Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

The wide presence of C–N bonds in biologically and pharmaceutically important compounds continues to drive the development of new C–N bond-forming transformations. Among the different strategies, electrophilic amination is an important synthetic approach for the direct formation of C–N bonds. Compared to electrophilic amination of organometallic reagents, direct amination of C–H bonds will provide a potentially more effective route towards C–N bond formation. Towards this, we proposed an electrophilic amination of C–H bonds via their reactive organometallic surrogate intermediates. Specifically, we are interested in organozinc intermediates and their *in situ* formation from C–H bonds.

This dissertation reports our development of direct amination of various C–H bonds using a H–Zn exchange/electrophilic amination strategy as a rapid and powerful way to access a variety of functionalized amines. We were able to achieve C–H zincation using strong and non-nucleophilic bases $\text{Zn}(\text{tmp})_2$ or $\text{tmpZnCl}\cdot\text{LiCl}$ and subsequent electrophilic amination of the corresponding zinc carbanions with copper as a catalyst and *O*-benzoylhydroxylamines as the electrophilic nitrogen source. With such a one-pot procedure, the synthesis of various amines from C–H bonds has been achieved, including α -amination of esters, amides, and phosphonates. Direct amination of heteroaromatic and aromatic C–H bonds has also been developed in good to high yields. It is important to note that mild reactivity of organozinc reagents offers a good compatibility with different functional groups, such as esters, amides, and halides.

Success in developing direct and efficient syntheses of these various amines is highly valuable. These new amination methods will greatly expand the chemical diversity and space of available amine skeletons, and will contribute to future advances in material science, medicinal chemistry and drug discovery.

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Abbreviations

Ac	acetate
acac	acetylacetone
Ar	aryl
bipyr	2,2'-bipyridine
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BPO	benzoyl peroxide
Bu	butyl
Bz	benzoyl
Cbz	carboxybenzyl
cod	cyclooctadiene
Cp	cyclopentadienyl
DCE	dichloroethane
DCM	dichloromethane
DG	directing group
DMA	dimethylacetamide
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	dimethylformamide
dppbz	1,2-bis(diphenylphosphino)benzene

dpppen	1,2-bis(diphenylphosphino)pentane
dtbpy	4,4'-di- <i>tert</i> -butyl-2,2'-dipyridyl
Et	ethyl
<i>i</i> -Pr	isopropyl
ICy•BF ₄	1,3-dicyclohexylimidazolium tetrafluoroborate salt
IMes•HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
iPr	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2 <i>H</i> -imidazol-2-ylidene
iPr•HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
JohnPhos	(2-Biphenyl)di- <i>tert</i> -butylphosphine
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
Me	methyl
MeCN	acetonitrile
<i>n</i> -BuLi	<i>n</i> -butyl lithium
NCS	<i>N</i> -chlorosuccinimide
Ph	phenyl
phen	1,10-Phenanthroline
pivOH	pivalic acid
Pr	propyl
RBF	round bottomed flask

rt	room temperature
SIMes•HBF ₄	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate
<i>t</i> -Bu	<i>tert</i> -butyl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
tmp	2,2,6,6-tetramethylpiperidide
TMSCl	chlorotrimethylsilane
trisyl	2,4,6-triisopropylbenzene
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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Chapter 1: Electrophilic amination for the synthesis of alkyl and aryl amines

1. Electrophilic amination for the synthesis of alkyl and aryl amines

1.1 Synthesis of amines via C–N bond formation

Amines containing either C(sp²)–N or C(sp³)–N bonds are privileged structural motifs that are present in many biologically and pharmaceutically relevant compounds (Figure 1).¹ For example, Plavix, which is an α -amino ester, is an antiplatelet drug used to

Figure 1. Examples of biologically and pharmaceutically relevant compounds containing C–N bonds

inhibit blood clots and was the second most prescribed drug in the world in 2010.² Safinamide, which contains an α -amino amide, is a Parkinson's drug candidate that was recently recommended as a therapy for the disease.³ Meanwhile, α -amino phosphonic acids alaphosphin and glyphosate contain interesting biological properties for medicine and agrochemistry, respectively.⁴ Examples of aryl amines include Abilify,⁵ which is an antipsychotic used for the treatment of schizophrenia and bipolar disorder, and

lerisetron,⁶ which is an antagonist at the 5HT₃ receptor and a potent antiemetic. The importance of nitrogen-containing compounds continues to drive the development of new C–N bond-forming transformations, therefore making amination reactions using simple and readily available compounds essential to organic synthesis.

Traditionally, C–N bonds have been synthesized using nucleophilic amines (Figure 2), with transition metal-mediated aminations providing a powerful method towards this end. The Buchwald-Hartwig amination,⁷⁻⁸ a cross-coupling reaction between aryl halides or triflates and amines, has been extensively used. The development of the Buchwald-Hartwig amination allowed for the facile synthesis of aryl amines while replacing harsher methods, such as nucleophilic aromatic substitution. On the other hand, the Chan-Lam coupling,⁹⁻¹¹ which is an oxidative amination of aryl boronic acids with amines, has been used as an alternative to the Buchwald-Hartwig amination. It provided notable advantages over the Buchwald-Hartwig amination as it could be run at room temperature and in the presence of air, but it was limited to primary amines and often required stoichiometric copper. More recently, oxidative C–H/N–H couplings have provided a complementary and direct method for the synthesis of amines.¹²⁻³⁴ However, despite the utility of the Buchwald-Hartwig amination and oxidative C–H/N–H couplings, they suffer from limitations, such as harsh reaction conditions that include high temperatures, strong oxidants, or acidic or basic additives. Moreover, transition metal-mediated aminations using nucleophilic amines are limited to the synthesis of aryl amines. Electrophilic aminations using $[\text{NR}_2]^+$ synthons offer a complementary method

to the conventional use of nucleophilic amines for aminations. In particular, direct C–H amination provides a new and potentially more effective C–N bond-formation approach.

Figure 2. Carbon-nitrogen bond-forming reactions for the synthesis of various amines

1.2 Electrophilic amination reagents and reactions

1.2.1 Electrophilic amination for the synthesis of alkyl and aryl amines

Electrophilic amination reactions have seen a considerable increase in interest over the past decade as an alternative method for the synthesis of ubiquitous C–N bonds.³⁵⁻⁴⁴ The key to these amination reactions is the use of $[\text{NR}_2]^+$ synthons as the nitrogen source. Many electrophilic aminations have been achieved using various organometallic reagents,⁴⁵⁻⁵⁸ while significant advances have also been achieved via C–H functionalization.⁵⁹⁻⁶⁴ Most of these transformations leverage the use of transition metals to facilitate the formation of the C–N bond. Electrophilic aminations offer advantages over traditional aminations that include mild reaction conditions and a broader amine scope that contains $\text{C}(\text{sp}^2)\text{--N}$ bonds as well as $\text{C}(\text{sp}^3)\text{--N}$ bonds. Additionally, C–H amination offers a direct method to introduce nitrogen-based groups onto molecules without stepwise functional group manipulations.

1.2.2 Electrophilic aminating reagents

Utilizing the umpolung concept in amine synthesis relies on the identification of useful electrophilic nitrogen sources. Several $[\text{NR}_2]^+$ synthons have been developed towards the advancement of electrophilic amination methods (Figure 3).³⁸ These reagents

Figure 3. Electrophilic aminating reagents for the synthesis of alkyl and aryl amines generally contain an electron-withdrawing group attached to the nitrogen in order to induce a partial positive charge on the nitrogen atom. Electrophilic aminating reagents can be divided into two groups—sp² and sp³ nitrogen-containing compounds. Early aminations took advantage of sp² nitrogen-containing compounds such as azides⁶⁵⁻⁶⁸ and diazene dicarboxylates.⁶⁹⁻⁸³ More recently, oxime esters⁸⁴⁻⁸⁹ and nitroso compounds⁹⁰⁻⁹⁶ have been used. However, for electrophilic amination reactions using sp² nitrogen-

containing compounds, the formation of the corresponding amine requires reduction of the N–N or N–O bond. Therefore, they are restricted to the formation of primary amines (the installation of an NH₂ group). To overcome this, several sp³ nitrogen-containing compounds have been developed for the synthesis of secondary and tertiary amines. These include oxaziridines,⁹⁷ *N*-haloamines,⁹⁸⁻¹⁰² and *O*-substituted hydroxylamines.^{45-64,103-108}

Of the various electrophilic aminating reagents, *O*-acylhydroxylamine derivatives occupy a prominent position in the development of umpolung C–N bond construction.³⁵ In particular, *O*-benzoylhydroxylamines have become increasingly popular for the synthesis of alkyl and aryl amines.^{45-64,103-108} They are easily prepared via oxidation of primary or secondary amines with benzoyl peroxide or the benzylation of hydroxylamines to give stable, often crystalline, compounds (Scheme 1).⁴⁸ Due to the labile nature of the N–O bond of *O*-benzoylhydroxylamines, electrophilic amination of different nucleophilic species is often achieved via transition metal catalysis.^{45-64,103-108}

Scheme 1. Preparation of *O*-benzoylhydroxylamines

1.2.3 Electrophilic amination reactions of organometallic reagents using *O*-benzoylhydroxylamines

O-Benzoylhydroxylamines have occupied a prominent role as [NR₂]⁺ synthons for electrophilic aminations. Numerous amination reactions that utilize *O*-

benzoylhydroxylamines have been achieved using carbanions. A large number of organometallic reagents are recognized to undergo the transformation including organozincs,⁴⁵⁻⁴⁸ Grignard reagents,⁴⁹ organoboron compounds,⁵⁰⁻⁵⁴ organosilicon reagents,⁵⁵⁻⁵⁶ organolithiums,⁵⁷ and organozirconium reagents.⁵⁸ Generally amination reactions of organometallics with *O*-benzoylhydroxylamines utilize transition metals such as copper or nickel to cleave the N–O bond and promote the formation of C–N bonds.

1.2.3.1 Electrophilic amination of organozinc compounds

The pioneering use of *O*-benzoylhydroxylamines for electrophilic amination was reported by Johnson and co-workers for the amination of diorganozinc compounds (Scheme 2).⁴⁵ Using [Cu(OTf)₂•C₆H₆] as the catalyst, they easily synthesized tertiary and

Scheme 2. Copper-catalyzed electrophilic amination of diorganozinc reagents

secondary aryl and alkyl amines in high yields. The reactions were run at room temperature, and many of the amine products were isolated by an acid-base extractive

workup. Their early method was limited to electron-rich aryl and alkyl groups; however using an I/Mg exchange of aryl iodides for the preparation of functionalized diarylzinc reagents, they were later able to extend their method so that nitriles, esters, halides, triflates, and nitro groups were also tolerated.⁴⁶

In their initial amination method, the Johnson group found a significant disparity in the reactivity of diorganozincs and organozinc halides with organozinc halides giving drastically lower yields (<30%).⁴⁵ To overcome this, they employed the use of nickel for the amination (Scheme 3).⁴⁷ They obtained the desired amines in good yields using various organozinc chlorides. Additionally, this method allowed for a decrease in the amount of aryl or alkyl substrate that was needed for the reaction. However despite mild reaction conditions and good yields, this method lacked the generality of the electrophilic amination of diorganozincs with secondary and tertiary zinc halides not yielding the desired products.

Scheme 3. Nickel-catalyzed electrophilic amination of organozinc halides

1.2.3.2 Electrophilic amination of Grignard reagents

Electrophilic amination of Grignard reagents using primary *O*-alkylhydroxylamines has been broadly used to synthesize primary amines.³⁵ However the use of *N*-substituted hydroxylamines has been more limited due to side reactions, such as *C*-acylation to form ketones. Following their reports on the electrophilic amination of organozincs,⁴⁵⁻⁴⁸ Johnson and co-workers developed a copper-catalyzed amination of Grignard reagents with *O*-benzoylhydroxylamines (Scheme 4).⁴⁹ Slow addition of the Grignard reagent to the reaction allowed for amination to occur faster than *C*-acylation. Aryl amines were synthesized in moderate to excellent yield. They were also able to synthesize alkyl amines using primary, secondary, and tertiary Grignard reagents. Overall, this reaction did not possess the scope of their previous protocol employing diorganozinc compounds; however in some cases it was operationally superior as a result of the absence of anhydrous zinc salts needed to generate the diorganozinc compounds.

Scheme 4. Copper-catalyzed electrophilic amination of Grignard reagents

1.2.3.3 Electrophilic amination of organoboron reagents

While organoboron reagents are typically building blocks used in cross-coupling reactions for the synthesis of C–C bonds, they have also been used for the synthesis of amines. In 2012, Miura and Lalic concurrently disclosed copper-catalyzed electrophilic aminations of aryl boronic esters.⁵⁰⁻⁵¹ In the work by Miura and co-workers, a wide variety of aniline derivatives were obtained in moderate to good yields by coupling aryl boronates with *O*-benzoylhydroxylamines using Cu(OAc)₂•H₂O as the catalyst (Scheme 5).⁵⁰ They were also able to combine their amination method with the iridium-catalyzed

Scheme 5. Copper-catalyzed electrophilic amination of aryl boronic esters developed by Miura and co-workers

direct C–H borylation developed by Hartwig¹⁰⁹ in order to synthesize aryl amines straight from the arene. (Scheme 5B). Meanwhile, Lalic and co-workers focused on a copper-catalyzed electrophilic amination of aryl boronic esters for the synthesis of sterically hindered aniline derivatives (Scheme 6).⁵¹ They found that boronic esters derived from

Scheme 6. Copper-catalyzed electrophilic amination of aryl boronic esters developed by Lalic and co-workers

neopentyl glycol were crucial for the reaction, and using a catalyst formed *in situ* from [CuOt-Bu]₄ and Xantphos gave the best yields for the various anilines. Both methods tolerated a variety of functional groups including halogens, esters, ketones, aldehydes, and carbamates. Additionally, Lalic and co-workers found that acidic functional groups

could be tolerated when excess CsF was used as the base rather than LiOt-Bu (Scheme 6B). However, both methods were limited to the use of *N,N*-dialkyl-*O*-benzoylhydroxylamines for the synthesis of only tertiary aryl amines.

In developing their amination methods, Miura and Lalic proposed possible mechanisms for their respective transformations (Schemes 7 and 8). Based on mechanistic studies, Miura and co-workers proposed that an anionic homocuprate was responsible for the amination step (Scheme 7).⁵⁰ On the other hand, Lalic and co-workers proposed that a neutral copper(I) complex was responsible for the amination step (Scheme 8).⁵¹ By either account, the presence of LiOt-Bu appeared to be critical for the generation of the active copper catalyst.

Scheme 7. Mechanism for amination of aryl boronates proposed by Miura and co-workers

Scheme 8. Mechanism for amination of aryl boronates proposed by Lalic and co-workers

Lalic and co-workers also reported the synthesis of tertiary amines from terminal alkenes (Scheme 9).⁵² They were able to develop a highly selective anti-Markovnikov hydroamination that involved the hydroboration of a terminal alkene followed by the copper-catalyzed electrophilic amination of the corresponding alkyl borane in one-pot. This method was compatible with a wide range of functional groups, but like the amination of aryl boronates, it was limited to the use of *N,N*-dialkyl-*O*-benzoylhydroxylamines for the synthesis of tertiary amines.

Scheme 9. Copper-catalyzed electrophilic amination of alkyl boranes

1.2.3.4 Electrophilic amination of organosilicon reagents

Organosilicon reagents can also undergo direct electrophilic amination. Miura and co-workers reported a copper-catalyzed amination of aryl silanes (Scheme 10).⁵⁵ The use of aryl[(2-hydroxymethyl)phenyl]dimethylsilanes was crucial because the an arylsilane is capable of selective aryl group transfer through facile formation of an intramolecularly pentacoordinated arylsilicate. Their method allowed for the efficient synthesis of aniline derivatives under mild conditions. Additionally, their method tolerated a wide range of functional groups, including halogens, nitriles, and esters.

Scheme 10. Copper-catalyzed electrophilic amination of arylsilanes

The electrophilic α -amination of carbonyl compounds has attracted considerable attention as an alternative way to access α -amino acids and their derivatives. Towards this, Miura and co-workers recently reported a copper-catalyzed electrophilic amination of silyl ketene acetals for the direct formation of C–N bonds at the α -position of esters (Scheme 11).⁵⁶ Different basic additives (NaHCO₃, Na₂CO₃, KOAc, and LiF) were used

in the reaction with the best additive for each reaction being dependent upon the steric and electronic nature of the silyl ketene acetal and *O*-benzoylhydroxylamine used. Various silyl ketene acetals underwent amination with *O*-benzoyl-*N,N*-dibenzylhydroxylamine to give the corresponding α -amino esters. In addition to *O*-benzoyl-*N,N*-dibenzylhydroxylamine, other acyclic and cyclic *O*-benzoylhydroxylamines participated in the reaction.

Scheme 11. Copper-catalyzed electrophilic amination of silyl ketene acetals

1.2.3.5 Electrophilic amination of organolithium reagents

Although organolithium reagents are commercially available or readily available through lithium–halogen exchange, their use for electrophilic amination has been limited due to low yields and often limited substrate scope. Therefore, organolithiums are often converted to other organometallic reagents.³⁵ Amos and co-workers developed a copper-

catalyzed amination of organolithiums exploiting a recoverable siloxane transfer agent (Scheme 12).⁵⁷ Inspired by Miura's amination of aryl silanes,⁵⁵ they prepared silanes *in situ* from the organolithiums, which readily underwent the electrophilic amination. The use of siloxane transfer agents offered a viable solution for the direct application of organolithiums in electrophilic amination. Through this amination method, they were able to access an array of aryl and heteroaryl amines.

Scheme 12. Copper-catalyzed electrophilic amination of organolithiums via a recoverable siloxane transfer agents

1.2.3.6 Electrophilic amination of organozirconium reagents

While electrophilic amination of organometallic reagents has primarily been achieved using organozincs, organoborons, and other main-group organometallics, Xi and co-workers have recently reported a synthesis of various enamines via a copper-catalyzed amination of alkenylzirconocenes (Scheme 13).⁵⁸ The corresponding enamines

were isolated via an extraction work-up, which is quite elegant since most enamines are sensitive to air and unsuitable for common column chromatography. The reaction yielded a wide range of enamines under mild reaction conditions. Moreover, the reaction tolerated an array of functional groups and could even be used to prepare hindered enamines.

^a Reaction run at 50 °C.

Scheme 13. Copper-catalyzed electrophilic amination of alkenylzirconocenes

1.3 Direct electrophilic amination of C–H bonds

Direct C–H amination provides a complementary approach to electrophilic aminations of carbanions. While remarkable progress in C–H amination has been accomplished via oxidative C–H/N–H coupling, current metal-catalyzed C–H aminations are still restricted in generality. Metallation of C–H bonds has primarily been achieved by

two strategies—1) directing group assisted *ortho*-metallation or 2) direct deprotonative metallation (Scheme 14).⁵⁹⁻⁶⁴

Scheme 14. Metal-catalyzed direct C–H amination

1.3.1 Directing group assisted *ortho*-metallation for C–H amination

Directing group-assisted metallation has proven to be a powerful tool for the synthesis of *ortho*-substituted arylamines. Toward this a range of catalyst systems have been developed, including palladium, ruthenium, rhodium and copper.⁵⁹⁻⁶³ The use of *O*-benzoylhydroxylamines for direct *ortho* C–H amination was first disclosed by Yu and co-workers via a palladium-catalyzed amination of *N*-aryl benzamides (Scheme 15A).⁵⁹ The reaction gave exclusive monoselectivity as well as good regioselectivity. The amination worked well for electron-donating benzamides; however, yields noticeably decreased for electron-withdrawn benzamides. For electron-withdrawn substrates, α,α,α -trifluorotoluene was necessary to obtain reasonable yields. In addition to the amination using *O*-benzoylhydroxylamines, they were able to demonstrate that a one-pot procedure using secondary amines in the presence of benzoyl peroxide was feasible (Scheme 15B).

Scheme 15. Palladium-catalyzed C–H amination of *N*-aryl benzamides

Despite the utility of the initial palladium-catalyzed C–H amination reported by Yu and co-workers, it was limited in substrate scope and had poor efficiency for electron-withdrawn benzamides. To overcome this limitation, they investigated different ligand scaffolds in the amination of triflyl-protected benzylamines, and found that pyridine and quinoline-based ligands promoted the amination (Scheme 16). Of the various pyridine and quinoline ligands, 2,4,5-trimethoxypyridine proved to be the best ligand. With this

particular ligand they were also able to extend the palladium-catalyzed *ortho* C–H amination to electron-withdrawn benzamides.⁶⁰

Scheme 16. Ligand-promoted palladium-catalyzed C–H amination

In addition to palladium, ruthenium and rhodium have also been shown to be effective catalysts for direct *ortho* C–H amination.^{61–62} Following their initial palladium-catalyzed *ortho* C–H amination,⁵⁹ Yu and co-workers disclosed a ruthenium-catalyzed *ortho* C–H amination of benzamides (Scheme 17).⁶¹ This reaction could be run at room temperature compared to higher temperatures required for their palladium catalyzed

method. In addition to benzamides, this reaction was also compatible with heterocycles including pyrazole, thiophene, furan, benzofuran, benzothiophene and indole. However, unlike their palladium-catalyzed methods, this ruthenium-catalyzed C–H amination was limited to cyclic *O*-benzoylhydroxylamines. Moreover, this method produced a mixture of mono- and diamination products for the more electron-withdrawn substrates.

Scheme 17. Ruthenium-catalyzed *ortho* C–H amination of arenes and heteroarenes

Zhang and Yao reported a rhodium-catalyzed aryl C–H amination using a pyrazolone moiety as an *ortho* directing group (Scheme 18).⁶² Their amination method is notable because they were able to introduce primary and secondary amines unlike previous palladium and ruthenium catalyzed aminations⁵⁹⁻⁶¹ reported by Yu and co-

workers. Moreover, they were able to conduct their amination under mild conditions to make novel analogues of neuroprotection drug edaravone.¹¹⁰⁻¹¹³

Scheme 18. Rhodium-catalyzed *ortho* C–H amination

1.3.2 Direct deprotonative metallation for C–H amination

Direct deprotonative metallation/amination using *O*-benzoylhydroxylamines has been less thoroughly explored; however it has been particularly useful for the amination of electron-deficient arenes. Miura and co-workers used this method for a copper-catalyzed direct amination of polyfluoroarenes and azoles (Scheme 19).⁶⁴ They were able

to synthesis the corresponding anilines and aminoazoles in moderate to good yields under mild reaction conditions.

Scheme 19. Copper-catalyzed direct C–H amination of polyfluoroarenes and azoles

1.4 Conclusions

Electrophilic amination is an important synthetic pathway for the direct formation of C–N bonds. Towards this, several methods using *O*-benzoylhydroxylamines as the electrophilic nitrogen source have been developed for the synthesis of alkyl and aryl amines with copper holding a prominent place for many transformations due to its low cost, low toxicity, and easy handling. While copper-catalyzed electrophilic amination of organometallic reagents is the state-of-art synthetic method for electrophilic amination, direct C–H amination provides a new and potentially more effective route towards C–N bond formation. However, the current methods often suffer from a limited nucleophile

scope (sp^2 C–H bonds) and poor efficiencies. This limitation is largely due to the challenging metallation step associated with the inherently high dissociation energy of sp^2 and sp^3 C–H bonds. Additionally, the use of high temperatures, strong oxidants, and acidic or basic additives considerably impacts functional group compatibility and potential applications.¹¹⁴ Therefore, further work is needed to expand the scope of direct C–H amination. It would be greatly desirable to develop a catalytic amination system effective for both sp^2 and sp^3 C–H bonds with broader applications in complex molecule synthesis.

In this dissertation, we report our work on the electrophilic amination of sp^2 and sp^3 C–H bonds. Specifically, we focused on direct deprotonative metallation for C–H amination. We proposed that a facile electrophilic C–H amination could be achieved via reactive organometallic intermediates of C–H bonds, such as organozinc intermediates that could be generated *in situ* using strong and non-nucleophilic zinc bases.¹¹⁵⁻¹²⁸ Such a H–Zn exchange/amination strategy would offer a rapid and powerful way to access a variety of highly functionalized complex amines. We were able to effectively deprotonate esters, amides, phosphonates, and heteroarenes to form organozinc reagents that readily undergo a copper-catalyzed electrophilic amination using *O*-benzoylhydroxylamines. Additionally, mild reactivity of organozinc reagents allowed for good compatibility with different functional groups, such as esters, amides, and halides. This method is especially attractive with the use of earth-abundant metals and readily available reagents.

Chapter 2: Selective α -amination and α -acylation of esters and amides via dual reactivity of *O*-acylhydroxylamines toward zinc enolates

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2. Selective α -amination and α -acylation of esters and amides via dual reactivity of *O*-acylhydroxylamines toward zinc enolates

2.1 α -Functionalization of esters and amides

α -Amino carbonyl and 1,3-dicarbonyl compounds are highly desirable motifs in organic synthesis and are present in many pharmaceutically and biologically relevant molecules.¹²⁹⁻¹³¹ α -Amino carbonyl compounds are of particular importance because of their presence in α -amino acids and derivatives, as well as α -amino aldehydes and α -amino alcohols. For example, Plavix is an antiplatelet drug used to inhibit blood clots and to prevent heart attack and stroke in people who are at high risk of these events (Figure 4), and in 2010, it was the second-most prescribed drug in the world.² Valaciclovir, another example of an α -amino carbonyl, is an antiviral drug used in the management of herpes—shingles and cold sores.¹³² Aspartame is used as an artificial sweetener in some food and beverages. As for 1,3-dicarbonyl compounds, they are often used as building blocks for the synthesis of drugs.¹³³ Therefore, it is important to be able to access these motifs. Functionalization of carbonyl enolates represents one of the most general and efficient approaches to access these biologically important α -functionalized carbonyl compounds.

Figure 4. Selected examples of biologically important α -amino carbonyls

2.1.1 α -Amination of carbonyl compounds

The ubiquity of nitrogen-containing compounds among functionally and biologically important molecules continues to drive the development of new C–N bond-forming transformations.¹ The formation of α -amino carbonyl compounds is of particular importance because of their presence in α -amino acids, α -amino aldehydes, and α -amino alcohols. However, the direct installation of diverse amines at the carbonyl α -position has been a long-standing challenge in organic synthesis.^{36-40,134} Umpolung electrophilic aminations have received significant attention as an alternative and complementary strategy to traditional nucleophilic aminations for C–N bond formation.³⁵⁻⁴² Electrophilic amination of α -carbanions represents one of most general and important methods for the synthesis of α -amino carbonyl compounds.³⁸⁻⁴⁰ Towards this, a variety of electrophilic nitrogen-transfer reagents have been developed for amination of enolates and eniminates (Figure 5). Electrophilic aminating reagents used for the preparation of α -aminocarbonyl

Figure 5. Electrophilic aminating reagents for amination of carbonyl compounds

compounds include diazene dicarboxylates,⁷⁰⁻⁸³ azides,⁶⁵ nitroso compounds,⁹⁰⁻⁹⁶ oxaziridines,⁹⁷ *O*-diarylphosphinyl hydroxylamine,¹³⁵ *N*-halo amines,⁹⁸⁻⁹⁹ and *O*-acylhydroxylamines.⁵⁶

2.1.1.1 Electrophilic α -aminations of carbonyl compounds via sp^2 *N*-containing reagents

Early electrophilic α -aminations of carbonyl compounds often utilized $[NR_2]^+$ synthons containing an sp^2 nitrogen. Many of these reactions exploited the use of diazene dicarboxylates for the amination of enolates because they are both stable and commercially available. The use of diazene dicarboxylates for electrophilic α -amination was first reported for achiral enolates of diethyl malonates,¹³⁶ acetylacetone and ethyl acetoacetate,¹³⁷ and cyclohexanone-derived enolates.¹³⁸ They have since been used in several asymmetric α -aminations (Scheme 20).⁷⁰⁻⁷⁵ Evans and co-workers used a chiral magnesium sulphonamide complex to generate chiral enolate derivatives of *N*-acyloxazolidinones (Scheme 20A).⁷⁵ Their amination procedure is applicable to a variety of aryl-substituted imides, and the α -amino compounds were obtained in good yield. Jørgensen and co-workers reported the catalytic asymmetric direct α -amination of 2-keto esters with modest yields (Scheme 20B).⁷³⁻⁷⁴ List⁷² and Jørgensen⁷⁰⁻⁷¹ independently reported asymmetric α -aminations of carbonyl compounds via enamine derivatives prepared using *L*-proline (Schemes 20C and 20D). In their respective reactions, good to high yields were obtained. For all of these asymmetric α -aminations, the chiral enolate or enamine derivatives were generated catalytically, and high enantioselectivities were observed in each transformation.⁷⁰⁻⁷⁵

of nitrosoformates (Scheme 21).⁹⁴ The nitrosoformates are produced by the *in situ* oxidation of *N*-hydroxycarbamate precursors. The reaction proceeded with good yield; however, it was limited to the construction of primary and secondary amines. Moreover, relatively harsh conditions are required for the cleavage of the resultant N–O bond of the aminated products.

Scheme 21. Copper-catalyzed *N*-selective nitrosoformate aldol reaction

2.1.1.2 Electrophilic α -aminations of carbonyl compounds via sp^3 *N*-containing reagents

In addition to sp^2 *N*-containing reagents, several sp^3 *N*-containing compounds have been developed for the electrophilic amination of α -carbanions.^{56,97-99,135} Collet and co-workers reported the synthesis of a series of *N*-protected oxaziridines for their use as electrophilic aminating reagents.⁹⁷ These oxaziridines reacted readily with propiophenone lithium enolate to afford the racemic α -*N*-Boc amino compound in modest yield (Scheme 22). They also observed a parallel aldol condensation between the released aldehyde from

the oxaziridine and enolate. Additionally, amide and ester enolates similarly afforded α -*N*-Boc amino compounds.

Scheme 22. Electrophilic amination of lithium enolates via oxaziridines

Direct amination of carbanions has also been reported using a variety of hydroxylamines as electrophilic $[\text{NH}_2]^+$ equivalents,³⁵ including *O*-diarylphosphinyl hydroxylamines.¹³⁵ With this in mind, Vedejs and co-workers reported enolate amination using *O*-diarylphosphinyl hydroxylamines as the nitrogen source (Scheme 23). Amination proceeded efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates, and phenylacetonitriles. Amination yields varied from moderate to excellent depending on the enolate and *O*-diarylphosphinyl hydroxylamine used for the reaction. The highly stabilized sodium and potassium enolates gave the best results, while the more basic phenylacetate and phenylacetonitrile anions also gave good yields. However, like other methods using sp^2 *N*-containing reagents, the use of oxaziridines and *O*-diarylphosphinyl hydroxylamines is limited to the construction of primary and secondary amines.

Scheme 23. Electrophilic amination of stabilized carbanions using *O*-diarylphosphinyl hydroxylamines

Recently, introducing tertiary amines at the α -position of esters has been successfully achieved by electrophilic amination of silyl ketene acetals using either *N*-chloramines or *O*-benzoylhydroxylamines.^{56,98} Previously, *N*-chloramines had been used to introduce an amino group at the α -position of carbonyls via their corresponding lithium enolates.^{99,140-141} However the substrate scope is limited due to the strongly basic reaction conditions as well as the competing chlorination reaction. To overcome this, the Murakami group developed a copper-catalyzed electrophilic amination of silyl ketene acetals using *N*-chloramines (Scheme 24).⁹⁸ Their mild reaction conditions readily afforded the corresponding α -amino esters in good to moderate yields. A variety of *N*-chloramines, cyclic and acyclic, worked well; however silyl ketene acetals were limited to aryl methyl esters.

Scheme 24. Copper-catalyzed electrophilic amination of silyl ketene acetals via *N*-chloramines

Simultaneously, Miura and co-workers developed a copper-catalyzed electrophilic amination of silyl ketene acetals using *O*-acylhydroxylamines as the electrophilic nitrogen source (Scheme 25).⁵⁶ Various silyl ketene acetals underwent amination with *O*-benzoyl-*N,N*-dibenzylhydroxylamine to give the corresponding α -amino esters. In addition to *O*-benzoyl-*N,N*-dibenzylhydroxylamine, other acyclic and cyclic *O*-benzoylhydroxylamines participated in the reaction. However, reaction conditions must be varied depending on the electronic and steric nature of different substrates, and in some cases only moderate yields were obtained. Additionally, both amination methods are efficient for ester precursors of silyl ketene acetals, but are not suitable for other carbonyl compounds (e.g., amides).^{4,142} Therefore, a general and direct α -amination method is highly desirable.

Scheme 25. Copper-catalyzed electrophilic amination of silyl ketene acetals via *O*-benzoylhydroxylamines

2.1.2 α -Acylation of carbonyl compounds

1,3-Dicarbonyl compounds constitute one of the most important classes of organic compounds as they are widely used as building blocks in organic synthesis and exhibit interesting biological properties.¹⁴³ They are traditionally synthesized by the Claisen condensation, either through a classic Claisen with two enolizable esters or crossed Claisen with an enolizable ester or ketone and nonenolizable ester (Scheme 26A).¹⁴⁴ In addition to the Claisen condensation, the Blaise reaction also allows for the synthesis of β -keto esters via the zinc-mediated reaction of nitriles with α -haloesters (Scheme 26 B).¹⁴⁵

Scheme 26. Traditional synthesis of 1,3-dicarbonyl compounds

2.1.3 Zinc enolates for α -functionalization of carbonyl compounds

Zinc enolates have received growing interest as valuable intermediates for carbonyl α -functionalization.^{125-126,146-162} In comparison to commonly used carbonyl α -alkali and alkaline-earth enolates, they offer an ideal combination of good reactivity and tolerance toward many functional groups.^{125-126,146-148} So far, zinc enolates have been successfully applied toward carbon-carbon bond formation with aldol additions to carbonyls,¹⁵⁷⁻¹⁵⁸ nucleophilic additions to alkenes,¹⁵⁹⁻¹⁶⁰ as well as a variety of transmetallation reactions such as α -arylation^{125-126,149-156} and α -allylation.¹⁶¹⁻¹⁶² However, the potential of zinc enolates remains underexplored for the synthesis of α -heteroatom substituted carbonyl molecules, such as α -amino carboxyl derivatives, one of the most biologically important carbonyl compounds.¹²⁹⁻¹³⁰

2.2 Results and Discussion

To develop a more direct and general α -amination strategy,^{56,98,135} we explored zinc enolates for the first time as a reactive intermediate toward electrophilic α -amination because of their good reactivity and tolerance toward many functional groups. We were interested in *O*-acylhydroxylamines as an electrophilic nitrogen source, inspired by the

pioneering work on electrophilic aminations between organometallic reagents and *O*-acylhydroxylamines.⁴⁵⁻⁵⁸ Simultaneously, we envisioned that various *O*-acylhydroxylamines could also act as an electrophilic acylating agent^{48-49,51} toward zinc enolates and lead to the alternative formation of 1,3-dicarbonyl compounds. Such dual reactivity of *O*-acylhydroxylamines is valuable and useful, providing a powerful and divergent strategy for direct and selective access to α -amino carbonyl and 1,3-dicarbonyl compounds, highly desirable motifs in organic synthesis and pharmaceuticals.¹²⁹⁻¹³¹

2.2.1 Electrophilic amination and acylation of esters and amides via zinc enolates

The initial goal of this project was to develop an electrophilic α -amination of zinc enolates of esters and amides using *O*-acylhydroxylamines as our electrophilic nitrogen source. During our studies, we found that the *O*-acylhydroxylamines could be used as either an aminating or acylating agent for selective α -amination and α -acylation reactions (Scheme 27). The developed amination conditions bypass the requirement for postreaction amine modification, such as the reduction of nitrogen-heteroatom bonds for aminations using sp^2 electrophilic nitrogen sources. Additionally, they overcome the limitation of a narrow amine scope under previous α -amination conditions. It provided the first example of electrophilic amination of zinc enolates for the direct installation of different amines at the carbonyl α -position in a one-step reaction. Such a direct and operationally convenient amination procedure represents a valuable advance in the synthesis of α -amino carbonyl compounds. We also identified that acylation effectively occurred upon the treatment of these zinc enolates with *O*-acylhydroxylamines alone at

elevated temperatures where *O*-acylhydroxylamines act as an acylating agent exclusively. Such an alternative α -acylation reaction provides an exceptionally simple entry to important 1,3-dicarbonyl compounds.¹³¹ Collectively, these studies on the dual electrophilic reactivity of *O*-acylhydroxylamines provide further insight into their potential for developing selective and complementary amination and acylation reactions in a broader range of C–H bonds.

Scheme 27. Selective α -amination and α -acylation of esters and amides via the dual reactivity of *O*-acylhydroxylamines

2.2.2 Initial amination studies using the Reformatsky reagent

The Reformatsky enolate was first reported by Sergey Reformatsky in the late 1800s for condensation with aldehydes and ketones to give β -hydroxy esters.¹⁶³⁻¹⁶⁴ The organozinc reagent is easily prepared by treating α -halo esters with zinc (Scheme 28) and is less nucleophilic than lithium enolates or Grignard reagents. With this we chose to start the development of our α -amination method using Reformatsky enolate **2**.

Scheme 28. Preparation of Reformatsky enolate **2**

Initial experiments screened Reformatsky enolate **2** and *O*-benzoylhydroxylamine **3** in the presence of CuCl and carbene ligands (Table 1). Using ICy•BF₄ as the ligand, α -

amino ester **4** was observed in 13% (entry 1). Minor amination was observed using IMes•HCl and iPr (entries 3 and 4), while no amination was observed for SIMes•HBF₄ or iPr•HCl (entries 2 and 5). It should be noted that 13% amination was observed when pre-formed catalyst [(iPr)CuCl] was used for the reaction. With these exciting results, ICy•BF₄ was used as the ligand for further screening and reaction optimization.

Table 1. Carbene ligand screen for the amination of Reformatsky enolate **2.**^a

entry	ligand	time (h) ^b	4 (%) ^c
1	ICy•BF ₄	2	13
2	SIMes•HBF ₄	2	0
3	IMes•HCl	2	trace
4	iPr	2	3
5 ^d	iPr•HCl	2	0

^a Reactions conducted on a 0.2-0.3 mmol scale. ^b Time required for the complete consumption of **3**. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^d Reaction with pre-formed catalyst [(iPr)CuCl] gave 13% amination.

After identifying ICy•BF₄ as our best ligand, we screened copper sources for the reaction (Table 2). In comparison to CuCl, CuCN and Cu(OTf)₂ were inferior (entries 2 and 3). On the other hand, CuBr, CuI, and Cu(acac)₂ gave increased amination yields with CuBr giving the best amination yields at 23% (entries 4–6). With this, CuBr was chosen as catalyst along with ICy•BF₄ as ligand for further reaction optimization.

Table 2. Copper catalyst screen for the amination of Reformatsky enolate **2.^a**

entry	catalyst	time (h) ^b	4 (%) ^c
1	CuCl	2	13
2	CuCN	2	0
3	Cu(OTf) ₂	2	0
4	CuBr	2	23
5	CuI	2	15
6	Cu(acac) ₂	2	17

^a Reactions conducted on a 0.2-0.3 mmol scale. ^b Time required for the complete consumption of **3**. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

Finally we finished reaction optimization by investigating the effect of the nucleophile, base, solvent, and reactant equivalence (Table 3). For the nucleophile effect we looked into two different ways of making the Reformatsky enolate. The Reformatsky enolate can either be prepared by treating the α -halo ester with zinc dust or by deprotonation of the ester with LDA followed by quenching with either ZnCl₂ or ZnBr₂. For the first method, amination was achieved in 23% (entry 1); however for the second method, β -keto ester **6** was the only product detected (entries 2 and 3). We believe this is due to the presence of excess lithium from *n*-BuLi, which can coordinate with the carbonyl of the *O*-acylhydroxylamine therefore increasing reactivity at the carbonyl

carbon. We next looked at the cation effect for the different *tert*-butoxide bases. As the metal cation increased in size, the amination amount decreased (entries 4 and 5). As for solvents, MeCN gave comparable results to THF, while toluene gave a mixture of amination and β -keto ester **6** (entries 7 and 8). Amination increased slightly when DCM was used (entry 9). Finally, we looked into the effects of nucleophile and electrophile equivalence as well as catalyst and ligand loading. To this point, we had only been using a slight excess of **2**. When the equivalence of **2** was increased to 2.0, the overall yield of the reaction doubled (entry 10). Conversely, when Reformatsky enolate **2** was used as the limiting reagent, the yield decreased slightly (entry 11). Lastly, we lowered the catalyst and ligand loading and observed comparable yields for the reaction (entry 12).

Table 3. Optimization of the Reformatsky enolate amination.^a

entry	enolate (equiv)	base (equiv)	solvent	time (h) ^b	temp (°C)	4 (%) ^c	6 (%) ^c
1	2 (1.1)	LiOt-Bu (1.1)	THF	2	60	23	0
2 ^d	2 (1.1)	LiOt-Bu (1.1)	THF	2	60	0	28
3 ^e	5 (1.1)	LiOt-Bu (1.1)	THF	2	60	0	38
4	2 (1.1)	NaOt-Bu (1.1)	THF	2.5	60	trace	0
5	2 (1.1)	KOt-Bu (1.1)	THF	2.5	60	0	0
6	2 (1.1)	LiOt-Bu (1.1)	THF	2	rt	11	0
7	2 (1.1)	LiOt-Bu (1.1)	MeCN	4	rt	11	0
8	2 (1.1)	LiOt-Bu (1.1)	tol	2	rt	8	13
9	2 (1.1)	LiOt-Bu (1.1)	DCM	2	rt	26	0
10	2 (2.0)	LiOt-Bu (1.2)	DCM	2	rt	52	0
11	2 (0.5)	LiOt-Bu (1.05)	DCM	2	rt	22	0
12 ^f	2 (2.0)	LiOt-Bu (1.2)	DCM	2	rt	49	0

^a Reactions conducted on a 0.2–0.3 mmol scale. ^b Time required for the complete consumption of **3**. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^d **2** was made by deprotonation of *tert*-butyl acetate with LDA then quenching the reaction with ZnBr₂. ^e **5** was made by deprotonation of *tert*-butyl acetate with LDA then quenching the reaction with ZnCl₂. ^f Reaction run using 5 mol% of CuBr and 5 mol% of ICy•BF₄.

2.2.3 Amination studies using Zn(tmp)₂ for zinc enolate formation

With promising results using the Reformatsky enolate, we wanted to look into the analogous and more reactive bis zinc enolate. Our study started from the amination reaction of ester **7** and *O*-benzoylhydroxylamine **3** as model substrates (Table 4). The generation of the nucleophilic zinc enolate was achieved by the treatment of ester **7** with Zn(tmp)₂ solution.¹²⁵⁻¹²⁶ In the initial examination of transition metal catalysts, CuCl was found effective to readily promote the desired amination reaction at room temperature, and the aminated product **4** was formed in 81% yield in 1.5 h (entry 1). Without a copper catalyst, no reaction occurred between zinc enolate of **7** and *O*-benzoylhydroxylamine **3** (entry 2). Next we evaluated the effect of ligands. The addition of 1,10-phenanthroline resulted in decreased yield of **4** while 2,2'-bipyridine provided quantitative yield of **4** (entries 3 and 4). We then screened the equivalence of *O*-benzoylhydroxylamine **3**. Comparable yields were observed when either 1.0 or 1.5 equivalents of **3** were used in the reaction; however when the equivalents of **3** was increased to 2.0, the yield of **4** decreased (entries 5–7). While screening amination conditions for **7**, we simultaneously screened amide **8**. We immediately found that the above conditions were not applicable to the amination of amide **8** (entry 8). Thus, we then looked into different copper sources. CuCN, [CuOTf]₂•tol and Cu(OAc)₂ were inferior to CuCl in the reaction of ester **1** while Cu(acac)₂ and CuCl₂ provided comparable efficacy (entries 9–14). Most encouragingly, the system of CuCl₂ and bipyridine was also effective for the amide substrate **7**, and afforded the desired product **9** in 53% yield (entry 16). Therefore, the use of CuCl₂ and 2,2'-bipyridine were selected as the standard amination conditions for subsequent studies.

Table 4. Condition optimization for electrophilic amination of ester **7a and amide **7b** with *O*-benzoylhydroxylamine **3**.^a**

entry	carbonyl	3 (equiv)	catalyst	ligand	time (h) ^b	results ^c
1	7	1.0	CuCl	—	1.5	4 (81%)
2	7	1.0	—	—	1.5	4 (0%)
3	7	1.0	CuCl	phen	24	4 (36%)
4	7	1.0	CuCl	bipyr	1.0	4 (99%)
5	7	0.5	CuCl	bipyr	1.0	4 (98%)
6	7	1.5	CuCl	bipyr	1.0	4 (98%)
7	7	2.0	CuCl	bipyr	24	4 (70%)
8	8	1.0	CuCl	bipyr	1.0	9 (6%)
9	7	1.0	CuCN	bipyr	24	4 (53%)
10	7	1.0	[CuOTf] ₂ •tol	bipyr	1.0	4 (35%)
11	7	1.0	Cu(OTf) ₂	bipyr	1.0	4 (36%)
12	7	1.0	Cu(acac) ₂	bipyr	1.0	4 (85%)
13	7	1.0	Cu(OAc) ₂	bipyr	1.0	4 (55%)
14	7	1.0	CuCl ₂	bipyr	1.0	4 (99%)
15 ^d	7	1.0	CuCl ₂	bipyr	1.0	4 (99%)

16	8	1.0	CuCl ₂	bipyr	1.0	9 (53%)
17	8	1.0	Cu(OTf) ₂	bipyr	1.0	9 (0%)
18	8	1.0	Cu(acac) ₂	bipyr	1.0	9 (15%)
19	8	1.0	Cu(OAc) ₂	bipyr	1.0	9 (0%)

^a Reactions conducted on a 0.2–0.3 mmol scale. **7** or **8** (2.1 equiv.), Zn(tmp)₂ (1.0 equiv.); **3** (1.0 equiv.); Cu catalyst (5 mol%), ligand (10 mol%). ^b Time required for the complete consumption of **3**. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^d Reaction run in the dark.

With conditions identified for α -amination, we surveyed the amine scope of the α -amination transformation using model substrate ester **7** with a variety of *O*-benzoylhydroxylamines derived from simple amines (Table 5). In addition to **3** (entry 1), functionalizing the α -position of **7** with different cyclic amines, such as **11** and **13**, was also achieved in excellent yields (entries 2 and 3). The amination reactions of acyclic *O*-benzoylhydroxylamines also proceeded efficiently with derivatives containing *N,N*-diethyl, *N,N*-dibenzyl, and *N*-benzyl-*N*-methyl groups (entries 4–6). Note that the benzyl moiety can be a useful synthetic handle for further manipulations after selective deprotection. Excitingly, the secondary hydroxylamine was effective for the direct amination (entry 7). Additionally, *O*-benzoylhydroxylamines containing carbamate, ester, and olefin groups all participated in the amination smoothly (entries 8–10), demonstrating the great compatibility of this transformation with diverse functionality. Importantly, the amination reaction of **26** gave the aminated product **27** exclusively in quantitative yield, and no pyrrolidine-containing compound was detected for a conceivable copper-catalyzed radical cyclization.¹⁶⁶

Table 5. Copper-catalyzed electrophilic α -amination of ester **7 with various *O*-benzoylhydroxylamines.^a**

$t\text{-BuO}-\text{C}(=\text{O})-\text{Me}$ **7**
 $\xrightarrow[\text{2) BzO}-\text{NR}^1\text{R}^2, \text{CuCl}_2, \text{bipyr}, \text{THF}, \text{rt}, 1 \text{ h}]{\text{1) Zn(tmp)}_2, \text{tol}, \text{rt}, 1 \text{ h}}$
 $t\text{-BuO}-\text{C}(=\text{O})-\text{CH}_2\text{NR}^1\text{R}^2$

entry	<i>O</i> -acylhydroxylamine	product	yield (%)	
1		3	4	98
2		10	11	98
3		12	13	95
4		14	15	98
5		16	17	99
6		18	19	96
7		20	21	42
8		22	23	97
9		24	25	98
10		26	27	99

^a Isolated yields. Reactions conducted in a 0.2–0.3 mmol scale: **7** (2.1 equiv), Zn(tmp)₂ (1.0 equiv), *O*-acylhydroxylamine (1.0 equiv), CuCl₂ (5 mol%), bipyridine (10 mol%).

We also examined the generality of α -amination using *O*-benzoylhydroxylamine **3** on a variety of zinc enolate derivatives (Table 6). Compared to the model substrate *tert*-butyl acetate **7**, other acetate ester including *iso*-propyl acetate **28** and ethyl acetate **30** also provided the aminated products in excellent yields (entries 1, 3 and 4). Besides **8**, other amides also effectively underwent electrophilic amination reactions (entries 5–7), while cyclic amides **32** and **34** proceeded more efficiently than acyclic amides **8** and **36**. However, the current conditions were ineffective for esters and amides bearing a substitution at the α -position, suggesting sterics may possibly influence the conformation of zinc enolates to impede an effective transmetallation reaction with the copper intermediate.^{125-126,157} The demonstrated generality of this copper-catalyzed α -amination transformation on a variety of zinc carbanions suggest its potential in the synthesis of functionally important α -amino carbonyl compounds.

Table 6. Copper-catalyzed electrophilic α -amination of esters and amides with *O*-acylhydroxylamine **3.^a**

1) Zn(tmp)₂, tol, rt
2) **3**
CuCl₂, bipyr, THF, rt

entry	ester or amide		time (h) ^b	product	yield (%)
1		7	1; 1	4	98
2		8	1; 1.5	9	53
3		28	1; 1.5	29	94
4		30	1; 3	31	90
5		32	1; 1.5	33	95
6		34	2; 3	35	70
7		36	0.5; 3	37	51

^a Isolated yields. Reactions conducted in a 0.2–0.3 mmol scale: ester or amide (2.1 equiv), Zn(tmp)₂ (1.0 equiv), **3** (1.0 equiv), CuCl₂ (5 mol%), bipyr (10 mol%). ^b Reaction time for step 1 and 2, respectively.

2.2.4 α -Acylation of ester and amide zinc enolates

During our studies, we found that acylated product **6** was formed in 58% yield when **3** was treated with the zinc enolate of ester **7** in the absence of a copper catalyst at

room temperature for an extended period of time (24 h). At 60°C, this reaction proceeded more rapidly and provided β -keto ester **6** in 82% yield within 3 h (Table 7). We were intrigued by such a highly selective acylation resulting from the dual reactivity of *O*-benzoylhydroxylamine **3** toward the zinc enolate of ester **7**.

Table 7. α -Acylation of ester **7 using *O*-benzoylhydroxylamine **3**.^a**

entry	temp (°C)	time (h) ^b	6 (%) ^c
1	rt	1.5	0
2	rt	24	58
3	60	3	82

^a Reactions conducted on a 0.2–0.3 mmol scale. ^b Time required for the complete consumption of **3**. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

We then examined the generality of this acylation transformation for the preparation of 1,3-dicarbonyl compounds (Table 8). With model substrate ester **7**, all reactions provided the desired 1,3-dicarbonyl products in good yields (61–92%, entries 1–4). These results also suggest that the efficiency of the acylation reaction is independent of the amine moiety (entries 1 and 2). Similarly, acylation reactions of hydroxylamine **3** with different ester and amide substrates also proceeded efficiently (entries 5–10). Once again, zinc enolates derived from α -substituted esters and amides were found unreactive toward acylation, suggesting that the steric hindrance significantly reduces their

nucleophilicity. Despite current limitations, the α -acylation transformation nevertheless offers a rapid and efficient approach to prepare simple 1,3-dicarbonyl compounds.

Table 8. α -Acylation of esters and amides via *O*-acylhydroxylamines.^a

$ \begin{array}{c} \text{Y}-\text{C}(=\text{O})-\text{Me} \xrightarrow[2) \text{R}^1-\text{C}(=\text{O})-\text{O}-\text{N}(\text{R}^2)\text{R}^3]{1) \text{Zn}(\text{tmp})_2, \text{tol}, \text{rt}} \text{Y}-\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{R}^1 \\ \text{THF, 60 } ^\circ\text{C} \end{array} $						
entry	ester or amide	<i>O</i> -acylhydroxylamine	time (h) ^b	product	yield (%)	
1			1; 3	6	82	
2	7		1; 5	6	81	
3	7		1; 3	39	92	
4	7		1; 5	41	61	
5		3	1; 3	42	90	
6		3	1; 3	43	87	
7		3	1; 5	44	61	
8		3	1; 5	45	71	
9		3	1; 5	46	75	
10		3	1; 5	47	68	

^a Isolated yields. Reactions conducted in a 0.2–0.3 mmol scale: ester or amide (2.1 equiv), Zn(tmp)₂ (1.0 equiv), *O*-acylhydroxylamine (1.0 equiv). ^b Reaction time for step 1 and 2, respectively.

2.2.5 Proposed mechanism for the α -amination and α -acylation reactions

Based on our results, a plausible reaction mechanism is proposed in Scheme 29 for the observed dual reactivity of *O*-acylhydroxylamines (e.g. **3**) toward zinc enolate (**I**) in the amination and acylation of ester **7**. When a copper catalyst is present (condition A),

Scheme 29. Reaction pathways for the amination and acylation of zinc enolates with *O*-acylhydroxylamine **3**

the transmetalation between copper and zinc enolate (**I**) occurs and the resulting intermediate **(IIIA)** subsequently undergoes oxidative addition of *O*-acylhydroxylamine **3**. Finally, the reactive copper complex **(IVA)** would readily undergo reductive elimination to afford the aminated product **4** and regenerate the copper catalyst. A radical pathway cannot be excluded despite lacking indication of any radical intermediates involved in the amination reactions. Additionally, we cannot exclude an alternative that includes (1) oxidative addition of the hydroxylamine to a low-valent copper species, (2) transmetalation with a zinc enolate, and (3) reductive elimination to form desired C–N

bond. On the other hand, in the absence of a copper catalyst (condition B), the nucleophilic zinc enolate (**I**) would preferably attack the electrophilic carbonyl group of **3**, possibly via an intermediate (**IIB**), and selectively afford the acylated product **6**.

2.3 Conclusion

In summary, we describe the development of selective α -amination and α -acylation of simple carbonyl compounds on the basis of the dual reactivity of *O*-acylhydroxylamines. α -Amination of esters and amides has been achieved by a copper-catalyzed electrophilic amination of their zinc enolates using *O*-acylhydroxylamines. In the absence of a copper catalyst, the direct treatment of zinc enolates with *O*-acylhydroxylamines exclusively formed α -acylated 1,3-dicarbonyl products. These interesting results also provide insight into the dual electrophilic reactivity of *O*-acylhydroxylamines for selective amination and acylation reactions of other C–H bonds. Currently, studies on α -amination of substituted carbonyl compounds are underway.

2.4 Supplemental Information

2.4.1 General Information

General Procedures. Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in Biotage 8 mL microwave vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 x 20 cm) of Drierite, unless otherwise noted. Reaction vials were sealed with Teflon tape. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic syringes or glass pipets were used to transfer liquid reagents.

Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO_4 stain. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Flash-column chromatography was performed on silica gel (60 Å, standard grade) or on a CombiFlash companion system with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.).

Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich or Strem and used as received. Dry THF and toluene were obtained using an Innovative Technologies solvent purification system. *O*-acylhydroxylamine derivatives were prepared according to literature procedure.⁴⁸

Instrumentation. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 or 125 MHz respectively) spectrometer at ambient temperature. Chemical shifts for ^1H NMR are reported in parts per million (ppm, δ) and referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.26). Chemical shifts for ^{13}C NMR are reported in ppm and referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), integration. Infrared spectroscopic data was obtained using an Thermo Scientific Nicolet 380 FT-IR. IR data is reported in wavenumbers (cm^{-1}) with only select peaks shown. High-resolution

mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer.

2.4.2 Experimental procedures

Procedure for formation of Reformatsky enolate **2**.¹⁶⁵

To activated Zn powder (305 mg, 4.67 mmol, 1.15 equiv) in 2-neck RBF was added THF (10 mL) and TMSCl (0.06 mL, 0.41 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 10 min then warmed to 40 °C for an additional 20 min. The reaction mixture was brought to reflux and **1** (0.6 mL, 4.06 mmol, 1.0 equiv) was added dropwise. After 2.5 h, the reaction was removed from heat. Reformatsky solution turned a pale green color.

General experimental procedure for the amination of Reformatsky enolate **2**.

O-Acylhydroxylamine **3** (0.200 mmol, 1.0 equiv), CuBr (0.01 mmol, 0.05 equiv), ICy•BF₄ (0.01 mmol, 0.05 equiv), and LiOt-Bu (0.220 mmol, 1.1 equiv) added to microwave tube. Flask evacuated and refilled with N₂ (3x). DCM (1 mL) added followed by Reformatsky enolate **2** (0.36M, 0.400 mmol, 2.0 equiv). Reaction stirred at room temperature. Consumption of *O*-acylhydroxylamine **3** monitored by TLC (50:50 ethyl

acetate–hexanes). Upon complete consumption of *O*-acylhydroxylamine **3**, the reaction was quenched with NaHCO₃ (10 mL), extracted into Et₂O (2 x 20 mL). Organic layers were combined and washed with brine (20 mL), and dried over Na₂SO₄. The mixture was filtered and evaporated under reduced pressure.

Typical procedure 1 (TP1): General experimental procedure for the α -amination reaction using Zn(tmp)₂ as base.

To an 8 mL microwave tube was added Zn(tmp)₂ (0.5 M solution in tol, 0.36 mL, 0.18 mmol, 1.0 equiv) followed by dropwise addition of the carbonyl compound (0.37 mmol, 2.1 equiv). The reaction was stirred at room temperature for 1 h and was added dropwise a mixture of *O*-acylhydroxylamine (0.18 mmol, 1.0 equiv), CuCl₂ (0.0089 mmol, 0.05 equiv), and 2,2'-bipyridyl (0.018 mmol, 0.1 equiv) in THF (2 mL). The reaction mixture was allowed to stir at room temperature. Upon complete consumption of *O*-acylhydroxylamine (monitored by TLC–50% ethyl acetate–hexanes), the reaction was diluted with a saturated aqueous solution of NaHCO₃ (10 mL) and extracted into Et₂O. The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by either column chromatography or acid-base extraction using 2M HCl and 2M NaOH.

Typical procedure 2 (TP2): General experimental procedure for the α -acylation reaction using $\text{Zn}(\text{tmp})_2$ as base.

To an 8 mL microwave tube was added $\text{Zn}(\text{tmp})_2$ (0.5 M solution in toluene, 0.36 mL, 0.18 mmol, 1.0 equiv) followed by dropwise addition of the carbonyl compound (0.37 mmol, 2.1 equiv). The reaction was stirred at room temperature for 1 h and was added dropwise a solution of *O*-acylhydroxylamine (0.20 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was heated to 60 °C. Upon complete consumption of *O*-acylhydroxylamine (monitored by TLC–50% ethyl acetate–hexanes), the reaction was diluted with a saturated aqueous solution of NaHCO_3 (10 mL) and extracted into Et_2O . The combined organic layers were washed with brine (10 mL) and dried over MgSO_4 . The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography.

2.4.3 Characterization of compounds

***tert*-Butyl-2-morpholinoacetate (4).** Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **4** as a pale yellow oil (35.1 mg, 98%); $R_f = 0.28$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.75 (t, $J = 4.8$ Hz, 4H), 3.10 (s, 2H), 2.57 (t, $J = 4.8$ Hz, 4H), 1.46 (s, 9H); ^{13}C NMR (CDCl_3 ,

100 MHz): δ 169.2, 81.1, 66.7, 60.2, 53.2, 28.0; FTIR (thin film): cm^{-1} 2854, 1741, 1147, 1115; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{20}\text{NO}_3$) ($[\text{M}+\text{H}]^+$): 202.1438; found 202.1441.

***N,N*-Diethyl-2-morpholinoacetamide (9).** Compound prepared according to TP1. Purification by acid-base extraction gave **9** as a pale yellow oil (18.9 mg, 53%); R_f = 0.10 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): 3.72 (t, J = 4.8 Hz, 4H), 3.38 (q, J = 7.2 Hz, 2H), 3.35 (q, J = 7.2 Hz, 2H), 3.14 (s, 2H), 2.52 (t, J = 4.8 Hz, 4H), 1.18 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): 168.1, 66.8, 61.1, 53.7, 41.6, 40.0, 14.3, 12.9; FTIR (thin film): cm^{-1} 2851, 1629, 1131, 1113, 1069; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{21}\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 201.1598; found 201.1601.

***tert*-Butyl-2-(piperidin-1-yl)acetate (11).** Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **11** as a pale yellow oil (34.8 mg, 98%); R_f = 0.38 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.07 (s, 2H), 2.49 (t, J = 5.4 Hz, 4H), 1.60 (quin, J = 5.4 Hz, 4H), 1.45 (s, 9H), 1.42–1.40 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.9, 80.8, 60.8, 54.2, 28.1, 25.9, 24.0; FTIR (thin film): cm^{-1} 2933, 2853, 1746, 1367, 1149; HRMS-ESI (m/z) Calcd for ($\text{C}_{11}\text{H}_{22}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 200.1645; found 200.1647.

tert-Butyl-2-(pyrrolidin-1-yl)acetate (13). Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **13** as a pale yellow oil (31.3 mg, 95%); R_f = 0.37 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.23 (s, 2H), 2.65–2.62 (m, 4H), 1.80 (t, J = 3.6 Hz, 2H), 1.78 (t, J = 3.6 Hz, 2H), 1.5 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.7, 81.0, 57.3, 53.7, 28.1, 23.5; FTIR (thin film): cm^{-1} 2930, 1744, 1151; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{20}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 186.1489; found 186.1488.

tert-Butyl-2-(dibenzylamino)acetate (15). Compound prepared according to TP1. Purification by column chromatography (25% ethyl acetate–hexanes) gave **15** as a white solid (54.3 mg, 98%); R_f = 0.80 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.40 (d, J = 7.2, 4H), 7.32 (t, J = 7.2 Hz, 4H), 7.26 (t, J = 7.2 Hz, 2H), 3.80 (s, 4H), 3.18 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 170.8, 139.2, 128.9, 128.2, 127.0, 80.7, 57.6, 54.4, 28.2; FTIR (thin film): cm^{-1} 3026, 2802, 1719, 1364, 1137; HRMS-ESI (m/z) Calcd for ($\text{C}_{20}\text{H}_{26}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 312.1958; found 312.1959.

tert-Butyl-2-(benzyl(methyl)amino)acetate (17). Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **17** as a pale yellow oil (41.7 mg, 99%); R_f = 0.66 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 ,

400 MHz): δ 7.36–7.25 (m, 5H), 3.68 (s, 2H), 3.17 (s, 2H), 2.37 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.3, 138.5, 129.1, 128.2, 127.1, 80.8, 60.9, 58.4, 42.0, 28.2; FTIR (thin film): cm^{-1} 2976, 2930, 1730, 1366, 1149; HRMS-ESI (m/z) Calcd for ($\text{C}_{14}\text{H}_{22}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 236.1645; found 236.1649.

***tert*-Butyl-2-(diethylamino)acetate (19).** Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **19** as a pale yellow oil (32.0 mg, 96%); R_f = 0.21 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.23 (s, 2H), 2.61 (q, J = 7.2 Hz, 4H), 1.46 (s, 9H), 1.07 (t, J = 7.2 Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.6, 80.7, 54.7, 47.6, 28.2, 12.3; FTIR (thin film): cm^{-1} 2970, 2931, 1733, 1367, 1151; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{22}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 188.1645; found 188.1646.

***tert*-Butyl-2-(benzylamino)acetate (21).** Compound prepared according to TP1. Purification by column chromatography (20% ethyl acetate–hexanes) gave **21** as a white solid (16.5 mg, 42%); R_f = 0.58 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): 7.34–7.24 (m, 5H), 3.79 (s, 2H), 3.31 (s, 2H), 1.93 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): 171.6, 139.6, 128.3, 128.2, 127.0, 81.0, 53.2, 50.9, 28.0; FTIR (thin film): cm^{-1} 3370, 2977, 1728, 1453, 1226, 1150; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{20}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 222.1489; found 222.1492.

tert-Butyl-4-(2-(tert-butoxy)-2-oxoethyl)piperazine-1-carboxylate (23). Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **23** as a pale yellow solid (51.8 mg, 97%); R_f = 0.52 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): 3.46 (t, J = 5.0 Hz, 4H), 3.12 (s, 2H), 2.51 (t, J = 5.0 Hz, 4H), 1.45, (s, 9H), 1.44 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.4, 154.7, 81.2, 79.6, 60.0, 52.6 (2C), 28.4, 28.1; FTIR (thin film): cm^{-1} 2975, 2861, 1741, 1688, 1365, 1147, 1124; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{29}\text{N}_2\text{O}_4$) ($[\text{M}+\text{H}]^+$): 301.2122; found 301.2126.

Ethyl-1-(2-(tert-butoxy)-2-oxoethyl)piperidine-4-carboxylate (25). Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **25** as a pale yellow oil (47.3 mg, 98%); R_f = 0.56 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): 4.11 (q, J = 7.2 Hz, 2H), 3.09 (s, 2H), 2.89 (dt, J = 11.6, 3.6 Hz, 2H), 2.29–2.20 (m, 3H), 1.90–1.76 (m, 4H), 1.44 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 174.9, 169.7, 81.0, 60.2, 52.5 (2C), 40.7, 28.1 (2C), 14.2; FTIR (thin film): cm^{-1} 2977, 2932, 2812, 1726, 1366, 1141; HRMS-ESI (m/z) Calcd for ($\text{C}_{14}\text{H}_{26}\text{NO}_4$) ($[\text{M}+\text{H}]^+$): 272.1856; found 272.1860.

tert-Butyl-2-(butyl(2-methylpent-4-en-1-yl)amino)acetate (27). Compound prepared according to TP1. Purification by column chromatography (20% ethyl acetate–hexanes) gave **27** as a pale yellow oil (47.8 mg, 99%); R_f = 0.83 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): 5.84–5.74 (m, 1H), 5.01–4.96 (m, 2H), 3.19 (s, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.42 (dd, J = 12.8, 7.2 Hz, 1H), 2.32 (dd, J = 12.8, 7.2 Hz, 1H), 2.22 (dt, J = 13.8, 4.8 Hz, 1H), 1.81 (dt, J = 13.8, 4.8 Hz, 1H), 1.69–1.61 (m, 1H), 1.50–1.45 (m, 2H), 1.45 (s, 9H), 1.32 (q, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.3, 137.5, 115.5, 80.5, 61.0, 56.5, 54.4, 39.7, 39.2, 28.2, 20.4, 17.8, 14.0; FTIR (thin film): cm^{-1} 2956, 2929, 1733, 1457, 1367, 1148, 910; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{32}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 270.2428; found 270.2431.

Isopropyl-2-morpholinoacetate (29). Compound prepared according to TP1. Purification by column chromatography (50% ethyl acetate–hexanes) gave **29** as a pale yellow oil (31.3 mg, 94%); R_f = 0.20 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 5.06 (tt, J = 6.4, 6.4 Hz, 1H), 3.75 (t, J = 4.6 Hz, 4H), 3.17 (s, 2H), 2.58 (t, J = 4.6 Hz, 4H), 1.25 (d, J = 6.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.6, 68.2, 66.8, 59.9, 53.3, 21.8; FTIR (thin film): cm^{-1} 2855, 1741, 1199, 1114; HRMS-ESI (m/z) Calcd for ($\text{C}_9\text{H}_{19}\text{NO}_3$) ($[\text{M}+\text{H}]^+$): 188.1281; found 188.128.

Ethyl-2-morpholinoacetate (31). Compound prepared according to TP1. Purification by column chromatography (60% ethyl acetate–hexanes) gave **31** as a pale yellow oil (27.8 mg, 90%); $R_f = 0.16$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.18 (q, $J = 7.2$ Hz, 2H), 3.74 (t, $J = 4.8$ Hz, 4H), 3.19 (s, 2H), 2.57 (t, $J = 4.8$ Hz, 4H), 1.26 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.0, 66.8, 60.6, 59.7, 53.3, 14.2; FTIR (thin film): cm^{-1} 2930, 2854, 1745, 1161, 1115; HRMS-ESI (m/z) Calcd for ($\text{C}_8\text{H}_{16}\text{NO}_3$) ($[\text{M}+\text{H}]^+$): 174.1125; found 174.1128.

1-(3-Methylpiperidin-1-yl)-2-morpholinoethanone (33). Compound prepared according to TP1. Purification by acid-base extraction gave **33** (1:1 ratio of two conformers) as a white solid (38.3 mg, 95%); ^1H NMR (CDCl_3 , 400 MHz, 25 °C): δ 4.40 (d, $J = 13.2$ Hz, 1H_a), 4.37 (d, $J = 13.2$ Hz, 1H_b), 3.94 (d, $J = 13.2$ Hz, 1H_a), 3.86 (d, $J = 13.2$ Hz, 1H_b), 3.71 (t, $J = 4.4$ Hz, 8H_{a+b}), 3.22 (dd, $J = 13.2, 7.2$ Hz, 2H_{a+b}), 3.10 (dd, $J = 13.2, 7.2$ Hz, 2H_{a+b}), 2.93 (td, $J = 11.6, 3.2$ Hz, 2H_{a+b}), 2.62 (dd, $J = 12.8, 10.8$ Hz, 2H_{a+b}), 2.54 (td, $J = 11.6, 3.2$ Hz, 2H_{a+b}), 2.50 (t, $J = 4.4$ Hz, 8H_{a+b}), 2.25 (dd, $J = 12.8, 10.8$ Hz, 2H_{a+b}), 1.81 (d, $J = 12.8$ Hz, 2H_{a+b}), 1.73–1.64 (m, 2H_{a+b}), 1.60–1.35 (m, 4H_{a+b}), 1.19–1.07 (m, 1H_{a+b}), 0.91 (d, $J = 6.8$ Hz, 3H_a), 0.89 (d, $J = 6.8$ Hz, 3H_b); ^{13}C NMR (CDCl_3 , 100 MHz): δ 167.3, 66.9, 61.6, 61.5, 53.5, 53.2, 49.2, 46.2, 42.4, 33.0, 33.0,

32.0, 31.2, 26.0, 25.0, 19.0, 18.9; FTIR (thin film): cm^{-1} 2927, 2850, 1640, 1455, 1262, 1115; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{23}\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 227.1754; found 227.1755.

***tert*-Butyl-4-(2-morpholinoacetyl)piperazine-1-carboxylate (35).** Compound prepared according to TP1. Purification by column chromatography (80% ethyl acetate–hexanes) gave **35** as a white solid (39.1 mg, 70%); R_f = 0.15 (90% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.70 (t, J = 4.6 Hz, 4H), 3.57 (t, J = 5.2 Hz, 4H), 3.45 (t, J = 5.6 Hz, 2H), 3.39 (t, J = 5.6 Hz, 2H), 3.19 (s, 2H), 2.50 (t, J = 4.6 Hz, 4H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 167.8, 154.5, 80.3, 66.8, 61.7, 53.5 (2C), 51.9, 45.5, 41.6, 28.3; FTIR (thin film): cm^{-1} 2902, 1679, 1628, 1249, 1234, 1130, 1111; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{28}\text{N}_3\text{O}_4$) ($[\text{M}+\text{H}]^+$): 314.2074; found 314.2077.

***N*-Methyl-2-morpholino-*N*-phenylacetamide (37).** Compound prepared according to TP1. Purification by acid-base extraction gave **37** as a white solid (21.3 mg, 51%); ^1H NMR (CDCl_3 , 400 MHz): δ 7.41 (t, J = 7.6 Hz, 2H), 7.36–7.32 (m, 1H), 7.20 (d, J = 7.6 Hz, 2H), 3.66 (t, J = 4.2 Hz, 4H), 3.27 (s, 3H), 2.91 (s, 2H), 2.44 (s, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.1, 143.4, 129.7, 127.9, 127.2, 66.8, 59.9, 53.6, 37.4; FTIR (thin film): cm^{-1} 2954, 2852, 2801, 1656, 1594, 1262, 1112; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 235.1441; found 235.1447.

tert-Butyl-3-oxo-3-phenylpropanoate (6). Compound prepared according to TP2. Purification by column chromatography (20% ethyl acetate–hexanes) gave **6** as a colorless oil (32.1 mg, 82%); $R_f = 0.78$ (20% ethyl acetate-hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 12.72 (s, 1H *enol tautomer*), 7.94 (dt, $J = 6.4$, 1.6 Hz, 2H), 7.76 (dt, $J = 6.4$, 1.6 Hz, 2H *enol tautomer*), 7.58 (tt, $J = 6.4$, 1.6 Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.44–7.38 (m, 3H *enol tautomer*), 5.58 (s, 1H *enol tautomer*), 3.89 (s, 2H), 1.54 (s, 9H *enol tautomer*), 1.43 (s, 9H); Spectroscopic data was identical to that reported previously.¹⁶⁷

tert-Butyl-3-(4-nitrophenyl)-3-oxopropanoate (39). Compound prepared according to TP2. Purification by column chromatography (20% ethyl acetate–hexanes) gave **39** as a yellow oil (43.2 mg, 92%); $R_f = 0.80$ (50% ethyl acetate-hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 12.70 (s, 1H *enol tautomer*), 8.33 (dt, $J = 9.2$, 2.0 Hz, 2H), 8.26 (dt, $J = 9.2$, 2.0 Hz, 2H *enol tautomer*), 8.10 (dt, $J = 9.2$, 2.0 Hz, 2H), 7.91 (dt, $J = 9.2$, 2.0 Hz, 2H *enol tautomer*), 5.68 (s, 1H *enol tautomer*), 3.94 (s, 2H), 1.55 (s, 9H *enol tautomer*), 1.43 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.4, 172.4, 167.7, 165.8, 140.6, 139.7, 129.5, 126.8, 123.9, 123.7, 91.8, 82.8, 82.1, 47.6, 28.3, 27.9; FTIR (thin film): cm^{-1} 2979, 2931, 1729, 1694, 1593, 1523, 1342, 1149; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{14}\text{NO}_5$) ($[\text{M}-\text{H}]$): 264.0877; found 264.0882.

tert-Butyl-3-oxobutanoate (41). Compound prepared according to TP2. Purification by column chromatography (50% ethyl acetate–hexanes) gave **41** as a colorless oil (17.1 mg, 61%); R_f = 0.85 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 3.34 (s, 2H), 2.24 (s, 3H), 1.46 (s, 9H); Spectroscopic data was identical to that reported previously.¹⁶⁸

Isopropyl-3-oxo-3-phenylpropanoate (42). Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30% ethyl acetate–hexanes) gave **42** as a pale yellow oil (37.0 mg, 90%); R_f = 0.64 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 12.65 (s, 1H *enol tautomer*), 7.94 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H *enol tautomer*), 7.59 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.44–7.40 (m, 3H *enol tautomer*), 5.63 (s, 1H *enol tautomer*), 5.18–5.12 (m, 1H *enol tautomer*), 5.10–5.04 (m, 1H), 3.95 (s, 2H), 1.31 (d, J = 6.4 Hz, 6H *enol tautomer*), 1.22 (d, J = 6.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.6, 167.0, 136.1, 133.6, 131.1, 128.7, 128.4, 126.0, 87.8, 69.0, 67.8, 46.3, 21.9, 21.6; FTIR (thin film): cm^{-1} 2980, 1732, 1685, 1266, 1103; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{15}\text{O}_3$) ($[\text{M}+\text{Na}]^+$): 229.0835; found 229.0836.

Ethyl-3-oxo-3-phenylpropanoate (43). Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30% ethyl acetate–hexanes) gave **43** as a pale yellow oil (33.3 mg, 87%); $R_f = 0.79$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 12.6 (s, 1H *enol tautomer*), 7.95 (dt, $J = 6.4, 1.6$ Hz, 2H), 7.78 (dt, $J = 6.4, 1.6$ Hz, 2H *enol tautomer*), 7.60 (tt, $J = 6.4, 1.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.45–7.40 (m, 3H *enol tautomer*), 4.27 (q, $J = 7.2$ Hz, 2H *enol tautomer*), 4.22 (q, $J = 7.2$ Hz, 2H), 3.99 (s, 2H), 1.34 (t, $J = 7.2$ Hz, 3H *enol tautomer*), 1.26 (t, $J = 7.2$ Hz, 3H); Spectroscopic data was identical to that reported previously.¹⁶⁹

N,N-Diethyl-3-oxo-3-phenylpropanamide (44). Compound prepared according to TP2. Purification by column chromatography (20% ethyl acetate–hexanes) gave **44** as a colorless oil (23.8 mg, 61%); $R_f = 0.64$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.02 (dt, $J = 8.0, 2.0$ Hz, 2H), 7.77 (dd, $J = 8.0, 1.6$ Hz, 2H *enol tautomer*), 7.58 (tt, $J = 7.2, 2.0$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.43–7.40 (m, 3H *enol tautomer*), 5.73 (s, 1H *enol tautomer*), 4.06 (s, 2H), 3.52–3.35 (m, 4H *enol tautomer*), 3.39 (dq, $J = 19.6, 7.2$ Hz, 4H), 1.66 (br s, 1H *enol tautomer*), 1.28–1.16 (m, 6H *enol tautomer*), 1.16 (dt, $J = 20.4, 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 194.2, 171.4, 171.3, 166.0, 136.4, 135.3, 133.5, 130.5, 128.7, 128.7, 128.4, 125.9, 110.0, 84.9, 45.8, 42.7, 40.2, 14.2,

12.9; FTIR (thin film): cm^{-1} 2974, 2933, 1690, 1627, 1281; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{18}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 220.1332; found 220.1334.

1-(3-Methylpiperidin-1-yl)-3-phenylpropane-1,3-dione (45). Compound prepared according to TP2. Purification by column chromatography (20% ethyl acetate–hexanes) gave **45** as a colorless oil (31.0 mg, 71%); R_f = 0.58 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.03 (d, J = 7.6 Hz, 2H), 7.77 (dd, J = 8.0, 1.6 Hz, 2H *enol tautomer*), 7.58 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.43–7.37 (m, 3H *enol tautomer*), 5.83 (s, 1H *enol tautomer*), 4.49–4.38 (m, 1H), 4.10 (s, 1H), 3.76–3.65 (m, 1H *enol tautomer*), 3.00 (tt, J = 11.2, 2.8 Hz, 1H *enol tautomer*), 2.70 (dd, J = 10.8, 2.4 Hz, 1H), 2.63 (tt, J = 11.2, 2.8 Hz, 1H *enol tautomer*), 2.33 (dd, J = 10.8, 2.4 Hz, 1H), 1.90–1.75 (m, 2H + *enol tautomer*), 1.75–1.40 (m, 5H + *enol tautomer*), 1.25–1.08 (m, 1H), 1.21 (s, 1H *enol tautomer*), 0.95 (d, J = 6.8 Hz, 2H), 0.86 (t, J = 6.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 193.9, 193.9, 171.4, 170.4, 164.8, 136.1, 136.1, 135.1, 133.4, 130.3, 128.6, 128.5, 128.2, 125.7, 84.2, 54.0, 45.9, 42.4, 32.7, 31.5, 30.7, 24.6, 18.8, 18.7, 18.7; FTIR (thin film): cm^{-1} 2926, 2850, 1686, 1628; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{20}\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 246.1489; found 246.1494.

tert-Butyl-4-(3-oxo-3-phenylpropanoyl)piperazine-1-carboxylate (46). Compound prepared according to TP2 on a 0.20 mmol scale. Purification by column chromatography (80% ethyl acetate–hexanes) gave **46** as a pale yellow oil (49.7 mg, 75%); $R_f = 0.59$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.01 (d, $J = 7.2$ Hz, 2H), 7.77 (d, $J = 7.2$ Hz, 2H *enol tautomer*), 7.60 (t, $J = 7.2$ Hz, 1H), 7.48 (t, $J = 7.2$ Hz, 2H), 7.44–7.39 (m, 3H *enol tautomer*), 5.79 (s, 1H *enol tautomer*), 4.13 (s, 2H), 3.63 (t, $J = 4.8$ Hz, 2H), 3.45 (br s, 2H), 3.42 (t, $J = 4.8$ Hz, 4H), 1.48 (s, 9H *enol tautomer*), 1.45 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 193.7, 154.5, 135.9, 133.8, 130.8, 128.8, 128.7, 128.4, 125.9, 80.3, 46.4, 45.8, 43.7, 42.9, 41.8, 28.3; FTIR (thin film): cm^{-1} 2974, 2926, 2860, 1686, 1637, 1412, 1160; HRMS-ESI (m/z) Calcd for ($\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_4$) ($[\text{M}+\text{H}]^+$): 333.1809; found 333.1809.

N-Methyl-3-oxo-N,3-diphenylpropanamide (47). Compound prepared according to TP2. Purification by column chromatography (20% ethyl acetate–hexanes) gave **47** as a white solid (30.7 mg, 68%); $R_f = 0.61$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.77 (d, $J = 8.4$ Hz, 2H), 7.56–7.50 (m, 4H + *enol tautomer*), 7.46–7.44 (m, 4H + *enol tautomer*), 7.42–7.24 (m, 10H + *enol tautomer*), 5.39 (s, 1H *enol tautomer*), 3.86 (s, 2H), 3.38 (s, 3H), 3.34 (s, 3H *enol tautomer*), 1.66 (br s, 1H *enol tautomer*); ^{13}C

NMR (CDCl₃, 100 MHz): δ ; HRMS-ESI (m/z) Calcd for (C₁₆H₁₅NO₂) ([M+H]⁺): 194.1, 180.2, 172.1, 167.0, 143.7, 143.4, 130.5, 129.9, 129.7, 128.5, 1128.3, 128.2, 128.2, 127.7, 127.3, 127.2, 125.8, 86.8, 45.5, 37.4; FTIR (thin film): cm⁻¹ 3061, 2924, 1690, 1653, 1624, 1346, 1123; HRMS-ESI (m/z) Calcd for (C₁₆H₁₆NO₂) ([M+H]⁺): 254.1176; found 254.1183.

Chapter 3: Copper-catalyzed α -amination of phosphonates and phosphine oxides: a direct approach to α -amino phosphonic acids and derivatives

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3. Copper-catalyzed α -amination of phosphonates and phosphine oxides: a direct approach to α -amino phosphonic acids and derivatives

3.1 Significance of α -amino phosphonic acids and derivatives

α -Amino phosphonic acids and their derivatives have found a wide range of interesting applications in agrochemistry and medicine (Figure 6).⁴ Most notably they have been used as herbicides¹⁷⁰⁻¹⁷¹ and antibiotics.¹⁷²⁻¹⁷³ They have also been used as plant virucides,¹⁷⁴⁻¹⁷⁶ anticancer agents,¹⁷⁷⁻¹⁷⁸ and inhibitors of HIV proteases.¹⁷⁹⁻¹⁸¹ α -Amino phosphonic acids can serve as functional surrogates for α -amino acids, and the tetrahedral configurations of phosphonic acids mimic intermediary tetrahedral structures in the reactions of carboxylic acid derivatives.^{177,182-184} The biological importance of this class of compounds continues to drive efforts toward their efficient and rapid synthesis.^{67-69,185-209} Among them, the electrophilic α -amination of phosphonates represents an attractive strategy for a rapid and direct access to α -amino phosphonic acids and derivatives.

Figure 6. Selected examples of biologically important α -amino phosphonic acids

3.1.1 Synthesis of α -amino phosphonic acids

3.1.1.1 Synthesis of α -amino phosphonic acids through formation of C–P, C–C, or C–H bonds

The importance of this class of α -amino phosphonic acids continues to drive efforts toward their efficient and rapid synthesis. They are generally prepared through formation of C–P bonds, for example, by the Pudovik reaction (Scheme 30, pathway a) or the Kabachnik-Fields reaction (Scheme 30, pathway b). The Pudovik reaction involves the hydrophosphonylation of an imine¹⁸⁵⁻¹⁹⁴ or an amide,¹⁹⁵ whereas, the Kabachnik-Fields reaction is a three-component reaction of an amine, an aldehyde, and a dialkyl phosphite.¹⁹⁶⁻¹⁹⁸ Alternatively, α -amino phosphonic acids can be prepared through C–C bond formation, either through the addition of an anionic phosphonic analogue of glycine to an electrophilic carbon atom (Scheme 30, pathway c) or through the addition of a nucleophile to a cationic phosphoglycine equivalent (Scheme 30, pathway d).¹⁹⁹⁻²⁰² α -Amino phosphonic acids have also been prepared through formation of C–H bonds through catalytic hydrogenation of enamido phosphonates (Scheme 30, pathway e).²⁰³⁻²⁰⁶

Scheme 30. Synthetic approaches toward the preparation of α -amino phosphonic acids

3.1.1.2 Synthesis of α -amino phosphonic acids through formation of C–N bonds

Complementarily, C–N bond formation using an electrophilic aminating agent represents an attractive approach that provides α -amino phosphonic acids and their derivatives directly (Scheme 30, pathway f).^{67-69,207-209} Previous studies on α -amination reactions of phosphonic acid derivatives involved the use of highly reactive electrophilic nitrogen sources, such as azodicarboxylate esters or arylsulfonyl azides, and focused on stereoselective α -aminations of substrates containing chiral auxiliaries. For example, Denmark and co-workers reported the asymmetric amination of chiral

oxazaphosphorinanes with 2,4,6-triisopropylbenzenesulfonyl (trisyl) azide for the synthesis of α -amino phosphonic acids (Scheme 31A).⁶⁷ The reaction involved the amination of phosphorus-stabilized α -anions and the trapping of the triazine intermediates with either acetic acid (Method A) or acetic anhydride (Method B). However, the efficiency of the reaction was contingent on the structure of the auxiliary, the nature of the *P*-alkyl substituent, and the amination method. Additionally, the selectivity was moderate to poor for most substrates. In a similar manner, Hanessian investigated the asymmetric amination of chiral phosphonamides derived from (1*R*,2*R*)-*N,N'*-dimethylcyclohexane-1,2-diamine. The amination employed trisyl azide as the electrophilic nitrogen and proceeded in moderate to excellent yields and enantioselectivities (Scheme 31B).⁶⁸ In 2005, Jørgensen reported a catalytic enantioselective amination of β -keto phosphonates catalyzed by a chiral bisoxazolinezinc ditriflate with dibenzyl azodicarboxylate as the aminating agent (Scheme 31C).⁶⁹

Scheme 31. Previous methods for the electrophilic α -amination of phosphonic acid derivatives

For these electrophilic α -amination reactions using either arylsulfonyl azides or azodicarboxylates, the formation of the corresponding α -amino phosphonic acids required reduction of the N–N bond. Therefore, it is restricted to the formation of primary amines (the installation of an NH_2 group) as well as a narrow range of phosphonates. Although C–N bond formation represents a powerful and direct approach to installing an α -amino group onto phosphonates, its potential in preparing α -amino phosphonic acids and derivatives remains underexplored. So far no examples of C–N bond formation have been reported for directly introducing secondary or tertiary amines to the α -position of phosphonates, thus limiting the synthesis and discovery of novel α -amino phosphonic

acids of biological importance.^{142,184,210} Therefore, it is of great value to develop a general amination method under mild reaction conditions and thus significantly extend the scope of the synthesis of α -aminophosphonates.

3.2 Results and Discussion

We proposed that a novel amination approach to α -amino phosphonic acids could be achieved by a copper-catalyzed amination of phosphonate α -zincates using electrophilic *O*-benzoylhydroxylamines. This strategy was inspired by pioneering studies on the electrophilic amination of arylzinc reagents with hydroxylamines.⁴⁵⁻⁴⁸ We surmised that an analogous amination strategy involving phosphonate-derived α -zincates might offer an opportunity to address the previous problems in α -amino phosphonic acid synthesis through C–N bond formation.

3.2.1 Electrophilic amination via phosphonate-derived α -zincates

Toward this end, we explored the formation of α -zincates of phosphonates through deprotonation with $\text{Zn}(\text{tmp})_2$, and we examined the reactivity of the α -zincates toward electrophilic amination using *O*-benzoylhydroxylamines (Scheme 32). Different from those organozinc reagents typically prepared from their organolithium or Grignard precursors,⁴⁵⁻⁴⁸ the phosphonate α -zincates are proposed to form via an H/Zn exchange.^{125-126,211} This strategy is direct and more efficient than previous electrophilic α -aminations of phosphonic acid derivatives. Additionally, it allowed a broader substrate scope and better functional group compatibility. This α -amination strategy provided the first example enabling the direct introduction of a variety of acyclic and cyclic amines to the α -position of phosphonates and phosphine oxides.

Scheme 32. Direct approach to α -amino phosphonates

3.2.2 Amination studies of phosphonate-derived α -zincates

Our studies began with the amination reaction of the model substrate **48** with *O*-benzoylhydroxylamine **3** (Table 9). Having successfully obtained the α -zincate through deprotonation of **48** with $\text{Zn}(\text{tmp})_2$, we examined the formation of α -aminophosphonate **49** under various conditions. No amination occurred when the α -zincate was treated with *O*-benzoylhydroxylamine **3** alone (entry 1). However, amination product **49** was obtained when a catalytic amount of a copper salt was added, with CuCN giving the best result (entries 2–8). Using either 2,2'-bipyridine or 1,10-phenanthroline as the ligand gave little improvement to the CuCN -catalyzed reaction (entries 9 and 10), whereas both ligands significantly accelerated the amination reaction catalyzed by CuCl_2 (entries 11 and 12). The use of *N,N'*-dimethylethylenediamine with CuCl_2 gave improved yields; however the amination reaction rate was still slow (entry 13). Therefore, the use of CuCl_2 and 2,2'-bipyridine were selected as the standard amination conditions for subsequent studies.

Table 9. Optimization studies for the copper-catalyzed amination of phosphonate **48 with *O*-benzoylhydroxylamine **3**.^a**

entry	48 (equiv)	Zn(tmp)₂ (equiv)	3 (equiv)	copper (10 mol%)	ligand (20 mol%)	time (h) ^b	49 (%) ^c
1	2.1	1.0	1.0	—	—	24	0
2	2.1	1.0	1.0	CuCl	—	20	77
3	2.1	1.0	1.0	[CuOTf] ₂ •tol	—	2	16
4	2.1	1.0	1.0	CuCN	—	20	96
5	2.1	1.0	1.0	CuCl ₂	—	18	78
6	2.1	1.0	1.0	Cu(OAc) ₂	—	18	78
7	2.1	1.0	1.0	Cu(OTf) ₂	—	18	31
8	2.1	1.0	1.0	Cu(acac) ₂	—	18	52
9	2.1	1.0	1.0	CuCN	phen	20	48 ^d
10	2.1	1.0	1.0	CuCN	bipyr	20	99
11	2.1	1.0	1.0	CuCl ₂	phen	1	96
12	2.1	1.0	1.0	CuCl ₂	bipyr	4	99
13	2.1	1.0	1.0	CuCl ₂	DMEDA	20	99
14	1.1	0.5	1.0	CuCl ₂	bipyr	24	26 ^e

^a Reactions run on a 0.2 mmol scale. ^b Time required for complete consumption of **3** in step 2. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^d **3** recovered in 24% yield. ^e **3** recovered in 25% yield.

With effective α -amination conditions identified, we examined the scope of phosphonates and derivatives using **3** (Table 10). Similar to the model substrate **48**, dibutyl butylphosphonate and ethyldiphenyl phosphine oxide both readily afforded the desired aminated products **50** and **51**. The simple analogous substrates, such as dimethyl and diethyl methylphosphonates as well as methyldiphenylphosphine oxide, also proceeded smoothly to give **52–54** in excellent yields. Besides a methyl group, other substituents at the α -position are also compatible with the amination reaction, including allyl, phenyl, and aryl groups (**55–59**). Regardless of an electron-donating or electron-withdrawing group present on the aryl ring, the reactions all occurred efficiently. Especially useful is the tolerance of the chloro- and bromo- groups in aminated products **58** and **59**, thus allowing additional functionalization by transition-metal-catalyzed couplings. However, attempts to aminate disubstituted phosphonates were unsuccessful.

A defining attribute of this new amination method is its ability to install a wide variety of amino groups in the α -position. On this basis, we did an extensive study of aminations using phosphonate **60** (Table 11). A diverse range of cyclic amine-based phosphonates were readily formed, including the piperazine derivative **62**, the diazepane **63**, the tetrahydroisoquinoline **64**, and the piperidines **65** and **66**. Various acyclic amines similarly gave the corresponding phosphonates **67–70** in excellent yields. However, phosphonate **60** did not undergo amination with sterically hindered *O*-benzoyl-*N,N*-diisopropylhydroxylamine. Interestingly, the phosphonate **61**, which lacks an α -substituent, gave the desired *N,N*-diisopropylamino derivative **72** in 90% yield. Furthermore, the aminated products **73** and **74**, which contain a secondary amine group,

were obtained from the corresponding phosphonates **60** and **61** in 40% and 78% yield, respectively. This suggests that both the electronic nature and the steric nature of the phosphonates and the *O*-benzoylhydroxylamines can affect the efficiency of the amination step.

Table 10. α -Amination of different phosphonates and phosphine oxides.^a

^a Isolated yields. Standard reaction conditions: phosphonate or phosphine oxide (2.1 equiv), **3** (1.0 equiv), Zn(tmp)₂ (1.0 equiv), CuCl₂ (10 mol %), bipy (20 mol %), rt. Reactions typically run on 0.2 mmol scale.

Table 11. Amine scope of phosphonate amination.^a

^a Isolated yields. Standard reaction conditions: **60** or **61** (2.1 equiv), *O*-acylhydroxylamine (1.0 equiv), Zn(tmp)₂ (1.0 equiv), CuCl₂ (10 mol %), bipyridine (20 mol %), rt. Reactions typically run on 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy using CH₂Br₂ as a quantitative internal standard, and confirmed by GC/MS.

Finally, we evaluated the efficacy of this transformation on a larger scale with a lower catalyst loading of only 0.5 mol % of CuCl₂ and 1 mol% of bipyridine ligand (Scheme 33). Although a longer reaction time (36 h) was required in this case, the aminated product **75** was formed in 96% yield, thus demonstrating high efficiency and practical utility of this amination reaction.

Scheme 33. An efficient scale-up amination reaction with 0.5 mol % catalyst loading

3.2.3 Mechanism studies

To probe the reaction for the possible formation of radical intermediates in the copper-catalyzed amination step, we performed two control experiments (Scheme 34).

Scheme 34. Control experiments to probe possible radical intermediates

First, we examined the reaction of the model *O*-benzoylhydroxylamine **3** with phosphonate **76**, which contains a cyclopropyl substituent at the α -position. This reaction gave the aminated product **77** exclusively in excellent yield, and the ring-opened product **78** was not observed.⁵⁰ Next, we examined the reaction of *O*-benzoyl-*N*-butyl-*N*-(2-methyl-pent-4-en-1-yl)hydroxylamine **79** with model phosphonate **60**, and we obtained the desired amination product **80** exclusively; we did not detect any cyclization product

such as pyrrolidine **81**, which might have formed through a previously reported copper-catalyzed 5-*exo* radical cyclization.¹⁶⁶ On the basis of these results, we suggested that no long-lived aminyl radical species or copper-coordinated radical complex is formed in the amination pathway.

Although the detailed mechanism for C–N bond formation remains obscure, a possible mechanism is proposed for the amination step based on these experimental results and observations (Scheme 35). The bisphosphonate zincate **A** could transmetallate with copper(I) to generate a reactive copper complex (**C**), which subsequently reacts with *O*-benzoylhydroxylamines to form the desired C–N bond. However, we cannot exclude an alternative that includes—1) oxidative addition of the hydroxylamine to a low-valent copper species, 2) transmetallation with a α -phosphonate zinc carbanion, and 3) reductive elimination to form the desired C–N bond. We believe that the zincate intermediate **B** did not undergo transmetallation to form the copper complex **C** as a stoichiometric amount of the zincate (**A**) was needed for the complete conversion of the *O*-benzoylhydroxylamines.

Scheme 35. Proposed reaction pathway for the α -amination of phosphonates and phosphine oxides

3.2.4 Alternative method for the α -zincation of phosphonates

Despite the utility of the amination using $\text{Zn}(\text{tmp})_2$ as the base for zincation, it was not without some limitations. Most importantly, the use of $\text{Zn}(\text{tmp})_2$ required the sacrifice of an additional equivalent of the phosphonate moiety. To overcome this drawback, we explored the amination of an alternative monozinc intermediate using $\text{tmpZnCl}\cdot\text{LiCl}$ ¹¹⁹⁻¹²⁴ in the C–H metallation step (Table 12). Using the previously established amination conditions, we were pleased to observe amination in 46% yield (entry 1). Because an increased amination temperature of 50 °C only lead to a slightly improved yield (entry 2), further amination screenings were run at room temperature. Next, we screened several copper salts with CuCN giving the best yield (entries 3–7). The use of 2,2'-bipyridine, 1,10-phenanthroline, and *N,N*-dimethylethylenediamine as ligands gave lower yields for the CuCN-catalyzed reaction (entries 8–10). When the equivalence of *O*-benzoylhydroxylamine **3** was increased, we saw little improvement for the reaction (entries 11 and 12). Although using $\text{tmpZnCl}\cdot\text{LiCl}$ as the base for the amination of phosphonates seemed promising, the yields were not comparable to those observed using $\text{Zn}(\text{tmp})_2$ as the base.

Table 12. Catalyst screen for the amination of phosphonate **60 using tmpZnCl•LiCl for α -zincation.^a**

entry	copper (10 mol%)	ligand (20 mol%)	temp (°C)	56 (%) ^b
1	CuCl ₂	bipyr	rt	46
2	CuCl ₂	bipyr	50	50
3	[CuOTf] ₂ •tol	—	rt	26
4	CuCN	—	rt	66
5	CuCl ₂	—	rt	35
6	Cu(OTf) ₂	—	rt	11
7	Cu(OAc) ₂	—	rt	trace
8	CuCN	bipyr	rt	40
9	CuCN	phen	rt	30
10	CuCN	DMEDA	rt	32
11 ^c	CuCN	—	rt	60
12 ^d	CuCN	—	rt	58

^a Reactions run on a 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^c 1.2 equivalents of *O*-benzoylhydroxylamine **3** used. ^d 1.5 equivalents of *O*-benzoylhydroxylamine **3** used.

Next, we decided to look into α -zincation that was achieved via *n*-BuLi deprotonation followed by Li/Zn exchange using ZnCl₂ (Scheme 36). We attempted the amination using either 0.5 or 1.05 equivalents of ZnCl₂ for the Li/Zn exchange, which mimicked the bis and mono α -zincates, respectively. When 0.5 equivalents of ZnCl₂ was used only trace amount of amination was observed (Scheme 36A). On the other hand, when 1.05 equivalents of ZnCl₂ was used, α -amino phosphonate **56** was observed in 47% (Scheme 36B). This was interesting since previously the bis α -zincate formed from Zn(tmp)₂ deprotonation gave superior results to the mono α -zincate from tmpZnCl•LiCl deprotonation. It is likely that the bis α -zincate does not form via the zincation method in Scheme 36A; therefore, amination was limited.

Scheme 36. Phosphonate amination using a Li/Zn exchange for α -zincation

We attempted to optimize the amination reaction using a Li/Zn exchange for α -zincation (Table 13). Copper(I) and copper(II) salts were screened (entries 2–5); however yields were still not comparable with the Zn(tmp)₂ method. Next, we looked into increased temperature for the amination step (entries 6–9). Unfortunately, increased

amination temperatures did not provide noticeable improvement for the reaction. Despite only moderate yields, we chose to continue using this α -zincation method for the amination of more difficult phosphonate substrates (i.e. disubstituted phosphonates).

Table 13. Optimization of phosphonate amination using a Li/Zn exchange for α -zincation.^a

$ \begin{array}{ccc} \text{EtO}-\text{P}(=\text{O})(\text{EtO})-\text{CH}_2\text{Ph} & \xrightarrow[\text{3) BzO}-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{O} \end{array} \text{3 (1.2 equiv)}]{\begin{array}{l} \text{1) } n\text{-BuLi (1.05 equiv), THF, } -78^\circ\text{C} \\ \text{2) ZnCl}_2 \text{ (1.05 equiv), THF, } -78^\circ\text{C to rt} \\ \text{Cu catalyst, ligand, THF, rt} \end{array}} & \text{EtO}-\text{P}(=\text{O})(\text{EtO})-\text{CH}(\text{Ph})-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{O} \end{array} \\ \text{60 (1.0 equiv)} & & \text{56} \end{array} $				
entry	copper (10 mol%)	ligand (20 mol%)	amination temp (°C)	56 (%) ^b
1	CuCl ₂	bipyr	rt	47
2	CuCl	—	rt	59
3	CuI	—	rt	27
4	CuCl ₂	—	rt	49
5	Cu(OAc) ₂	—	rt	55
6	CuCl	—	50	50
7	CuI	—	50	57
8	CuCl ₂	—	50	53
9	Cu(OAc) ₂	—	50	38

^a Reactions run on a 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

3.2.5 α -Amination of disubstituted phosphonates

Attempts to aminate disubstituted phosphonates were unsuccessful using $\text{Zn}(\text{tmp})_2$ because deprotonation did not provide the required α -zincates (Scheme 37A). This is most likely due to the increased steric hindrance. To see if deprotonation of the α -proton was possible, we used $n\text{-BuLi}$ for deprotonation of phosphonate **82** followed by a deuterium quench. We were pleased to observe full deuterium incorporation at the α -position (Scheme 37B). Next, we tried the Li/Zn exchange towards α -zincation and subsequent amination of disubstituted phosphonate **82**. After slight optimization of reaction conditions, α -amino phosphonate **84** was isolated in 11% yield (Scheme 37C).

Scheme 37. Deprotonation studies and amination of disubstituted phosphonate **82**

3.2.6 Development of an asymmetric α -amination

The previous aminations developed by Denmark,⁶⁷ Hanessian,⁶⁸ and Jørgensen⁶⁹ for the synthesis of α -amino phosphonic acids were enantioselective; however they were restricted to the formation of primary amines. On the other hand, secondary and tertiary α -amino phosphonates could be synthesized with our Zn(tmp)₂-mediated amination, but it was limited to the formation of racemic α -amino phosphonates and required the sacrifice of one equivalent of phosphonate. Therefore, an asymmetric electrophilic amination for the synthesis of secondary and tertiary α -amino phosphonic acids and derivatives is needed. Moreover, this would be the first example of an asymmetric α -amination of phosphonates incorporating primary and secondary amines. Towards this we sought to develop an asymmetric amination from two approaches—chiral ligands and chiral auxiliaries.

3.2.6.1 Asymmetric α -amination of phosphonates via chiral ligands

We started our development of an asymmetric amination by screening CuCl₂ with various chiral ligands (Table 14). To reduce the equivalence of phosphonate **60** used in the reaction, we initially chose to use tmpZnCl•LiCl as the base for the reaction. Using PyBOX ligand **85**, α -aminated phosphonate **56** was isolated in 31% yield (entry 1). Next BOX ligands **86–88** were screened in the reaction (entries 2–4). Amination was also observed albeit in low yields. However, the reactions using the PyBOX and BOX ligands were not stereoselective.

Table 14. Chiral ligand screen for the development of an asymmetric α -amination of phosphonates using tmpZnCl•LiCl for α -zincation.^a

entry	ligand (8 mol%)		yield (%) ^b	<i>ee</i> (%)
1		85	31	0
2		86	28	0
3		87	28	0
4		88	24	0

^a Reactions run on 0.2 mmol scale. ^b Isolated yields.

Next, we screened chiral ligands for the amination using the Li/Zn exchange for α -zincation (Table 15). Excitingly, α -aminated phosphonate **56** was isolated in 21% yield and 14% *ee* using PyBOX ligand **85** (entry 1). This was the first time we were able to induce enantioselectivity using a catalyst and chiral ligand for the amination of phosphonate **60**. Next we screened different BOX ligands for the amination (entries 2–6). For ligands **86–89**, amination was observed in slight enantiomeric excess. For ligand **90**,

α -amino phosphonate **56** was isolated in 27% yield; however *ee* was not observed. Diamine ligands **91–94** were also screened (entries 7–10). For ligand **91**, which also contained phosphine groups, amination was not observed. For reactions using diamine ligands **92–94**, α -amino phosphonate **56** was isolated in low yields; however, they did not induce enantioselectivity for the amination.

Table 15. Chiral ligand screen for the development of an asymmetric α -amination of phosphonates using a Li/Zn exchange for α -zincation.^a

$ \begin{array}{c} \text{EtO}-\text{P}(=\text{O})(\text{EtO})-\text{CH}_2\text{Ph} \\ \text{60 (1.0 equiv)} \end{array} \xrightarrow[\begin{array}{c} \text{3 (1.2 equiv)} \\ \text{CuCl}_2 \text{ (5 mol\%), ligand, THF, rt} \end{array}]{ \begin{array}{c} \text{1) } n\text{-BuLi (1.05 equiv), THF, } -78^\circ\text{C} \\ \text{2) ZnCl}_2 \text{ (1.05 equiv), THF, } -78^\circ\text{C to rt} \end{array} } \begin{array}{c} \text{EtO}-\text{P}(=\text{O})(\text{EtO})-\text{CH}(\text{Ph})-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}) \\ \text{56} \end{array} $				
entry	ligand (8 mol%)		yield (%) ^b	<i>ee</i> (%)
1		85	21	14
2		86	40	4
3		87	39	10
4		88	11	2

5		89	26	10
6		90	27	0
7		91	0	—
8		92	15	0
9		93	24	0
10		94	24	0

^a Reactions run on 0.2 mmol scale. ^b Isolated yields.

We found it interesting that the asymmetric amination reaction using tmpZnCl•LiCl for α -zincation gave our desired product without *ee* while the Li/Zn exchange method gave α -amino phosphonate **56** with slight *ee* using certain PyBOX and BOX ligands. We hypothesized that this phenomena was due to the presence of 2,2,6,6-tetramethylpiperadine, which could also act as a ligand, when tmpZnCl•LiCl was used as the base. To test this hypothesis, after the Li/Zn exchange for α -zincation, 2,2,6,6-

tetramethylpiperadine was added prior to the amination step (Scheme 38). The desired α -amino phosphonate **56** was isolated in 26% yield and 0% *ee* suggesting that the presence of 2,2,6,6-tetramethylpiperadine in the reaction may have a negative effect on the stereochemical control.

Scheme 38. Study of the effect of 2,2,6,6-tetramethylpiperadine on stereoselectivity of the asymmetric α -amination of phosphonates

3.2.6.2 Asymmetric α -amination of chiral phosphonates and phosphonamides

In addition to a catalytic asymmetric α -amination, we also worked to develop an asymmetric amination of chiral phosphonates and phosphonamides. For these reactions stereochemistry would be set at deprotonation thus allowing a subsequent stereoselective amination. We started our studies using the chiral phosphonate and phosphonamides shown in Figure 7. The chiral phosphonate and phosphonamides could be easily synthesized from the corresponding chiral alcohol or amine and phosphorous dichloride. Furthermore, hydrolysis would allow for easy removal of the auxiliary to obtain chiral α -amino phosphonic acids.

Figure 7. Chiral phosphonates and phosphonamides for asymmetric α -amination

First, we attempted the amination of chiral phosphonate **95** using the Li/Zn exchange method for α -zincation (Table 16). Copper(I) and copper(II) salts were screened. Despite consumption of *O*-benzoylhydroxylamine **3** in the reactions, amination was not observed.

Table 16. Screen of copper salts for the amination of chiral phosphonate **95.^a**

entry	Cu catalyst (10 mol%)	yield (%) ^b	<i>dr</i> (%)
1	CuCl	0	—
2	CuI	0	—
3	CuCl ₂	0	—
4	Cu(OAc) ₂	0	—

^a Reactions run on a 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

Next, we screened chiral phosphonamides **96** and **97** for the amination (Table 17). We hoped to achieve amination using *O*-benzoylhydroxylamine **3** or *O*-benzoyl-*N,N*-dibenzylhydroxylamine **14** with CuCl₂ as the catalyst. In these attempted reactions, the corresponding *O*-benzoylhydroxylamine was consumed; however amination was not observed.

Table 17. Asymmetric amination of chiral phosphonamides.^a

entry	phosphonamide (1.0 equiv)	hydroxylamine	product	yield (%) ^b
1	93	3		99 0
2	93	14		100 0
3	94	3		101 0
4	94	14		102 0

^a Reaction run on a 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

3.3 Conclusion

In summary, we have developed an effective method for the α -amination of phosphonates through C–N bond formation, providing access to various α -amino phosphonates, thereby greatly extending the scope of available products beyond that of primary α -amino phosphonates. Studies on an asymmetric version of the amination

reaction are still currently underway in our laboratory. Of our two current methods for asymmetric amination, the Li/Zn exchange and subsequent amination using a copper catalyst with chiral PyBOX and BOX ligands shows the most promise. Success in developing direct and efficient stereoselective syntheses of α -amino phosphonic acids and their derivatives is highly valuable, especially in medicinal chemistry and drug discovery, and will contribute to future advances in the understanding of these important compounds.

3.4 Supplemental Information

3.4.1 General Information

General Procedures. Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in Biotage 8 mL microwave vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 x 20 cm) of Drierite, unless otherwise noted. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Flash-column

chromatography was performed on silica gel (60 Å, standard grade) or on a CombiFlash companion system with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.).

Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich and used as received. Zn(tmp)₂ (0.5 M solution in tol) was purchased from Sigma-Aldrich. Dry THF was obtained using an Innovative Technologies solvent purification system. *O*-acylhydroxylamine derivatives were prepared according to literature procedure.⁴⁸

Instrumentation. Proton and carbon nuclear magnetic resonance (¹H and ¹³C NMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 MHz respectively) or Bruker 500 (500 MHz and 125 MHz respectively) spectrometer at ambient temperature unless otherwise indicated. Chemical shifts for ¹H NMR are reported in parts per million (ppm, δ) and referenced to residual protium in the NMR solvent (CHCl₃: δ 7.26). Chemical shifts for ¹³C NMR are reported in ppm and referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), integration. Infrared spectroscopic data was obtained using an Thermo Scientific Nicolet 380 FT-IR. IR data is reported in wavenumbers (cm⁻¹) with only select peaks shown. High-resolution mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer.

3.4.2 Initial deprotonation of phosphonates

As the α -zincation of substituted phosphonates has not been reported previously, we first confirmed that the corresponding α -zincate of **48** was effectively formed upon the treatment with $\text{Zn}(\text{tmp})_2$. The deprotonation of **48** was conducted at room temperature then subsequently quenched with D_2O . Deuterium incorporation on **48** was observed by both ^1H NMR and GC/MS.

3.4.3 Experimental Procedures

General Experimental Procedure for the Amination Reaction using $\text{Zn}(\text{tmp})_2$.

A mixture of $\text{Zn}(\text{tmp})_2$ (0.5 M solution in toluene, 0.4 mL, 0.2 mmol, 1.0 equiv) and phosphonate or phosphine oxide (0.42 mmol, 2.1 equiv) was stirred at room temperature for 1 h. To the above mixture, was added a mixture of *O*-benzoylhydroxylamine (0.2 mmol, 1.0 equiv), CuCl_2 (2.7 mg, 0.02 mmol, 0.1 equiv), and 2,2'-bipyridyl (6.2 mg, 0.04 mmol, 0.2 equiv) in THF (1 mL). The reaction mixture was allowed to stir at room temperature. Upon complete consumption of *O*-benzoylhydroxylamine (monitored by TLC–50% ethyl acetate–hexanes, typically 2–6 h), the reaction mixture was filtered through silica and washed with isopropanol. The filtered solution was concentrated under reduced pressure. The crude residue was purified by column chromatography.

3.4.4 Characterization of compounds

Diethyl-(1-morpholinoethyl)phosphonate (49). Purification by column chromatography (5% isopropanol–hexanes) gave **49** as a colorless oil (96%); $R_f = 0.26$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 4.21–4.08 (m, 4H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.93 (dq, $J = 18.8, 7.2$ Hz, 1H), 2.81 (dt, $J = 11.6, 4.4$ Hz, 2H), 2.62 (dt, $J = 11.6, 4.4$ Hz, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.23 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 67.4, 62.0 (d, $J_{\text{C-P}} = 157.9$ Hz), 58.1, 56.8, 50.3, 50.3, 16.6, 16.5, 9.4; FTIR (thin film): cm^{-1} 2852, 1227, 1019, 959; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{23}\text{NO}_4\text{P}$) ($[\text{M}+\text{H}]^+$): 252.1359; found: 252.1364.

Dibutyl-(1-morpholinobutyl)phosphonate (50). Purification by column chromatography (5% isopropanol–hexanes) gave **50** as a colorless oil (65%); $R_f = 0.30$ (5% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.10–3.97 (m, 4H), 3.68–3.59 (m, 4H), 2.85–2.70 (m, 5H), 1.77–1.5 (m, 7H), 1.42–1.34 (m, 5H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 67.7, 65.7 (d, $J_{\text{C-P}} = 6.9$ Hz), 64.8 (d, $J_{\text{C-P}} = 6.9$ Hz), 61.9 (d, $J_{\text{C-P}} = 139.1$ Hz),

50.4, 32.8 (d, $J_{C-P} = 5.5$ Hz), 32.7 (d, $J_{C-P} = 5.5$ Hz), 28.3 (d, $J_{C-P} = 5.0$ Hz), 20.5, 20.4, 18.8, 13.7, 13.6; FTIR (thin film): cm^{-1} 2956, 2872, 1232, 1116, 1020, 971; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{35}\text{NO}_4\text{P}$) ($[\text{M}+\text{H}]^+$): 336.2298; found: 336.2296.

(1-Morpholinoethyl)diphenylphosphine oxide (51). Purification by column chromatography (30% isopropanol–hexanes) gave **51** as a white solid (85%); $R_f = 0.44$ (30% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.89–7.79 (m, 4H), 7.52–7.42 (m, 6H), 3.56–3.53 (m, 4H), 3.43 (dt, $J = 15.8, 7.2$ Hz, 1H), 2.93 (dt, $J = 11.2, 4.8$ Hz, 2H), 2.47 (dt, $J = 11.2, 4.8$ Hz, 2H), 1.28 (dd, $J = 15.8, 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 132.8 (d, $J_{C-P} = 8.5$ Hz), 132.1 (d, $J_{C-P} = 16.3$ Hz), 131.6, 131.5 (d, $J_{C-P} = 7.1$ Hz), 131.0 (d, $J_{C-P} = 8.5$ Hz), 128.5 (d, $J_{C-P} = 10.8$ Hz), 128.1 (d, $J_{C-P} = 11.3$ Hz), 67.2, 59.6 (d, $J_{C-P} = 87.8$ Hz), 50.5, 6.0 (d, $J_{C-P} = 1.8$ Hz); FTIR (thin film): cm^{-1} 2961, 2852, 1452, 1180, 1114; HRMS-ESI (m/z) Calcd for ($\text{C}_{18}\text{H}_{23}\text{NO}_2\text{P}$) ($[\text{M}+\text{H}]^+$): 316.1461; found: 316.1462.

Dimethyl-(morpholinomethyl)phosphonate (52). Purification by column chromatography (100% ethyl acetate pretreated with 2% Et_3N) gave **52** as a colorless oil

(95%); R_f = 0.09 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 3.76 (s, 3H), 3.73 (s, 3H), 3.66 (t, J = 4.4 Hz, 4H), 2.75 (d, J = 12 Hz, 2H), 2.59 (br s, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 66.8, 55.2, 54.3, 52.8; FTIR (thin film): cm^{-1} 2852, 1112, 1020, 864, 809; HRMS-ESI (m/z) Calcd for $(\text{C}_7\text{H}_{17}\text{NO}_4\text{P})$ ($[\text{M}+\text{H}]^+$): 210.089; found: 210.0895.

Diethyl-(morpholinomethyl)phosphonate (53). Purification by column chromatography (100% ethyl acetate pretreated with 2% Et_3N) gave **53** as a colorless oil (98%); R_f = 0.08 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 4.20–4.11 (m, 4H), 3.71 (t, J = 4.6 Hz, 4H), 2.77 (d, J = 11.6 Hz, 2H), 2.65 (br s, 4H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 66.9, 62.1 (d, $J_{\text{C-P}}$ = 6.8 Hz), 55.2 (d, $J_{\text{C-P}}$ = 10.2 Hz), 53.5, 16.4 (d, $J_{\text{C-P}}$ = 5.7 Hz); FTIR (thin film): cm^{-1} 2853, 1218, 1113, 1018, 958; HRMS-ESI (m/z) Calcd for $(\text{C}_9\text{H}_{21}\text{NO}_4\text{P})$ ($[\text{M}+\text{H}]^+$): 238.1203; found: 238.1207.

(Morpholinomethyl)diphenylphosphine oxide (54). Purification by column chromatography (30% isopropanol–hexanes) gave **54** as a white solid (90%); R_f = 0.23 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.82–7.77 (m, 4H), 7.54–7.41 (m,

6H), 3.62 (t, $J = 4.8$ Hz, 4H), 3.22 (d, $J = 6.4$ Hz, 2H), 2.63 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 132.7, 131.9, 131.8, 131.2 (d, $J_{\text{C-P}} = 8.7$ Hz), 130.7, 138.8, 128.5, 128.4, 66.9, 58.7 (d, $J_{\text{C-P}} = 87.7$ Hz), 55.7, 55.7; FTIR (thin film): cm^{-1} 2920, 2852, 1437, 1180, 1117; HRMS-ESI (m/z) Calcd for ($\text{C}_{17}\text{H}_{21}\text{NO}_2\text{P}$) ($[\text{M}+\text{H}]^+$): 302.1304; found: 302.1312.

Diethyl-(1-morpholinobut-3-en-1-yl)phosphonate (55). Purification by column chromatography (5% isopropanol–hexanes) gave **55** as a colorless oil (75%); $R_f = 0.18$ (5% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 5.94–5.84 (m 1H), 5.14–5.03 (m, 2H), 4.20–4.05 (m, 4H), 3.63 (dt, $J = 5.6, 2.8$ Hz, 4H), 2.89 (ddd, $J = 17.2, 9.6, 5.2$ Hz, 1H), 2.82–2.79 (m, 4H), 2.60–2.40 (m, 2H), 1.32 (dt, $J = 7.6, 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 136.1 (d, $J_{\text{C-P}} = 13.7$ Hz), 116.6, 67.6, 62.5 (d, $J_{\text{C-P}} = 144.3$ Hz), 62.3 (d, $J_{\text{C-P}} = 6.7$ Hz), 61.2 (d, $J_{\text{C-P}} = 6.7$ Hz), 50.5, 50.5, 30.7 (d, $J_{\text{C-P}} = 6.0$ Hz), 16.6 (d, $J_{\text{C-P}} = 5.3$ Hz), 16.5 (d, $J_{\text{C-P}} = 5.3$ Hz); FTIR (thin film): cm^{-1} 2977, 2850, 1639, 1452, 1228, 1115, 1018, 953; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{25}\text{NO}_4\text{P}$) ($[\text{M}+\text{H}]^+$): 278.1516; found: 278.1519.

Diethyl-(morpholino(phenyl)methyl)phosphonate (56). Purification by column chromatography (5% isopropanol–hexanes) gave **56** as a colorless oil (96%); $R_f = 0.30$ (5% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.47–7.45 (m, 2H), 7.38–7.32 (m, 3H), 4.25–4.17 (m, 2H), 3.93–3.88 (m, 1H), 3.81 (d, $J = 21.2$ Hz, 1H), 3.70 (t, $J = 4.4$ Hz, 4H), 3.70–3.63 (m, 1H), 2.82–2.79 (br m, 2H), 2.60–2.49 (br m, 2H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 132.4, 130.4 ($J_{\text{C-P}} = 8.0$ Hz), 128.2, 128.1, 68.6 ($J_{\text{C-P}} = 159.9$ Hz), 67.2, 62.8, 62.4, 51.9, 51.8, 16.6, 16.2; FTIR (thin film): cm^{-1} 2852, 1241, 1024, 962; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{25}\text{NO}_4\text{P}$) ($[\text{M}+\text{H}]^+$): 314.1516; found: 314.1512.

Diethyl-(morpholino(*p*-tolyl)methyl)phosphonate (57). Purification by column chromatography (5% isopropanol–hexanes) gave **57** as a pale yellow solid (98%); $R_f = 0.25$ (5% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.32 (d, $J = 7.6$ Hz, 2H), 7.14 (d, $J = 7.6$ Hz, 2H), 4.26–4.14 (m, 2H), 3.94–3.87 (m, 1H), 3.76 (d, $J = 21.2$ Hz, 1H), 3.70–3.64 (m, 1H), 3.67 (t, $J = 5.2$ Hz, 4H), 2.78 (dt, $J = 11.2, 4.4$ Hz, 2H), 2.49 (dt, $J = 11.2, 4.4$ Hz, 2H), 2.33 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C

NMR (CDCl₃, 125 MHz): δ 137.8, 130.3 (d, J_{C-P} = 8.4 Hz), 129.1, 128.9, 68.2 (d, J_{C-P} = 160.6 Hz), 67.2 62.8 (d, J_{C-P} = 6.2 Hz), 62.3 (d, J_{C-P} = 6.2 Hz), 51.8, 51.7, 21.1, 16.5 (d, J_{C-P} = 5.2 Hz), 16.2 (d, J_{C-P} = 5.2 Hz); FTIR (thin film): cm⁻¹ 2977, 2851, 1453, 1239, 1115, 1012, 958; HRMS-ESI (m/z) Calcd for (C₁₆H₂₇NO₄P) ([M+H]⁺): 328.1672; found: 328.1668.

Diethyl-((4-chlorophenyl)(morpholino)methyl)phosphonate (58). Purification by column chromatography (5% isopropanol–hexanes) gave **58** as a colorless oil (94%); R_f = 0.20 (5% isopropanol–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.39 (d, J = 9.6 Hz, 2H), 7.29 (d, J = 9.6 Hz, 2H), 4.28–4.13 (m, 2H), 3.97–3.88 (m, 1H), 3.76 (d, J = 23.2 Hz, 1H), 3.74–3.69 (m, 1H), 3.67 (t, J = 4.8 Hz, 4H), 2.67 (dt, J = 11.6, 4.8 Hz, 2H), 2.49 (dt, J = 11.6, 4.8 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 134.1, 131.6 (d, J_{C-P} = 8.1 Hz), 131.1, 128.4, 67.8 (d, J_{C-P} = 152.0 Hz), 67.2, 63.0, 62.3, 51.8, 51.7, 16.5 (d, J_{C-P} = 5.2 Hz), 16.2 (d, J_{C-P} = 5.2 Hz); FTIR (thin film): cm⁻¹ 2978, 2851, 1487, 1238, 1115, 1014, 957; HRMS-ESI (m/z) Calcd for (C₁₅H₂₄ClNO₄P) ([M+H]⁺): 348.1126; found: 348.1126.

Diethyl-((3-bromophenyl)(morpholino)methyl)phosphonate (59). Purification by column chromatography (5% isopropanol–hexanes) gave **59** as a colorless oil (94%); R_f = 0.34 (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.58–7.56 (m, 1H), 7.47–7.42 (m, 2H), 7.25–7.20 (m, 1H), 4.26–4.15 (m, 2H), 3.97–3.91 (m, 1H), 3.77–3.71 (m, 1H), 3.74 (d, J = 25.6 Hz, 4H), 2.78 (dt, J = 11.2, 4.8 Hz, 2H), 2.53 (dt, J = 11.2, 4.8 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 135.1, 133.1 (d, $J_{\text{C-P}}$ = 9.0 Hz), 131.2, 129.8, 128.9 (d, $J_{\text{C-P}}$ = 7.5 Hz), 122.3, 68.0 (d, $J_{\text{C-P}}$ = 160.1 Hz), 67.2, 63.0, 62.4, 51.9, 51.8, 16.5 (d, $J_{\text{C-P}}$ = 5.6 Hz), 16.2 (d, $J_{\text{C-P}}$ = 5.6 Hz); FTIR (thin film): cm^{-1} 2977, 2851, 1473, 1238, 1115, 1020, 959, 864; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{24}\text{BrNO}_4\text{P}$) ($[\text{M}+\text{H}]^+$): 392.0721; found: 392.0727.

tert-Butyl-4-((diethoxyphosphoryl)(phenyl)methyl)piperazine-1-carboxylate (62). Purification by column chromatography (50% ethyl acetate–hexanes) gave **62** as a white solid (98%); R_f = 0.65 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.44–7.41 (m, 2H), 7.35–7.28 (m, 3H), 4.27–4.15 (m, 2H), 3.93–3.85 (m, 1H), 3.85 (d, J = 22.8 Hz,

1H), 3.72–3.63 (m, 1H), 3.43–3.35 (br m, 4H), 2.80–2.76 (br m, 2H), 2.45–2.35 (br m, 2H), 1.38 (s, 9H), 1.33 (t, $J = 6.8$ Hz, 3H), 1.01 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 154.5, 132.1, 130.4 (d, $J_{\text{C-P}} = 8.5$ Hz), 126.9, 79.5, 68.1 (d, $J_{\text{C-P}} = 160.5$ Hz), 62.9 (d, $J_{\text{C-P}} = 3.9$ Hz), 62.2 (d, $J_{\text{C-P}} = 3.9$ Hz), 51.0 (2H), 44.1, 43.5, 28.3, 16.5 (d, $J_{\text{C-P}} = 5.5$ Hz), 16.1 (d, $J_{\text{C-P}} = 5.5$ Hz); FTIR (thin film): cm^{-1} 2976, 2929, 1688, 1420, 1242, 1160, 1020, 955; HRMS-ESI (m/z) Calcd for ($\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_5\text{P}$) ($[\text{M}+\text{H}]^+$): 413.2200; found: 413.2203.

***tert*-Butyl-4-((diethoxyphosphoryl)(phenyl)methyl)-1,4-diazepane-1-carboxylate**

(63). Purification by column chromatography (5% isopropanol–hexanes) gave **63** as a colorless oil (75%); $R_f = 0.46$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz, 60 °C): δ 7.50–7.47 (m, 2H), 7.35–7.28 (m, 3H), 4.24–4.17 (m, 2H), 4.07 (d, $J = 18.4$ Hz, 1H), 3.96–3.89 (m, 1H), 3.82–3.73 (m, 1H), 3.50–3.40 (m, 5H), 3.18–3.00 (m, 3H), 2.78–2.62 (m, 2H), 1.42 (s, 9H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.07 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz, 60 °C): δ 155.4, 134.1, 130.1 (d, $J_{\text{C-P}} = 16.9$ Hz), 128.2, 127.9, 79.3, 68.2 (d, $J_{\text{C-P}} = 157.8$ Hz), 62.9 (d, $J_{\text{C-P}} = 7.0$ Hz), 62.2 (d, $J_{\text{C-P}} = 7.0$ Hz), 55.1, 53.9, 47.8, 47.2, 45.3, 28.8, 16.7 (d, $J_{\text{C-P}} = 5.5$ Hz), 16.3 (d, $J_{\text{C-P}} = 5.5$ Hz); FTIR (thin film): cm^{-1} 2976, 2929, 1685, 1411, 1163, 1009, 958; HRMS-ESI (m/z) Calcd for ($\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_5\text{P}$) ($[\text{M}+\text{H}]^+$): 427.2356; found: 427.2357.

Diethyl-((3,4-dihydroisoquinolin-2(1*H*)-yl)(phenyl)methyl)phosphonate (64).

Purification by column chromatography (5% isopropanol–hexanes) gave **64** as a colorless oil (90%); $R_f = 0.54$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.56–7.54 (m, 2H), 7.39–7.30 (m, 3H), 7.09–7.04 (m, 3H), 6.98–6.96 (m, 1H), 4.25–4.17 (m, 2H), 4.08 (d, $J = 22.0$ Hz, 1H), 3.97–3.92 (m, 1H), 3.94 (d, $J = 11.6$ Hz, 1H), 3.78–3.71 (m, 1H), 3.76 (d, $J = 11.6$ Hz, 1H), 3.33 (dt, $J = 11.6, 5.2$ Hz, 1H), 2.96–2.79 (m, 2H), 2.70 (dt, $J = 11.6, 5.2$ Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.07 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 135.0, 134.2, 132.6, 130.5 (d, $J_{\text{C-P}} = 8.3$ Hz), 128.5, 128.1, 128.0, 126.5, 125.9, 125.4, 67.6 (d, $J_{\text{C-P}} = 159.7$ Hz), 63.0 (d, $J_{\text{C-P}} = 3.0$ Hz), 62.2 (d, $J_{\text{C-P}} = 3.0$ Hz), 54.0 (d, $J_{\text{C-P}} = 11.3$ Hz), 48.4 (d, $J_{\text{C-P}} = 6.9$ Hz), 29.5, 16.5 (d, $J_{\text{C-P}} = 5.7$ Hz), 16.2 (d, $J_{\text{C-P}} = 5.7$ Hz); FTIR (thin film): cm^{-1} 2978, 2904, 1453, 1243, 1012, 959; HRMS-ESI (m/z) Calcd for ($\text{C}_{20}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 360.1723; found: 360.1725.

Ethyl-1-((diethoxyphosphoryl)(phenyl)methyl)piperidine-4-carboxylate (65).

Purification by column chromatography (100% ethyl acetate) gave **65** as a colorless oil

(92%); R_f = 0.66 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.45–7.43 (m, 2H), 7.35–7.30 (m, 3H), 4.28–4.17 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.95–3.88 (m, 1H), 3.88 (d, J = 18.8 Hz, 1H), 3.75–3.69 (m, 1H), 3.40–3.37 (m, 1H), 2.94–2.91 (m, 1H), 2.35 (td, J = 11.2, 2.4 Hz, 1H), 2.10–2.05 (m, 1H), 1.93 (br t, J = 11.2 Hz, 1H), 1.84–1.67 (m, 4H), 1.34 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 175.1, 132.3, 130.5 (d, $J_{\text{C-P}}$ = 8.6 Hz), 128.0, 127.9, 68.2 ($J_{\text{C-P}}$ = 161 Hz), 63.1, 62.0, 60.2, 52.6 (d, $J_{\text{C-P}}$ = 14.3 Hz), 49.3, 40.8, 28.8, 28.7, 16.6 (d, $J_{\text{C-P}}$ = 5.6 Hz), 16.1 (d, $J_{\text{C-P}}$ = 5.1 Hz), 14.1; FTIR (thin film): cm^{-1} 2980, 1730, 1245, 1027, 962; HRMS-ESI (m/z) Calcd for ($\text{C}_{19}\text{H}_{31}\text{NO}_5\text{P}$) ($[\text{M}+\text{H}]^+$): 384.1934; found: 384.1935.

Diethyl-(phenyl(piperidin-1-yl)methyl)phosphonate (66). Purification by column chromatography (30% ethyl acetate–hexanes) gave **66** as a yellow oil (93%); R_f = 0.63 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.47–7.44 (m, 2H), 7.35–7.29 (m, 3H), 4.32–4.18 (m, 2H), 3.96–3.86 (m, 1H), 3.86 (d, J = 23.6 Hz, 1H), 3.77–3.67 (m, 1H), 2.85–2.77 (br m, 2H), 2.42–2.34 (br m, 2H), 1.58–1.51 (m, 4H), 1.35 (t, J = 6.8 Hz, 3H), 1.33–1.27 (m, 2H), 1.03 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 132.5, 130.5 (d, $J_{\text{C-P}}$ = 8.8 Hz), 127.9, 127.7, 68.6 (d, $J_{\text{C-P}}$ = 160.9 Hz), 63.1 (d, $J_{\text{C-P}}$ = 6.1 Hz), 61.9 (d, $J_{\text{C-P}}$ = 6.1 Hz), 52.5, 52.4, 26.4, 24.0, 16.5 (d, $J_{\text{C-P}}$ = 5.6 Hz), 16.1 (d, $J_{\text{C-P}}$ = 5.6 Hz); FTIR (thin film): cm^{-1} 2929, 2807, 1451, 1242, 1019, 953; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 312.1723; found: 312.1726.

Diethyl-((diethylamino)(phenyl)methyl)phosphonate (67). Purification by column chromatography (5% isopropanol–hexanes) gave **67** as a colorless oil (97%); $R_f = 0.43$ (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.48–7.45 (m, 2H), 7.34–7.28 (m, 3H), 4.24 (quin, $J = 7.2$ Hz, 2H), 4.16 (d, $J = 24.8$ Hz, 1H), 3.96–3.88 (m, 1H), 3.80–3.70 (m, 1H), 3.04–2.95 (m, 2H), 2.34–2.26 (m, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 133.5, 130.5 (d, $J_{\text{C-P}} = 8.6$ Hz), 128.0, 127.6, 62.8, 62.5 (d, $J_{\text{C-P}} = 155.6$ Hz), 61.5, 44.8, 44.7, 16.5 (d, $J_{\text{C-P}} = 4.9$ Hz), 16.2 (d, $J_{\text{C-P}} = 4.1$ Hz), 13.3; FTIR (thin film): cm^{-1} 2970, 1243, 1023, 958; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 300.1723; found: 300.1724.

Diethyl-((diallylamino)(phenyl)methyl)phosphonate (68). Purification by column chromatography (30% ethyl acetate–hexanes) gave **68** as a colorless oil (89%); $R_f = 0.51$ (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.48–7.45 (m, 2H), 7.37–7.31 (m, 3H), 5.87–5.76 (m, 2H), 5.21–5.13 (m, 4H), 4.27 (d, $J = 22.4$ Hz, 1H), 4.26–4.22 (m, 2H), 3.97–3.88 (m, 1H), 3.83–3.75 (m, 1H), 3.74 (ddd, $J = 14.4, 4.0, 2.0$ Hz, 1H), 2.73 (dd, $J = 14.4, 8.0$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 136.6, 132.2 (d, $J_{\text{C-P}} = 5.3$ Hz), 130.7 (d, $J_{\text{C-P}} = 8.9$ Hz), 128.1, 127.8, 117.4, 63.1 (d, $J_{\text{C-P}} = 5.0$ Hz), 61.9 (d, $J_{\text{C-P}} = 5.0$ Hz), 60.5 (d, $J_{\text{C-P}} = 163.0$ Hz).

Hz), 54.0, 54.0, 16.6 (d, $J_{C-P} = 5.6$ Hz), 16.1 (d, $J_{C-P} = 5.6$ Hz); FTIR (thin film): cm^{-1} 2978, 2818, 1641, 1452, 1241, 1022, 957; HRMS-ESI (m/z) Calcd for ($\text{C}_{17}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 324.1723; found: 324.1727.

Diethyl-((dibenzylamino)(phenyl)methyl)phosphonate (69). Purification by column chromatography (30% ethyl acetate–hexanes) gave **69** as a white solid (95%); $R_f = 0.75$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.50–7.47 (m, 2H), 7.44–7.37 (m, 7H), 7.34–7.30 (m, 4H), 7.27–7.22 (m, 2H), 4.32 (d, $J = 13.6$ Hz, 2H), 4.26–4.13 (m, 2H), 4.16 (d, $J = 25.6$ Hz, 1H), 3.92–3.85 (m, 1H), 3.72–3.65 (m, 1H), 3.26 (d, $J = 13.6$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 139.5, 131.8 (d, $J_{C-P} = 5.7$ Hz), 131.0 (d, $J_{C-P} = 8.6$ Hz), 128.9, 128.0, 126.9, 62.2 (d, $J_{C-P} = 6.6$ Hz), 62.0 (d, $J_{C-P} = 6.6$ Hz), 60.0 (d, $J_{C-P} = 161.1$ Hz), 55.1, 55.1, 16.5 (d, $J_{C-P} = 5.7$ Hz), 16.1 (d, $J_{C-P} = 5.7$ Hz); FTIR (thin film): cm^{-1} 3060, 2904, 1452, 1238, 1021, 954; HRMS-ESI (m/z) Calcd for ($\text{C}_{25}\text{H}_{31}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 424.2036; found: 424.2043.

Diethyl-((benzyl(methyl)amino)(phenyl)methyl)phosphonate (70). Purification by column chromatography (30% ethyl acetate–hexanes) gave **70** as a colorless oil (90%); $R_f = 0.44$ (30% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.55–7.48 (m, 2H),

7.41–7.30 (m, 7H), 7.27–7.25 (m, 1H), 4.30–4.18 (m, 2H), 4.04 (d, $J = 24.0$ Hz, 1H), 3.95–3.86 (m, 1H), 3.84 (d, $J = 13.2$ Hz, 1H), 3.76–3.65 (m, 1H), 3.39 (d, $J = 13.2$ Hz, 1H), 2.41 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H), 1.02 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 139.0, 132.0, 130.8 (d, $J_{\text{C-P}} = 8.6$ Hz), 128.9, 128.2, 128.1, 128.0, 127.0, 64.9 (d, $J_{\text{C-P}} = 161.0$ Hz), 62.5 (d, $J_{\text{C-P}} = 3.3$ Hz), 62.1 (d, $J_{\text{C-P}} = 3.3$ Hz), 59.8, (d, $J_{\text{C-P}} = 12.6$ Hz), 39.8 (d, $J_{\text{C-P}} = 4.6$ Hz), 16.5 (d, $J_{\text{C-P}} = 6.0$ Hz), 16.1 (d, $J_{\text{C-P}} = 6.0$ Hz); FTIR (thin film): cm^{-1} 2979, 2797, 1452, 1242, 1022, 957; HRMS-ESI (m/z) Calcd for ($\text{C}_{19}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 348.1723; found: 348.1728.

Diethyl-((diisopropylamino)methyl)phosphonate (72). Purification by column chromatography (10% isopropanol–hexanes) gave **72** as a pale yellow oil (90%); $R_f = 0.46$ (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.14 (quin, $J = 7.2$ Hz, 4H), 3.24–3.14 (m, 2H), 2.85 (d, $J = 10$ Hz, 2H), 1.31 (d, $J = 7.2$ Hz, 6H), 0.99 (d, $J = 6.4$, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 62.0 (d, $J_{\text{C-P}} = 6.5$ Hz), 48.7 (d, $J_{\text{C-P}} = 6.9$ Hz), 41.7 (d, $J_{\text{C-P}} = 173.2$ Hz), 20.4, 16.5 (d, $J_{\text{C-P}} = 5.6$ Hz); FTIR (thin film): cm^{-1} 2965, 1262, 1022, 956; HRMS-ESI (m/z) Calcd for ($\text{C}_{11}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 252.1723; found: 252.1725.

Diethyl-((butylamino)(phenyl)methyl)phosphonate (73). Purification by column chromatography (5% isopropanol–hexanes) gave **73** as a colorless oil (40%); $R_f = 0.59$ (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.42–7.27 (m, 5H), 4.09–4.06 (m, 2H), 4.01 (d, $J = 19.6$ Hz, 1H), 3.98–3.93 (m, 1H), 3.87–3.79 (m, 1H), 2.55–2.40 (m, 2H), 1.47 (quin, $J = 7.2$ Hz, 2H), 1.33–1.25 (m, 2H), 1.27 (d, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 136.3, 128.5 (d, $J_{\text{C-P}} = 6.0$ Hz), 128.3, 127.7, 62.8 (d, $J_{\text{C-P}} = 21.9$ Hz), 61.2 (d, $J_{\text{C-P}} = 151.5$ Hz), 47.8 (d, $J_{\text{C-P}} = 16.6$ Hz), 32.0, 29.7, 20.3, 16.4 (d, $J_{\text{C-P}} = 5.6$ Hz), 16.2 (d, $J_{\text{C-P}} = 5.6$ Hz), 13.9; FTIR (thin film): cm^{-1} 3305, 2926, 2857, 1453, 1240, 1022, 962; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{27}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 300.1729; found: 300.1727.

Diethyl-((butylamino)methyl)phosphonate (74). Purification by column chromatography (10% isopropanol–hexanes) gave **74** as a pale yellow oil (78%); $R_f = 0.34$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 4.19–4.07 (m, 4H), 2.97 (d, $J = 12.4$ Hz, 2H), 2.66 (t, $J = 7.2$ Hz, 2H), 1.64 (br s, 1H), 1.48–1.43 (m, 2H), 1.35–1.30 (m, 2H), 1.33 (t, $J = 7.2$ Hz, 6H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 62.0 (d, $J_{\text{C-P}} = 5.8$ Hz), 51.0 (d, $J_{\text{C-P}} = 15.0$ Hz), 45.2 (d, $J_{\text{C-P}} = 152.6$ Hz), 31.8, 20.2,

16.5 (d, $J_{\text{C-P}} = 5.5$ Hz), 13.9; FTIR (thin film): cm^{-1} 2929, 1229, 1098, 1023, 961; HRMS-ESI (m/z) Calcd for ($\text{C}_9\text{H}_{23}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 224.1410; found: 224.1411.

Diethyl-(1-(piperidin-1-yl)ethyl)phosphonate (75). Purification by column chromatography (5% isopropanol–hexanes) gave **75** as a yellow oil (96%); $R_f = 0.31$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 4.21–4.03 (m, 4H), 2.95 (dq, $J = 18.8, 7.6$ Hz, 1H), 2.76 (dt, $J = 11.6, 5.2$ Hz, 2H), 2.51 (dt, $J = 11.6, 5.2$ Hz, 2H), 1.53 (quin, $J = 5.6$ Hz, 4H), 1.42–1.37 (m, 2H), 1.32 (d, $J = 7.2$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 62.4 (d, $J_{\text{C-P}} = 6.5$ Hz), 61.0 (d, $J_{\text{C-P}} = 6.5$ Hz), 58.0 (d, $J_{\text{C-P}} = 150.7$ Hz), 51.2 51.1, 26.6, 24.4, 16.6 (d, $J_{\text{C-P}} = 5.3$ Hz), 16.5 (d, $J_{\text{C-P}} = 5.3$ Hz), 9.5 (d, $J_{\text{C-P}} = 2.8$ Hz); FTIR (thin film): cm^{-1} 2931, 1232, 1018, 953; HRMS-ESI (m/z) Calcd for ($\text{C}_{11}\text{H}_{25}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 250.1567; found: 250.1565.

Diethyl-(cyclopropyl(morpholino)methyl)phosphonate (77). Purification by column chromatography (10% isopropanol–hexanes) gave **77** as a colorless oil (95%); $R_f = 0.20$ (10% isopropanol–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.19 (q, $J = 7.2$ Hz, 2H),

4.11 (q, $J = 7.2$ Hz, 2H), 3.67 (t, $J = 4.8$ Hz, 4H), 3.04 (dt, $J = 11.2, 4.8$ Hz, 2H), 2.73 (dt, $J = 11.2, 4.8$ Hz, 2H), 2.03 (dd, $J = 20.0, 10.8$ Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.15–1.07 (m, 1H), 0.73–0.59 (m, 2H), 0.38–0.30 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 68.1 (d, $J_{\text{C-P}} = 157.1$ Hz), 67.6, 62.8, 61.4, 51.4, 51.4, 16.6, 16.5, 6.4 (d, $J_{\text{C-P}} = 5.3$ Hz), 5.6 (d, $J_{\text{C-P}} = 16.8$ Hz), 3.4; FTIR (thin film): cm^{-1} 2851, 1238, 1021, 951; HRMS-ESI (m/z) Calcd for $(\text{C}_{12}\text{H}_{25}\text{NO}_4\text{P})$ ($[\text{M}+\text{H}]^+$): 278.1516; found: 278.1514.

Diethyl-((butyl(2-methylpent-4-en-1-yl)amino)(phenyl)methyl)phosphonate (80, as a mixture of diastereomers). Purification by column chromatography (30% ethyl acetate–hexanes) gave **80** as a colorless oil (89%); $R_f = 0.63$ (30% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.47–7.44 (m, 4H), 7.35–7.29 (m, 6H), 5.88–5.71 (m, 2H), 5.03–4.94 (m, 4H), 4.24–4.15 (m, 4H), 4.11 (dd, $J = 26.0, 7.6$ Hz, 2H), 3.92–3.85 (m, 2H), 3.75–3.67 (m, 2H), 3.04–2.94 (br m, 2H), 2.63–2.45 (m, 3H), 2.25–2.12 (m, 4H), 2.05–2.00 (m, 1H), 1.87–1.64 (m, 4H), 1.50–1.23 (br m, 6H), 1.34 (t, $J = 7.2$ Hz, 6H), 1.01 (t, $J = 7.2$ Hz, 6H), 0.97 (d, $J = 6.8$ Hz, 6H), 0.90 (t, $J = 7.2$ Hz, 6H), 0.80 (t, $J = 6.4$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 137.9, 137.3, 132.9 (t, $J_{\text{C-P}} = 7.4$ Hz), 136.8 (d, $J_{\text{C-P}} = 4.7$ Hz), 130.7 (d, $J_{\text{C-P}} = 4.7$ Hz), 127.9, 127.7, 62.3 (d, $J_{\text{C-P}} = 161.2$ Hz), 62.1, 62.0, 61.9, 58.1 (d, $J_{\text{C-P}} = 8.7$ Hz), 57.8 (d, $J_{\text{C-P}} = 8.7$ Hz), 51.3 (t, $J_{\text{C-P}} = 7.3$ Hz), 39.6,

38.7, 31.6, 31.5, 30.5, 20.3, 17.8, 17.6, 16.5, 16.1, 14.1; FTIR (thin film): cm^{-1} 2955, 2870, 1453, 1243, 1024, 956; HRMS-ESI (m/z) Calcd for ($\text{C}_{21}\text{H}_{37}\text{NO}_3\text{P}$) ($[\text{M}+\text{H}]^+$): 382.2506; found: 382.2505.

Chapter 4: Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes by C–H Zincation

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4. Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes by C–H Zincation

4.1 Synthesis of heteroaromatic and aryl amines

Heteroaromatic amines, especially 2-aminoazoles, are key structural motifs that are widely found in biologically important molecules and medicines.^{6,212-218} For example, the 2-piperazinylbenzimidazole derivative lerisetron is currently in clinical trials for the treatment of nausea associated with cancer chemotherapy (Figure 7).⁶ Other classes of heteroaryl amines, such as anti-HIV agent HM13N,²¹⁶ WRC-0571,²¹⁵ and linagliptin,²¹³ are also extensively used in drug discovery. Therefore, efficient methods for the synthesis of these important heteroaryl amines are highly valuable.

Figure 8. Selected examples of bioactive heteroaromatic amines.

4.1.1 Aryl amination reactions

Heteroaromatic and aryl amines are functionally and biologically important molecules.^{6,212-218} The importance of nitrogen-containing compounds continues to drive the development of new C–N bond-forming transformations (Scheme 39).¹ Traditionally,

C–N bonds have been synthesized using nucleophilic amines, with transition metal-mediated aminations providing a powerful method towards this end. Electrophilic aminations using $[\text{NR}_2]^+$ synthons offer a complementary method to the conventional use of nucleophilic amines for aminations. Moreover, direct C–H amination offers a direct method to introduce N-based groups into molecules without stepwise functional group manipulations.

A) Buchwald-Hartwig amination

B) Oxidative amination

a. *Chan-Lam oxidative amination*

b. *Oxidative C-H amination*

C) Electrophilic amination of organometallics

D) Electrophilic C-H amination

Scheme 39. Amination Strategies to Access $\text{Ar}-\text{NR}^1\text{R}^2$

4.1.1.1 Nucleophilic or Buchwald-Hartwig amination

Migita and co-workers reported the first aryl amination involving the palladium-catalyzed cross-coupling of aryl bromides with *N,N*-diethylamino-tributyltin in 1983.²¹⁹ More than a decade later Buchwald and co-workers reported a new catalytic aryl amination procedure based on Migita's amination.²²⁰ However, both of these methods

called for the use of stoichiometric tributyltin amides, which are both heat- and moisture-sensitive. In 1995, Buchwald and Hartwig concurrently reported the use of free amines in the presence of a strong base (e.g. NaOt-Bu) to replace the need for stoichiometric tributyltin.⁷⁻⁸ The resulting Buchwald-Hartwig amination became one of the first practical methods for the synthesis of arylamines (Scheme 40).

Scheme 40. The Buchwald-Hartwig amination for the synthesis of aryl amines

The Buchwald-Hartwig amination is the state-of-the-art method and most powerful tool for the synthesis of aryl amines. It is a transition metal-catalyzed cross-coupling reaction between aryl halides or triflates and amines (Scheme 2). The development of the Buchwald-Hartwig amination allowed for a facile synthesis of aryl amines while replacing harsher methods such as nucleophilic aromatic substitution. While palladium is typically used as the catalyst in the reaction, other transition metals have proven to be competent catalysts as well.²²¹⁻²²² Chelating phosphine-type ligands are used in the reaction, and the base has to be present in stoichiometric amounts. Overtime, reaction conditions have gradually become milder and traditionally unreactive aryl chlorides can be coupled with amines when the appropriate ligand is used.²²¹

4.1.1.2 Synthesis of aryl amines via oxidative amination

As a complementary strategy to the Buchwald-Hartwig amination, oxidative amination provides a potentially more effective synthetic approach to intermolecular C–N

bond formation and the synthesis of heteroaromatic and aromatic amines. In 1998, Chan and Lam reported the first copper-catalyzed oxidative coupling of amines with boronic acids (Scheme 41).⁹⁻¹⁰ It had notable advantages over the Buchwald-Hartwig amination as it could be run at room temperature and in the presence of air. Since the initial publication, others have continued to expand the reaction scope to aliphatic amines and amides as the nucleophilic nitrogen source.²²³⁻²²⁵

Scheme 41. Chan-Lam oxidative coupling for the synthesis of aryl amines

In addition to the Chan-Lam coupling, some progress in this area has also been accomplished by oxidative C–H amination reactions (Scheme 42).¹²⁻³⁴ The development of oxidative C–H/N–H coupling reactions has seen a surge in recent years. In 2006, Yu and co-workers reported their pioneering development of a copper-catalyzed oxidative amination of 2-phenylpyridine (Scheme 42A).³⁰ Subsequently, other groups have shown that 2-aryl pyridines can be used for copper-catalyzed oxidative C–H/N–H coupling to yield *ortho* aminated arenes.³¹⁻³³ However, the pyridine moiety for these methods is non-removable. Daugulis and co-workers reported an oxidative amination of arenes using 8-aminoquinoline as a directing auxiliary and Cu(OAc)₂ as catalyst (Scheme 42B).²² The 8-aminoquinoline auxiliary provided an alternative to pyridine directing groups. Their method provided a straightforward means for preparation of *ortho*-aminobenzoic acid derivatives. Most recently, Yu and co-workers reported a copper-catalyzed oxidative amination of arenes and heteroarenes (Scheme 42C).³⁴ They were able to use a wide

range of sulfonamides, amides, and anilines as amine donors for their reaction. In 2009, the Mori group reported the first direct oxidative C–H/N–H coupling of azoles with amines in the presence of sodium acetate and catalytic $\text{Cu}(\text{OAc})_2$ (Scheme 42D).¹⁹ The reaction conditions were extended to benzothiazole, benzoxazole, *N*-methylbenzimidazole, and 4,5-dimethylbenzimidazole using secondary amines. However, four equivalents of the amine nucleophile were required in order to prevent side reactions of the organocopper intermediate, thus limiting this method to simple and commercially available amines. Additional deprotonative, copper-catalyzed oxidative aminations of thiazoles and oxazoles have since been reported but are still limited by the excess of nucleophile needed.²⁴

Scheme 42. Oxidative C–H amination reactions

An alternative approach to direct oxidative C–H amination of arenes and heteroarenes was reported by Knochel and co-workers (Scheme 43).¹³⁻¹⁶ Knochel's oxidative amination started with the deprotonation of the arene or heteroarene with $\text{tmpMgCl}\cdot\text{LiCl}$ or Zn(tmp)_2 and then treatment of the anion with stoichiometric $\text{CuCl}\cdot 2\text{LiCl}$. The formed organocopper was reacted with excess lithium amide, then stoichiometric oxidant was added to provide the desired aryl or heteroaryl amine. However, the use of lithium amides, as well as oxidants, limited the functional group compatibility of the reaction. Additionally, the low temperatures and some times long

reaction times made this impractical for large-scale production of the desired aryl or heteroaryl amines.

A) C–H deprotonation with $\text{tmpMgCl}\cdot\text{LiCl}$

B) C–H deprotonation with $\text{Zn}(\text{tmp})_2$

Scheme 43. Oxidative amination developed by Knochel and co-workers

Several metal-free C–H/N–H coupling methods have also been developed via an oxidative re-aromatization pathway.^{27–29} Most recently, Reutrakul and co-workers reported a one-pot synthesis of *N*-substituted 2-aminoazole derivatives (Scheme 44).²⁹

^a Requires microwave irradiation

Scheme 44. Metal-free C–H/N–H coupling

Using iodine to mediate C–N bond formation, their transformation employed the use of simpleazole substrates for the synthesis of primary and secondary heteroaryl amines. To extend the scope to less reactive thiazoles and imidazoles, albeit in low yields, a microwave irradiation method was employed.

4.2 Electrophilic amination for the synthesis of aryl amines

Electrophilic amination reactions have seen a considerable increase in interest over the past decade as an alternative method for the synthesis of ubiquitous C–N bonds.³⁵⁻⁴⁴ To date, most electrophilic aminations have been achieved using various carbanions with $[\text{NR}_2]^+$ synthons. Many of these amination reactions leverage the use of transition metals.

4.2.1 Electrophilic amination of organometallics

The electrophilic amination of carbanions is well known with a large number of organometallic reagents used, including organozincs,^{45-48,102} Grignard reagents,^{35,49,101} organoboron reagents,⁵⁰⁻⁵¹ organosilicon reagents⁵⁵ and aryl and heteroaryl lithiums.⁵⁷ In 2004, Campbell and Johnson reported their pioneering work on the copper-catalyzed electrophilic amination of diorganozincs using *O*-acylhydroxylamines (Scheme 45A).⁴⁵ Using CuOTf as catalyst, they were able to prepare tertiary aryl amines in high yields under mild conditions. Many of the amine products were isolated by an acid-base extractive workup. While their early method was limited to electron-rich aryl and alkyl groups, using an I/Mg exchange of aryl iodides for the preparation of functionalized diarylzinc reagents allowed them able to extend their method so that nitriles, esters, halides, triflates, and nitro groups were also tolerated.⁴⁶ Later they were able to extend

their method to organozinc halides using a nickel catalyst (Scheme 45B).⁴⁷ However, despite mild reaction conditions and good yields, the nickel-catalyzed amination lacked the generality of their previous copper-catalyzed system.

Scheme 45. Electrophilic amination of organozincs using *O*-benzoylhydroxylamines

Following the work of the Johnson group, Barker and Jarvo reported a nickel-catalyzed coupling of diorganozincs with *N*-chloramines in good yield (Scheme 46).¹⁰² The use of *N*-chloramines added a significant advance to the electrophilic amination of organozincs, as they are easily prepared from treatment of the starting amine with bleach. Aside from isolated *N*-chloramines, a one-pot procedure starting from the corresponding amine and *N*-chlorosuccinimide (NCS) could be utilized, which increased the versatility of the method. However, the reaction was limited to *N*-chloramines generated from electron-rich secondary amines.

Scheme 46. Electrophilic amination of organozincs using *N*-chloramines

Electrophilic amination of Grignard reagents using primary *O*-alkylhydroxylamines and haloamines has been broadly used to synthesize primary amines;³⁵ however the use of *N*-substituted hydroxylamines and haloamines has been more limited due to side reactions such as *C*-acylation and halogenation. Following their reports on the electrophilic amination of organozincs,⁴⁵⁻⁴⁸ Johnson and co-workers reported a copper-catalyzed amination of Grignard reagent with *O*-acylhydroxylamines (Scheme 47).⁴⁹ Aryl amines were synthesized in moderate to excellent yield, and the slow

Scheme 47. Copper-catalyzed electrophilic amination of Grignard reagents via *O*-benzoylhydroxylamines

addition of the Grignard reagent to the reaction allowed for amination to occur faster than *C*-acylation. Although this reaction lacked the scope of their previous protocol employing

diorganozinc compounds,⁴⁵⁻⁴⁸ it was in some cases operationally superior as a result of the absence of anhydrous zinc salts needed to generate the diorganozinc compounds.

Using *N*-chloramines as the electrophilic nitrogen source, Jarvo and co-workers disclosed a titanium-mediated amination of aryl Grignards (Scheme 48). Their method was appealing because no prior isolation of the *N*-chloramines was necessary. This allowed for a diverse scope of both primary and secondary amines to be used. Their method was compatible with a range of functional groups that included esters, halides and nitriles.

Scheme 48. Titanium-mediated amination of aryl Grignard reagents

In 2010, Nakamura and co-workers reported a metal-free electrophilic amination of aryl Grignard reagents with *N*-chloramines (Scheme 49).¹⁰¹ Using *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as an additive they were able to synthesize a variety of arylamines in good to excellent yield. Additionally, ester and nitrile functional groups were compatible with their amination method.

Scheme 49. Metal-free amination of aryl Grignard reagents

Recently organoboron reagents have been used for the synthesis of aryl amines. In 2012, Miura and Lalic concurrently disclosed copper-catalyzed electrophilic aminations of aryl boronic esters.⁵⁰⁻⁵¹ In the work by Miura and co-workers, a wide variety of anilines were obtained in moderate to good yields by coupling aryl boronates with *O*-benzoylhydroxylamines using $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the catalyst (Scheme 50A).⁵⁰ Meanwhile, Lalic and co-workers focused on a copper-catalyzed electrophilic amination of aryl boronic esters for the synthesis of sterically hindered anilines (Scheme 50B).⁵¹ They found that boronic esters derived from neopentyl glycol were crucial for the reaction. Using a catalyst formed *in situ* from $[\text{CuOt-Bu}]_4$ and Xantphos gave the best yields for the various anilines. Both methods tolerated a variety of functional groups including halogens, esters, ketones, aldehydes, and carbamates.

Scheme 50. Copper-catalyzed electrophilic aminations of aryl boronic esters

Organosilicon reagents can also undergo direct electrophilic amination. Miura and co-workers reported a copper-catalyzed amination of aryl silanes (Scheme 51).⁵⁵ This method allowed for the efficient synthesis of aniline derivatives under mild conditions. Additionally, their method tolerated a wide range of functional groups, including halogens, nitriles, and esters.

Scheme 51. Copper-catalyzed electrophilic amination of arylsilanes

Although organolithium reagents are commercially available or readily available through lithium–halogen exchange, their use for electrophilic amination has been limited due to low yields and often limited substrate scope. Therefore, organolithiums are often converted to other organometallic reagents.³⁵ Amos and co-workers developed a copper-catalyzed amination of organolithiums using *O*-benzoylhydroxylamines as the electrophilic nitrogen source (Scheme 52).⁵⁷ They used a recoverable siloxane as a transfer agent to prepare silanes *in situ* from the organolithiums. Additionally, the use of siloxane transfer agents offered a viable solution for the direct application of organolithiums in electrophilic amination. Through this amination method, they were able to access a diverse array of aryl and heteroaryl amines.

Scheme 52. Electrophilic amination of organolithiums mediated by siloxane transfer agents

4.2.2 Electrophilic metal-catalyzed C–H amination

While remarkable progress in C–H amination has been accomplished via oxidative C–H/N–H coupling, current metal-catalyzed electrophilic C–H amination methods are still restricted in generality. Effective metal-catalyzed C–H aminations of arenes and heteroarenes have been achieved by various transition metals. Toward this, a range of catalyst systems have been developed, including palladium, ruthenium, rhodium and copper.^{59–62,64} Metallation of C–H bonds has been achieved by two strategies in most amination reactions—directing group assisted *ortho*-metallation or direct deprotonative metallation (Scheme 53). The first approach (Scheme 53A), involving directing group-assisted metallation, has proven to be powerful for the synthesis of *ortho*-substituted arylamines.^{59–62} The second approach (Scheme 53B), via direct deprotonative metallation, is particularly useful for the amination of electron-deficient arenes, such as 1,3,4-oxadiazoles and polyfluoroarenes.^{64,100}

A) Directing group assisted *ortho*-metalation

B) Direct deprotonative metalation

Scheme 53. Metal-catalyzed direct C–H aminations

4.2.2.1 Directing group assisted *ortho*-metallation for C–H amination

Directing group-assisted metallation has proven to be a powerful tool for the synthesis of *ortho*-substituted arylamines. Direct *ortho* C–H amination was first disclosed by Yu and co-workers with their palladium-catalyzed amination of *N*-aryl benzamides using *O*-benzoylhydroxylamines as the electrophilic nitrogen source (Scheme 54).⁵⁹ The amination worked well for electron-donating benzamides; however, yields noticeably decreased for electron-withdrawn benzamides. For electron-withdrawn substrates, α,α,α -trifluorotoluene was necessary to obtain reasonable yields. In addition to the amination using *O*-benzoylhydroxylamines, they were able to demonstrate that a one-pot procedure using secondary amines in the presence of benzoyl peroxide (BPO) was feasible (Scheme 54B).

Scheme 54. Palladium-catalyzed C–H amination of *N*-aryl benzamides

Despite the utility of the initial palladium-catalyzed C–H amination reported by Yu and co-workers, it was limited in substrate scope and had poor efficiency for electron-withdrawn benzamides. Recently, Yu and co-workers disclosed a palladium-catalyzed *ortho* C–H amination in which pyridine and quinoline-based ligands promoted the amination of these more difficult substrates (Scheme 55).⁶⁰ Of the various pyridine and quinoline ligands, 2,4,5-trimethoxypyridine proved to be the best ligand. With this particular ligand they were also able to extend the palladium-catalyzed *ortho* C–H amination to triflyl-protected benzylamines as well as electron-withdrawn benzamides.

Scheme 55. Ligand-promoted palladium-catalyzed C–H amination

In addition to palladium, ruthenium and rhodium have been shown to be effective catalysts for direct *ortho* C–H amination.^{61–62} Following their initial palladium-catalyzed *ortho* C–H amination,⁵⁹ Yu and co-workers disclosed a ruthenium-catalyzed *ortho* C–H amination of benzamides (Scheme 56).⁶¹ This reaction could be run at room temperature compared to higher temperatures required for palladium catalysis. In addition to benzamides, this reaction was also compatible with heterocycles including pyrazole, thiophene, furan, benzofuran, benzothiophene and indole. However, unlike their palladium-catalyzed methods, this ruthenium-catalyzed C–H amination was limited to incorporation of cyclic amines.

Scheme 56. Ruthenium-catalyzed *ortho* C–H amination of arenes and heteroarenes

Zhang and Yao reported a rhodium-catalyzed aryl C–H amination using a pyrazolone moiety as an *ortho* directing group (Scheme 57).⁶² Their amination method is notable because they were able to introduce primary and secondary amines under mild conditions to make novel analogues of the neuroprotection drug edaravone.¹¹⁰⁻¹¹³

Scheme 57. Rhodium-catalyzed *ortho* C–H amination

4.2.2.2 Direct deprotonative metallation for C–H amination

Direct deprotonative metallation/amination using *O*-benzoylhydroxylamines has been less thoroughly explored; however it has been particularly useful for the amination of electron-deficient arenes. Miura and co-workers used this method for a copper-catalyzed direct amination of polyfluoroarenes and azoles (Scheme 58).⁶⁴ They were able to synthesis the corresponding anilines and aminoazoles in moderate to good yields under mild reaction conditions.

Scheme 58. Copper-catalyzed direct C–H amination of polyfluoroarenes and azoles

4.2.3 Limitations of current methods

While progress towards the synthesis of heteroaryl and aryl amines has been made, the current methods often suffer from a limited arene scope and poor efficiencies, particularly on important skeletons including benzimidazoles, benzothiazoles, and thiazoles. This limitation is largely due to the challenging metallation step associated with the inherently high dissociation energy of sp^2 C–H bonds, and also leads to the common requirement of harsh reaction conditions (high temperatures, strong oxidants, and acidic or basic additives). Additionally, the use of high temperatures, strong oxidants, and acidic or basic additives considerably impacts functional group compatibility and potential applications.¹¹⁴ A more general C–H amination method is needed, and it would be greatly desirable to develop a catalytic amination system effective for sp^2 C–H bonds with broader applications in complex molecule synthesis to access highly valuable aminated heteroarenes. Mild reaction conditions are desirable to broaden the scope of its applications.¹¹⁴

4.3 Results and Discussion

4.3.1 Electrophilic amination of heteroarenes and arenes by C–H zincation

Inspired by the pioneering copper-catalyzed electrophilic amination of diarylzincs with *O*-benzoylhydroxylamines reported by Johnson and co-workers,^{45-46,48} we reported a C–H zincation and copper-catalyzed electrophilic amination as a modular and facile amination approach to rapidly access a broad scope of important heteroaromatic and aromatic amines (Scheme 59). Our approach was built on the use of strong and non-nucleophilic zinc bases,¹¹⁵⁻¹²⁸ such as $Zn(tmp)_2$ (pKa of the conjugate acid=37),¹²⁵⁻¹²⁸ to

generate the corresponding organozincates from a wide range of heteroarenes and arenes. Importantly, the resulting organozinc intermediates could serve as a more reactive surrogate of C–H bonds toward amination. Thus, this strategy would overcome the narrow substrate scope and harsh reaction conditions of the previous C–H amination methods. In comparison to organozinc intermediates prepared from the heteroaryl halides and Grignard reagents,^{45,226} our approach using the direct H–Zn exchange would make use of various arenes and heteroarenes as more convenient starting materials, and offer a better functional-group compatibility.^{146-147,227-228} Based on this hypothesis, we developed an operationally convenient one-step C–H amination procedure and examined its efficiency on a wide scope of heteroarenes and arenes, including both electron-rich and electron-deficient substrates. It is particularly useful because of its high efficacy for substrates, such as benzimidazoles, pyridines, benzothiophenes, and less acidic C–H bonds, which were isolated in poor yields under previous amination conditions.^{13-26,64,100}

Scheme 59. C–H zincation and copper-catalyzed electrophilic amination heteroarenes and arenes

4.3.2 Amination studies using Zn(tmp)₂ for C–H zincation

Our studies began with the amination of *N*-methylbenzimidazole (**103**) with the *O*-benzoylhydroxylamine **3** via the formation of its organozinc intermediate using Zn(tmp)₂ (Table 18). We focused on *O*-benzoylhydroxylamines as the electrophilic

nitrogen source because of their easy availability and previous use in the electrophilic amination of different organometallic reagents.⁴⁵⁻⁵⁸ To our delight, the aminated product **104** was formed upon treating the diarylzinc intermediate with **3** and a copper catalyst, among which Cu(OAc)₂ was most effective (entries 2–10). Without a copper catalyst, no aminated product was observed (entry 1). Furthermore, a stoichiometric amount of the diarylzinc intermediate was needed to fully convert **3** into **104**, thus suggesting that the resulting monoarylzinc benzoate was ineffective for the amination under these reaction conditions (entries 11 and 12).

One of the important attributes of this new amination approach is its potential to directly access a broad array of heteroaromatic amines, including those inaccessible from other C–H amination methods.^{13-26,64,100} Toward this end, we first examined the amination reactions of different azoles using *O*-benzoylhydroxylamine **3** (Table 19). We first looked into simple azoles, including both the electron-deficient benzothiazole **105** and benzoxazole **107**, and electron-rich benzofuran **109** and benzothiophene **111**. For electron-rich benzofuran **109** and benzothiophene **111**, Zn(tmp)₂•LiCl•MgCl₂ were in order to stabilize the zinc intermediate. All the reactions successfully provided the aminated products (entries 2–5). Analogous reactions with the imidazole **113**, oxazole **115**, and thiazole **117** also occurred in excellent yields (entries 6–8). Next we examined the amination of functionalized azoles (entries 9–14), including the bromobenzoxazole **119**, bromothiazoles **121** and **123**, disubstituted oxazole **125**, caffeine **127**, and 1,3,4-oxadiazole **129**. These reactions gave the corresponding aminated azoles in 82–96% yields.

Table 18. Optimization studies for copper-catalyzed amination of *N*-methylbenzimidazole (103) and *O*-benzoylhydroxylamine 3.^a

entry	103 (equiv)	Zn(tmp)₂ (equiv)	copper (10 mol%)	time (h) ^b	104 (%) ^c
1	2.1	1.0	—	72 ^d	0
2	2.1	1.0	CuI	4	82
3	2.1	1.0	CuBr	19	80
4	2.1	1.0	CuCl	4	88
5	2.1	1.0	CuCN	19	81
6	2.1	1.0	[CuOTf] ₂ •tol	4	71
7	2.1	1.0	CuCl ₂	3.5	89
8	2.1	1.0	Cu(acac) ₂	3.5	82
9	2.1	1.0	Cu(OTf) ₂	5	76
10	2.1	1.0	Cu(OAc) ₂	5	99
11	1.4	0.6	Cu(OAc) ₂	72 ^d	56
12	1.05	0.5	Cu(OAc) ₂	72 ^d	40

^a Reactions run on a 0.2 mmol scale. ^b Time required for complete consumption of **3** in step 2. ^c Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. ^d **3** not fully consumed after 72 h.

Table 19. Amination of azole compounds.^a

$\text{Ar-H} \xrightarrow[\text{Cu(OAc)}_2 \text{ (10 mol\%), THF, rt}]{\begin{array}{l} 1) \text{ Zn(tmp)}_2, \text{ THF, rt} \\ 2) \text{ BzO-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array} \text{ 3 (1.0 equiv)} \end{array}} \text{Ar-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array}$				
entry	Ar-H	time (h) ^b	product	yield (%)
1		1; 5		96
2		1; 5		93
3		1; 5		95
4		1; ^c 5		71
5		1; ^c 5		70
6		1; 12		82
7		1; 12		92
8		1; 12		95
9		1; 24		96
10		1; 5		85
11		1; 5		90
12		1; 4		89
13		1; ^d 24		82
14		1; 4		91

^a Isolated yields. Reactions typically run on 0.2 mmol scale. Ar-H (2.1 equiv), **3** (1.0 equiv, 0.08 M), Zn(tmp)₂ (1.0 equiv). ^b Reaction time for deprotonation and amination step respectively. ^c Zn(tmp)₂•LiCl•MgCl₂¹⁶ was used as base. ^d Deprotonation step run in CH₂Cl₂ because of the poor solubility of **127** in THF.

We next wanted to expand the heteroarene and arene scope beyond azole compounds (Table 20). In the examination of this method on pyridinyl C–H bonds, the reactions of the pyridines **131**, **133**, **135**, and **137** all proceeded smoothly, thus affording the aminated products **132**, **134**, **136**, **138**, albeit elevated amination temperatures were necessary (50 °C; entries 1–4). Lastly, the amination of the arene **139** also proceeded smoothly in 75% yield (entry 5).

Table 20. Amination of pyridines and arenes.^a

$\text{Ar-H} \xrightarrow[\text{Cu(OAc)}_2 \text{ (10 mol\%), THF, rt}]{\begin{array}{l} \text{1) Zn(tmp)}_2, \text{ THF, rt} \\ \text{2) BzO-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array} \text{ 3 (1.0 equiv)} \end{array}} \text{Ar-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array}$					
entry	Ar-H		time (h) ^b	product	yield (%)
1		131	2; 12 ^c		132 81
2		133	2; 12 ^c		134 79
3		135	2; 12 ^c		136 91
4		137	2; 12 ^c		138 74
5		139	1; 12		140 75

^a Isolated yields. Reactions typically run on 0.2 mmol scale. Ar-H (2.1 equiv), **3** (1.0 equiv, 0.08 M), Zn(tmp)₂ (1.0 equiv). ^b Reaction time for deprotonation and amination step respectively. ^c Amination step run at 50 °C.

The high regioselectivity observed in the aminated products of these heteroarenes and arenes is presumably derived from the selective zinc metallation. It is noteworthy that many functionalities were well tolerated, and include halide, ester, nitro, and nitrile groups. Many of these groups would be incompatible with amination conditions by C–H lithiation to form organozinc intermediates. Such a broad scope demonstrates the value of our amination protocol, which proceeds by C–H zinc metallation in comparison to other amination strategies.

The scope of the amines is also crucial for extensive utility of this amination method. Next we examined different *O*-benzoylhydroxylamines derived from simple dialkylamines in the amination reactions with representative heteroarenes and arenes (Table 21). We were pleased to find that all the reactions proceeded smoothly in modest to excellent yields (67–97%), thus allowing the introduction of a variety of cyclic and acyclic alkylamino groups. Notably, the cleavage of the benzyl group or allyl group can additionally afford either a secondary amine or a primary amine (e.g., **150–154**).

Table 21. Scope of *O*-benzoylhydroxylamines.^a

^a Isolated yields. Reactions run on 0.2 mmol scale. Conditions: Ar-H (2.1 equiv), Zn(tmp)₂ (1.0 equiv), rt, 1 h; BzONR¹R² (1.0 equiv, 0.08 M), Cu(OAc)₂ (10 mol %), rt, 5 h. ^b Amination step run for 24 h.

4.3.3 Amination studies using tmpZnCl•LiCl for C–H zincation

Recognizing that the use of Zn(tmp)₂ required the sacrifice of an additional equivalent of the arene moiety, we next explored the amination of an alternative monoarylzinc intermediate using tmpZnCl•LiCl¹¹⁹⁻¹²⁴ in the C–H metallation (Table 22). First we looked at lowering the equivalent of **103**, and encouragingly, we saw amination

in 79% (entry 1). Next, we looked into using *N*-methylbenzimidazole **103** as the limiting reagent (entries 2 and 3). We were able increase amination up to 89% yield.

Table 22. Condition optimization using tmpZnCl•LiCl for C–H zincation.

entry	103 (equiv)	3 (equiv)	tmpZnCl•LiCl (equiv)	time (h) ^a	104 (%) ^b
1	1.1	1	1	4	79
2	1.05	1.2	1	4	88
3	1	1.2	1	3	89

^a Time required for complete consumption of **3** in step 2. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

With amination conditions identified, we next examined the generality of the transformation (Table 23). Encouragingly, these reactions from both electron-deficient and electron-rich substrates all provided the aminated products in excellent yields. These preliminary results suggest that arylzinc chloride was equally effective as diarylzinc for electrophilic amination under the current reaction conditions and extend the synthetic utility of this amination with the flexibility of using heteroarenes as the limiting reagent.

Table 23. Direct amination using a tmpZnCl•LiCl-mediated metallation.^a

^a Isolated yields. Reactions run on 0.2 mmol scale and 10 mol% Cu(OAc)₂ used. ^b Amination step run at 50 °C. ^c Deprotonation step run in CH₂Cl₂ because of the poor solubility of **127** in THF. ^d Deprotonation step run at 65 °C. ^e Deprotonation run for 1.5 h.

Given the broad generality and operational simplicity of this amination reaction, its utility for the synthesis of medicinally valuable agents was demonstrated by the rapid

synthesis of lerisetron **167** (Scheme 60). This 5-HT₃ receptor antagonist was readily prepared from the simple benzimidazole **165** by using the standard amination conditions.

Scheme 60. A rapid synthesis of lerisetron via C–H zincation and amination

Finally, we evaluated the efficacy of this transformation on a larger scale. For the amination scale-up, we decided to use 3-fluoropyridine **168** (Scheme 61) because of the increasing presence of amine-substituted pyridines in pharmaceutical sciences.²²⁹⁻²³¹ The amination reaction was set-up on a 50 mmol scale. Additionally catalyst loading was lowered to 5 mol%. Excitingly, the large-scale amination of 3-fluoropyridine **168** gave aminated pyridine **156** in 58% yield.

Scheme 61. Large-scale amination of 3-fluoropyridine 168

4.3.4 Proposed mechanism for the amination

Based on current experimental observations and related mechanistic studies,^{49,64} a possible mechanism is proposed for this copper-catalyzed amination reaction (Scheme 62). It involves (1) the transmetalation of the pre-formed organozinc intermediate, either diarylzinc (**I**) or monoarylzinc chloride (**I'**), with a Cu(I) catalyst [upon initial reduction when Cu(II) catalyst was used] to form the aryl copper complex (**III**), (2) an oxidative

addition with *O*-acylhydroxylamine to form a high-valent copper species (**IV**), and (3) reductive elimination to form the C–N bond and regenerate the copper catalyst. In addition, the results from Table 19, entries 11 and 12 suggest that benzoyloxyarylzinc intermediate (**II**) is unable to undergo effective transmetallation under the current conditions. It should be noted that the detailed mechanism for C–N bond formation still remains obscure. For example, we cannot exclude an alternative that involves (1) oxidative addition of the hydroxylamine to the copper (I) species, (2) transmetallation with an organozinc intermediate, and (3) reductive elimination to form a C–N bond.

Scheme 62. Proposed reaction pathway for heteroarenes and arenes

4.4 Conclusion

In summary, we have developed a direct and facile amination reaction of heteroarenes and arenes, including both electron-poor and electron-rich substrates. This transformation was achieved by a one-pot C–H zincation and copper-catalyzed electrophilic amination using *O*-benzoylhydroxylamines. It is especially attractive with

the use of low cost copper catalyst and readily available reagents. The reaction features broad substrate scope, high efficiency, mild reaction conditions, and good functional-group compatibility. Additionally, it demonstrates great potential as a rapid and powerful way to access a variety of highly functionalized complex heteroaromatic amines, which are of broad interest in organic synthesis and drug discovery.

4.5 Supplemental Information

4.5.1 General Information

General Procedures. Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in Biotage 8 mL microwave vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 x 20 cm) of Drierite, unless otherwise noted. Reaction vials were sealed with Teflon tape. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Flash-column chromatography was performed on silica gel (60 Å, standard grade) or on a CombiFlash companion system with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.).

Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich or Strem and used as received. Dry THF and toluene were obtained using an Innovative Technologies solvent purification system. $\text{tmpZnCl}\cdot\text{LiCl}$ was prepared according to literature procedure.¹²⁴ *O*-acylhydroxylamine derivatives were prepared according to literature procedure.⁴⁸

Instrumentation. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 or 125 MHz respectively) spectrometer at ambient temperature. Chemical shifts for ^1H NMR are reported in parts per million (ppm, δ) and referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.26). Chemical shifts for ^{13}C NMR are reported in ppm and referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), integration. Infrared spectroscopic data was obtained using an Thermo Scientific Nicolet 380 FT-IR. IR data is reported in wavenumbers (cm^{-1}) with only select peaks shown. High-resolution mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer

4.5.2 Experimental procedures

Typical Procedure 1 (TP1): General Experimental Procedure for C–H Amination via $\text{Zn}(\text{tmp})_2$ Mediated Metallation.

To an 8 mL microwave tube charged with heteroaryl compound (0.420 mmol, 2.1 equiv)

was added THF (1 mL) followed by dropwise addition of Zn(tmp)₂ (0.5 M solution in toluene, 0.40 mL, 0.200 mmol, 1.0 equiv) under N₂. The reaction was stirred at room temperature for 1–2 h and then a mixture of *O*-benzoylhydroxylamine (0.200 mmol, 1.0 equiv) and Cu(OAc)₂ (0.020 mmol, 0.10 equiv) in THF (1 mL) was added to the reaction. The reaction mixture was allowed to stir at room temperature. Upon complete consumption of *O*-benzoylhydroxylamine (monitored by TLC–50% ethyl acetate–hexanes), the reaction mixture was flushed through a plug of aluminum oxide and washed with Et₂O. The filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by either column chromatography or Kugelrohr distillation.

Typical Procedure 2 (TP2): General Experimental Procedure for C–H Amination via tmpZnCl•LiCl Mediated Metallation.

To an 8 mL microwave tube charged with heteroaryl compound (0.200 mmol, 1.0 equiv) was added THF (1 mL) followed by dropwise addition of tmpZnCl•LiCl solution (0.200 mmol, 1.0 equiv) under N₂. The resulting mixture was stirred vigorously at room temperature for 1 h. Then a mixture of Cu(OAc)₂ (0.020 mmol, 0.10 equiv) and *O*-benzoylhydroxylamine (0.240 mmol, 1.2 equiv) in THF (1 mL) was added dropwise to the heteroarylzinc mixture under N₂. Upon complete consumption of the heteroarene (determined by TLC analysis with a small aliquot reaction sample that was quenched with a saturated aqueous solution of NaHCO₃ and extracted into EtOAc), the reaction was quenched by dropwise addition of a saturated aqueous solution of NH₄Cl (1 mL). The reaction mixture was subsequently basified with saturated aqueous solution of Na₂CO₃ (5 mL) and extracted with Et₂O (3 × 5 mL). The combined organic layers were

washed with brine (5 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash-column chromatography.

4.5.3 Characterization of compounds

4-(1-Methyl-1H-benzo[d]imidazol-2-yl)morpholine (104). Compound prepared according to TP1. Purification by flash-column chromatography (100% ethyl acetate) gave **104** as a white solid (41.6 mg, 96%); $R_f = 0.32$ (100% ethyl acetate); ¹H NMR (CDCl₃, 400 MHz): δ 7.63–7.60 (m, 1H), 7.22–7.17 (m, 3H), 3.90 (t, $J = 4.6$ Hz, 4H), 3.62 (s, 3H), 3.32 (t, $J = 4.6$ Hz, 4H); Spectroscopic data was identical to that reported previously.²³²

4-(Benzo[d]thiazol-2-yl)morpholine (106). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **106** as a pale yellow solid (40.6 mg, 93%); $R_f = 0.57$ (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.61 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.31 (td, $J = 7.6$, 1.2 Hz, 1H), 7.10 (td, $J = 7.6$, 1.2 Hz, 1H), 3.83 (t, $J = 4.8$ Hz, 4H), 3.62 (t, $J = 4.8$ Hz, 4H); Spectroscopic data was identical to that reported previously.²³²

2-Morpholinobenzo[d]oxazole (108). Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–hexanes) gave **108** as a yellow solid (38.9 mg, 95%); R_f = 0.64 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.38 (dd, J = 8.0, 0.8 Hz, 1H), 7.27 (dd, J = 8.0, 0.8 Hz, 1H), 7.18 (td, J = 7.6, 1.2 Hz, 1H), 7.04 (td, J = 7.6, 1.2 Hz, 1H), 3.82 (t, J = 4.8 Hz, 4H), 3.69 (t, J = 4.8 Hz, 4H); Spectroscopic data was identical to that reported previously.²³²

4-(Benzofuran-2-yl)morpholine (110). Compound prepared according to TP1. Deprotonation of **109** achieved with $\text{Zn}(\text{tmp})_2 \cdot \text{LiCl} \cdot \text{MgCl}_2$ at room temperature for 24 h. Purification by flash-column chromatography (10% ethyl acetate–hexanes) gave **110** as a white solid (28.9 mg, 71%); R_f = 0.64 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.32 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 5.47 (s, 1H), 3.86 (t, J = 4.8 Hz, 4H), 3.29 (t, J = 4.8 Hz, 4H); Spectroscopic data was identical to that previously reported.¹⁵

4-(Benzo[b]thiophen-2-yl)morpholine (112). Compound prepared according to TP1. Deprotonation of **111** achieved with $\text{Zn}(\text{tmp})_2 \cdot \text{LiCl} \cdot \text{MgCl}_2$ at room temperature for 24 h. Purification by flash-column chromatography (10% ethyl acetate–hexanes) gave **112** as a white solid (30.7 mg, 70%); R_f = 0.66 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 ,

400 MHz): δ 7.61 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 6.23 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.25 (t, J = 4.8 Hz, 4H); Spectroscopic data was identical to that reported previously.¹⁶

4-(1-Methyl-1H-imidazol-2-yl)morpholine (114). Compound prepared according to TP1. Purification by flash-column chromatography (100% ethyl acetate) gave **114** as a colorless oil (27.4 mg, 82%); R_f = 0.07 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 6.80 (d, J = 1.4 Hz, 1H), 6.67 (d, J = 1.4 Hz, 1H), 3.83 (t, J = 4.8 Hz, 4H), 3.50 (s, 3H), 3.08 (t, J = 4.8 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 151.8, 125.0, 118.3, 66.8, 51.1, 31.9; FTIR (thin film): cm^{-1} 2854, 1527, 1285, 1115; HRMS-ESI (m/z) Calcd for ($\text{C}_8\text{H}_{14}\text{N}_3\text{O}$) ($[\text{M}+\text{H}]^+$): 168.1131; found 168.1133.

4-(Oxazol-2-yl)morpholine (116). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **116** as a white solid (28.3 mg, 92%); R_f = 0.27 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.23 (s, 1H), 6.83 (s, 1H), 3.78 (t, J = 4.9 Hz, 4H), 3.48 (t, J = 4.9 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 161.8, 132.8, 126.8, 66.2, 46.0; FTIR (thin film): cm^{-1} 2922, 1655, 1483, 1116; HRMS-ESI (m/z) Calcd for ($\text{C}_7\text{H}_{11}\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 155.0815; found 155.0811.

4-(Thiazol-2-yl)morpholine (118). Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–hexanes) gave **118** as a colorless oil (32.3 mg, 95%); R_f = 0.49 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.21 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 3.81 (t, J = 5.0 Hz, 4H), 3.46 (t, J = 5.0 Hz, 4H); Spectroscopic data was identical to that reported previously.²³²

5-Bromo-2-morpholinobenzo[d]oxazole (120). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **120** as a white solid (54.3 mg, 96%); R_f = 0.52 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.46 (dd, J = 2.0, 0.8 Hz, 1H), 7.15–7.09 (m, 2H), 3.81 (t, J = 4.6 Hz, 4H), 3.68 (t, J = 4.6 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 162.6, 147.7, 144.7, 123.5, 119.4, 116.8, 109.9, 66.1, 45.6; FTIR (thin film): cm^{-1} 2869, 1567, 1452, 1113, 791; HRMS-ESI (m/z) Calcd for ($\text{C}_{11}\text{H}_{12}\text{BrN}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 283.0077; found 283.0080.

4-(5-Bromothiazol-2-yl)morpholine (122). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **122** as a pale yellow solid (42.3 mg, 85%); R_f = 0.71 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.09 (s, 1H), 3.80 (t, J = 5.0 Hz, 4H), 3.40 (t, J = 5.0 Hz, 4H); ^{13}C

NMR (CDCl₃, 125 MHz): δ 171.8, 140.4, 95.3, 66.0, 48.2; FTIR (thin film): cm⁻¹ 2869, 1537, 1448, 1114, 634; HRMS-ESI (m/z) Calcd for (C₇H₁₀BrN₂OS) ([M+H]⁺): 248.9692; found 248.9691.

4-(2-Bromothiazol-5-yl)morpholine (124). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **124** as a white solid (44.7 mg, 90%); R_f = 0.65 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 6.75 (s, 1H), 3.82 (t, J = 4.8 Hz, 4H), 3.05 (t, J = 4.8 Hz, 4H); Spectroscopic data was identical to that reported previously.¹⁵

Ethyl-2-morpholino-5-(4-nitrophenyl)oxazole-4-carboxylate (126). Compound prepared according to TP1. Purification by flash-column chromatography (60% ethyl acetate–hexanes) gave **126** as a neon yellow solid (61.8 mg, 89%); R_f = 0.18 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 8.26 (dt, J = 8.8, 2.0 Hz, 2H), 8.19 (dt, J = 8.8, 2.0 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 3.83 (t, J = 4.8 Hz, 4H), 3.66 (t, J = 4.8 Hz, 4H), 1.42 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 162.3, 159.6, 147.2, 146.2, 133.3, 130.2, 127.7, 123.6, 66.0, 61.8, 45.6, 14.2; FTIR (thin film): cm⁻¹ 2859, 1713, 1619, 1323, 1116; HRMS-ESI (m/z) Calcd for (C₁₇H₁₈N₃O₆) ([M+H]⁺): 348.1190; found 348.1193.

1,3,7-Trimethyl-8-morpholino-3,7-dihydro-1H-purine-2,6-dione (128). Compound prepared according to TP1. Deprotonation of **127** was done in CH_2Cl_2 due to low solubility in THF. Purification by flash-column chromatography (80% ethyl acetate–hexanes) gave **128** as a white solid (45.8 mg, 82%); $R_f = 0.24$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 3.84 (t, $J = 4.8$ Hz, 4H), 3.76 (s, 3H), 3.52 (s, 3H), 3.38 (s, 3H), 3.26 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 155.9, 155.0, 151.7, 147.3, 105.5, 66.3, 49.9, 32.4, 29.7, 27.7; FTIR (thin film): cm^{-1} 2852, 1693, 1647, 1611, 1432, 1114; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{18}\text{N}_5\text{O}_3$) ($[\text{M}+\text{H}]^+$): 280.1404; found 280.1405.

4-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)morpholine (130). Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–hexanes) gave **130** as a white solid (56.4 mg, 91%); $R_f = 0.08$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.76 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 3.82 (t, $J = 4.6$ Hz, 4H), 3.57 (t, $J = 4.6$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 164.0, 158.8, 132.1, 127.1, 125.0, 123.3, 65.9, 46.1; FTIR (thin film): cm^{-1} 2857, 1547, 1481, 1273, 1116; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{13}\text{BrN}_3\text{O}_2$) ($[\text{M}+\text{H}]^+$): 310.0186; found 310.0188.

2-Morpholinonicotinonitrile (132). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (20% ethyl acetate–hexanes) gave **132** as a pale yellow solid (30.6 mg, 81%); R_f = 0.50 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz) δ 8.36 (dd, J = 4.8, 2.0 Hz, 1H), 7.79 (dd, J = 7.6, 2.0 Hz, 1H), 6.79 (dd, J = 7.6, 4.8 Hz, 1H), 3.84 (t, J = 4.8 Hz, 4H), 3.71 (t, J = 4.8 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.7, 151.9, 143.9, 117.9, 114.5, 95.2, 66.7, 48.4; FTIR (thin film): cm^{-1} 3026, 2845, 2210, 1580, 1552, 1231, 1116; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{12}\text{N}_3\text{O}$) ($[\text{M}+\text{H}]^+$): 190.0975; found: 190.0975.

4-(3,5-Dichloropyridin-2-yl)morpholine (134). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (20% ethyl acetate–hexanes) gave **134** as a pale yellow solid (36.8 mg, 91%); R_f = 0.82 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.13 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 3.85 (t, J = 4.8 Hz, 4H), 3.34 (t, J = 4.8 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 156.6, 144.3, 138.3, 124.5, 122.6, 66.8, 49.5; FTIR (thin film): cm^{-1} 2961, 2852, 2360, 1573, 1436, 1271, 1117; HRMS-ESI (m/z) Calcd for ($\text{C}_9\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}$) ($[\text{M}+\text{H}]^+$): 233.0243; found: 233.0243.

4-(3,5-Difluoropyridin-4-yl)morpholine (136). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **136** as a pale yellow solid (36.2 mg, 91%); R_f = 0.48 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.16 (br s, 2H), 3.81 (t, J = 4.4 Hz, 4H), 3.41 (t, J = 4.4 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 152.6 (d, J = 251.7 Hz), 134.9 (d, J = 23.9 Hz), 134.0 (t, J = 8.6 Hz), 67.1, 50.5; FTIR (thin film): cm^{-1} 2970, 2920, 2872, 1603, 1506, 1447, 1254, 1114, 1016; HRMS-ESI (m/z) Calcd for ($\text{C}_9\text{H}_{11}\text{F}_2\text{N}_2\text{O}$) ($[\text{M}+\text{H}]^+$): 201.0834; found: 201.0837.

4-(2-(Thiophen-2-yl)pyridin-3-yl)morpholine (138). Compound prepared according to TP1. Amination step run at 50 °C. Compound prepared according to TP1. Purification by flash-column chromatography (20% ethyl acetate–hexanes) gave **138** as a pale yellow solid (36.4 mg, 74%); R_f = 0.53 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.55–8.53 (m, 1H), 8.34–8.31 (m, 1H), 7.71–7.66 (m, 1H), 7.32 (d, J = 5.6 Hz, 1H), 7.10–7.07 (m, 1H), 7.02 (d, J = 5.6 Hz, 1H), 3.86 (t, J = 4.4 Hz, 4H), 3.00 (t, J = 4.4 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 133.9, 130.5, 129.2, 128.4 (2C), 128.3 (2C), 127.7, 107.6, 65.0, 40.0; FTIR (thin film): cm^{-1} 3051, 2956, 2848, 1578, 1535, 1214,

1028; HRMS-ESI (m/z) Calcd for (C₁₃H₁₅N₂OS) ([M+H]⁺): 247.0900; found: 247.0909.

4-(Perfluorophenyl)morpholine (140). Compound prepared according to TP1. Purification by kugelröhr distillation gave **140** as a yellow oil (37.9 mg, 75%); *R_f* = 0.88 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 3.81 (t, *J* = 4.6 Hz, 4H), 3.20 (t, *J* = 4.6 Hz, 4H); Spectroscopic data was identical to that reported previously.²³³

tert-Butyl 4-(1-methyl-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (141). Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–hexanes) gave **141** as a white solid (54.1 mg, 86%); *R_f* = 0.36 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.61– 7.58 (m, 1H), 7.22–7.17 (m, 3H), 3.62 (s, 3H), 3.62 (t, *J* = 5.2 Hz, 4H), 3.26 (t, *J* = 5.2 Hz, 4H), 1.49 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz, 60 °C): δ 157.5, 154.7, 141.4, 135.7, 121.6, 121.2, 118.1, 108.3, 79.9, 50.2, 43.4, 30.2, 28.3; FTIR (thin film): cm⁻¹ 2935, 1634, 1575, 1459, 739; HRMS-ESI (m/z) Calcd for (C₁₇H₂₅N₄O₂) ([M+H]⁺): 317.1972; found: 317.1974.

tert-Butyl 4-(1-methyl-1H-benzo[d]imidazol-2-yl)-1,4-diazepane-1-carboxylate (142). Compound prepared according to TP1. Purification by flash-column chromatography

(90% ethyl acetate–hexanes) gave **142** as a colorless oil (44.1 mg, 67%); $R_f = 0.34$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 500 MHz, 60 °C): δ 7.53 (d, $J = 6.5$ Hz, 1H), 7.18–7.07 (m, 3H), 3.69–3.45 (m, 8H), 3.59 (s, 3H), 1.99 (br s, 2H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz, 60 °C) as a mixture of conformers: δ 158.5, 155.3, 141.7, 136.0, 121.6, 120.8, 117.6, 108.1, 79.6, 53.5, 52.0, 48.1, 47.5, 46.1, 45.5, 30.9, 28.5; FTIR (thin film): cm^{-1} 2971, 1682, 1526, 1159, 738; HRMS-ESI (m/z) Calcd for ($\text{C}_{18}\text{H}_{27}\text{N}_4\text{O}_2$) ($[\text{M}+\text{H}]^+$): 331.2129; found: 331.2129.

1-Methyl-2-(pyrrolidin-1-yl)-1H-benzo[d]imidazole (143). Compound prepared according to TP1. Purification by flash-column chromatography (100% ethyl acetate) gave **143** as a white solid (27.1 mg, 67%); $R_f = 0.31$ (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.48 (dt, $J = 7.6, 1.0$ Hz, 1H), 7.13–7.05 (m, 3H), 3.63 (s, 3H), 3.64–3.60 (m, 4H), 2.00–1.92 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 157.3, 142.1, 136.2, 121.3, 119.6, 116.5, 107.4, 50.3, 31.1, 25.6; FTIR (thin film): cm^{-1} 2968, 1541, 1469, 1285, 740; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{16}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 202.1339; found: 202.1341.

1-Methyl-2-(piperidin-1-yl)-1H-benzo[d]imidazole (144). Compound prepared according to TP1. Purification by flash-column chromatography (30% ethyl

acetate–hexanes) gave **144** as white solid (36.9 mg, 86%); $R_f = 0.45$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.60–7.58 (m, 1H), 7.19–7.14 (m, 3H), 3.59 (s, 3H), 3.25 (t, $J = 5.2$ Hz, 4H), 1.79–1.73 (m, 4H), 1.68–1.65 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 158.9, 141.5, 135.6, 121.4, 120.8, 117.8, 108.2, 51.5, 30.4, 25.7, 24.2; FTIR (thin film): cm^{-1} 2932, 2849, 1522, 1469, 1283; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{18}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 214.1495; found: 214.1497.

2-(Piperidin-1-yl)benzo[d]oxazole (145). Compound prepared according to TP1. Purification by kugelröhr distillation followed by flash-column chromatography (15% ethyl acetate–hexanes) gave **145** as a white solid (35.0 mg, 87%); $R_f = 0.28$ (15% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 500 MHz): δ 7.34 (d, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 7.8$ Hz, 1H), 6.98 (t, $J = 7.8$ Hz, 1H), 3.65 (br s, 4H), 1.67 (br s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 162.4, 148.7, 143.4, 123.8, 120.2, 116.0, 108.5, 46.6, 25.2, 24.1; FTIR (thin film): cm^{-1} 2935, 1634, 1575, 1459, 739; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$) ($[\text{M}+\text{H}]^+$): 203.1179; found: 203.1181.

1-Methyl-2-(3-methylpiperidin-1-yl)-1H-benzo[d]imidazole (146). Compound prepared according to TP1. Purification by flash-column chromatography (10% ethyl acetate–hexanes) gave **146** as a white solid (37.0 mg, 81%); $R_f = 0.26$ (30% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.59–7.57 (m, 1H), 7.16–7.14 (m, 3H),

3.57 (s, 3H), 3.49–3.44 (m, 2H), 2.90 (td, $J = 11.2, 3.6$ Hz, 1H), 2.65 (dd, $J = 12.4, 10.4$ Hz, 1H), 1.87–1.76 (m, 4H), 1.14–1.09 (m, 1H), 0.96 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 158.7, 141.5, 135.6, 121.4, 120.8, 117.8, 108.2, 58.0, 51.1, 32.7, 30.9, 30.4, 25.2, 19.2; FTIR (thin film): cm^{-1} 2925, 1521, 1280, 1122, 742; HRMS-ESI (m/z) Calcd for ($\text{C}_{14}\text{H}_{20}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 230.1652; found: 230.1555.

Ethyl-1-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (147).

Compound prepared according to TP1. Purification by flash-column chromatography (40% ethyl acetate–hexanes) gave **147** as a yellow oil (43.9 mg, 76%); $R_f = 0.36$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.60–7.58 (m, 1H), 7.19–7.16 (m, 3H), 4.17, (q, $J = 7.2$ Hz, 2H), 3.60 (s, 3H), 3.56 (dt, $J = 12.8, 3.2$, 2H), 3.05 (td, 12.4, 2.4 Hz, 2H), 2.52 (tt, 11.2, 4.0 Hz, 1H), 2.10–2.06 (m, 2H), 1.99–1.89 (m, 2H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 174.5, 158.1, 141.3, 135.3, 121.5, 121.0, 117.9, 108.3, 60.4, 50.0, 40.8, 30.3, 27.9, 14.1; FTIR (thin film): cm^{-1} 2926, 1723, 1520, 1041, 743; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_2$) ($[\text{M}+\text{H}]^+$): 288.1707; found: 288.1707.

Ethyl-1-(benzo[d]thiazol-2-yl)piperidine-4-carboxylate (148). Compound prepared according to TP1. Purification by flash-column chromatography (gradient from 5% ethyl acetate–hexanes to 15% ethyl acetate–hexanes) gave **148** as a yellow powder (46.1 mg,

79%); R_f = 0.20 (15% ethyl acetate–hexanes); ^1H NMR (CD_2Cl_2 , 500 MHz): δ 7.65 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33–7.29 (m, 1H), 7.11–7.08 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.07 (tt, J = 13.5, 3.5 Hz, 2H), 3.23 (ddd, J = 13.5, 11.5, 3.0 Hz, 2H), 2.57 (tt, J = 11.0, 3.8 Hz, 1H), 2.04–2.01 (m, 2H), 1.86–1.72 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CD_2Cl_2 , 125 MHz): δ 174.5, 169.1, 153.6, 131.6, 126.4, 121.7, 121.2, 119.3, 61.1, 48.5, 41.3, 28.1, 16.6; FTIR (thin film): cm^{-1} 2925, 1726, 1529, 1174, 1038, 752; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$) ($[\text{M}+\text{H}]^+$): 291.1162; found: 291.1164.

***N,N*-Diethyl-1-methyl-1*H*-benzo[*d*]imidazol-2-amine (149).** Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–hexanes) gave **149** as a clear oil (37.3 mg, 92%); R_f = 0.35 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.60–7.58 (m, 1H), 7.19–7.12 (m, 3H), 3.59 (s, 3H), 3.32 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 157.8, 141.6, 135.5, 121.4, 120.7, 117.7, 108.2, 46.0, 30.4, 12.9; FTIR (thin film): cm^{-1} 2969, 1521, 1439, 1323, 741; HRMS-ESI (m/z) Calcd for ($\text{C}_{12}\text{H}_{18}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 204.1495; found: 204.1499.

***N*-Benzyl-*N*,1-dimethyl-1*H*-benzo[*d*]imidazol-2-amine (150).** Compound prepared according to TP1. Purification by flash-column chromatography (50% ethyl acetate–

hexanes) gave **150** as a white solid (45.2 mg, 90%); $R_f = 0.46$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.62–7.60 (m, 1H), 7.41–7.35 (m, 4H), 7.32–7.30 (m, 1H), 7.22–7.16 (m, 3H), 4.47 (s, 2H), 3.65 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 158.9, 141.3, 137.3, 135.8, 128.6, 127.8, 127.5, 121.6, 120.9, 117.7, 108.3, 58.2, 39.3, 30.7; FTIR (thin film): cm^{-1} 3029, 1532, 1445, 1392, 740; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{18}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 252.1495; found: 252.1504.

***N,N*-Diallyl-1-methyl-1*H*-benzo[*d*]imidazol-2-amine (151).** Compound prepared according to TP1. Purification by flash-column chromatography (5% ethyl acetate–dichloromethane) gave **151** as a clear oil (36.5 mg, 80%); $R_f = 0.17$ (15% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.59–7.57 (m, 1H), 7.20–7.14 (m, 3H), 5.94 (ddt, $J = 17.2, 10.0, 6.0$ Hz, 2H), 5.28 (dd, $J = 17.2, 1.6$ Hz, 2H), 5.20 (dd, $J = 10.0, 1.6$ Hz, 2H), 3.92 (d, $J = 6.0$ Hz, 4H), 3.62 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 157.8, 141.5, 135.7, 133.9, 121.5, 120.8, 118.0, 117.8, 108.2, 53.7, 30.6; FTIR (thin film): cm^{-1} 2920, 1533, 1393, 1284, 923, 741; HRMS-ESI (m/z) Calcd for ($\text{C}_{14}\text{H}_{18}\text{N}_3$) ($[\text{M}+\text{H}]^+$): 228.1495; found: 228.1494.

***N,N*-Diallylbenzo[*d*]oxazol-2-amine (152).** Compound prepared according to TP1. Purification by kugelröhr distillation followed by flash-column chromatography (15%

ethyl acetate–hexanes) gave **152** as a clear oil (28.1 mg, 66%); $R_f = 0.51$ (15% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.38–7.35 (m, 1H), 7.26–7.24 (m, 1H), 7.15 (td, $J = 7.6, 1.2$ Hz, 1H), 7.00 (td, $J = 7.6, 1.2$ Hz, 1H), 5.87 (ddt, $J = 22.4, 10.4, 5.8$ Hz, 2H), 5.27–5.26 (m, 2H), 5.22 (t, $J = 1.2$ Hz, 2H), 4.16 (d, $J = 5.8$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 162.3, 148.9, 143.3, 132.5, 123.9, 120.3, 117.8, 116.1, 108.7, 49.9; FTIR (thin film): cm^{-1} 2923, 1631, 1577, 1459, 1243, 740; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}$) ($[\text{M}+\text{H}]^+$): 215.1178; found: 215.1178.

***N,N*-Dibenzyl-2,3,5,6-tetrafluoroaniline (153).** Compound prepared according to TP1. Purification by flash- column chromatography (100% hexanes) gave **153** as a clear oil (58.7 mg, 85%); $R_f = 0.33$ (100% hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.31–7.26 (m, 10H), 6.71 (tt, $J = 10.0, 7.2$ Hz, 1H), 4.30 (s, 4H); Spectroscopic data was identical to that reported previously.⁶⁴

***N,N*-Dibenzyl-2,3,4,5,6-pentafluoroaniline (154).** Compound prepared according to TP1. Purification by flash-column chromatography (5% dichloromethane–hexanes) gave **154** as a clear oil (58.1 mg, 80%); $R_f = 0.39$ (5% dichloromethane–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.30–7.22 (m, 10H), 4.23 (s, 4H); Spectroscopic data was identical

to that reported previously.⁶⁴

Ethyl-1-(perfluorophenyl)piperidine-4-carboxylate (155). Compound prepared according to TP1. Purification by flash-column chromatography (gradient of 100% hexanes to 20% ethyl acetate–hexanes) gave **155** as a yellow oil (50.6 mg, 78%); R_f = 0.35 (5% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.16 (q, J = 7.2 Hz, 2H), 3.28–3.24 (m, 2H), 3.14–3.07 (m, 2H), 2.43 (tt, J = 11.2, 4.0 Hz, 1H), 2.00–1.96 (m, 2H), 1.89–1.81 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 143.3 (dd, $J_{\text{C-F}}$ = 246.3, 5.5 Hz), 139.0–135.9 (m, 2C), 126.5 (t, $J_{\text{C-F}}$ = 11.3 Hz); FTIR (thin film): cm^{-1} 2959, 1730, 1516, 1498, 985; HRMS-ESI (m/z) Calcd for ($\text{C}_{14}\text{H}_{15}\text{F}_5\text{NO}_2$) ($[\text{M}+\text{H}]^+$): 324.1017; found: 324.1014.

tert-Butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate (156). Compound prepared according to TP2. Amination step run at 50 °C. Purification by flash-column chromatography (20% ethyl acetate–hexanes) gave **156** as a yellow solid (37.0 mg, 65%); R_f = 0.55 (20% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ : 8.00 (dt, J = 4.8, 1.6 Hz, 1H), 7.23 (ddd, J = 12.8, 8.0, 1.6 Hz, 1H), 6.77 (ddd, J = 12.8, 8.0, 4.8 Hz, 1H), 3.57–3.54 (m, 4H), 3.44–3.42 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3 , 60 °C) δ : 154.6, 149.8 ($J_{\text{C-F}}$ = 255.0 Hz), 149.6 ($J_{\text{C-F}}$ = 6.2 Hz), 142.6 ($J_{\text{C-F}}$ = 5.2 Hz), 122.9

(J_{C-F} = 18.9 Hz), 115.7, 79.5, 47.3 (J_{C-F} = 5.0 Hz), 43.6, 28.3; IR (thin film): cm^{-1} 2974, 2846, 1686, 1603, 1410, 1291; HRMS (ESI) $[M + H]$ Calcd for $\text{C}_{14}\text{H}_{21}\text{FN}_3\text{O}_2$: 282.1612; found 282.1612.

4-(3-Bromopyridin-2-yl)morpholine (157). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Amination step run at 50 °C. Purification by flash-column chromatography (20% ethyl acetate–hexanes) gave **157** as a yellow oil (50.6 mg, 90%); R_f = 0.74 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.24 (dd, J = 4.8, 1.6 Hz, 1H), 7.79 (dd, J = 7.6, 1.6 Hz, 1H), 6.80 (dd, J = 7.6, 4.8 Hz, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.34 (t, J = 4.8 Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 159.2, 146.5, 142.3, 118.7, 112.8, 66.9, 50.0; FTIR (thin film): cm^{-1} 2956, 2847, 1717, 1575, 1427, 1110, 1011, 941; HRMS-ESI (m/z) Calcd for ($\text{C}_9\text{H}_{12}\text{BrN}_2\text{O}$) ($[M+H]^+$): 243.0128; found: 243.0127.

4-(2-Chloro-3-nitropyridin-4-yl)morpholine (158). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Purification by flash-column chromatography (40% ethyl acetate–hexanes) gave **158** as a bright yellow solid (78.9 mg, 81%); R_f = 0.30 (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.16 (d, J = 6.0 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H), 3.76 (t, J = 4.8 Hz, 4H), 3.20 (t, J = 4.8 Hz, 4H); ^{13}C NMR

(CDCl₃, 125 MHz): δ 150.4, 149.8, 144.0, 137.3, 112.7, 66.1, 49.4; FTIR (thin film): cm⁻¹ 3053, 2862, 1585, 1530, 1263, 968; HRMS-ESI (m/z) Calcd for (C₉H₁₁ClN₃O₃) ([M+H]⁺): 244.0483; found: 244.0485.

4-(3,6-Dichloropyridazin-4-yl)morpholine (159). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Purification by flash-column chromatography (40% ethyl acetate–hexanes) gave **159** as a yellow solid (84.1 mg, 90%); R_f = 0.40 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 6.86 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.30 (t, J = 4.8 Hz, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 155.7, 149.3, 149.2, 115.8, 66.0, 49.5; FTIR (thin film): cm⁻¹ 2962, 2853, 1714, 1548, 1110, 966; HRMS-ESI (m/z) Calcd for (C₈H₁₀Cl₂N₃O) ([M+H]⁺): 234.0195; found: 234.0195.

4-(2,6-Difluoro-3-nitrophenyl)morpholine (160). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Purification by flash-column chromatography (10% ethyl acetate–hexanes) gave **160** as a yellow solid (95.5 mg, 98%); R_f = 0.83 (50% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.74–7.69 (m, 1H), 6.99–6.93 (m, 1H), 3.81 (t, J = 4.8 Hz, 4H), 3.26–3.23 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 160.7 (d, J = 262.4 Hz), 138.4 (d, J = 11.3 Hz), 130.8 (d, J = 5.9 Hz), 129.8, 128.7,

113.2, 102.3 (d, $J = 15.6$ Hz), 67.4, 50.9 (d, $J = 3.7$ Hz); FTIR (thin film): cm^{-1} 3062, 2971, 2861, 1578, 1528, 1380, 1068, 1019; HRMS-ESI (m/z) Calcd for ($\text{C}_{10}\text{H}_{11}\text{F}_2\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 285.0033; found: 285.0029.

4-Bromo-2-fluoro-3-morpholinobenzonitrile (161). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Deprotonation step run at 65 °C. Purification by flash-column chromatography (10% ethyl acetate–hexanes) gave **161** as a yellow solid (102.6 mg, 90%); $R_f = 0.74$ (50% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.48 (d, $J = 8.4$ Hz, 1H), 7.21 (dd, $J = 8.4, 6.0$ Hz, 1H), 3.84 (t, $J = 4.4$ Hz, 4H), 3.18 (br s, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.7 (d, $J = 262.4$ Hz), 138.4 (d, $J = 11.3$ Hz), 130.8 (d, $J = 5.9$ Hz), 129.8, 128.7, 113.2, 102.3 (d, $J = 15.6$ Hz), 67.4, 50.9 (d, $J = 3.7$ Hz); FTIR (thin film): cm^{-1} 2958, 2853, 2234, 1589, 1438, 1112, 1024; HRMS-ESI (m/z) Calcd for ($\text{C}_{11}\text{H}_{11}\text{BrFN}_2\text{O}$) ($[\text{M}+\text{H}]^+$): 285.0033; found: 285.0029.

2-Morpholinobenzo[*b*]thiophene-3-carbaldehyde (162). Compound prepared according to TP2. Purification by flash-column chromatography (30% ethyl acetate–hexanes) gave **162** as a white solid (35.6 mg, 72%); $R_f = 0.25$ (30% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 10.18 (s, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.45–7.38 (m, 1H), 7.30–7.26 (m, 1H), 3.93 (t, $J = 4.8$ Hz, 4H),

3.45 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 182.4, 151.5, 137.3, 131.4, 124.0, 121.6, 116.6, 66.2, 55.0; FTIR (thin film): cm^{-1} 2854, 1650, 1514, 1462, 1437, 1115, 1011, 754; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{14}\text{NO}_2\text{S}$) ($[\text{M}+\text{H}]^+$): 248.0740; found: 248.0734.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)piperazine-1-carboxylate (163).** Compound prepared according to TP2. Purification by flash-column chromatography (gradient from 5% ethyl acetate–hexanes to 20% ethyl acetate–hexanes) gave **163** as a white solid (55.0 mg, 86%); $R_f = 0.28$ (20% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.62–7.59 (m, 1H), 7.57–7.55 (m, 1H), 7.33–7.28 (m, 1H), 7.11–7.07 (m, 1H), 3.63–3.54 (m, 8H), 1.48 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 168.5, 154.6, 152.7, 130.9, 126.0, 121.6, 120.7, 119.4, 80.3, 48.3, 43.2, 28.4; FTIR (thin film): cm^{-1} 2974, 1696, 1536, 1444, 1167; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$) ($[\text{M}+\text{H}]^+$): 320.1427; found: 320.1429.

***tert*-Butyl-4-(2,3,5,6-tetrafluorophenyl)piperazine-1-carboxylate (164).** Compound prepared according to TP2. Purification by flash-column chromatography (5% ethyl acetate–dichloromethane) gave **164** as a clear oil (59.6 mg, 89%); $R_f = 0.51$ (15% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 6.71 (tt, $J = 9.6, 7.1$ Hz, 1H), 3.54 (t, J

= 5.0 Hz, 4H), 3.19 (br s, 4H), 1.48 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz, 60 °C): δ 154.7, 147.7–145.5 (m), 143.5–141.4 (m), 130.8 (t, J = 9.9 Hz), 99.2 (t, J = 23.0 Hz), 50.8, 44.4, 28.4; FTIR (thin film): cm^{-1} 2976, 2859, 1696, 1503, 1005, 924; HRMS-ESI (m/z) Calcd for ($\text{C}_{15}\text{H}_{19}\text{F}_4\text{N}_2\text{O}_2$) ($[\text{M}+\text{H}]^+$): 335.1377; found: 335.1378.

***tert*-Butyl-4-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)piperazine-1-carboxylate (166).**

Compound prepared according to TP2. Reaction run on 0.960 mmol scale. Purification by flash-column chromatography (70% ethyl acetate–hexanes) gave **166** as a pale yellow solid (331 mg, 88%); R_f = 0.57 (100% ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.65 (d, J = 7.6 Hz, 1H), 7.36–7.29 (m, 3H), 7.20 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.17–7.15 (m, 2H), 7.11 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.05–7.03 (m, 1H), 5.24 (s, 2H), 3.53 (t, J = 4.8 Hz, 4H), 3.19 (t, J = 4.8 Hz, 4H), 1.46 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 157.7, 154.7, 141.4, 136.1, 135.4, 129.0, 127.7, 126.0, 122.1, 121.7, 118.3, 109.4, 80.1, 50.5, 47.6, 43.2, 28.4; FTIR (thin film): cm^{-1} 3070, 2845, 1691, 1520, 1114, 998; HRMS-ESI (m/z) Calcd for ($\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_2$) ($[\text{M}+\text{H}]^+$): 394.2285; found: 394.2284.

4-(1-Benzyl-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-ium chloride (168). To an 8 mL vial charged with boc-protected amine **166** (89.3 mg, 0.23 mmol, 1.0 equiv) was added Et_2O (2 mL) followed by HCl (2.0 M solution in Et_2O , 1.1 mL, 2.3 mmol, 10 equiv). The

reaction was stirred at room temperature. Upon consumption of **166** (monitored by TLC–100% ethyl acetate), the reaction was filtered. The salt was washed with copious amounts of Et₂O. The salt then washed into separate filter flask with MeOH. Filtrate collected and concentrated under reduced pressure giving **168** as a pale yellow solid (73.3 mg, 98%). ¹H NMR (D₂O, 400 MHz): δ 7.64–7.62 (m, 1H), 7.51–7.38 (m, 6H), 7.29–7.27 (m, 2H), 5.53 (s, 2H), 3.81 (t, *J* = 5.2 Hz, 4H), 3.42 (t, *J* = 5.2 Hz, 4H); ¹³C NMR (D₂O, 125 MHz): δ 151.8, 133.9, 132.1, 129.9, 129.1, 129.0, 129.8, 126.2, 125.8, 113.5, 112.4, 46.7, 43.1; HRMS-ESI (*m/z*) Calcd for (C₁₈H₂₁N₄) ([M-HCl]⁺): 293.1761; found: 293.1763.

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Biography

Stacey L. McDonald is the daughter of Michael and Carolyn Turner. She was born on March 13, 1987 in Charlotte, NC and was raised just over the SC-NC border in Fort Mill, SC. In 2009, Stacey graduated from Wofford College with a B.S. in Chemistry and matriculated into Department of Chemistry at Duke University to pursue her Ph.D.

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Publications

McDonald, S. L.; Wang, Q. "α-Amination of Phosphonates: A Direct Synthesis of α-Amino Phosphonic Acids and Their Derivatives," *Synlett* **2014**, 25, 2233–2238. (invited contribution)

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Presentations

McDonald, S. L.; Hendrick, C. E.; Wang, Q. Copper Catalyzed Electrophilic Amination of C–H Bonds. Local Section Conference North Carolina Section ACS (Poster), Durham, NC, November 2014.

McDonald, S. L. and Wang, Q. Copper-catalyzed Electrophilic α -Amination of Esters, Amides, and Phosphonates. Southeastern Regional Meeting of the American Chemical Society, Nashville, TN, October 2014.

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