N_2, was added to the round bottom flask. A solution of freshly prepared SmI_2 (0.1 M, 15.0 mL, 1.5 mmol, 7.1 equiv) was then added slowly. The deep burgundy solution was stirred under N_2 at 40 ºC until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was dry loaded onto Celite and purified via column chromatography to afford **34** (25 mg, 63%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 7.5, 1.1 Hz, 1H), 6.93 (ddd, J = 7.8, 6.1, 2.8 Hz, 1H), 6.90 – 6.79 (m, 2H), 4.35 (s, 1H), 3.85 (s, 3H), 1.75 (s, 6H), 1.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 133.5, 122.0, 120.9, 119.6, 114.5, 110.0, 55.5, 55.4, 48.5, 28.3; IR 3370, 2870, 1587, 1493, 1245, 1100, 1050, 772, 740 HRMS (EI) *m/z* 190.1113 (190.1106 calcd for $C_{11}H_{14}N_2O$ $[M]^+$).

1-(4-methoxyphenyl)-5,5-dimethyl-3-(4-nitrophenyl)-2-thioxoimidazolidin-4-one (39): A mixture of isothiocyanate **S-15** (27 mg, 0.15 mmol) and **33** (19 mg, 0.10 mmol)

in DMF (0.1 mL) was stirred at 40 °C for 24 h. To this mixture were added methanol (1.0 mL) and 2 N HCl (0.25 mL). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$, dry loaded onto Celite, and purified via column chromatography to afford **39** (24 mg, 68 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.33 (m, 2H), 7.71 – 7.63 (m, 2H), 7.26 – 7.19 (m, 2H), 7.07 – 7.00 (m, 2H), 3.86 (s, 3H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 175.4, 160.2, 147.5, 138.6, 130.6, 129.5, 127.5, 124.2, 115.0, 66.2, 55.5, 23.6; IR (ATR) 3080, 2919, 2850, 1749, 1513, 1433, 1346, 1305, 1248, 834; HRMS (EI) *m/z* 371.0943 (371.0940 calcd for $C_{18}H_{17}N_3O_4S$ $[M]^+$)

References

[1] Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, *16*, 501–502.

8.4 Supporting Information for Chapter 6: An Intramolecular Radical Coupling Reaction with Nitrosoarenes for the Synthesis of Amino Alcohols

Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of N_2 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 or anisaldehyde. 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 (at 100, 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 100 FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility.

General Procedure A

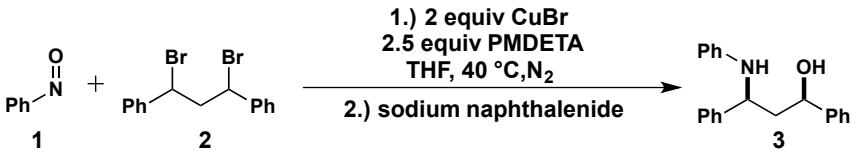
To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (0.1 mmol) in THF (4 mL) was added to the reaction mixture via

syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® *in vacuo*, and purified via column chromatography

General Procedure B

A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 μL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes,

quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol.

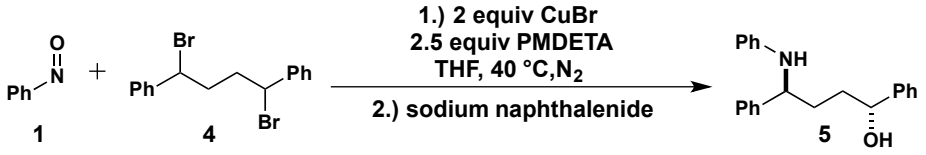


1,3-Diphenyl-3-(phenylamino)propan-1-ol (3):

To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **3** (20 mg, 67%, 2:1 dr).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 9H), 7.23 – 7.18 (m, 1H), 7.08 (q, J = 8.1 Hz, 2H), 6.72 – 6.61 (m, 1.36H major), 6.57 (d, J = 8.0 Hz, 0.66H minor), 6.52 (d, J = 8.0 Hz,

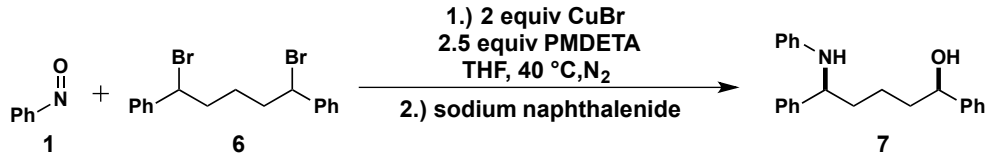
1H), 4.86 (dd, J = 9.2, 3.3 Hz, 1H), 4.65 – 4.53 (m, 1H), 2.28 (ddt, J = 18.4, 14.6, 9.7 Hz, 1H), 2.16 (ddd, J = 14.1, 8.4, 3.5 Hz, 0.36H minor), 2.05 (dt, J = 14.5, 4.2 Hz, 0.78H major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.1, 128.7, 128.6, 128.6, 127.8, 127.7, 127.2, 127.0, 126.3, 126.2, 125.7, 118.2, 114.5, 113.9, 73.8, 71.8, 58.2, 47.3, 46.6.



1,4-Diphenyl-4-(phenylamino)butan-1-ol (5): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite

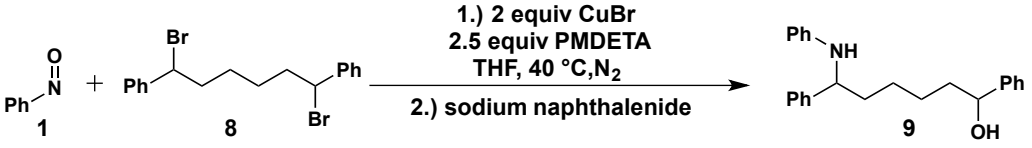
and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **5** (21 mg, 66%, 2:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 9H), 7.25 – 7.20 (m, 1H), 7.12 – 7.05 (m, 2H), 6.67 – 6.61 (m, 1H), 6.54 – 6.48 (m, 2H), 4.73 – 4.65 (m, 1H), 4.37 – 4.29 (m, 1H), 2.14 – 1.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.26, 147.24, 144.37, 144.32, 143.81, 143.74, 129.07, 128.58, 128.56, 128.54, 127.72, 127.69, 126.98, 126.40, 126.38, 125.86, 125.82, 117.34, 117.31, 113.43, 113.36, 74.33, 74.25, 58.31, 58.22, 35.72, 35.58, 34.88, 34.66; IR (ATR) 3424, 3054, 2936, 2861, 1603, 1324, 755, 702 cm^{-1}; HRMS (EI) *m/z* 317.1783 (317.1780 calcd for $C_{22}H_{23}NO$ $[M]^+$).



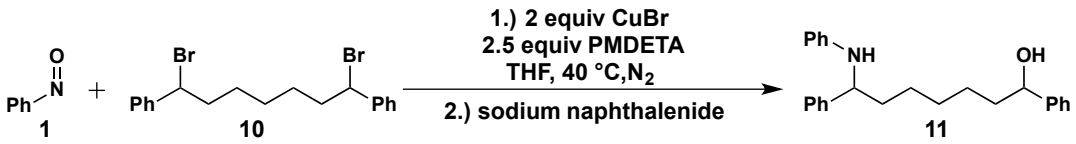
1,5-Diphenyl-5-(phenylamino)pentan-1-ol (7): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was

reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **7** (17 mg, 51%, 2:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 9H), 7.25 – 7.17 (m, 1H), 7.07 (t, *J* = 7.7 Hz, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 4.65 (dd, *J* = 7.7, 5.6 Hz, 1H), 4.29 (t, *J* = 6.8 Hz, 1H), 1.93 – 1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.31, 144.59, 144.01, 129.04, 128.54, 128.50, 127.63, 126.88, 126.28, 125.78, 117.10, 113.17, 74.43, 74.37, 58.06, 58.03, 38.73, 38.67, 22.79, 22.64; IR (ATR) 3417, 3032, 2940, 2866, 1601, 1503, 1320, 751, 700 cm^{-1}; HRMS (EI) *m/z* 331.1933 (331.1936 calcd for $C_{23}H_{25}NO$ $[M]^+$).



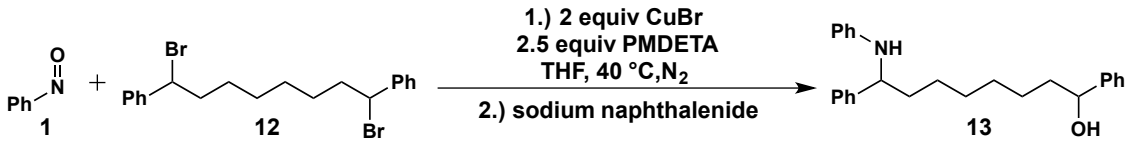
1,6-Diphenyl-6-(phenylamino)hexan-1-ol (9): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the

consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **9** (18 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 9H), 7.22 (ddt, *J* = 8.5, 5.7, 3.0 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.67 – 6.61 (m, 1H), 6.54 – 6.48 (m, 2H), 4.67 – 4.62 (m, 1H), 4.31 – 4.25 (m, 1H), 1.97 – 1.65 (m, 4H), 1.52 – 1.28 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.73, 129.06, 128.52, 128.46, 127.56, 126.88, 126.35, 125.84, 125.82, 117.20, 113.28, 74.51, 74.50, 58.18, 38.85, 38.82, 38.74, 26.17, 26.16, 25.65, 25.62; IR (ATR) 3431, 3062, 2938, 2860, 1603, 1506, 1322, 911, 736 cm^{-1}



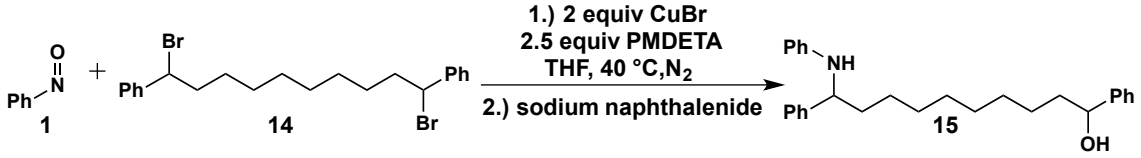
1,7-Diphenyl-7-(phenylamino)heptan-1-ol (11): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene

(0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **11** (21 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 9H), 7.25 – 7.19 (m, 1H), 7.11 – 7.05 (m, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 7.4 Hz, 2H), 4.65 (dd, J = 7.5, 5.8 Hz, 1H), 4.28 (t, J = 6.8 Hz, 1H), 1.92 – 1.63 (m, 3H), 1.57 (s, 1H), 1.36 (tdd, J = 30.4, 16.7, 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.80, 144.79, 129.06, 128.54, 128.51, 128.44, 128.03, 127.53, 126.87, 126.37, 125.86, 117.22, 113.32, 74.59, 74.58, 58.27, 38.92, 38.76, 29.34, 26.18, 26.17, 25.62, 25.60; IR (ATR) 3404, 3052, 3029, 2930, 2856, 1600, 1503, 1318, 749, 699 cm^{-1}



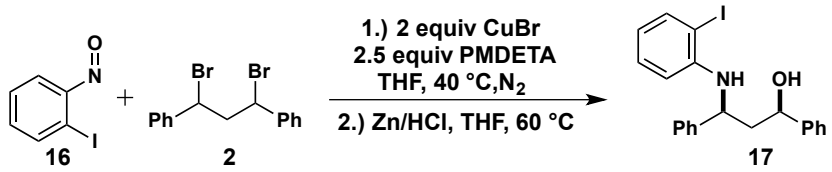
1,8-Diphenyl-8-(phenylamino)octan-1-ol (13): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **13** (21 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 9H), 7.25 – 7.19 (m, 1H), 7.08 (t, J = 7.7 Hz, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 7.9 Hz, 2H), 4.65 (t, J = 6.7 Hz, 1H), 4.28 (t, J = 6.8 Hz, 1H), 1.94 – 1.50 (m, 6H), 1.46 – 1.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.39, 144.82, 144.22, 129.05, 128.49, 128.42, 127.50, 126.82,

126.33, 125.85, 117.08, 113.18, 74.62, 58.17, 38.98, 38.89, 29.34, 29.32, 26.21, 25.69; IR (ATR) 3420, 3064, 3032, 2933, 2857, 1602, 1505, 1454, 1320, 751, 702 cm^{-1}



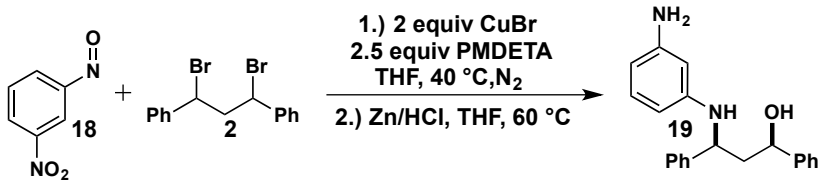
1,10-Diphenyl-10-(phenylamino)decan-1-ol (15): A round bottom flask containing a suspension of CuBr (30 mg, 0.2 mmol, 2 equiv) and PMDTA (52 µL, 0.25 mmol, 2.5 equiv) with a magnetic stir bar in THF (30 mL) was sparged for 30 minutes with N_2. Meanwhile a round bottom flask containing a solution of the dibromide (0.1 mmol) and the nitrosoarene (0.15 mmol, 1.5 equiv) in THF (10 mL) was sparged for 10 minutes. The flask containing the copper suspension was heated to 50 °C in an oil bath, and the nitrosoarene-dibromide solution was added dropwise via syringe pump over 10 hours. After TLC indicated the consumption of starting material (12-16 hours), the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting concentrated suspension was washed with aq. EDTA (0.5 M, 20 mL, pH 7), extracted with DCM (3 x 15 mL), and dried with brine (1 x 15 mL) and sodium sulfate. DCM was removed *in vacuo* and the crude N–O heterocycle was reconstituted in THF (5 mL) and sparged with N_2 for 5 minutes. A freshly prepared solution of sodium naphthalenide (0.15 M) was added dropwise until a dark green color persisted. The resulting solution was stirred for 3 minutes, quenched with isopropanol (10 mL), washed with aq. sodium bicarbonate (1.14 M, 30 mL), extracted with DCM (3 x 15 mL), dried with brine (1 x 15 mL) and sodium sulfate. The crude reaction mixture was dry loaded onto Celite and purified via column chromatography (Hexanes/EtOAc) to afford the corresponding amino alcohol **15** (14 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 9H), 7.24 –

7.18 (m, 1H), 7.12 – 7.04 (m, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 7.9 Hz, 2H), 4.66 (dd, J = 7.5, 5.7 Hz, 1H), 4.28 (t, J = 6.8 Hz, 1H), 1.85 – 1.63 (m, 5H), 1.44 – 1.18 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.90, 129.05, 128.49, 128.42, 127.48, 126.82, 126.36, 125.87, 113.27, 74.68, 58.28, 39.08, 29.44, 29.40, 29.37, 26.29, 25.77; IR (ATR) 3423, 3066, 3055, 2929, 2854, 1601, 1504, 1319, 750, 701 cm^{-1}



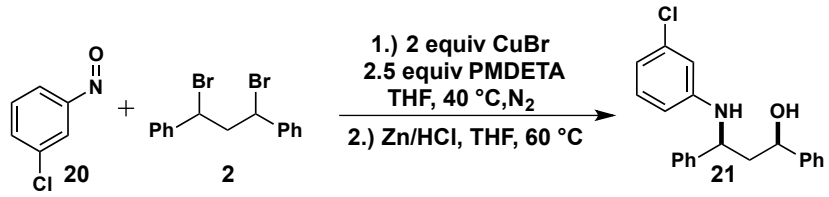
3-((2-Iodophenyl)amino)-1,3-diphenylpropan-1-ol (17): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (35 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **17** (10 mg, 24%, 3:1 dr). ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 9H), 7.25 – 7.18 (m, 1H), 7.14 – 7.05 (m, 2H), 6.69 (t, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.56 (m, 1.56H major), 6.56 – 6.50 (m, 0.44H minor), 4.88 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.61 (dd, *J* = 9.2, 5.1 Hz, 1H), 2.28 (dt, *J* = 14.5, 9.1 Hz, 1H), 2.07 (ddd, *J* = 14.4, 5.0, 3.3 Hz, 1H); IR (ATR) 3383, 3026, 2922, 1600, 1494, 1452, 1264, 1060, 911, 868, 748 cm^{-1}; HRMS (CI) *m/z* 429.0581 (429.0590 calcd for $C_{21}H_{20}NOI$ $[M]^+$).



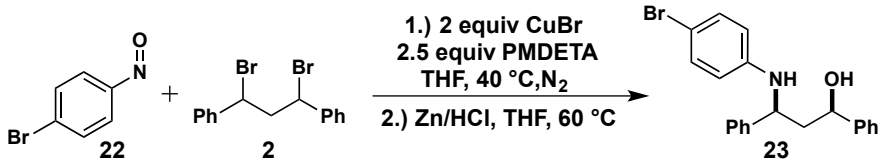
3-((3-Nitrophenyl)amino)-1,3-diphenylpropan-1-ol (19): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (23 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via

column chromatography to afford amino alcohol **19** (21 mg, 66%, 5:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 9H), 7.15 – 7.11 (m, 1H), 6.84 – 6.77 (m, 1H), 6.00 – 5.91 (m, 2H), 5.84 (t, *J* = 2.2 Hz, 1H 0.84 major), 5.77 (t, *J* = 2.2 Hz, 0.16H minor), 4.77 (dt, *J* = 8.7, 3.4 Hz, 1H), 4.50 (ddd, *J* = 17.3, 8.8, 4.5 Hz, 1H), 2.26 – 2.11 (m, 1H), 2.00 – 1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.36, 147.25, 144.47, 143.84, 129.94, 129.92, 128.67, 128.62, 128.58, 128.56, 127.72, 127.65, 127.07, 126.93, 126.27, 126.16, 125.75, 125.71, 105.55, 105.48, 105.06, 104.93, 101.09, 100.34, 73.81, 71.83, 57.92, 55.22, 47.48, 46.80; IR (ATR) 3340, 3019, 2914, 1610, 1489, 698 cm^{-1}



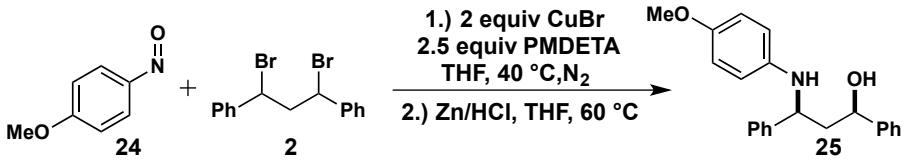
3-((2-Chlorophenyl)amino)-1,3-diphenylpropan-1-ol (21): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (21 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous

saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **21** (24 mg, 75%, 2:1 dr). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 9H), 7.16 (dt, *J* = 6.4, 2.1 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.55 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.46 (t, *J* = 2.2 Hz, 1H), 6.32 (dd, *J* = 8.1, 2.4 Hz, 1H), 4.75 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.47 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.20 (dt, *J* = 14.6, 9.0 Hz, 1H), 1.98 (ddd, *J* = 14.5, 5.4, 3.3 Hz, 1H); Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 9H), 7.19 – 7.14 (m, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.55 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 6.46 (t, *J* = 2.1 Hz, 1H), 6.32 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 4.76 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.47 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.20 (dt, *J* = 14.5, 9.1 Hz, 1H), 1.98 (ddd, *J* = 14.5, 5.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.29, 143.20, 130.03, 128.81, 128.68, 127.93, 127.33, 126.16, 125.66, 117.58, 113.82, 112.06, 104.99, 73.60, 57.74, 47.35; IR (ATR) 3382, 3028, 2921, 1595, 1482, 1323, 988, 908, 761 cm^{-1}; HRMS (EI) *m/z* 337.1229 (337.1229 calcd for $C_{21}H_{20}NOCl$ $[M]^+$).



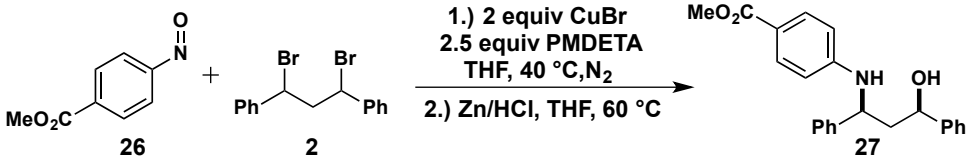
3-((4-Bromophenyl)amino)-1,3-diphenylpropan-1-ol (23): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (28 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and

extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **23** (17 mg, 45%, 3:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 10H), 7.18 – 7.14 (m, 2H), 6.45 – 6.40 (m, 2H), 4.84 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.53 (dd, *J* = 8.9, 5.3 Hz, 1H), 2.28 (dt, *J* = 14.4, 9.0 Hz, 1H), 2.06 (ddd, *J* = 14.5, 5.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.26, 144.30, 143.24, 131.75, 128.78, 128.65, 127.90, 127.29, 126.15, 125.63, 115.58, 104.99, 73.65, 57.88, 47.38, 29.69; IR (ATR) 3372, 2924, 1594, 1491, 1454, 1072, 813, 757 cm^{-1}



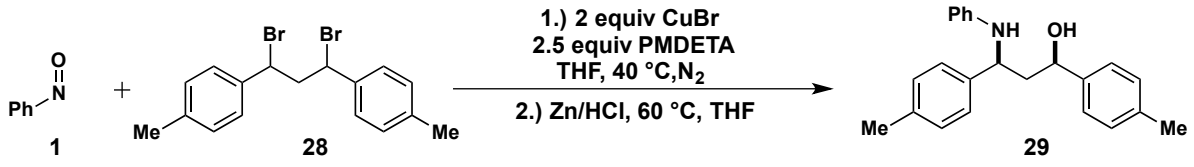
3-((4-Methoxyphenyl)amino)-1,3-diphenylpropan-1-ol (25): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (21 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered,

concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **25** (12 mg, 35%, 2:1 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 9H), 7.19 (tt, *J* = 6.1, 2.2 Hz, 1H), 6.70 – 6.65 (m, 2H), 6.58 – 6.54 (m, 1.31H major), 6.50 – 6.46 (m, 0.65H minor), 4.91 (td, *J* = 9.3, 8.8, 3.4 Hz, 1H), 4.53 (dd, *J* = 9.5, 4.5 Hz, 0.64H major), 4.50 (dd, *J* = 8.8, 3.8 Hz, 0.32H minor), 3.68 (d, *J* = 5.4 Hz, 3H), 2.30 – 2.14 (m, 1H), 2.04 (ddd, *J* = 14.5, 4.5, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.80, 144.49, 143.62, 140.86, 128.68, 128.61, 128.56, 128.51, 127.63, 127.58, 127.15, 126.98, 126.27, 126.17, 125.70, 125.65, 116.33, 115.42, 114.73, 114.68, 74.20, 71.99, 59.68, 56.38, 55.68, 55.65, 47.33, 46.54; IR (ATR) 3377, 3027, 2919, 2850, 1501, 1452, 1233, 1028, 818, 751 cm^{-1}; HRMS (CI) *m/z* 333.1731 (333.1729 calcd for $C_{22}H_{23}NO_2$ $[M]^+$).



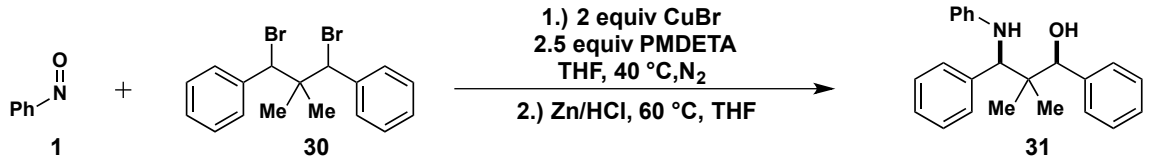
Methyl 4-((3-hydroxy-1,3-diphenylpropyl)amino)benzoate (27): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosoarene (25 mg, 0.15 mmol, 1.5 equiv) and 1,3-dibromo-1,3-

diphenylpropane (35 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **27** (23 mg, 65%, 2:1 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H), 7.40 – 7.22 (m, 10H), 6.46 (d, J = 8.5 Hz, 2H), 4.79 (dd, J = 9.2, 3.3 Hz, 1H), 4.61 (dd, J = 8.7, 5.6 Hz, 1H), 3.79 (s, 3H), 2.30 (dt, J = 14.5, 9.0 Hz, 1H), 2.06 (ddd, J = 14.5, 5.6, 3.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.27, 151.14, 144.22, 142.90, 131.28, 128.82, 128.69, 127.98, 127.36, 126.14, 125.62, 118.53, 112.57, 73.35, 57.16, 51.47, 47.20; IR (ATR) 3368, 3029, 2948, 1685, 1601, 1523, 1434, 1274, 1172, 836, 771 cm^{-1}; HRMS (EI) *m/z* 361.1674 (361.1670 calcd for $C_{23}H_{23}NO_3$ $[M]^+$).



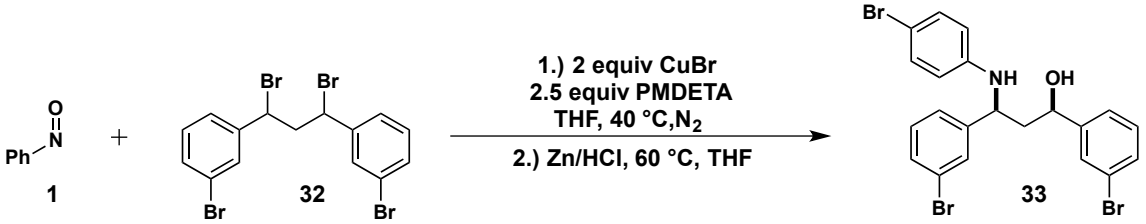
3-(Phenylamino)-1,3-di-*p*-tolylpropan-1-ol (29): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of

nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (38 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **29** (19 mg, 58%, 3:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 7.19 – 7.03 (m, 6H), 6.73 – 6.62 (m, 1H), 6.62 – 6.49 (m, 2H), 4.82 (dt, J = 6.9, 3.4 Hz, 1H), 4.57 (dt, J = 9.0, 5.2 Hz, 1H), 2.40 – 2.20 (m, 7H), 2.03 (ddd, J = 14.5, 5.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.19, 141.50, 140.60, 137.42, 136.64, 129.36, 129.31, 129.25, 129.21, 129.07, 129.05, 126.22, 126.09, 125.72, 125.65, 117.88, 117.36, 114.28, 113.62, 73.60, 71.74, 57.65, 55.07, 47.39, 46.64, 21.12, 21.07; IR (ATR) 3366, 3011, 2912, 1596, 1499, 812, 689 cm^{-1}; HRMS (CI) *m/z* 331.1935 (331.1936 calcd for $C_{23}H_{25}NO$ $[M]^+$).

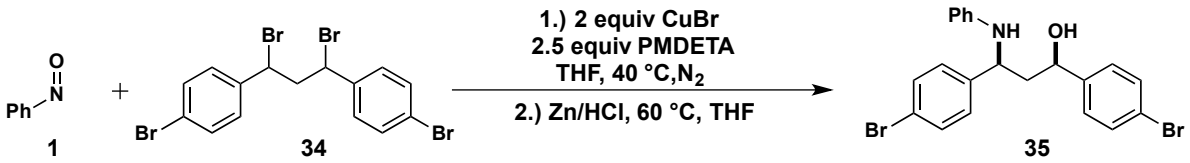


2,2-Dimethyl-1,3-diphenyl-3-(phenylamino)propan-1-ol (31): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of

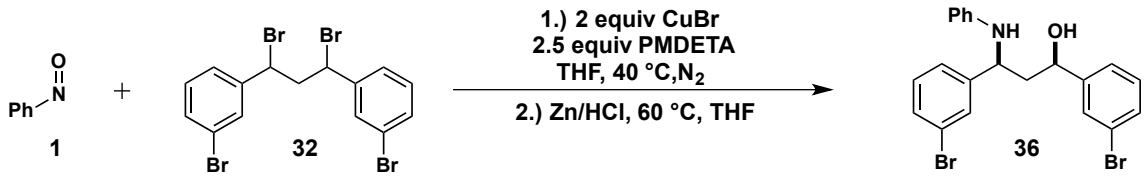
nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (38 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **31** (13 mg, 40%, 2:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 9H), 7.24 – 7.18 (m, 1H), 7.12 – 7.04 (m, 2H), 6.71 – 6.65 (m, 0.67 H, minor), 6.64 – 6.58 (m, 1.63H, major + minor), 6.57 – 6.53 (m, 0.7H, minor), 4.80 (s, 0.67H, major), 4.70 (s, 0.33H, minor), 4.46 (s, 0.67H, major), 4.36 (s, 0.33H, minor), 1.13 (s, 2H major), 0.96 (s, 1H minor), 0.92 (s, 1H minor), 0.62 (s, 2H major); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.76, 141.60, 140.09, 129.03, 128.86, 128.64, 128.04, 127.89, 127.84, 127.77, 127.68, 127.60, 127.53, 127.04, 126.91, 118.29, 116.93, 114.84, 113.50, 81.04, 80.43, 65.72, 65.41, 42.24, 29.70, 22.81, 22.23, 21.99, 15.81; IR (ATR) 3375, 3018, 2961, 2917, 1595, 1496, 1024, 748 cm^{-1}; HRMS (EI) *m/z* 331.1934 (331.1936 calcd for $C_{23}H_{25}NO$ $[M]^+$).



1,3-Bis(3-bromophenyl)-3-((4-bromophenyl)amino)propan-1-ol (33): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (51 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **33** (33 mg, 62%, 7:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dt, *J* = 3.5, 1.9 Hz, 2H), 7.45 – 7.35 (m, 2H), 7.30 – 7.16 (m, 7H), 6.44 – 6.39 (m, 2H), 4.79 (dd, *J* = 9.5, 3.1 Hz, 1H), 4.55 (dd, *J* = 8.4, 3.0 Hz, 0.13H minor) 4.49 (dd, *J* = 8.9, 5.3 Hz, 0.87H major), 2.25 – 2.16 (m, 1H), 1.98 (ddd, *J* = 14.4, 5.3, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.41, 145.81, 145.67, 131.89, 131.04, 130.61, 130.48, 130.28, 129.27, 128.77, 124.80, 124.22, 123.05, 122.82, 115.62, 109.94, 72.93, 57.56, 47.15; IR (ATR) 3365, 3047, 2909, 1587, 1487, 1067, 810, 780 cm^{-1};

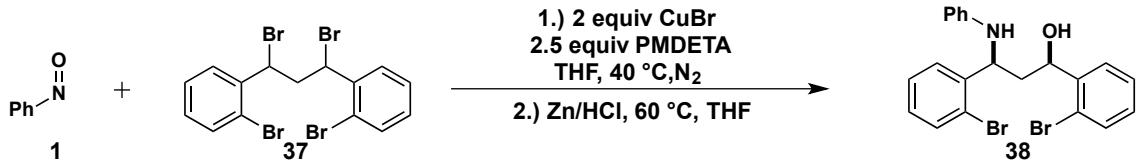


1,3-Bis(4-bromophenyl)-3-(phenylamino)propan-1-ol (35): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (51 mg 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **35** (35 mg, 66%, 4:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 4H), 7.25 – 7.16 (m, 4H), 7.15 – 7.06 (m, 2H), 6.76 – 6.66 (m, 1H), 6.52 (ddt, *J* = 16.1, 6.9, 1.1 Hz, 2H), 4.80 (dd, *J* = 9.4, 3.4 Hz, 1H), 4.53 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.19 (dt, *J* = 14.5, 9.2 Hz, 1H), 1.95 (ddd, *J* = 14.4, 5.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.61, 143.19, 143.04, 142.49, 131.85, 131.78, 131.70, 129.20, 129.17, 128.04, 127.95, 127.38, 121.61, 121.52, 120.92, 118.42, 117.90, 114.32, 113.67, 73.00, 71.16, 57.41, 54.83, 47.18, 46.38; IR (ATR) 3374, 3042, 2913, 1596, 1480, 1067, 1006, 822, 748 cm^{-1}



1,3-Bis(3-bromophenyl)-3-(phenylamino)propan-1-ol (36):

To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 µL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (51 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **36** (25 mg, 46%, 8:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.38 (m, 2H), 7.32 – 7.08 (m, 6H), 6.77 – 6.69 (m, 1H), 6.61 – 6.50 (m, 2H), 4.82 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.62 (dd, *J* = 8.7, 3.4 Hz, 0.12H minor), 4.55 (dd, *J* = 9.1, 5.0 Hz, 0.88H major), 2.20 (dt, *J* = 14.5, 9.3 Hz, 1H), 1.98 (ddd, *J* = 14.5, 5.0, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.63, 146.50, 146.04, 130.89, 130.44, 130.39, 130.21, 129.28, 129.19, 128.76, 124.82, 124.25, 122.93, 122.74, 118.43, 114.30, 73.12, 57.75, 47.22; IR (ATR) 3376, 3044, 2914, 1596, 1500, 1066, 780, cm^{-1}; HRMS (EI) *m/z* 458.9840 (458.9833 calcd for $C_{21}H_{19}NOBr_2$ $[M]^+$).



1,3-Bis(2-bromophenyl)-3-(phenylamino)propan-1-ol (38): To a sparged suspension of CuBr (29 mg, 0.20 mmol, 2 equiv) in THF (7 mL) was added PMDETA (52 μL, 0.25 mmol, 2.5 equiv). The resulting solution was heated to 40 °C with stirring and a sparged solution of nitrosobenzene (17 mg, 0.15 mmol, 1.5 equiv) and dibromide (51 mg, 0.1 mmol) in THF (4 mL) was added to the reaction mixture via syringe pump over 10 hours with stirring. The reaction was quenched with 0.5M aqueous EDTA (15 mL, pH 7) and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated in vacuo, and used without further purification. The crude mixture was dissolved in THF (0.75 mL), treated with 1.5 N HCl (1.5 mL) and Zn (130 mg, 20 equiv), and heated to 60 °C with stirring until the starting material was consumed as indicated by TLC (usually 1 hr). The mixture was cooled to room temperature, neutralized with aqueous saturated $NaHCO_3$ (7 mL), and extracted 3x with EtOAc (15 mL). The organics were combined, dried over $MgSO_4$, filtered, dry-loaded onto Celite® in vacuo, and purified via column chromatography to afford amino alcohol **38** (27 mg, 50%, 2:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 6.85 (m, 10H), 6.87 – 6.47 (m, 3H), 5.44 – 5.20 (m, 1H), 5.07 (ddd, J = 23.6, 8.9, 3.8 Hz, 0.5H), 4.74 – 4.69 (m, 0.5H), 2.37 – 1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.07, 143.35, 133.05, 132.61, 129.12, 128.87, 128.69, 127.99, 127.78, 127.20, 127.00, 126.19, 118.19, 114.52, 114.19, 113.34, 73.19, 72.92, 58.77, 57.74, 45.75, 44.22; IR (ATR) 3377, 2913, 1597, 1500, 1020, 748 cm^{-1}; HRMS (CI) *m/z* 458.9819 (458.9833 calcd for $C_{21}H_{19}NOBr_2$ $[M]^+$).

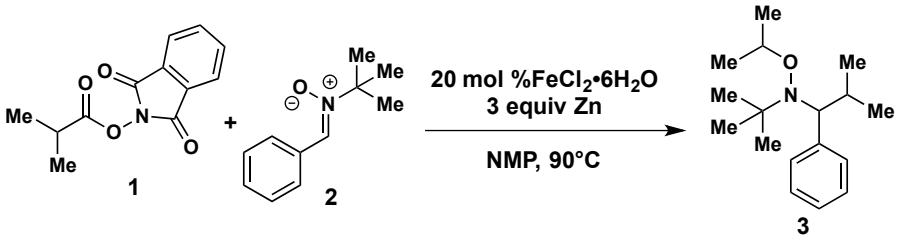
8.5 Supporting Information for Chapter 7: Coupling of Redox Active Esters with Nitrones

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of N_2 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 or anisaldehyde. 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 (at 100, 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 100 FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility. Nitrones were all made according to literature precedent.[1]

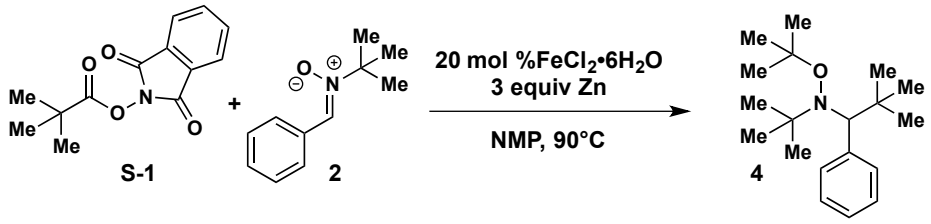
General Procedure:

An oven-dried 1 dram vial equipped with a teflon septa re-sealable screw-cap and a Teflon-coated magnetic stir bar was sequentially charged with zinc powder (Zn, 3 equiv), iron(III) chloride ($FeCl_3$ 0.05 mmol), nitrone (0.25 mmol), and NMP (0.25 mL). The mixture was sparged for 2 min under N_2, heated to 40 °C and then redox ester (3 equiv, 1.5

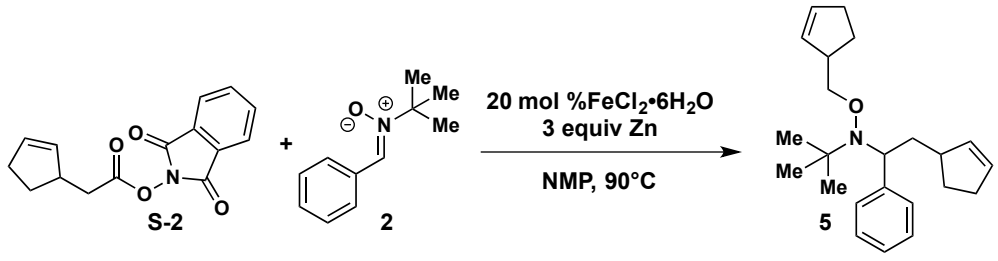
mmol) in sparged NMP (0.5 mL) was added over 10 hr via syringe pump. After the nitrone was completely consumed as indicated by TLC analysis, the reaction mixture was cooled, diluted w/ 0.5 mL EtOAc, run through a plug of silica (~15 g) with 30:1 Hexanes/EtoAc (100 mL) and concentrated *in vacuo*.



***N*-(*tert*-butyl)-*O*-isopropyl-*N*-(2-methyl-1-phenylpropyl)hydroxylamine (3):** An oven-dried 1 dram vial equipped with a teflon septa re-sealable screw-cap and a Teflon-coated magnetic stir bar was sequentially charged with zinc powder (Zn, 3 equiv), iron(III) chloride ($FeCl_3$ 0.05 mmol), nitrone (0.25 mmol), and NMP (0.25 mL). The mixture was sparged for 2 min under N_2, heated to 40 °C and then redox ester (3 equiv, 1.5 mmol) in sparged NMP (0.5 mL) was added over 10 hr via syringe pump. After the nitrone was completely consumed as indicated by TLC analysis, the reaction mixture was cooled, diluted w/ 0.5 mL EtOAc, run through a plug of silica (~15 g) with 30:1 Hexanes/EtoAc (100 mL) and concentrated *in vacuo* to afford to afford **3** (50 mg, 76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.33 – 7.18 (m, 2H), 4.18 (hept, J = 5.6 Hz, 1H), 3.45 (d, J = 10.7 Hz, 1H), 2.30 – 2.13 (m, 1H), 1.39 – 1.19 (m, 10H), 1.02 (s, 9H), 0.51 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.38, 131.20, 127.18, 126.20, 74.42, 71.99, 60.04, 32.55, 28.42, 22.49, 22.45, 21.89, 21.41; HRMS (EI) *m/z* 263.2247 (263.2249 calcd for $C_{17}H_{29}NO$ $[M]^+$).



***N*,*O*-di-*tert*-butyl-*N*-(2,2-dimethyl-1-phenylpropyl)hydroxylamine (4):** An oven-dried 1 dram vial equipped with a teflon septa re-sealable screw-cap and a Teflon-coated magnetic stir bar was sequentially charged with zinc powder (Zn, 3 equiv), iron(III) chloride ($FeCl_3$ 0.05 mmol), nitrone (0.25 mmol), and NMP (0.25 mL). The mixture was sparged for 2 min under N_2, heated to 40 °C and then redox ester (3 equiv, 1.5 mmol) in sparged NMP (0.5 mL) was added over 10 hr via syringe pump. After the nitrone was completely consumed as indicated by TLC analysis, the reaction mixture was cooled, diluted w/ 0.5 mL EtOAc, run through a plug of silica (~15 g) with 30:1 Hexanes/EtoAc (100 mL) and concentrated *in vacuo* to afford to afford **4** (27 mg, 56%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (bs, 2H), 7.29 – 7.20 (m, 3H), 3.81 (s, 1H), 1.50 (s, 9H), 1.08 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.86, 133.41, 126.33, 125.95, 79.56, 73.96, 61.59, 35.86, 30.11, 29.36, 28.94, HRMS (CI) *m/z* 292.2635 (292.2640 calcd for $C_{19}H_{34}NO$ $[M+H]^+$).



***N*-(*tert*-butyl)-*N*-(2-(cyclopent-2-en-1-yl)-1-phenylethyl)-*O*-(cyclopent-2-en-1-ylmethyl)hydroxylamine (5):** An oven-dried 1 dram vial equipped with a teflon septa re-sealable screw-cap and a Teflon-coated magnetic stir bar was sequentially charged with zinc

powder (Zn, 3 equiv), iron(III) chloride ($FeCl_3$ 0.05 mmol), nitrone (0.25 mmol), and NMP (0.25 mL). The mixture was sparged for 2 min under N_2, heated to 40 °C and then redox ester (3 equiv, 1.5 mmol) in sparged NMP (0.5 mL) was added over 10 hr via syringe pump. After the nitrone was completely consumed as indicated by TLC analysis, the reaction mixture was cooled, diluted w/ 0.5 mL EtOAc, run through a plug of silica (~15 g) with 30:1 Hexanes/EtoAc (100 mL) and concentrated *in vacuo* to afford to afford **5** (15 mg, 19%) ^{1}H NMR (400 MHz, CDCl3) δ 7.60 – 7.09 (m, 5H), 6.16 – 5.39 (m, 4H), 4.28 – 3.51 (m, 3H), 2.73 – 1.40 (m, 11H), 0.92 (s, 9H); HRMS (EI) *m/z* 339.2559 (339.2562 calcd for $C_{23}H_{33}NO$ $[M]^+$).

References

(1) Hinton, R. D.; Janzen, E. G. *J. Org. Chem.* **1992**, *57*, 2646.