Springer Theses
Recognizing Outstanding Ph.D. Research

Stacey L. McDonald

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

Springer

Springer Theses

Recognizing Outstanding Ph.D. Research

Aims and Scope

The series "Springer Theses" brings together a selection of the very best Ph.D. theses from around the world and across the physical sciences. Nominated and endorsed by two recognized specialists, each published volume has been selected for its scientific excellence and the high impact of its contents for the pertinent field of research. For greater accessibility to non-specialists, the published versions include an extended introduction, as well as a foreword by the student's supervisor explaining the special relevance of the work for the field. As a whole, the series will provide a valuable resource both for newcomers to the research fields described, and for other scientists seeking detailed background information on special questions. Finally, it provides an accredited documentation of the valuable contributions made by today's younger generation of scientists.

Theses are accepted into the series by invited nomination only and must fulfill all of the following criteria

- They must be written in good English.
- The topic should fall within the confines of Chemistry, Physics, Earth Sciences, Engineering and related interdisciplinary fields such as Materials, Nanoscience, Chemical Engineering, Complex Systems and Biophysics.
- The work reported in the thesis must represent a significant scientific advance.
- If the thesis includes previously published material, permission to reproduce this must be gained from the respective copyright holder.
- They must have been examined and passed during the 12 months prior to nomination.
- Each thesis should include a foreword by the supervisor outlining the significance of its content.
- The theses should have a clearly defined structure including an introduction accessible to scientists not expert in that particular field.

More information about this series at http://www.springer.com/series/8790

Stacey L. McDonald

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

Doctoral Thesis accepted by
Duke University, Durham, NC, USA

Springer

Author
Dr. Stacey L. McDonald
Department of Chemistry
Duke University
Durham, NC
USA

Supervisor
Prof. Qiu Wang
Department of Chemistry
Duke University
Durham, NC
USA

ISSN 2190-5053 ISSN 2190-5061 (electronic)
Springer Theses
ISBN 978-3-319-38877-9 ISBN 978-3-319-38878-6 (eBook)
DOI 10.1007/978-3-319-38878-6

Library of Congress Control Number: 2016947779

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Supervisor's Foreword

It is my great pleasure to introduce Dr. Stacey L. McDonald's work for publication in Springer Theses. The importance of nitrogen-containing molecules is evident in biomedical research and drug discovery; 874 of 1035 FDA-approved small-molecule drugs contain at least one N-atom. In the past few decades, the development of new and efficient amination methods has made a broad impact on organic synthesis, material science, and drug discovery. Among different approaches for the C–N bond formation, direct amination of C–H bonds offers an attractive and potentially more effective route.

The thesis of Stacey L. McDonald explores the amination of C–H bonds using electrophilic amino sources for the synthesis of α-amino carboxyl acid and α-amino phosphonic acid derivatives as well as a wide range of amino arenes and heteroarenes. A crucial technical innovation demonstrated in this thesis is the implementation of a direct H–Zn exchange that allows for the formation of organozinc intermediates that are suitable for copper-catalyzed amino transfer reactions. Selective H–Zn exchange on a broad range of C–H bonds, including both sp^2 and sp^3 C–H bonds, has been achieved by the use of strong and non-nucleophilic bases $Zn(tmp)_2$ or tmpZnCl•LiCl. Success in developing the direct and efficient access to diverse and novel amine-containing structures 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. Simultaneously, these findings in Stacey's amination work have inspired further work in the research group where we are exploring the applicability of selective H–Zn exchange in conjugation with different electrophilic partners for a general and powerful platform for C–H functionalization.

Stacey L. McDonald's thesis is written in a very clear style and is accompanied by a good review of previous electrophilic amination work for the synthesis of different alkyl and aryl amines. Exciting advancements in this thesis will be of interest to a broad audience ranging from organometallics to heterocyclic and organophosphorus chemistry.

Durham, NC
March 2016

Prof. Qiu Wang, Ph.D.

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 toward C–N bond formation. Toward 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 an 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, non-nucleophilic bases $Zn(tmp)_2$ or tmpZnCl•LiCl and subsequent electrophilic amination of the corresponding zinc carbanions with catalytic copper 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.

Parts of this thesis have been published in the following journal articles:

McDonald, S. L.; Hendrick, C. E.; Bitting K. J.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroaromatic and Aromatic C–H Bonds via TMPZnCl·LiCl Mediated Metalation," *Org. Synth.* **2015**, *92*, 356−372.

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)

McDonald, S. L.; Hendrick, C. E.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes via C–H Zincation," *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670. (highlighted in Synfacts)

McDonald, S. L.; Wang, Q. "Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives," *Angew. Chem. Int. Ed.* **2014**, *53*, 1867–1871. (highlighted in Synfacts)

McDonald, S. L.; Wang, Q. "Selective α-amination and α-acylation of esters and amides *via* dual reactivity of *O*-acylhydroxylamines toward zinc enolates," *Chem. Comm.* **2014**, *50*, 2535−2538.

Acknowledgements

A number of individuals deserve my gratitude for personal and scientific support during my time at Duke and prior to this time. I would like to mention a few.

First and foremost, I must thank my husband, Michael. You have been very patient through this entire process, and without your love and support, I can't imagine how I would have survived these past 6 years. I am also grateful to my mom and dad, Carolyn and Michael Turner. Thank you for your encouragement and support in all my academic pursuits and for always pushing me to be my best, both personally and academically.

I would also like to extend my gratitude to my research advisor, Qiu Wang. Thank you for taking me in and pushing me to be the best scientist I could be each and every day. Your guidance and encouragement over the past 3 years have been greatly appreciated. It has been a distinct privilege working with you, and I am extremely grateful for this experience.

Lastly, I need to thank my fellow graduate students who have worked with me in the Wang laboratory. To Chuck Hendrick, Jerry Ortiz, and Lily Du: You guys have been there since the beginning, and it has been wonderful to work with you. I couldn't imagine better people to have by my side going through this experience. Thank you so much for being there through the research lows and highs and for putting up with me. Thanks also to the rest of the Wang laboratory, and you have all helped me in various ways and made my time spent in the laboratory even more worthwhile. Again, thank you to all of those who have supported me through my time in graduate school.

Contents

Abbreviations

Ac	Acetate
acac	Acetylacetone
Ar	Aryl
bipyr	2,2′-Bipyridine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPO	Benzoyl peroxide
Bu	Butyl
Bz	Benzoyl
Cbz	Carboxybenzyl
cod	Cyclooctadiene
Cp	Cyclopentadienyl
DCE	Dichloroethane
DCM	Dichloromethane
DG	Directing group
DMA	Dimethylacetamide
DMEDA	*N,N′*-Dimethylethylenediamine
DMF	Dimethylformamide
dppbz	1,2-Bis(diphenylphosphino)benzene
dpppen	1,2-Bis(diphenylphosphino)pentane
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
Et	Ethyl
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*H*-imidazol-2-ylidene
i-Pr	Isopropyl
iPr•HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide

LDA	Lithium diisopropylamide
Me	Methyl
MeCN	Acetonitrile
n-BuLi	*n*-Butyl lithium
NCS	*N*-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
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
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

List of Figures

List of Tables

List of Schemes

Chapter 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(sp^2)–N or C(sp^3)–N bonds are privileged structural motifs that are present in many biologically and pharmaceutically relevant compounds (Fig. 1.1) [1]. For example, Plavix, which is an α-amino ester, is an antiplatelet drug used to 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 $5HT_3$ 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 (Fig. 1.2), 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

S.L. McDonald, *Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds*, Springer Theses, DOI 10.1007/978-3-319-38878-6_1

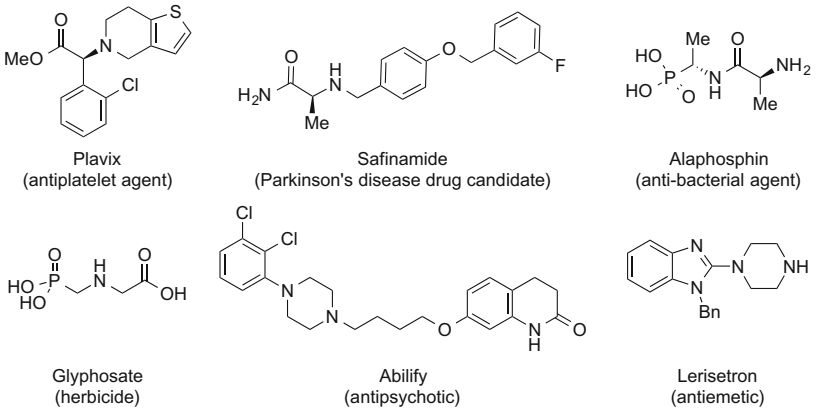


Fig. 1.1 Examples of biologically and pharmaceutically relevant compounds containing C–N bonds

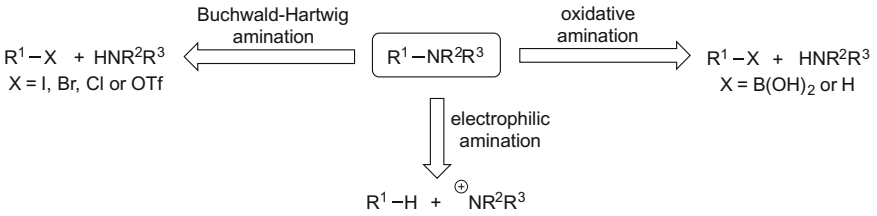


Fig. 1.2 Carbon-nitrogen bond-forming reactions for the synthesis of various amines

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 $[NR_2]^+$ 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.

1.1.1 Electrophilic Amination Reagents and Reactions

1.1.1.1 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 $[NR_2]^+$ 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 C(sp^2)–N bonds as well as C(sp^3)–N bonds. Additionally, C–H amination offers a direct method to introduce nitrogen-based groups onto molecules without stepwise functional group manipulations.

1.1.1.2 Electrophilic Aminating Reagents

Utilizing the umpolung concept in amine synthesis relies on the identification of useful electrophilic nitrogen sources. Several $[NR_2]^+$ synthons have been developed towards the advancement of electrophilic amination methods (Fig. 1.3) [38]. These reagents 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—sp^2 and sp^3 nitrogen-containing compounds. Early aminations took advantage of sp^2 nitrogen-containing compounds such as azides [65–68] and diazene dicarboxylates [69–83]. More recently, oxime esters [84–89] and nitroso compounds [90–96] have been used. However, for electrophilic amination reactions using sp^2 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 NH_2 group). To overcome this, several sp^3 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 benzoylation of hydroxylamines to give stable, often crystalline,

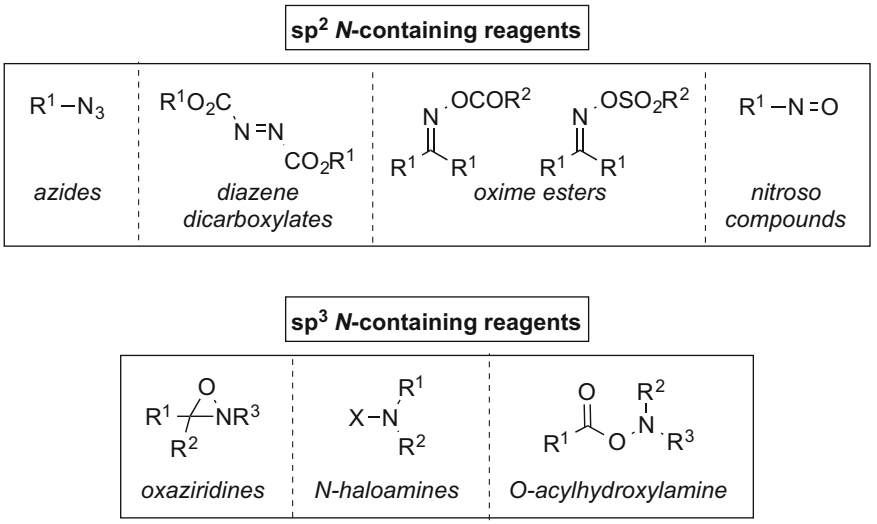
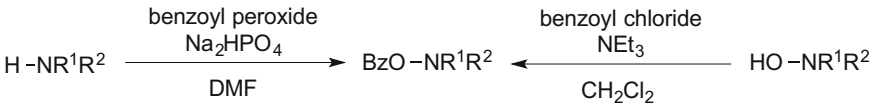


Fig. 1.3 Electrophilic aminating reagents for the synthesis of alkyl and aryl amines



Scheme 1.1 Preparation of *O*-benzoylhydroxylamines

compounds (Scheme 1.1) [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].

1.1.1.3 Electrophilic Amination Reactions of Organometallic Reagents Using *O*-Benzoylhydroxylamines

O-Benzoylhydroxylamines have occupied a prominent role as $[NR_2]^+$ 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.

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 1.2a) [45]. Using $[Cu(OTf)]_2 \cdot C_6H_6$ as the catalyst, they easily synthesized tertiary and 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].

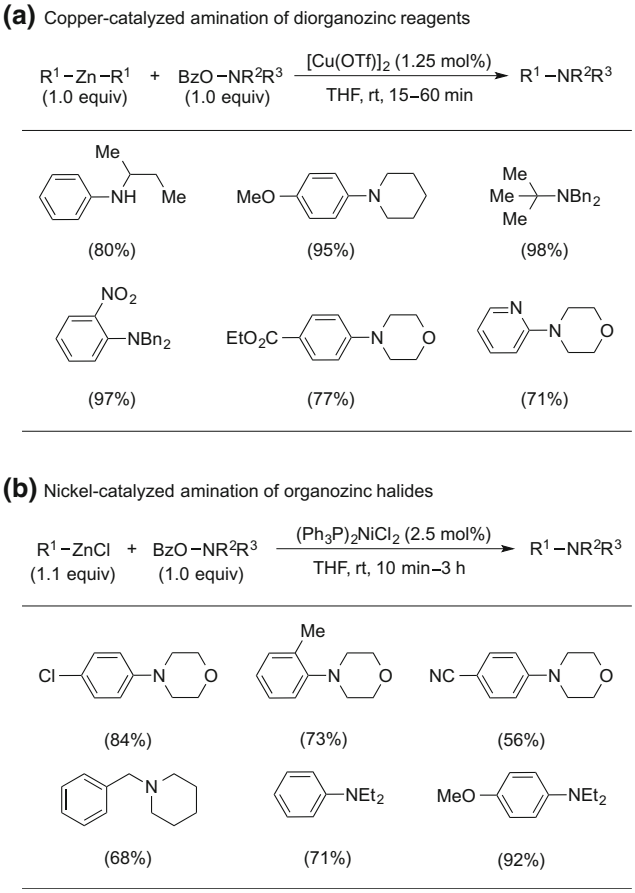
In their initial amination method, the Johnson group found a significant disparity in the reactivity of diorganozincs and organozinc halides with organozinc halides giving drastically lower yields (<30 %) [45]. To overcome this, they employed the use of nickel for the amination (Scheme 1.2b) [47]. They 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 alkyl zinc halides not yielding the desired products.

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 1.3) [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. However, this reaction did not possess the scope of their previous protocol employing diorganozinc compounds.

Electrophilic Amination of Organoboron Reagents

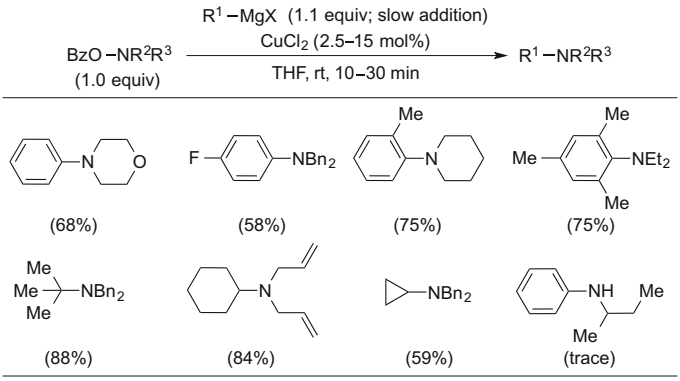
While organoboron reagents are typically building blocks used in cross-coupling reactions for the synthesis of C–C bonds, in 2012, Miura and Lalic concurrently disclosed copper-catalyzed electrophilic aminations of aryl boronic esters [50, 51]. In the work by Miura and co-workers, a wide variety of aniline derivatives were



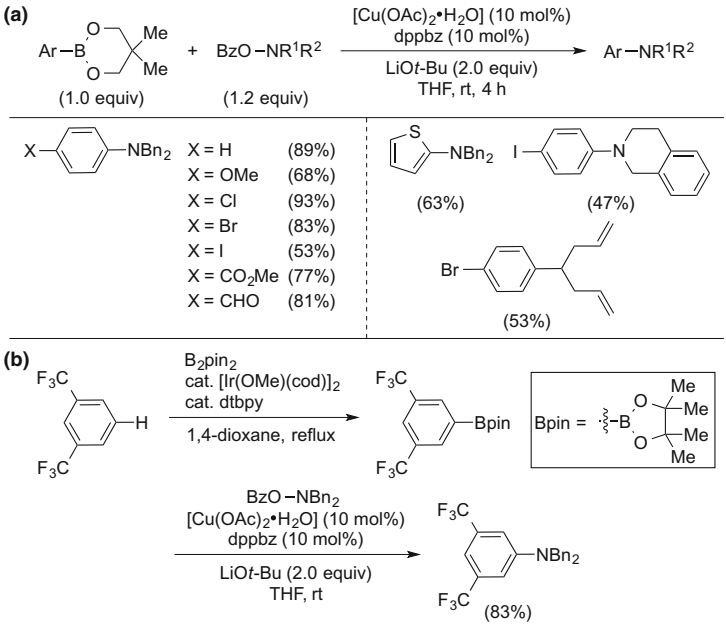
Scheme 1.2 Electrophilic amination of organozinc reagents

obtained in moderate to good yields (Scheme 1.4) [50]. Moreover, they were also able to combine their amination method with the iridium-catalyzed direct C–H borylation developed by Hartwig [109] in order to synthesize aryl amines directly from the arene (Scheme 1.4b).

Meanwhile, Lalic and co-workers focused on the synthesis of sterically hindered aniline derivatives (Scheme 1.5) [51]. They found that boronic esters derived from neopentyl glycol were crucial for the reaction, and using a catalyst formed in situ from $[CuO\textit{t}\text{-Bu}]_4$ and Xantphos gave the best yields for the various anilines. Additionally, they found that acidic functional groups could be tolerated when excess CsF was used as the base rather than Li*O*t-Bu (Scheme 1.5b). While both methods tolerated a variety of functional groups including halogens, esters, carbonyls, and carbamates, they were limited to the synthesis of only tertiary aryl amines.

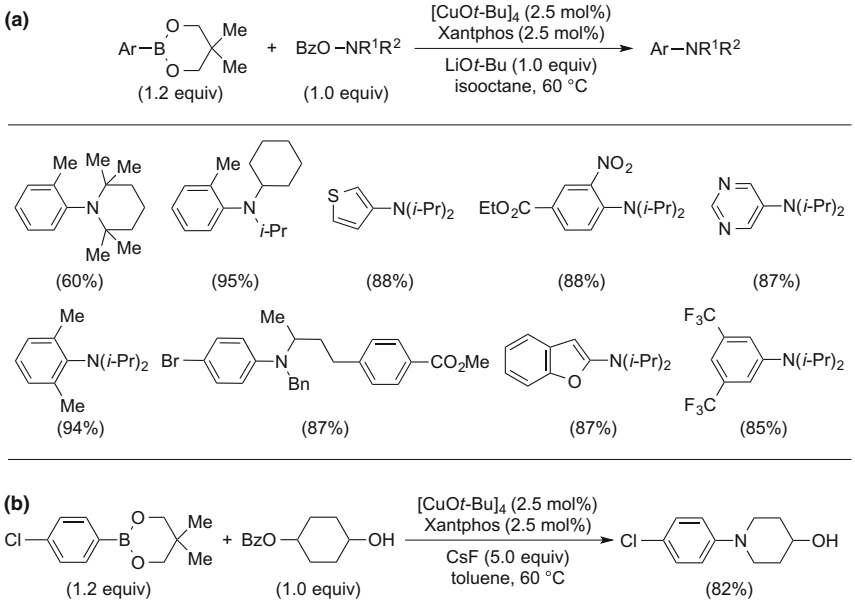


Scheme 1.3 Copper-catalyzed electrophilic amination of Grignard reagents



Scheme 1.4 Copper-catalyzed electrophilic amination of aryl boronic esters developed by Miura and co-workers

In developing their amination methods, Miura and Lalic proposed possible mechanisms for their respective transformations (Schemes 1.6 and 1.7). Based on mechanistic studies, Miura and co-workers proposed that an anionic homocuprate was responsible for the amination step (Scheme 1.6) [50]. On the other hand, Lalic and co-workers proposed that a neutral copper(I) complex was responsible for the



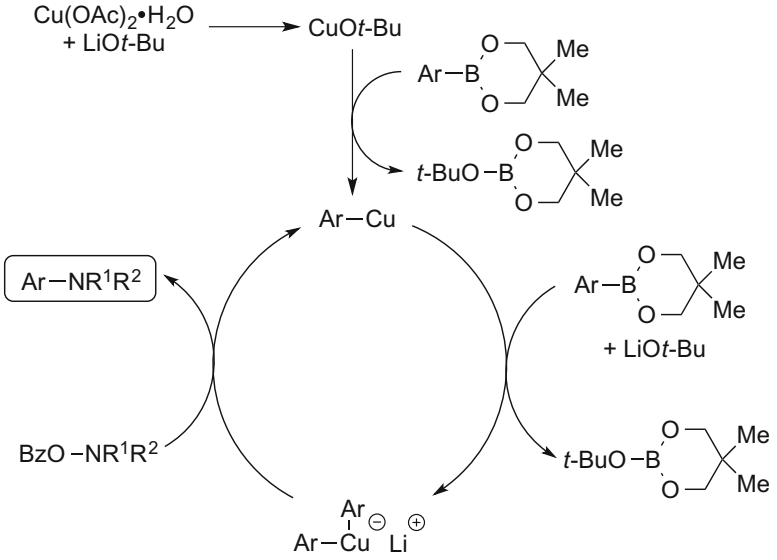
Scheme 1.5 Copper-catalyzed electrophilic amination of aryl boronic esters developed by Lalic and co-workers

amination step (Scheme 1.7) [51]. By either account, the presence of LiO*t*-Bu appeared to be critical for the generation of the active copper catalyst.

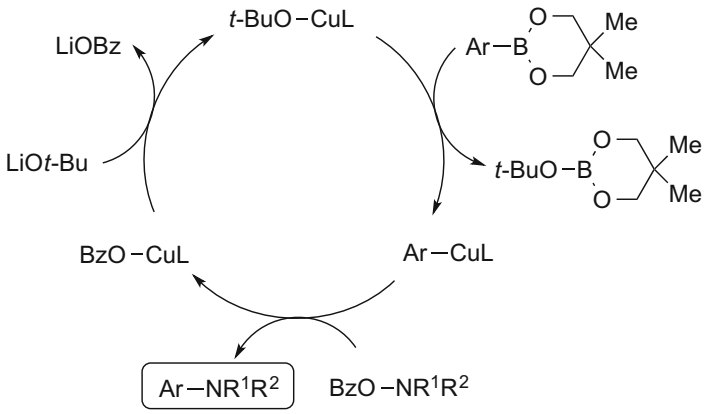
Lalic and co-workers also reported the synthesis of tertiary amines from terminal alkenes (Scheme 1.8) [52]. They were able to develop a highly selective anti-Markovnikov hydroamination that involved the hydroboration of a terminal alkene followed by the copper-catalyzed electrophilic amination of the 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.

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 1.9) [55]. The use of aryl[(2-hydroxymethyl)phenyl]dimethylsilanes was crucial since the 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.

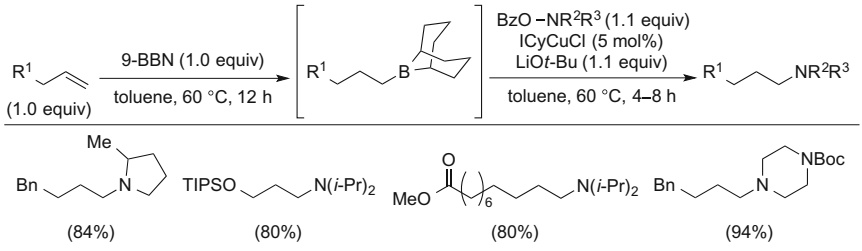


Scheme 1.6 Mechanism for amination of aryl boronates proposed by Miura and co-workers

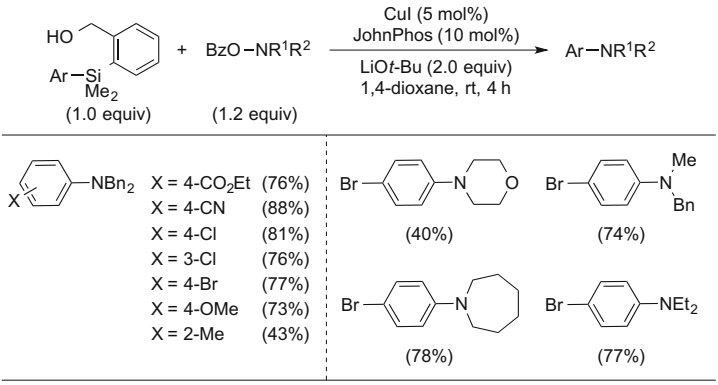


Scheme 1.7 Mechanism for amination of aryl boronates proposed by Lalic and co-workers

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 1.10) [56]. Different basic additives ($NaHCO_3$, Na_2CO_3, 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



Scheme 1.8 Copper-catalyzed electrophilic amination of alkyl boranes

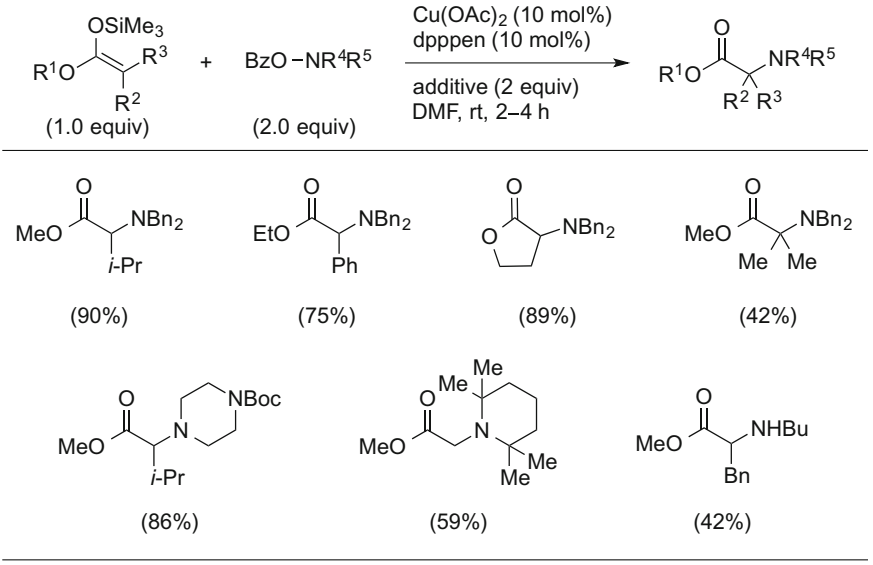


Scheme 1.9 Copper-catalyzed electrophilic amination of arylsilanes

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.

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 1.11) [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



Scheme 1.10 Copper-catalyzed electrophilic amination of silyl ketene acetals

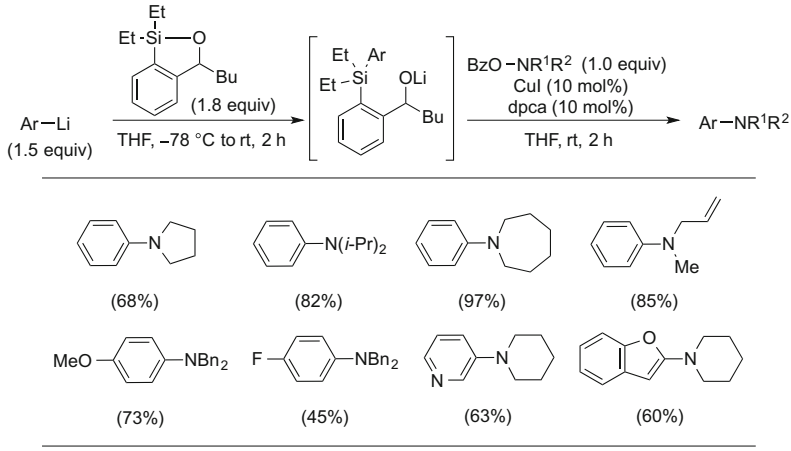
electrophilic amination. Through this amination method, they were able to access an array of aryl and heteroaryl amines.

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 1.12) [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.

1.1.2 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



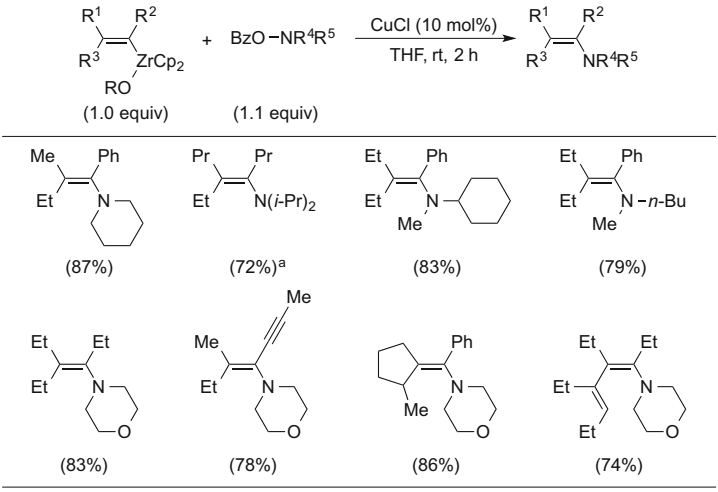
Scheme 1.11 Copper-catalyzed electrophilic amination of organolithiums via a recoverable siloxane transfer agents

been achieved by two strategies—(1) directing group assisted *ortho*-metallation or (2) direct deprotonative metallation (Scheme 1.13) [59–64].

1.1.2.1 Directing Group Assisted *Ortho*-Metallation for C–H Amination

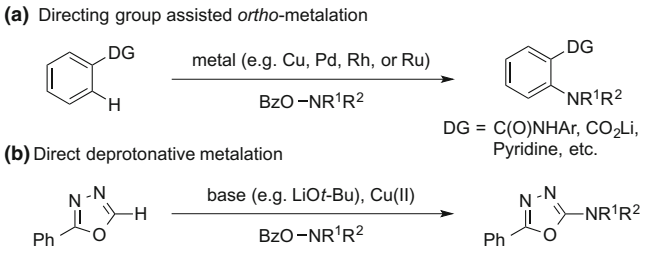
Directing group-assisted metallation has proven to be a powerful tool for the synthesis of *ortho*-substituted arylamines. Toward this a range of catalyst systems have been developed, including palladium, ruthenium, rhodium and copper [59–63]. The use of *O*-benzoylhydroxylamines for direct *ortho* C–H amination was first disclosed by Yu and co-workers via a palladium-catalyzed amination of *N*-aryl benzamides (Scheme 1.14a) [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 1.14b).

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 1.15). Of the various pyridine and quinoline ligands,



a Reaction run at 50 °C.

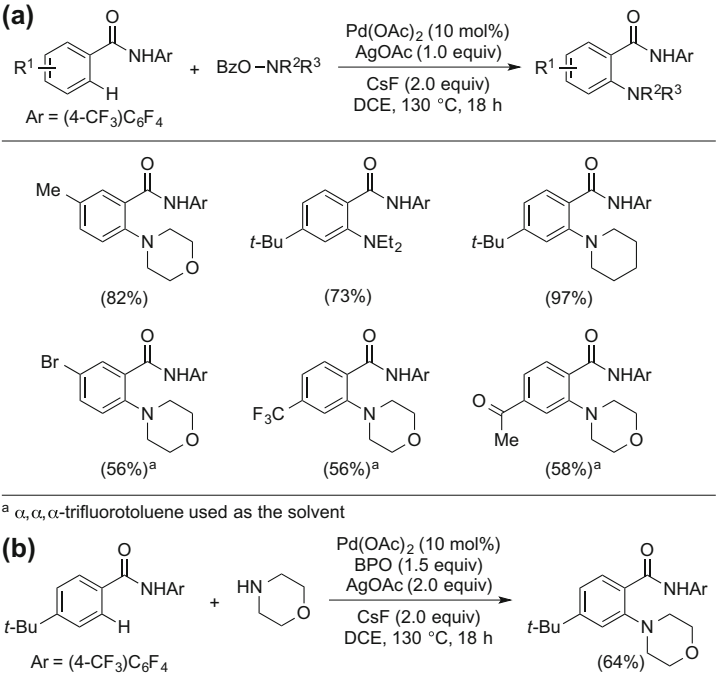
Scheme 1.12 Copper-catalyzed electrophilic amination of alkenylzirconocines



Scheme 1.13 Metal-catalyzed direct C–H amination

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 (Scheme 1.15b) [60].

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 1.16) [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.

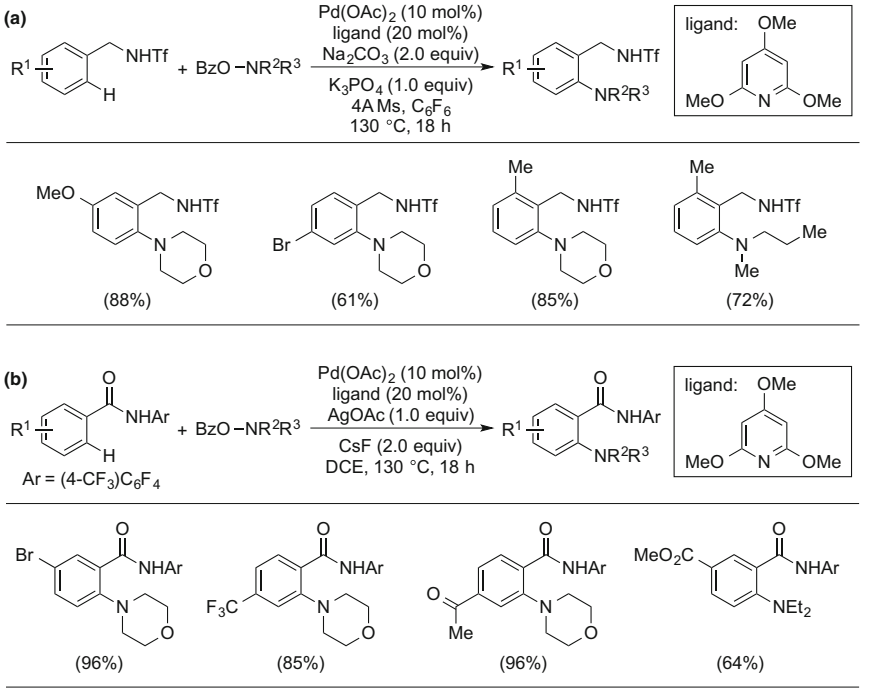


Scheme 1.14 Palladium-catalyzed C–H amination of *N*-aryl benzamides

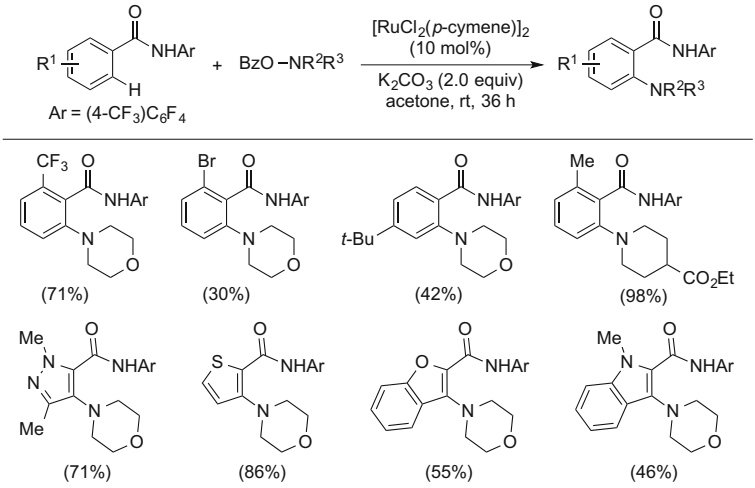
Zhang and Yao reported a rhodium-catalyzed aryl C–H amination using a pyrazolone moiety as an *ortho* directing group (Scheme 1.17) [62]. Their amination method is notable because they were able to introduce primary and secondary amines unlike previous palladium and ruthenium catalyzed aminations [59–61] 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].

1.1.2.2 Direct Deprotonative Metallation for C–H Amination

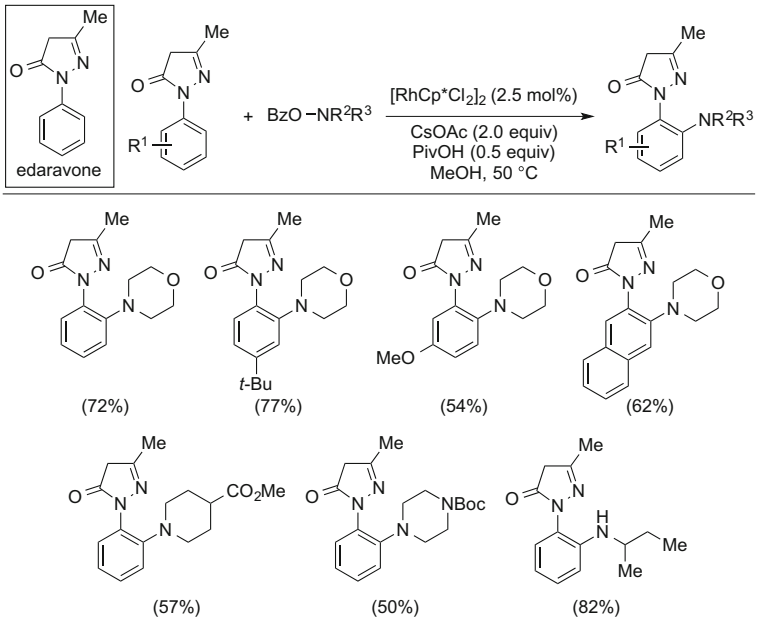
Direct deprotonative metallation/amination using *O*-benzoylhydroxylamines has been less thoroughly explored; however it has been particularly useful for the amination of electron-deficient arenes. Miura and co-workers used this method for a copper-catalyzed direct amination of polyfluoroarenes and azoles (Scheme 1.18) [64]. They were able to synthesize the corresponding anilines and aminoazoles in moderate to good yields under mild reaction conditions.



Scheme 1.15 Ligand-promoted palladium-catalyzed C–H amination



Scheme 1.16 Ruthenium-catalyzed *ortho* C–H amination of arenes and heteroarenes

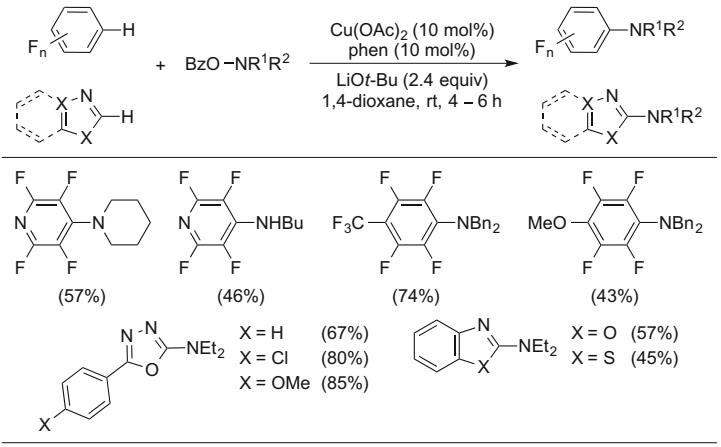


Scheme 1.17 Rhodium-catalyzed *ortho* C–H amination

1.1.3 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



Scheme 1.18 Copper-catalyzed direct C–H amination of polyfluoroarenes and azoles

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.

References

1. Hili R, Yudin AK (2006) Making carbon-nitrogen bonds in biological and chemical synthesis. Nat Chem Biol 2(6):284–287
2. Topol EJ, Schork NJ (2011) Catapulting clopidogrel pharmacogenomics forward. Nat Med 17(1):40–41
3. Lawrence J (2015) Safinamide recommended for approval as Parkinson's disease therapy. The Pharmaceutical Journal doi:10.1211/PJ.2015.20067595
4. Mucha A, Kafarski P, Berlicki L (2011) Remarkable potential of the α-Aminophosphonate/phosphinate structural motif in medicinal chemistry. J Med Chem 54(17):5955–5980
5. Davies MA, Sheffler DJ, Roth BL (2004) Aripiprazole: a novel atypical antipsychotic drug with a uniquely robust pharmacology. CNS Drug Rev 10(4):317–336
6. Orjales A, Mosquera R, Labeaga L, Rodes R (1997) New 2-piperazinylbenzimidazole derivatives as 5-HT_3 antagonists: synthesis and pharmacological evaluation. J Med Chem 40(4):586–593

7. Guram AS, Rennels RA, Buchwald SL (1995) A simple catalytic method for the conversion of aryl bromides to arylamines. Angew Chem Int Ed 34(12):1348–1350
8. Louie J, Hartwig JF (1995) Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. Tetrahedron Lett 36(21):3609–3612
9. Chan DMT, Monaco KL, Wang RP, Winters MP (1998) New N- and O-arylations with phenylboronic acids and cupric acetate. Tetrahedron Lett 39(19):2933–2936
10. Lam PYS, Clark CG, Saubern S, Adams J, Winters MP, Chan DMT, Combs A (1998) New aryl/heteroaryl C–N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. Tetrahedron Lett 39(19):2941–2944
11. Evans DA, Katz JL, West TR (1998) Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. Tetrahedron Lett 39(19):2937–2940
12. Cho SH, Kim JY, Lee SY, Chang S (2009) Silver-mediated direct amination of benzoxazoles: Tuning the amino group source from formamides to parent amines. Angew Chem Int Ed 48(48):9127–9130
13. Boudet N, Dubbaka SR, Knochel P (2008) Oxidative amination of cuprated pyrimidine and purine derivatives. Org Lett 10(9):1715–1718
14. del Amo V, Dubbaka SR, Krasovskiy A, Knochel P (2006) General preparation of primary, secondary, and tertiary aryl amines by the oxidative coupling of polyfunctional aryl and heteroaryl amidocuprates. Angew Chem Int Ed 45(46):7838–7842
15. Kienle M, Dunst C, Knochel P (2009) Oxidative amination of heteroaromatic zinc reagents mediated by $PhI(OAc)_2$. Org Lett 11(22):5158–5161
16. Kienle M, Wagner AJ, Dunst C, Knochel P (2011) Preparation of heterocyclic amines by an oxidative amination of zinc organometallics mediated by Cu^I: A new Oxidative cycloamination for the preparation of annulated indole derivatives. Chem Asian J 6(2):517–523
17. Li Y, Xie Y, Zhang R, Jin K, Wang X, Duan C (2011) Copper-catalyzed direct oxidative C–H amination of benzoxazoles with formamides or secondary amines under mild conditions. J Org Chem 76(13):5444–5449
18. Mitsuda S, Fujiwara T, Kimigafukuro K, Monguchi D, Mori A (2012) Copper-catalyzed oxidative C–H, N–H coupling of azoles and thiophenes. Tetrahedron 68(18):3585–3590
19. Monguchi D, Fujiwara T, Furukawa H, Mori A (2009) Direct amination of azoles via catalytic C−H, N−H coupling. Org Lett 11(7):1607–1610
20. Sun K, Li Y, Xiong T, Zhang JP, Zhang QA (2011) Palladium-catalyzed C−H aminations of anilides with N-fluorobenzenesulfonimide. J Am Chem Soc 133(6):1694–1697
21. Thu HY, Yu WY, Che CM (2006) Intermolecular amidation of unactivated sp^2 and sp^3 C−H bonds via palladium-catalyzed cascade C−H activation/nitrene insertion. J Am Chem Soc 128(28):9048–9049
22. Tran LD, Roane J, Daugulis O (2013) Directed amination of non-acidic arene C–H bonds by a copper–silver catalytic system. Angew Chem Int Ed 52(23):6043–6046
23. Wagh YS, Bhanage BM (2012) $Cu(acac)_2$ catalyzed oxidative C–H bond amination of azoles with amines under base-free conditions. Tetrahedron Lett 53(48):6500–6503
24. Wang Q, Schreiber SL (2009) Copper-mediated amidation of heterocyclic and aromatic C−H bonds. Org Lett 11(22):5178–5180
25. Xiao B, Gong TJ, Xu J, Liu ZJ, Liu L (2011) Palladium-catalyzed intermolecular directed C −H amidation of aromatic ketones. J Am Chem Soc 133(5):1466–1474
26. Xu J, Li JR, Wei Z, Zhang Q, Shi DX (2013) Direct amination of azoles using $CuCl_2$ complexes of amines under mild conditions. RSC Adv. 3(25):9622–9624
27. Lamani M, Prabhu KR (2011) Iodine-catalyzed amination of benzoxazoles: a metal-free route to 2-Aminobenzoxazoles under mild conditions. J Org Chem 76(19):7938–7944
28. Wertz S, Kodama S, Studer A (2011) Amination of benzoxazoles and 1,3,4-oxadiazoles using 2,2,6,6-tetramethylpiperidine-N-oxoammonium tetrafluoroborate as an organic oxidant. Angew Chem Int Ed 50(48):11511–11515

29. Yotphan S, Beukeaw D, Reutrakul V (2013) A convenient one-pot synthesis of N-substituted 2-aminoazole derivatives. Synthesis 45(7):936–942
30. Chen X, Hao X-S, Goodhue CE, Yu J-Q (2006) Cu(II)-catalyzed functionalizations of aryl C −H bonds using O_2 as an oxidant. J Am Chem Soc 128(21):6790–6791
31. John A, Nicholas KM (2011) Copper-catalyzed amidation of 2-phenylpyridine with oxygen as the terminal oxidant. J Org Chem 76(10):4158–4162
32. Shuai Q, Deng G, Chua Z, Bohle DS, Li C-J (2010) Copper-catalyzed highly regioselective oxidative C–H bond amidation of 2-arylpyridine derivatives and 1-methylindoles. Adv Synth Catal 352(4):632–636
33. Uemura T, Imoto S, Chatani N (2006) Amination of the ortho C–H bonds by the $Cu(OAc)_2$-mediated reaction of 2-phenylpyridines with anilines. Chem Lett 35(8):842–843
34. Shang M, Sun S-Z, Dai H-X, Yu J-Q (2014) Cu(II)-mediated C–H amidation and amination of arenes: exceptional compatibility with heterocycles. J Am Chem Soc 136(9):3354–3357
35. Erdik E, Ay M (1989) Electrophilic amination of carbanions. Chem Rev 89(8):1947–1980
36. Greck C, Genet JP (1997) Electrophilic amination: new synthetic applications. Synlett 1997 (7):741–748
37. Dembech P, Seconi G, Ricci A (2000) The electrophilic amination of carbanions: an unconventional new entry to C−N bond formation. Chem Eur J 6(8):1281–1286
38. Erdik E (2004) Electrophilic α-Amination of carbonyl compounds. Tetrahedron 60(40):8747–8782
39. Greck C, Drouillat B, Thomassigny C (2004) Asymmetric electrophilic α-Amination of carbonyl groups. Eur J Org Chem 2004(7):1377–1385
40. Ciganek E (2009) Electrophilic amination of carbanions, enolates, and their surrogates. John Wiley & Sons, Inc.
41. Seebach D (1979) Methods of reactivity umpolung. Angew Chem Int Ed 18(4):239–258
42. Barker TJ, Jarvo ER (2011) Developments in transition-metal-catalyzed reactions using electrophilic nitrogen sources. Synthesis 24:3954–3964
43. Lalic G, Rucker RP (2013) Copper-catalyzed electrophilic amination of organoboron compounds. Synlett 24(3):269–275
44. Yan X, Yang X, Xi C (2014) Recent progress in copper-catalyzed electrophilic amination. Catal Sci Technol 4(12):4169–4177
45. Berman AM, Johnson JS (2004) Copper-catalyzed electrophilic amination of diorganozinc reagents. J Am Chem Soc 126(18):5680–5681
46. Berman AM, Johnson JS (2005) Copper-catalyzed electrophilic amination of functionalized diarylzinc reagents. J Org Chem 70(1):364–366
47. Berman AM, Johnson JS (2005) Nickel-catalyzed electrophilic amination of organozinc halides. Synlett 11:1799–1801
48. Berman AM, Johnson JS (2006) Copper-catalyzed electrophilic amination of organozinc nucleophiles: documentation of O-benzoyl hydroxylamines as broadly useful $R_2N(+)$ and RHN(+) synthons. J Org Chem 71(1):219–224
49. Campbell MJ, Johnson JS (2007) Mechanistic studies of the copper-catalyzed electrophilic amination of diorganozinc reagents and development of a zinc-free protocol. Org Lett 9 (8):1521–1524
50. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of arylboronates with N,N-dialkylhydroxylamines. Angew Chem Int Ed 51(15):3642–3645
51. Rucker RP, Whittaker AM, Dang H, Lalic G (2012) Synthesis of hindered anilines: copper-catalyzed electrophilic amination of aryl boronic esters. Angew Chem Int Ed 51 (16):3953–3956
52. Rucker RP, Whittaker AM, Dang H, Lalic G (2012) Synthesis of tertiary alkyl amines from terminal alkenes: copper-catalyzed amination of alkyl boranes. J Am Chem Soc 134 (15):6571–6574
53. Xiao Q, Tian LM, Tan RC, Xia Y, Qiu D, Zhang Y, Wang JB (2012) Transition-metal-free electrophilic amination of arylboroxines. Org Lett 14(16):4230–4233

54. Sakae R, Hirano K, Satoh T, Miura M (2013) Formal anti-markovnikov hydroamination of terminal aryl alkynes with pinacolborane and hydroxylamines via Zr/Cu sequential catalysis. Chem Lett 42(10):1128–1130
55. Miki Y, Hirano K, Satoh T, Miura M (2013) Copper-catalyzed electrophilic amination of arylsilanes with hydroxylamines. Org Lett 15(1):172–175
56. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of ketene silyl acetals with hydroxylamines: electrophilic amination approach to α-Amino acids. Angew Chem Int Ed 51(47):11827–11831
57. Nguyen MH, Smith AB (2013) Copper-catalyzed electrophilic amination of organolithiums mediated by recoverable siloxane transfer agents. Org Lett 15(18):4872–4875
58. Yan X, Chen C, Zhou Y, Xi C (2012) Copper-catalyzed electrophilic amination of alkenylzirconocenes with O-benzoylhydroxylamines: an efficient method for synthesis of enamines. Org Lett 14(18):4750–4753
59. Yoo EJ, Ma S, Mei T-S, Chan KSL, Yu J-Q (2011) Pd-catalyzed intermolecular C–H amination with alkylamines. J Am Chem Soc 133(20):7652–7655
60. Zhu D, Yang G, He J, Chu L, Chen G, Gong W, Chen K, Eastgate MD, Yu J-Q (2015) Ligand-promoted ortho-C–H amination with Pd catalysts. Angew Chem Int Ed 54 (8):2497–2500
61. Shang M, Zeng S-H, Sun S-Z, Dai H-X, Yu J-Q (2013) Ru(II)-catalyzed ortho-C–H amination of arenes and heteroarenes at room temperature. Org Lett 15(20):5286–5289
62. Wu K, Fan Z, Xue Y, Yao Q, Zhang A (2014) Rh(III)-catalyzed intermolecular C–H amination of 1-aryl-1H-pyrazol-5(4H)-ones with alkylamines. Org Lett 16(1):42–45
63. Li G, Jia C, Sun K, Lv Y, Zhao F, Zhoua K, Wu H (2015) Copper(II)-catalyzed electrophilic amination of quinoline N-oxides with O-benzoyl hydroxylamines. Org Biomol Chem 13(11):3207–3210
64. Matsuda N, Hirano K, Satoh T, Miura M (2011) Copper-catalyzed direct amination of electron-deficient arenes with hydroxylamines. Org Lett 13(11):2860–2863
65. Scriven EFV, Turnbull K (1988) Azides: their preparation and synthetic uses. Chem Rev 88(2):297–368
66. Reed JN, Snieckus V (1983) Ortho-amination of lithiated tertiary benzamides. Short route to polysubstituted anthranilamides. Tetrahedron Lett 24(36):3795–3798
67. Denmark SE, Chatani N, Pansare SV (1992) Asymmetric electrophilic amination of chiral phosphorus-stabilized anions. Tetrahedron 48(11):2191–2208
68. Hanessian S, Bennani YL (1994) Electrophilic amination and azidation of chiral α-alkyl phosphonamides: asymmetric syntheses of α-Amino α-alkyl phosphonic-acids. Synthesis 1994(12):1272–1274
69. Bernardi L, Zhuang W, Jørgensen KA (2005) An easy approach to optically active α-Amino phosphonic acid derivatives by chiral Zn(II)-catalyzed enantioselective amination of phosphonates. J Am Chem Soc 127(16):5772–5773
70. Kumaragurubaran N, Juhl K, Zhuang W, Bøgevig A, Jørgensen KA (2002) Direct L-proline-catalyzed asymmetric α-Amination of ketones. J Am Chem Soc 124(22): 6254–6255
71. Bøgevig A, Juhl K, Kumaragurubaran N, Zhuang W, Jørgensen KA (2002) Direct organo-catalytic asymmetric α-Amination of aldehydes—a simple approach to optically active α-amino aldehydes, α-Amino alcohols, and α-Amino acids. Angew Chem Int Ed 41 (10):1790–1793
72. List B (2002) Direct catalytic asymmetric α-Amination of aldehydes. J Am Chem Soc 124 (20):5656–5657
73. Juhl K, Jørgensen KA (2002) Catalytic asymmetric direct α-Amination reactions of 2-keto esters: a simple synthetic approach to optically active *syn*-β-Amino-α-Hydroxy esters. J Am Chem Soc 124(11):2420–2421
74. Marigo M, Juhl K, Jørgensen KA (2003) Catalytic, highly enantioselective, direct amination of β-ketoesters. Angew Chem Int Ed 42(12):1367–1369

75. Evans DA, Nelson SG (1997) Chiral magnesium bis(sulfonamide) complexes as catalysts for the merged enolization and enantioselective amination of N-acyloxazolidinones. A catalytic approach to the synthesis of arylglycines. J Am Chem Soc 119(27):6452–6453
76. Bui T, Hernandez-Torres G, Milite C, Barbas CF (2010) Highly enantioselective organocatalytic α-Amination reactions of aryl oxindoles: developing designer multifunctional alkaloid catalysts. Org Lett 12(24):5696–5699
77. Hasegawa Y, Watanabe M, Gridnev ID, Ikariya T (2008) Enantioselective direct amination of α-Cyanoacetates catalyzed by bifunctional chiral Ru and Ir amido complexes. J Am Chem Soc 130(7):2158–2159
78. Konishi H, Lam TY, Malerich JP, Rawal VH (2010) Enantioselective α-Amination of 1,3-dicarbonyl compounds using squaramide derivatives as hydrogen bonding catalysts. Org Lett 12(9):2028–2031
79. Mashiko T, Kumagai N, Shibasaki M (2009) Managing highly coordinative substrates in asymmetric catalysis: a catalytic asymmetric amination with a lanthanum-based ternary catalyst. J Am Chem Soc 131(41):14990–14999
80. Nandakumar MV, Ghosh S, Schneider C (2009) Enantioselective synthesis of a novel chiral 2,9-disubstituted 1,10-phenanthroline and first applications in asymmetric catalysis. Eur J Org Chem 2009(36):6393–6398
81. Simon L, Goodman JM (2012) Mechanism of amination of beta-keto esters by azadicarboxylates catalyzed by an axially chiral guanidine: acyclic keto esters react through an E enolate. J Am Chem Soc 134(40):16869–16876
82. Terada M, Nakano M, Ube H (2006) Axially chiral guanidine as highly active and enantioselective catalyst for electrophilic amination of unsymmetrically substituted 1,3-dicarbonyl compounds. J Am Chem Soc 128(50):16044–16045
83. Zhou F, Ding M, Liu YL, Wang CH, Ji CB, Zhang YY, Zhou J (2011) Organocatalytic asymmetric α-Amination of unprotected 3-aryl and 3-aliphatic substituted oxindoles using di-*tert*-butyl azodicarboxylate. Adv Synth Catal 353(16):2945–2952
84. Erdik E, Ay M (1989) Effect of copper (I) iodide and magnesium chloride on amination of aryl grignards with ketoximes. Synth React Inorg Met-Org Chem 19(7):663–668
85. Tsutsui H, Hayashi Y, Narasaka K (1997) Preparation of primary amines by the copper(I) catalyzed reaction of 4,4′-bis(trifluoromethyl)benzophenone O-methylsulfonyloxime and alkyl grignard reagents. Chem Lett 26(4):317–318
86. Kitamura M, Chiba S, Narasaka K (2003) Synthesis of primary amines and N-methylamines by the electrophilic amination of grignard reagents with 2-imidazolidinone O-sulfonyloxime. Bull Chem Soc Jpn 76(5):1063–1070
87. Narasaka K (2002) Metal-assisted amination with oxime derivatives. Pure Appl Chem 74 (1):143–149
88. Daşkapan T (2006) Preparation of primary arylamines via arylzinc chlorides in good yields. Tetrahedron Lett 47(17):2879–2881
89. Daşkapan T, Yeşilbağ F, Koca S (2009) Cosolvent-promoted electrophilic amination of organozinc reagents. Appl Organomet Chem 23(6):213–218
90. Kano T, Ueda M, Takai J, Maruoka K (2006) Direct asymmetric hydroxyamination reaction catalyzed by an axially chiral secondary amine catalyst. J Am Chem Soc 128(18):6046–6047
91. Lopez-Cantarero J, Cid MB, Poulsen TB, Bella M, Ruano JLG, Jørgensen KA (2007) Intriguing behavior of cinchona alkaloids in the enantioselective organocatalytic hydroxyamination of α-substituted-α-cyanoacetates. J Org Chem 72(18):7062–7065
92. Momiyama N, Yamamoto H (2002) Simple synthesis of α-Hydroxyamino carbonyl compounds: new scope of the nitroso aldol reaction. Org Lett 4(21):3579–3582
93. Momiyama N, Yamamoto H (2005) Brønsted acid catalysis of achiral enamine for regio- and enantioselective nitroso aldol synthesis. J Am Chem Soc 127(4):1080–1081
94. Sandoval D, Frazier CP, Bugarin A, de Alaniz JR (2012) Electrophilic α-amination reaction of β-ketoesters using N-hydroxycarbamates: merging aerobic oxidation and lewis acid catalysis. J Am Chem Soc 134(46):18948–18951

95. Shen K, Liu XH, Wang G, Lin LL, Feng XM (2011) Facile and efficient enantioselective hydroxyamination reaction: synthesis of 3-hydroxyamino-2-oxindoles using nitrosoarenes. Angew Chem Int Ed 50(20):4684–4688
96. Yanagisawa A, Fujinami T, Oyokawa Y, Sugita T, Yoshida K (2012) Catalytic enantioselective N-nitroso aldol reaction of γ,δ-unsaturated δ-lactones. Org Lett 14(10):2434–2437
97. Vidal J, Damestoy S, Guy L, Hannachi JC, Aubry A, Collet A, Aubry A (1997) N-alkyloxycarbonyl-3-aryloxaziridines: their preparation, structure, and utilization as electrophilic amination reagents. Chem Eur J 3(10):1691–1709
98. Miura T, Morimoto M, Murakami M (2012) Copper-catalyzed amination of silyl ketene acetals with N-chloroamines. Org Lett 14(20):5214–5217
99. Yamada S, Oguri T, Shioiri T (1972) α-Amination of carboxylic acids: a new synthesis of α-amino-acids. J Chem Soc Chem Commun 1972(10):623a
100. Kawano T, Hirano K, Satoh T, Miura M (2010) A new entry of amination reagents for heteroaromatic C–H bonds: copper-catalyzed direct amination of azoles with chloroamines at room temperature. J Am Chem Soc 132(20):6900–6901
101. Hatakeyama T, Yoshimoto Y, Ghorai SK, Nakamura M (2010) Transition-metal-free electrophilic amination between aryl grignard reagents and N-chloroamines. Org Lett 12(7):1516–1519
102. Barker TJ, Jarvo ER (2009) Umpolung amination: nickel-catalyzed coupling reactions of N, N-dialkyl-N-chloroamines with diorganozinc reagents. J Am Chem Soc 131(43): 15598–15599
103. Miki Y, Hirano K, Satoh T, Miura M (2013) Copper-catalyzed intermolecular regioselective hydroamination of styrenes with polymethylhydrosiloxane and hydroxylamines. Angew Chem Int Ed 52(41):10830–10834
104. Zhu S, Niljianskul N, Buchwald SL (2013) Enantio- and regioselective CuH-catalyzed hydroamination of alkenes. J Am Chem Soc 135(42):15746–15749
105. Zhu S, Buchwald SL (2014) Enantioselective CuH-catalyzed anti-markovnikov hydroamination of 1,1-disubstituted alkenes. J Am Chem Soc 136(45):15913–15916
106. Niljianskul N, Zhu S, Buchwald SL (2015) Enantioselective synthesis of α-Aminosilanes by copper-catalyzed Hydroamination of vinylsilanes. Angew Chem Int Ed 54(5):1638–1641
107. Hirano K, Satoh T, Miura M (2011) Copper-catalyzed annulative amination of ortho-alkynylphenols with hydroxylamines: synthesis of 3-aminobenzofurans by umpolung amination strategy. Org Lett 13(9):2395–2397
108. Matsuda N, Hirano K, Satoh T, Miura M (2012) An annulative electrophilic amination approach to 3-aminobenzoheteroles. J Org Chem 77(1):617–625
109. Ishiyama T, Takagi J, Ishida K, Miyaura N, Anastasi NR, Hartwig JF (2002) Mild iridium-catalyzed borylation of arenes. High turnover numbers, room temperature reactions, and isolation of a potential intermediate. J Am Chem Soc 124(3):390–391
110. Watanabe T, Tahara M, Todo S (2008) The novel antioxidant edaravone: from bench to bedside. Cardiovasc Ther 26(2):101–114
111. Abe K, Yuki S, Kogure K (1988) Strong attenuation of ischemic and postischemic brain edema in rats by a novel free radical scavenger. Stroke 19:480–485
112. Tabrizch R (2000) Edaravone mitsubishi-tokyo. curr. opin. invest. Drugs 1(3):347–354
113. Jin Y-J, Mima T, Raicu V, Park KC, Shimizu K (2002) Combined argatroban and edaravone caused additive neuroprotection against 15 min of forebrain ischemia in gerbils. Neurosci Res 43(1):75–79
114. Wencel-Delord J, Droge T, Liu F, Glorius F (2011) Towards mild metal-catalyzed C–H bond activation. Chem Soc Rev 40(9):4740–4761
115. Clegg W, Dale SH, Harrington RW, Hevia E, Honeyman GW, Mulvey RE (2006) Post-metalation structural insights into the use of alkali-metal-mediated zincation for directed ortho-metalation of a tertiary aromatic amide. Angew Chem Int Ed 45(15):2374–2377

116. Clegg W, Dale SH, Hevia E, Honeyman GW, Mulvey RE (2006) Pre-metalation structural insights into the use of alkali-metal-mediated zincation for directed ortho-metalation of a tertiary aromatic amide. Angew Chem Int Ed 45(15):2370–2374
117. Kondo Y, Shilai M, Uchiyama M, Sakamoto T (1999) TMP-zincate as highly chemoselective base for directed ortho metalation. J Am Chem Soc 121(14):3539–3540
118. Nguyen TT, Marquise N, Chevallier F, Mongin F (2011) Deprotonative metalation of aromatic compounds by using an amino-based lithium cuprate. Chem Eur J 17(37): 10405–10416
119. Haas B, Mosrin M, Ila H, Malakhov V, Knochel P (2011) Regio- and chemoselective metalation of arenes and heteroarenes using hindered metal amide bases. Angew Chem Int Ed 50(42):9794–9824
120. Bresser T, Monzon G, Mosrin M, Knochel P (2010) Scaleable preparation of sensitive functionalized aromatics and heteroaromatics via directed metalation using tmpZnCl·LiCl. Org Process Res Dev 14(6):1299–1303
121. Bresser T, Mosrin M, Monzon G, Knochel P (2010) Regio- and chemoselective zincation of sensitive and moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl. J Org Chem 75(14):4686–4695
122. Mosrin M, Bresser T, Knochel P (2009) Regio- and chemoselective multiple functionalization of chloropyrazine derivatives. Application to the synthesis of coelenterazine. Org Lett 11(15):3406–3409
123. Mosrin M, Knochel P (2009) TMPZnCl·LiCl: A new active selective base for the directed zincation of sensitive aromatics and heteroaromatics. Org Lett 11(8):1837–1840
124. Unsinn A, Ford MJ, Knochel P (2013) New preparation of TMPZnCl·LiCl by Zn insertion into TMPCl. Application to the functionalization of dibromodiazines. Org Lett 15(5):1128–1131
125. Hlavinka ML, Hagadorn JR (2006) Structures of zinc ketone enolates. Organometallics 25 (14):3501–3507
126. Hlavinka ML, Hagadorn JR (2007) $Zn(tmp)_2$: A versatile base for the selective functionalization of C−H bonds. Organometallics 26(17):4105–4108
127. Wunderlich SH, Knochel P (2007) $(tmp)_2Zn2{\cdot}MgCl_2{\cdot}2LiCl$: a chemoselective base for the directed zincation of sensitive arenes and heteroarenes. Angew Chem Int Ed 46(40): 7685–7688
128. Balloch L, Kennedy AR, Mulvey RE, Rantanen T, Robertson SD, Snieckus V (2011) Concerning the structures of alkali-metal-mediated *ortho* zincation of benzamides and phenyl O-carbamate. Organometallics 30(1):145–152

Chapter 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 [1–3]. 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 (Fig. 2.1), and in 2010, it was the second-most prescribed drug in the world [4]. Valaciclovir, another example of an α-amino carbonyl, is an antiviral drug used in the management of herpes—shingles and cold sores [5]. 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 [6]. 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.

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 [7]. The formation of α-amino carbonyl compounds

Portions of this chapter have been published: McDonald, S.L.; Wang, Q. "Selective α-amination and α-acylation of esters and amides via dual reactivity of *O*-acylhydroxylamines toward zinc enolates," *Chem. Commun.* **2014**, *50*, 2535–2538.

S.L. McDonald, *Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds*, Springer Theses, DOI 10.1007/978-3-319-38878-6_2

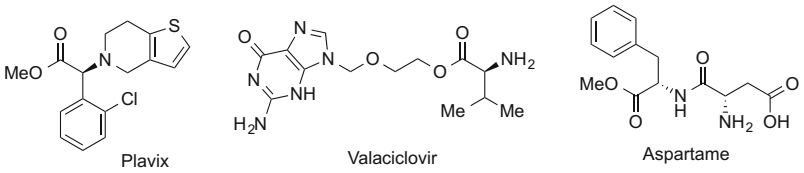


Fig. 2.1 Selected examples of biologically important α-amino carbonyls

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 [8–13]. Umpolung electrophilic aminations have received significant attention as an alternative and complementary strategy to traditional nucleophilic aminations for C–N bond formation [14–16]. Electrophilic amination of α-carbanions represents one of the most general and important methods for the synthesis of α-amino carbonyl compounds [10–12]. Towards this, a variety of electrophilic nitrogen-transfer reagents have been developed for the amination of enolates and eniminates (Fig. 2.2). Electrophilic aminating reagents used for the preparation of α-aminocarbonyl compounds include diazene dicarboxylates [17–30], azides [31], nitroso compounds [32–38], oxaziridines [39], *O*-diarylphosphinyl hydroxylamine [40], *N*-halo amines [41, 42], and *O*-acylhydroxylamines [43].

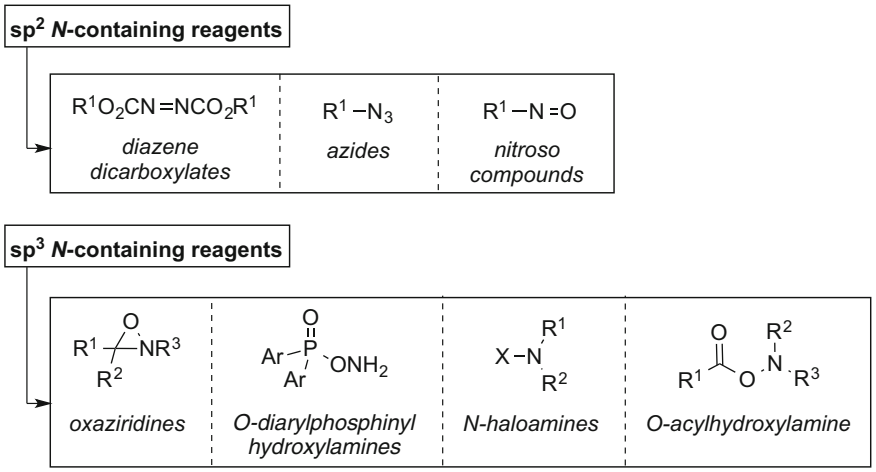
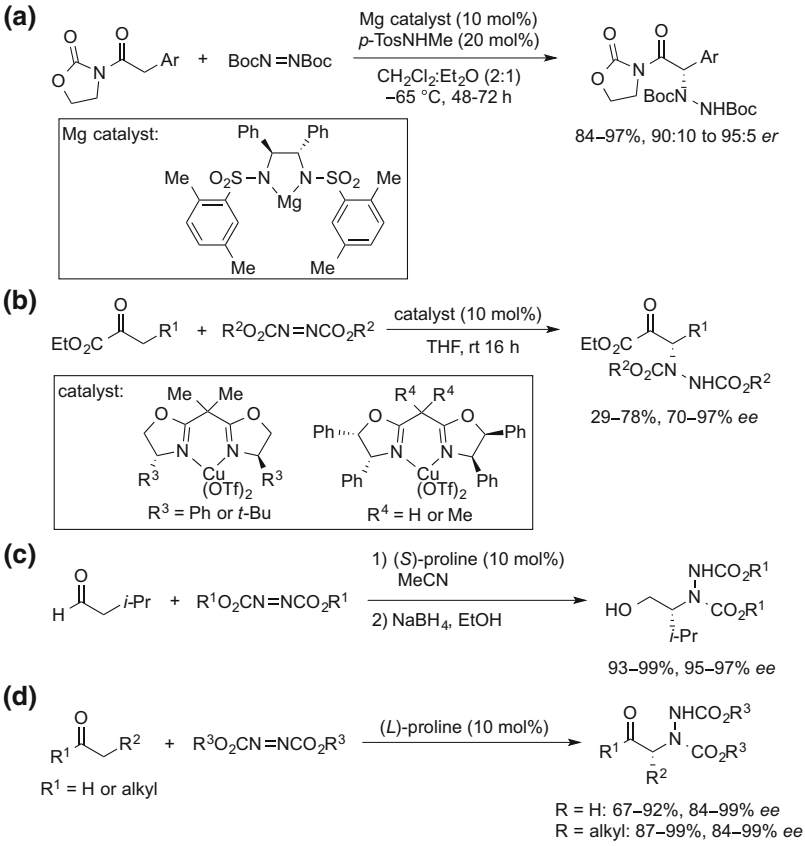


Fig. 2.2 Electrophilic aminating reagents for amination of carbonyls compounds

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 [44], acetylacetone and ethyl acetoacetate [45], and cyclohexanone-derived enolates [46]. They have since been used in several asymmetric α-aminations (Scheme 2.1) [17–22]. Evans and co-workers used a chiral magnesium sulphonamide complex to generate chiral enolate derivatives of *N*-acyloxazolidinones (Scheme 2.1a) [22].



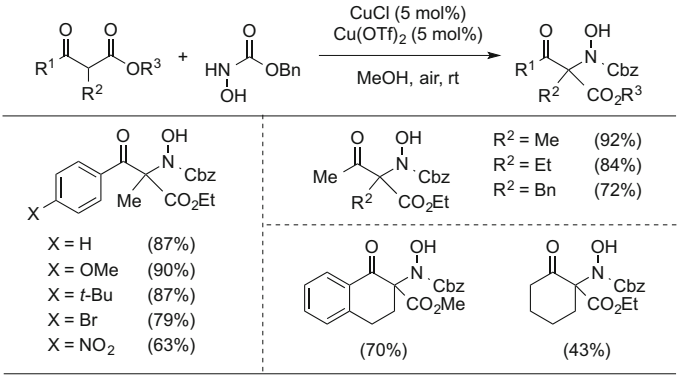
Scheme 2.1 Direct asymmetric catalytic α-amination of carbonyl derivatives using diazene dicarboxylates

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 2.1b) [17, 18]. List [19] and Jørgensen [20, 21] independently reported asymmetric α-aminations of carbonyl compounds via enamine derivatives prepared using *L*-proline (Schemes 2.1c, d). 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 [17–22].

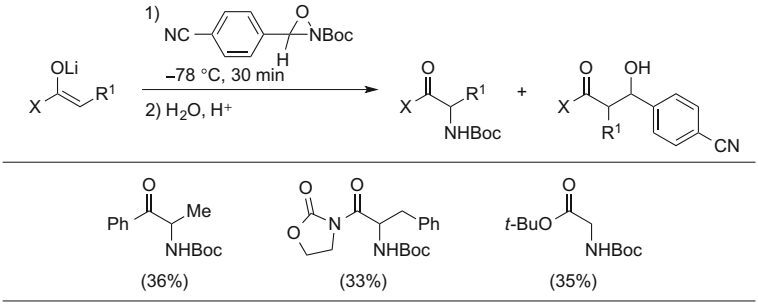
Organic azides and nitroso compounds have also been used for the electrophilic α-amination of carbonyls. Because azides can also function as diazo transfer agents [47], their use for the amination of enolates has been limited [31]. Nitroso compounds, on the other hand, have been used for *N*-selective nitroso aldol reactions [32–38]. Read de Alaniz and co-workers recently reported the copper-catalyzed *N*-selective nitroso aldol reaction of nitrosoformates (Scheme 2.2) [36]. 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.

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 [39–43]. Collet and



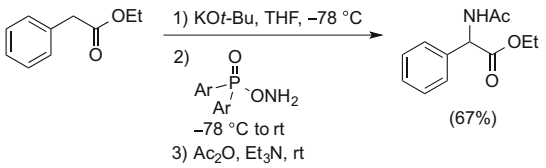
Scheme 2.2 Copper-catalyzed *N*-selective nitrosoformate aldol reaction



Scheme 2.3 Electrophilic amination of lithium enolates via oxaziridines

co-workers reported the synthesis of a series of *N*-protected oxaziridines and their use as electrophilic aminating reagents [39]. These oxaziridines reacted readily with a propiophenone lithium enolate to afford the racemic α-*N*-Boc amino compound in modest yield (Scheme 2.3). 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.

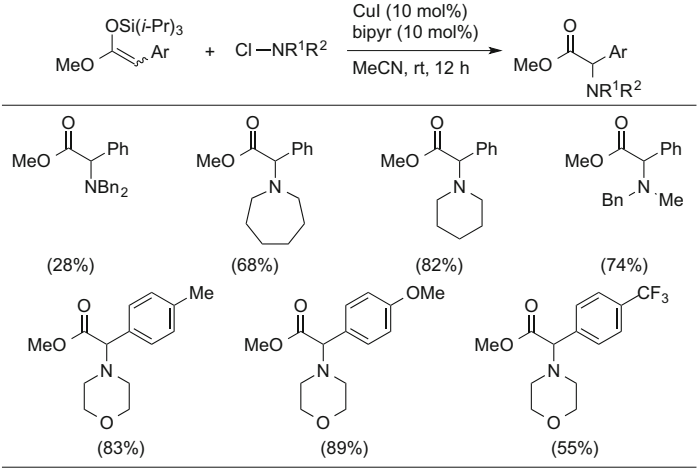
Direct amination of carbanions has also been reported using a variety of hydroxylamines as electrophilic $[NH_2]^+$ equivalents [14], including *O*-diarylphosphinyl hydroxylamines [40]. With this in mind, Vedejs and co-workers reported enolate amination using *O*-diarylphosphinyl hydroxylamines as the nitrogen source (Scheme 2.4). 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.



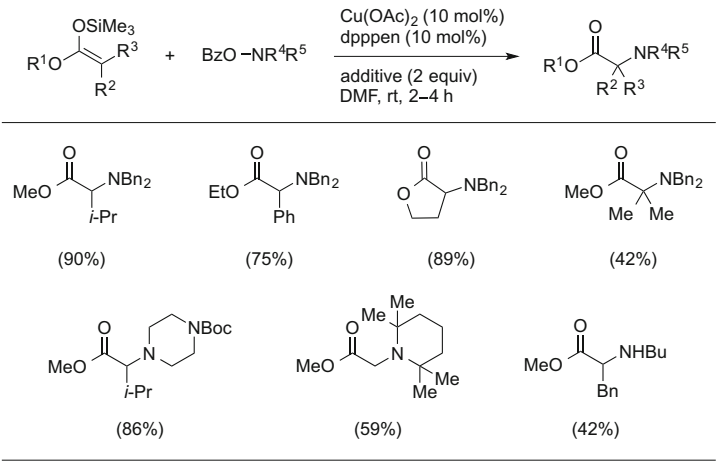
Scheme 2.4 Electrophilic amination of stabilized carbanions using *O*-diarylphosphinyl hydroxylamines

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 [41, 43]. Previously, *N*-chloramines had been used to introduce an amino group at the α-position of carbonyls via their corresponding lithium enolates [42, 48, 49]. 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 2.5) [41]. 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 benzyl methyl esters.

Simultaneously, Miura and co-workers developed a copper-catalyzed electrophilic amination of silyl ketene acetals using *O*-acylhydroxylamines as the electrophilic nitrogen source (Scheme 2.6) [43]. 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) [50, 51]. Therefore, a general and direct α-amination method is highly desirable.



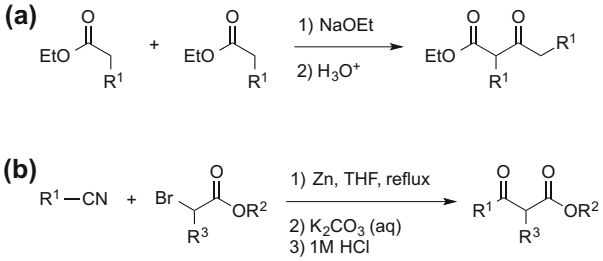
Scheme 2.5 Copper-catalyzed electrophilic amination of silyl ketene acetals via *N*-chloramines



Scheme 2.6 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 [52]. 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 2.7a) [53]. In addition to the Claisen condensation, the Blaise reaction also



Scheme 2.7 Traditional synthesis of 1,3-dicarbonyl compounds

allows for the synthesis of β-keto esters via the zinc-mediated reaction of nitriles with α-haloesters (Scheme 2.7b) [54].

2.1.3 *Zinc Enolates for α-Functionalization of Carbonyl Compounds*

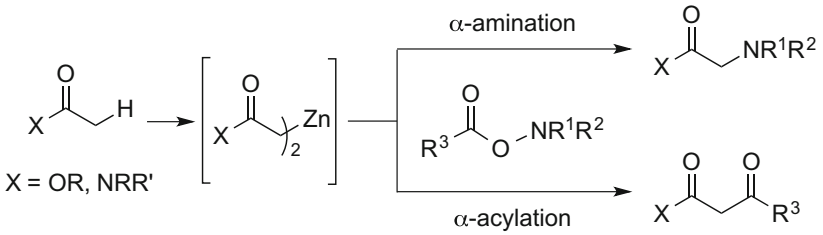
Zinc enolates have received growing interest as valuable intermediates for carbonyl α-functionalization [55–73]. In comparison to commonly used carbonyl α-alkali and alkaline-earth enolates, they offer an ideal combination of good reactivity and tolerance toward many functional groups [55–59]. So far, zinc enolates have been successfully applied toward carbon–carbon bond formation with aldol additions to carbonyls [68, 69], nucleophilic additions to alkenes [70, 71], as well as a variety of transmetallation reactions such as α-arylation [55, 56, 60–67] and α-allylation [72, 73]. 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 [1, 2].

2.2 Results and Discussion

To develop a more direct and general α-amination strategy [40, 41, 43], 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 [74–87]. Simultaneously, we envisioned that various *O*-acylhydroxylamines could also act as an electrophilic acylating agent [77, 78, 80] 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 [1, 2].

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



Scheme 2.8 Selective α-amination and α-acylation of esters and amides via the dual reactivity of *O*-acylhydroxylamines

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 2.8). 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 [3]. 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.

2.2.2 *Initial Amination Studies Using the Reformatsky Reagent*

The Reformatsky enolate was first reported by Sergey Reformatsky in the late 1800 s for condensation with aldehydes and ketones to give β-hydroxy esters [88, 89]. The organozinc reagent is easily prepared by treating α-halo esters with zinc (Scheme 2.9) and is less nucleophilic than lithium enolates or Grignard reagents.

Scheme 2.9 Preparation of Reformatsky enolate **2** [90]

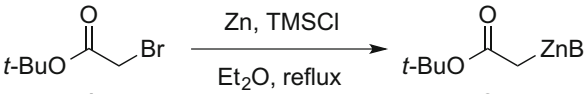
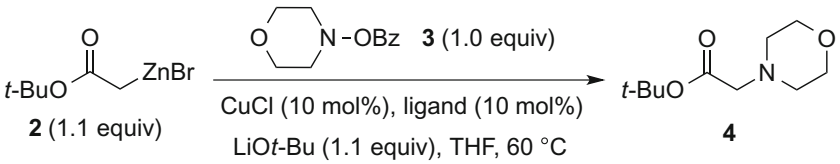


Table 2.1 Carbene ligand screen for the amination of Reformatsky enolate **2**[a]



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 ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard
[d]Reaction with pre-formed catalyst [(iPr)CuCl] gave 13 % amination

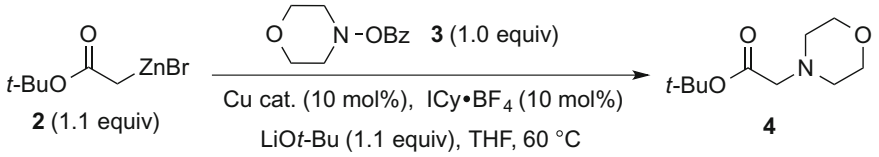
With this we chose to start the development of our α-amination method using Reformatsky enolate **2**.

Initial experiments screened Reformatsky enolate **2** and *O*-benzoylhydroxylamine **3** in the presence of CuCl and carbene ligands (Table 2.1). Using ICy·BF_4 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·HBF_4 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·BF_4 was used as the ligand for further screening and reaction optimization.

After identifying ICy·BF_4 as our best ligand, we screened copper sources for the reaction (Table 2.2). 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·BF_4 as ligand for further reaction optimization.

Finally we finished reaction optimization by investigating the effect of the nucleophile, base, solvent, and reactant equivalence (Table 2.3). 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 $ZnCl_2$ or $ZnBr_2$. 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

Table 2.2 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

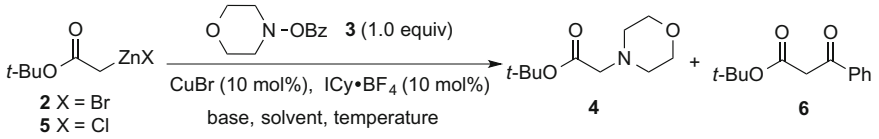
[a]Reactions conducted on a 0.2–0.3 mmol scale
[b]Time required for the complete consumption of **3**
[c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard

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).

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 2.4). The generation of the nucleophilic zinc enolate was achieved by the treatment of ester **7** with $Zn(tmp)_2$ solution [55, 56]. 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

Table 2.3 Optimization of the Reformatsky enolate amination[a]



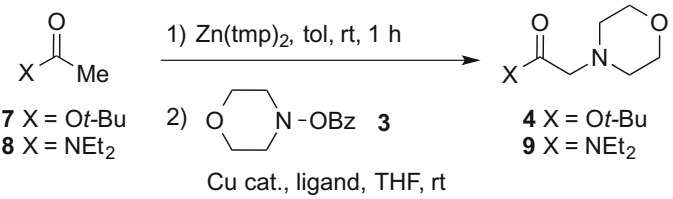
Entry	Enolate (equiv)	Base (equiv)	Solvent	Time (h)[b]	Temp (°C)	4 (%)[c]	6 (%)[c]
1	**2** (1.1)	LiO*t*-Bu (1.1)	THF	2	60	23	0
2[d]	**2** (1.1)	LiO*t*-Bu (1.1)	THF	2	60	0	28
3[e]	**5** (1.1)	LiO*t*-Bu (1.1)	THF	2	60	0	38
4	**2** (1.1)	NaO*t*-Bu (1.1)	THF	2.5	60	Trace	0
5	**2** (1.1)	KO*t*-Bu (1.1)	THF	2.5	60	0	0
6	**2** (1.1)	LiO*t*-Bu (1.1)	THF	2	rt	11	0
7	**2** (1.1)	LiO*t*-Bu (1.1)	MeCN	4	rt	11	0
8	**2** (1.1)	LiO*t*-Bu (1.1)	tol	2	rt	8	13
9	**2** (1.1)	LiO*t*-Bu (1.1)	DCM	2	rt	26	0
10	**2** (2.0)	LiO*t*-Bu (1.2)	DCM	2	rt	52	0
11	**2** (0.5)	LiO*t*-Bu (1.05)	DCM	2	rt	22	0
12[f]	**2** (2.0)	LiO*t*-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 ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard
[d]**2** was made by deprotonation of *tert*-butyl acetate with LDA then quenching the reaction with $ZnBr_2$
[e]**5** was made by deprotonation of *tert*-butyl acetate with LDA then quenching the reaction with $ZnCl_2$
[f]Reaction run using 5 mol% of CuBr and 5 mol% of ICy·BF_4

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 $CuCl_2$ provided comparable efficacy (entries 9–14). Most encouragingly, the system of $CuCl_2$ and bipyr was also effective for the amide

Table 2.4 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 ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard
[d] Reaction run in the dark

substrate **7**, and afforded the desired product **9** in 53 % yield (entry 16). Therefore, the use of $CuCl_2$ and 2,2′-bipyridine were selected as the standard amination conditions for subsequent studies.

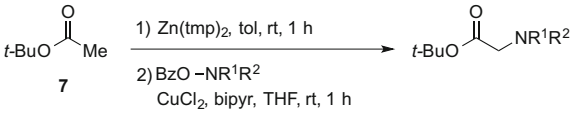
With conditions identified for α-amination, we surveyed the amine scope of the α-amination transformation using model substrate ester **7** with a variety of *O*-benzoylhydroxylamines derived from simple amines (Table 2.5). In addition to **3** (entry 1), functionalizing the α-position of **7** with 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 [91].

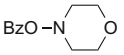
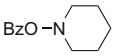
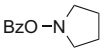
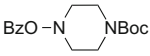
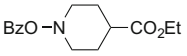
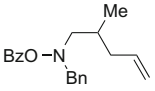
We also examined the generality of α-amination using *O*-benzoylhydroxylamine **3** on a variety of zinc enolate derivatives (Table 2.6). Compared to the model substrate *tert*-butyl acetate **7**, other acetate ester including *iso*-propyl acetate **28** and ethyl acetate **30** also provided the aminated 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 [55, 56, 68]. 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.

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 2.7). 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**.

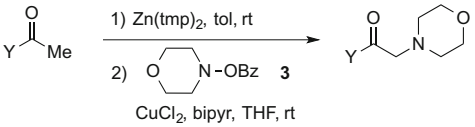
Table 2.5 Copper-catalyzed electrophilic α-amination of ester **7** with various *O*-benzoylhydroxylamines[a]

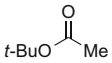
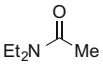
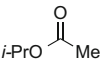
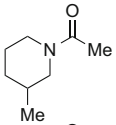
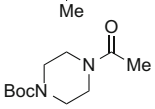
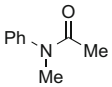


entry	*O*-acylhydroxylamine		product	yield (%)
1		**3**	**4**	98
2		**10**	**11**	98
3		**12**	**13**	95
4		**14**	**15**	98
5		**16**	**17**	99
6		**18**	**19**	96
7		**20**	**21**	42
8		**22**	**23**	97
9		**24**	**25**	98
10		**26**	**27**	99

[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), $CuCl_2$ (5 mol%), bipyr (10 mol%)

Table 2.6 Copper-catalyzed electrophilic α-amination of esters and amides with *O*-acylhydroxylamine **3**[a]



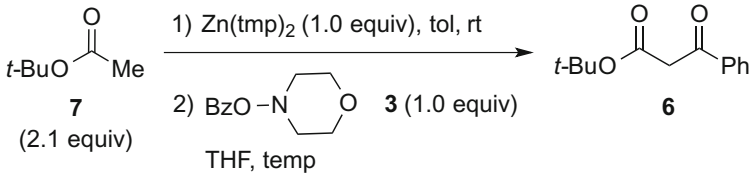
entry	ester or amide		time (h)[b]	product	yield (%)
1		**7**	1; 1	**4**	98
2		**8**	1; 1.5	**9**	53
3		**28**	1; 1.5	**29**	94
4		**30**	1; 3	**31**	90
5		**32**	1; 1.5	**33**	95
6		**34**	2; 3	**35**	70
7		**36**	0.5; 3	**37**	51

[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), $CuCl_2$ (5 mol%), bipyr (10 mol%)

[b]Reaction time for step 1 and 2, respectively

We then examined the generality of this acylation transformation for the preparation of 1,3-dicarbonyl compounds (Table 2.8). 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

Table 2.7 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

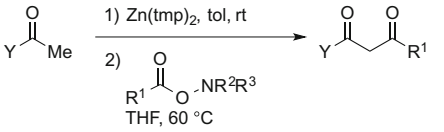
[a]Reactions conducted on a 0.2–0.3 mmol scale
[b]Time required for the complete consumption of **3**
[c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard

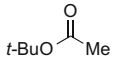
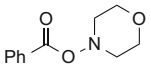
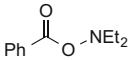
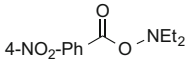
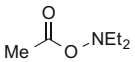
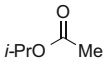
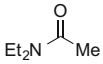
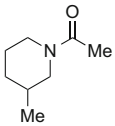
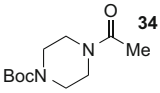
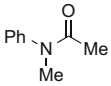
and amides were found unreactive toward acylation, suggesting that the steric hindrance significantly reduces their nucleophilicity. Despite current limitations, the α-acylation transformation nevertheless offers a rapid and efficient approach to prepare simple 1,3-dicarbonyl compounds.

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 2.10 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), the transmetallation 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) transmetallation 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**.

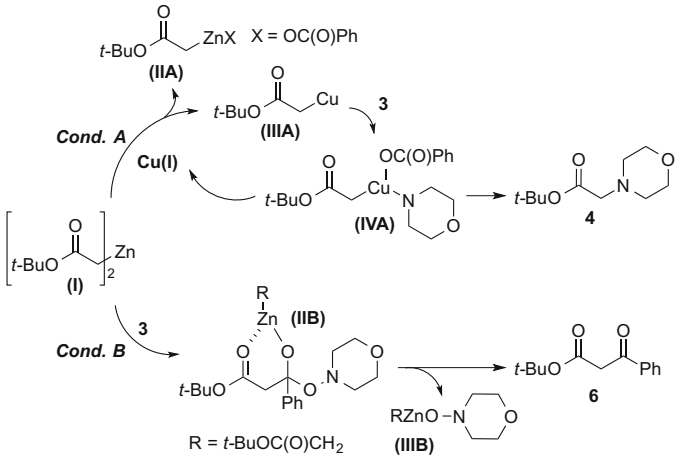
Table 2.8 α-Acylation of esters and amides via *O*-acylhydroxylamines[a]



entry	ester or amide		*O*-acylhydroxylamine		time (h)[b]	product	yield (%)
1		**7**		**3**	1; 3	**6**	82
2	**7**			**18**	1; 5	**6**	81
3	**7**			**38**	1; 3	**39**	92
4	**7**			**40**	1; 5	**41**	61
5		**28**	**3**		1; 3	**42**	90
6		**30**	**3**		1; 3	**43**	87
7		**8**	**3**		1; 5	**44**	61
8		**32**	**3**		1; 5	**45**	71
9		**34**	**3**		1; 5	**46**	75
10		**36**	**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



Scheme 2.10 Reaction pathways for the amination and acylation of zinc enolates with *O*-acylhydroxylamine **3**

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.

2.3.1 Supplemental Information

2.3.1.1 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

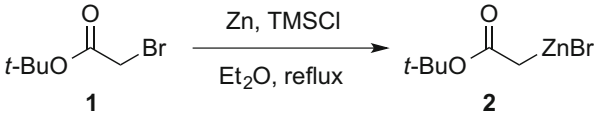
vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 × 20 cm) of Drierite, unless otherwise noted. Reaction vials were sealed with Teflon tape. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic 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 [77].

Instrumentation. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}CNMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 or 125 MHz respectively) spectrometer at ambient temperature. Chemical shifts for ^{1}H 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.

2.3.1.2 Experimental Procedures

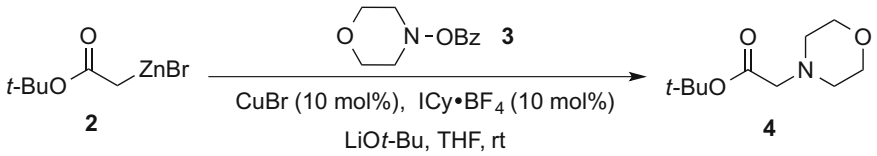
Procedure for formation of Reformatsky enolate 2 [90]



1 **2**

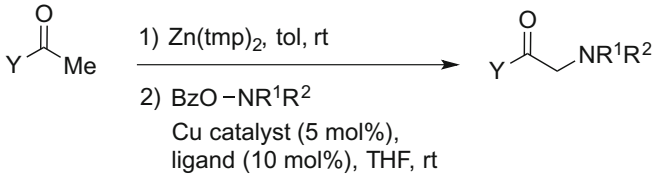
To activated Zn powder (305 mg, 4.67 mmol, 1.15 equiv) in 2-neck RBF was added THF (10 mL) and TMSCl (0.06 mL, 0.41 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 10 min then warmed to 40 °C for an additional 20 min. The reaction mixture was brought to reflux and **1** (0.6 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·BF_4 (0.01 mmol, 0.05 equiv), and LiO*t*-Bu (0.220 mmol, 1.1 equiv) added to microwave tube. Flask evacuated and refilled with N_2 (3x). DCM (1 mL) added followed by Reformatsky enolate **2** (0.36 M, 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 $NaHCO_3$ (10 mL), extracted into Et_2O (2 × 20 mL). Organic layers were combined and washed with brine (20 mL), and dried over Na_2SO_4. The mixture was filtered and evaporated under reduced pressure.

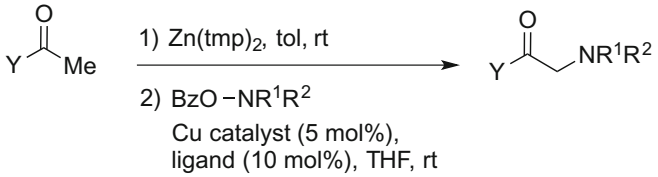
Typical procedure 1 (TP1): General experimental procedure for the α-amination reaction using $Zn(tmp)_2$ as base



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), $CuCl_2$ (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

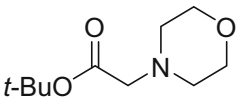
acetate–hexanes), the reaction was diluted with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted into Et_2O. The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by either column chromatography or acid-base extraction using 2 M HCl and 2 M NaOH.

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



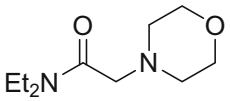
To an 8 mL microwave tube was added $Zn(tmp)_2$ (0.5 M solution in tol, 0.36 mL, 0.18 mmol, 1.0 equiv) followed by dropwise addition of the carbonyl compound (0.37 mmol, 2.1 equiv). The reaction was stirred at room temperature for 1 h and was added dropwise a solution of *O*-acylhydroxylamine (0.20 mmol, 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.

2.3.2 Characterization of Compounds

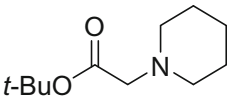


***tert*-Butyl-2-morpholinoacetate (4)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate–hexanes) gave **4** as a pale yellow oil (35.1 mg, 98 %); R_f = 0.28 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75 (t, *J* = 4.8 Hz, 4H), 3.10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

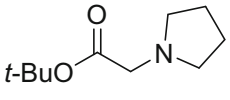
4H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 81.1, 66.7, 60.2, 53.2, 28.0; FTIR (thin film): cm^{-1} 2854, 1741, 1147, 1115; HRMS-ESI (m/z) Calcd for ($C_{10}H_{20}NO_3$) ($[M + H]^+$): 202.1438; found 202.1441.



***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); ^{1}H 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 ($C_{10}H_{21}N_2O_2$) ($[M + H]^+$): 201.1598; found 201.1601.

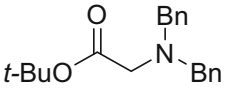


***tert*-Butyl-2-(piperidin-1-yl)acetate (11)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **11** as a pale yellow oil (34.8 mg, 98 %); R_f = 0.38 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.07 (s, 2H), 2.49 (t, *J* = 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 ($C_{11}H_{22}NO_2$) ($[M + H]^+$): 200.1645; found 200.1647.

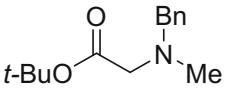


***tert*-Butyl-2-(pyrrolidin-1-yl)acetate (13)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **13** as a pale yellow oil (31.3 mg, 95 %); R_f = 0.37 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.23 (s, 2H), 2.65–2.62 (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,

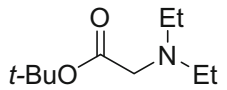
57.3, 53.7, 28.1, 23.5; FTIR (thin film): cm^{-1} 2930, 1744, 1151; HRMS-ESI (m/z) Calcd for ($C_{10}H_{20}NO_2$) ([M + H]$^+$): 186.1489; found 186.1488.



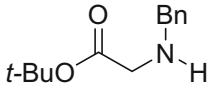
***tert*-Butyl-2-(dibenzylamino)acetate (15)**. Compound prepared according to TP1. Purification by column chromatography (25 % ethyl acetate-hexanes) gave **15** as a white solid (54.3 mg, 98 %); R_f = 0.80 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J* = 7.2, 4H), 7.32 (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 ($C_{20}H_{26}NO_2$) ([M + H]$^+$): 312.1958; found 312.1959.



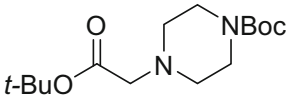
***tert*-Butyl-2-(benzyl(methyl)amino)acetate (17)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **17** as a pale yellow oil (41. 7 mg, 99 %); R_f = 0.66 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (m, 5H), 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 ($C_{14}H_{22}NO_2$) ([M + H]$^+$): 236.1645; found 236.1649.



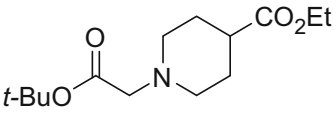
***tert*-Butyl-2-(diethylamino)acetate (19)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **19** as a pale yellow oil (32.0 mg, 96 %); R_f = 0.21 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.23 (s, 2H), 2.61 (q, *J* = 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 ($C_{10}H_{22}NO_2$) ([M + H]$^+$): 188.1645; found 188.1646.



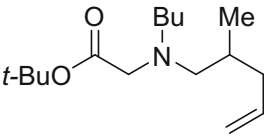
***tert*-Butyl-2-(benzylamino)acetate (21)**. Compound prepared according to TP1. Purification by column chromatography (20 % ethyl acetate-hexanes) gave **21** as a white solid (16.5 mg, 42 %); R_f = 0.58 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.34–7.24 (m, 5H), 3.79 (s, 2H), 3.31 (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 ($C_{13}H_{20}NO_2$) ([M + H]$^+$): 222.1489; found 222.1492.



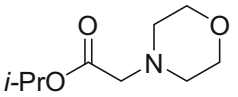
***tert*-Butyl-4-(2-(*tert*-butoxy)-2-oxoethyl)piperazine-1-carboxylate (23)**. Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **23** as a pale yellow solid (51.8 mg, 97 %); R_f = 0.52 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 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 ($C_{15}H_{29}N_2O_4$) ([M + H]$^+$): 301.2122; found 301.2126.



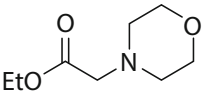
Ethyl-1-(2-(*tert*-butoxy)-2-oxoethyl)piperidine-4-carboxylate (25). Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **25** as a pale yellow oil (47.3 mg, 98 %); R_f = 0.56 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): 4.11 (q, 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 ($C_{14}H_{26}NO_4$) ([M + 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); ^{1}H 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 ($C_{16}H_{32}NO_2$) ([M + H]$^+$): 270.2428; found 270.2431.

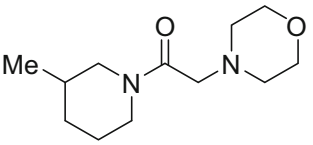


Isopropyl-2-morpholinoacetate (29). Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave **29** as a pale yellow oil (31.3 mg, 94 %); R_f = 0.20 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.06 (tt, *J* = 6.4, 6.4 Hz, 1H), 3.75 (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 ($C_9H_{19}NO_3$) ([M + H]$^+$): 188.1281; found 188.128.

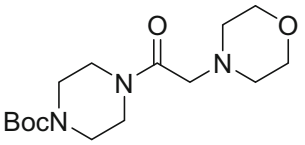


Ethyl-2-morpholinoacetate (31). Compound prepared according to TP1. Purification by column chromatography (60 % ethyl acetate-hexanes) gave **31** as a pale yellow oil (27.8 mg, 90 %); R_f = 0.16 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.18 (q, *J* = 7.2 Hz, 2H), 3.74 (t, *J* = 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 ($CDCl_3$,

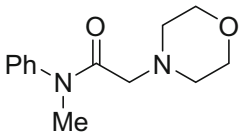
100 MHz): δ 170.0, 66.8, 60.6, 59.7, 53.3, 14.2; FTIR (thin film): cm^{-1} 2930, 2854, 1745, 1161, 1115; HRMS-ESI (m/z) Calcd for ($C_8H_{16}NO_3$) ($[M + H]^+$): 174.1125; found 174.1128.



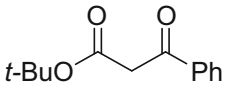
1-(3-Methylpiperidin-1-yl)-2-morpholinoethanone (33). Compound prepared according to TP1. Purification by acid-base extraction gave **33** (1:1 ratio of two conformers) as a white solid (38.3 mg, 95 %); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 4.40 (d, J = 13.2 Hz, $1H_a$), 4.37 (d, J = 13.2 Hz, $1H_b$), 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 ($C_{12}H_{23}N_2O_2$) ($[M + H]^+$): 227.1754; found 227.1755.



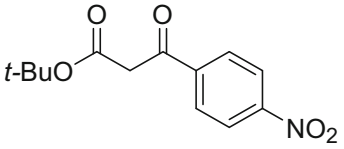
***tert*-Butyl-4-(2-morpholinoacetyl)piperazine-1-carboxylate (35)**. Compound prepared according to TP1. Purification by column chromatography (80 % ethyl acetate-hexanes) gave **35** as a white solid (39.1 mg, 70 %); R_f = 0.15 (90 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (t, 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 ($C_{15}H_{28}N_3O_4$) ($[M + H]^+$): 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 %); ^{1}H 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 ($C_{13}H_{19}N_2O_2$) ($[M + H]^+$): 235.1441; found 235.1447.

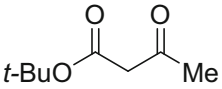


***tert*-Butyl-3-oxo-3-phenylpropanoate (6)**. Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave **6** as a colorless oil (32.1 mg, 82 %); R_f = 0.78 (20 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.72 (s, 1H *enol tautomer*), 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 [92].

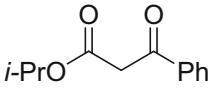


***tert*-Butyl-3-(4-nitrophenyl)-3-oxopropanoate (39)**. Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave **39** as a yellow oil (43.2 mg, 92 %); R_f = 0.80 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.70 (s, 1H *enol tautomer*), 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,

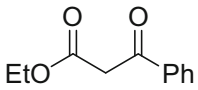
1342, 1149; HRMS-ESI (m/z) Calcd for ($C_{13}H_{14}NO_5$) ([M − H]): 264.0877; found 264.0882.



***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); ^{1}H 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 [93].

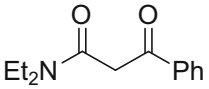


Isopropyl-3-oxo-3-phenylpropanoate (42). Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30 % ethyl acetate-hexanes) gave **42** as a pale yellow oil (37.0 mg, 90 %); R_f = 0.64 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.65 (s, 1H *enol 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 ($C_{12}H_{15}O_3$) ($[M + Na]^+$): 229.0835; found 229.0836.

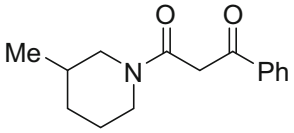


Ethyl-3-oxo-3-phenylpropanoate (43). Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30 % ethyl acetate-hexanes) gave **43** as a pale yellow oil (33.3 mg, 87 %); R_f = 0.79 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.6 (s, 1H *enol 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

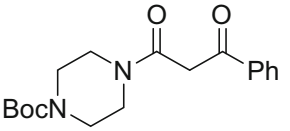
(s, 2H), 1.34 (t, J = 7.2 Hz, 3H *enol tautomer*), 1.26 (t, J = 7.2 Hz, 3H); Spectroscopic data was identical to that reported previously [94].



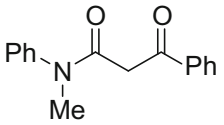
***N,N*-Diethyl-3-oxo-3-phenylpropanamide (44)**. Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave **44** as a colorless oil (23.8 mg, 61 %); R_f = 0.64 (50 % ethyl acetate-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (dt, J = 8.0, 2.0 Hz, 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 ($C_{13}H_{18}NO_2$) ([M + 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); ^{1}H 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 ($C_{15}H_{20}NO_2$) ([M + 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); ^{1}H 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 ($C_{18}H_{25}N_2O_4$) ($[M + H]^+$): 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); ^{1}H 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 ($CDCl_3$, 100 MHz): δ; HRMS-ESI (m/z) Calcd for ($C_{16}H_{15}NO_2$) ($[M + H]^+$): 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 ($C_{16}H_{16}NO_2$) ($[M + H]^+$): 254.1176; found 254.1183.

References

1. Ohfune Y (1992) Stereoselective routes toward the synthesis of unusual amino-acids. Accounts Chem Res 25(8):360–366
2. Duthaler RO (1994) Recent developments in the stereoselective synthesis of α-aminoacids. Tetrahedron 50(6):1539–1650
3. Kel'in AV, Maioli A (2003) Recent advances in the chemistry of 1,3-diketones: Structural modifications and synthetic applications. Curr Org Chem 7(18):1855–1886
4. Topol EJ, Schork NJ (2011) Catapulting clopidogrel pharmacogenomics forward. Nat Med 17 (1):40–41
5. O'Brien JJ, Campoli-Richards DM (1989) Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 37(3):233–309
6. Andrushko V, Andrushko N (2013) Stereoselective synthesis of drugs and natural products. Wiley, New York
7. Hili R, Yudin AK (2006) Making carbon-nitrogen bonds in biological and chemical synthesis. Nat Chem Biol 2(6):284–287
8. Greck C, Genet JP (1997) Electrophilic amination: New synthetic applications. Synlett 1997 (7):741–748
9. Dembech P, Seconi G, Ricci A (2000) The electrophilic amination of carbanions: an unconventional new entry to C–N bond formation. Chem Eur J 6(8):1281–1286
10. Erdik E (2004) Electrophilic α-Amination of carbonyl compounds. Tetrahedron 60(40):8747–8782
11. Greck C, Drouillat B, Thomassigny C (2004) Asymmetric electrophilic α-Amination of carbonyl groups. Eur J Org Chem 2004(7):1377–1385
12. Ciganek E (2009) Electrophilic amination of carbanions, enolates, and their surrogates. Wiley, New York
13. Janey JM (2005) Recent advances in catalytic, enantioselective α-Aminations and α-Oxygenations of carbonyl compounds. Angew Chem Int Ed 44(28):4292–4300
14. Erdik E, Ay M (1989) Electrophilic amination of carbanions. Chem Rev 89(8):1947–1980
15. Seebach D (1979) Methods of reactivity umpolung. Angew Chem Int Ed 18(4):239–258
16. Barker TJ, Jarvo ER (2011) Developments in transition-metal-catalyzed reactions using electrophilic nitrogen sources. Synthesis 2011(24):3954–3964
17. Juhl K, Jørgensen KA (2002) Catalytic asymmetric direct α-Amination reactions of 2-Keto Esters: a simple synthetic approach to optically active syn-β-Amino-α-hydroxy Esters. J Am Chem Soc 124(11):2420–2421
18. Marigo M, Juhl K, Jørgensen KA (2003) Catalytic, highly enantioselective, direct amination of β-Ketoesters. Angew Chem Int Ed 42(12):1367–1369
19. List B (2002) Direct catalytic asymmetric α-Amination of aldehydes. J Am Chem Soc 124 (20):5656–5657
20. Kumaragurubaran N, Juhl K, Zhuang W, Bøgevig A, Jørgensen KA (2002) Direct L-proline-catalyzed asymmetric α-Amination of ketones. J Am Chem Soc 124(22):6254–6255
21. Bøgevig A, Juhl K, Kumaragurubaran N, Zhuang W, Jørgensen KA (2002) Direct organo-catalytic asymmetric α-Amination of aldehydes—a simple approach to optically active α-Amino aldehydes, α-Amino alcohols, and α-Amino acids. Angew Chem Int Ed 41 (10):1790–1793
22. Evans DA, Nelson SG (1997) Chiral Magnesium Bis(sulfonamide) complexes as catalysts for the merged enolization and enantioselective amination of N-Acyloxazolidinones. A catalytic approach to the synthesis of arylglycines. J Am Chem Soc 119(27):6452–6453
23. Bui T, Hernandez-Torres G, Milite C, Barbas CF (2010) Highly enantioselective organocatalytic α-Amination reactions of aryl oxindoles: developing designer multifunctional alkaloid catalysts. Org Lett 12(24):5696–5699

24. Hasegawa Y, Watanabe M, Gridnev ID, Ikariya T (2008) Enantioselective direct amination of α-Cyanoacetates catalyzed by bifunctional chiral ru and ir amido complexes. J Am Chem Soc 130(7):2158–2159
25. Konishi H, Lam TY, Malerich JP, Rawal VH (2010) Enantioselective α-Amination of 1,3-Dicarbonyl Compounds using squaramide derivatives as hydrogen bonding catalysts. Org Lett 12(9):2028–2031
26. Mashiko T, Kumagai N, Shibasaki M (2009) Managing highly coordinative substrates in asymmetric catalysis: a catalytic asymmetric amination with a lanthanum-based ternary catalyst. J Am Chem Soc 131(41):14990–14999
27. Nandakumar MV, Ghosh S, Schneider C (2009) Enantioselective synthesis of a novel chiral 2,9-disubstituted 1,10-phenanthroline and first applications in asymmetric catalysis. Eur J Org Chem 2009(36):6393–6398
28. Simon L, Goodman JM (2012) Mechanism of amination of beta-Keto esters by Azadicarboxylates catalyzed by an axially chiral guanidine: Acyclic Keto esters react through an E Enolate. J Am Chem Soc 134(40):16869–16876
29. Terada M, Nakano M, Ube H (2006) Axially chiral guanidine as highly active and enantioselective catalyst for electrophilic amination of unsymmetrically substituted 1,3-dicarbonyl compounds. J Am Chem Soc 128(50):16044–16045
30. Zhou F, Ding M, Liu YL, Wang CH, Ji CB, Zhang YY, Zhou J (2011) Organocatalytic Asymmetric α-Amination of Unprotected 3-Aryl and 3-Aliphatic substituted oxindoles using Di-*tert*-butyl Azodicarboxylate. Adv Synth Catal 353(16):2945–2952
31. Scriven EFV, Turnbull K (1988) Azides: their preparation and synthetic uses. Chem Rev 88 (2):297–368
32. Kano T, Ueda M, Takai J, Maruoka K (2006) Direct asymmetric hydroxyamination reaction catalyzed by an axially chiral secondary amine catalyst. J Am Chem Soc 128(18):6046–6047
33. Lopez-Cantarero J, Cid MB, Poulsen TB, Bella M, Ruano JLG, Jørgensen KA (2007) Intriguing behavior of cinchona alkaloids in the enantioselective organocatalytic hydroxyamination of α-Substituted-α-cyanoacetates. J Org Chem 72(18):7062–7065
34. Momiyama N, Yamamoto H (2002) Simple synthesis of α-Hydroxyamino carbonyl compounds: new scope of the nitroso aldol reaction. Org Lett 4(21):3579–3582
35. Momiyama N, Yamamoto H (2005) Brønsted acid catalysis of achiral enamine for regio- and enantioselective nitroso aldol synthesis. J Am Chem Soc 127(4):1080–1081
36. Sandoval D, Frazier CP, Bugarin A, de Alaniz JR (2012) Electrophilic α-Amination reaction of β-Ketoesters using N-Hydroxycarbamates: merging aerobic oxidation and lewis acid catalysis. J Am Chem Soc 134(46):18948–18951
37. Shen K, Liu XH, Wang G, Lin LL, Feng XM (2011) Facile and efficient enantioselective hydroxyamination reaction: synthesis of 3-Hydroxyamino-2-Oxindoles using nitrosoarenes. Angew Chem Int Ed 50(20):4684–4688
38. Yanagisawa A, Fujinami T, Oyokawa Y, Sugita T, Yoshida K (2012) Catalytic Enantioselective N-Nitroso Aldol Reaction of γ,δ-Unsaturated δ-Lactones. Org Lett 14 (10):2434–2437
39. Vidal J, Damestoy S, Guy L, Hannachi JC, Aubry A, Collet A (1997) N-Alkyloxycarbonyl-3-aryloxaziridines: their preparation, structure, and utilization as electrophilic amination reagents. Chem Eur J 3(10):1691–1709
40. Smulik JA, Vedejs E (2003) Improved reagent for electrophilic amination of stabilized carbanions. Org Lett 5(22):4187–4190
41. Miura T, Morimoto M, Murakami M (2012) Copper-catalyzed amination of silyl ketene acetals with N-Chloroamines. Org Lett 14(20):5214–5217
42. Yamada S, Oguri T, Shioiri TJ (1972) α-Amination of carboxylic acids: a new synthesis of α-Amino-acids. Chem Soc Chem Commun 1972(10):623a

43. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of ketene silyl acetals with Hydroxylamines: electrophilic amination approach to α-Amino acids. Angew Chem Int Ed 51(47):11827–11831
44. Diels O, Behncke H (1924) Über derivate des cyclo-triazbutans. Chem Ber 57(4):653–656
45. Huisgen R, Jakab F (1954) Additionsreaktionen der NN-Doppelbindung II Der Chemismus einiger weiterer Reaktionen des Azodicarbonesters. Liebigs Ann Chem 590(1):37–54
46. Diels O (1922) Über die Azoesterreaktion der Amine und Enole. Liebgs Ann Chem 429(1):1–55
47. Regitz M, Mass G (1986) In diazo compounds, properties and synthesis. Academic, New York
48. Horiike M, Oda J, Inouye Y, Ohno M (1969) Synthesis of substituted aminomalonates by the reaction of chloramine with malonate carbanions. Agric Biol Chem 33(2):292–293
49. Oguri T, Shiori T, Yamada S (1975) Amino acids and peptides. XV.: a new synthesis of α-Amino acids by amination of α-Metalated carboxylic acids. Chem Pharm Bull 23(1):167–172
50. Mucha A, Kafarski P, Berlicki L (2011) Remarkable potential of the α-Aminophosphonate/Phosphinate structural motif in medicinal chemistry. J Med Chem 54(17):5955–5980
51. Naydenova ED, Todorov PT, Troev KD (2010) Recent synthesis of aminophosphonic acids as potential biological importance. Amino Acids 38(1):23–30
52. Kim DK, Shokova EA, Tafeenko VA, Kovalev VV (2014) Synthesis of 1,3-diketones from 3-(4-R-phenyl)propionic acids. Russian J Org Chem 50(4):464–468
53. Carey FA (2006) Organic chemistry, 6th edn. McGraw-HIll, New York
54. Rao HSP, Rafi S, Padmavathy K (2008) The Blaise reaction. Tetrahedron 64(35):8037–8043
55. Hlavinka ML, Hagadorn JR (2006) Structures of Zinc ketone enolates. Organometallics 25 (14):3501–3507
56. Hlavinka ML, Hagadorn JR (2007) $Zn(tmp)_2$: A versatile base for the selective functionalization of C−H bonds. Organometallics 26(17):4105–4108
57. Knochel P, Singer RD (1993) Preparation and reactions of polyfunctional organozinc reagents in organic synthesis. Chem Rev 93(6):2117–2188
58. Knochel P, Perea JJA, Jones P (1998) Organozinc mediated reactions. Tetrahedron 54 (29):8275–8319
59. Fürstner A (1989) Recent advancements in the reformatsky reaction. Synthesis 1989(8):571–590
60. Hama T, Ge S, Hartwig JF (2013) Palladium-Catalyzed α-Arylation of zinc enolates of esters: Reaction Conditions and Substrate Scope. J Org Chem 78(17):8250–8266
61. Hama T, Culkin DA, Hartwig JF (2006) Palladium-catalyzed intermolecular α-Arylation of zinc amide enolates under mild conditions. J Am Chem Soc 128(15):4976–4985
62. Hama T, Liu XX, Culkin DA, Hartwig JF (2003) Palladium-catalyzed α-Arylation of esters and amides under more neutral conditions. J Am Chem Soc 125(37):11176–11177
63. Fauvarque JF, Jutand A (1977) Arylation of the reformatsky reagent catalyzed by zerovalent complexes of palladium and nickel. J Organomet Chem 132(2):C17–C19
64. Fauvarque JF, Jutand A (1979) Catalysis of the arylation of the reformatsky reagent by palladium or nickel-complexes. Synthesis of Aryl Acid-Esters. J Organomet Chem 177 (1):273–281
65. Cossy J, De Filippis A, Pardo DG (2003) Palladium-catalyzed intermolecular α-Arylation of N-Protected 2-Piperidinones. Org Lett 5(17):3037–3039
66. Bentz E, Moloney MG, Westaway SM (2004) Palladium-catalysed α-arylation of esters and amides under microwave conditions. Tetrahedron Lett 45(40):7395–7397
67. Duez S, Bernhardt S, Heppekausen J, Fleming FF, Knochel P (2011) Pd-Catalyzed α-Arylation of nitriles and esters and γ-Arylation of unsaturated nitriles with TMPZnCl·LiCl. Org Lett 13(7):1690–1693
68. Dekker J, Schouten A, Budzelaar PHM, Boersma J, Vanderkerk GJM, Spek AL, Duisenberg AJM (1987) Zinc enolates: C- or O-metallation? J Organomet Chem 320(1):1–12
69. Hansen MM, Bartlett PA, Heathcock CH (1987) Preparation and reactions of an alkylzinc enolate. Organometallics 6(10):2069–2074

70. Perez-Luna A, Botuha C, Ferreira F, Chemla F (2008) Carbometalation of unactivated alkenes by zinc enolate derivatives. New J Chem 32(4):594–606
71. Denes F, Perez-Luna A, Chemla F (2010) Addition of metal enolate derivatives to unactivated carbon-carbon multiple bonds. Chem Rev 110(4):2366–2447
72. Kinoshita N, Kawabata T, Tsubaki K, Bando M, Fuji K (2006) Use of zinc enolate, free from other metals, in enantioselective palladium-catalyzed allylic alkylation. Tetrahedron 62 (8):1756–1763
73. Jarugumilli GK, Cook SP (2011) A simple, nontoxic iron system for the allylation of zinc enolates. Org Lett 13(8):1904-1907
74. Berman AM, Johnson JS (2004) Copper-catalyzed electrophilic amination of diorganozinc reagents. J Am Chem Soc 126(18):5680–5681
75. Berman AM, Johnson JS (2005) Copper-catalyzed electrophilic amination of functionalized diarylzinc reagents. J Org Chem 70(1):364–366
76. Berman AM, Johnson JS (2005) Nickel-catalyzed electrophilic amination of organozinc halides. Synlett 2005(11):1799–1801
77. Berman AM, Johnson JS (2006) Copper-catalyzed electrophilic amination of organozinc nucleophiles: documentation of O-Benzoyl Hydroxylamines as broadly useful $R_2N(+)$ and RHN(+) synthons. J Org Chem 71(1):219–224
78. Campbell MJ, Johnson JS (2007) Mechanistic studies of the Copper-catalyzed electrophilic amination of diorganozinc reagents and development of a Zinc-Free protocol. Org Lett 9 (8):1521–1524
79. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of Arylboronates with N,N-Dialkylhydroxylamines. Angew Chem Int Ed 51(15):3642–3645
80. Rucker RP, Whittaker AM, Dang H, Lalic G (2012) Synthesis of hindered anilines: copper-catalyzed electrophilic amination of aryl boronic esters. Angew Chem Int Ed 51 (16):3953–3956
81. Rucker RP, Whittaker AM, Dang H, Lalic G (2012) Synthesis of tertiary alkyl amines from terminal alkenes: Copper-catalyzed amination of alkyl boranes. J Am Chem Soc 134 (15):6571–6574
82. Xiao Q, Tian LM, Tan RC, Xia Y, Qiu D, Zhang Y, Wang JB (2012) Transition-Metal-Free electrophilic amination of arylboroxines. Org Lett 14(16):4230–4233
83. Sakae R, Hirano K, Satoh T, Miura M (2013) Formal anti-Markovnikov Hydroamination of terminal aryl alkynes with pinacolborane and hydroxylamines via Zr/Cu sequential catalysis. Chem Lett 42(10):1128–1130
84. Miki Y, Hirano K, Satoh T, Miura M (2013) Copper-catalyzed electrophilic amination of arylsilanes with hydroxylamines. Org Lett 15(1):172–175
85. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of ketene silyl acetals with hydroxylamines: electrophilic amination approach to α-Amino acids. Angew Chem Int Ed 51(47):11827–11831
86. Nguyen MH, Smith AB (2013) Copper-catalyzed electrophilic amination of organolithiums mediated by recoverable siloxane transfer agents. Org Lett 15(18):4872–4875
87. Yan X, Chen C, Zhou Y, Xi C (2012) Copper-catalyzed Electrophilic amination of alkenylzirconocenes with O-Benzoylhydroxylamines: an efficient method for synthesis of enamines. Org Lett 14(18):4750–4753
88. Reformatsky S (1887) Neue synthese zweiatomiger einbasischer Säuren aus den Ketonen. Ber Dtsch Chem Ges 20(1):1210–1211
89. Reformatsky SJ (1890) Action of zinc and ethyl chloroacetate on ketones and aldehydes. Russ Phys Chem Soc 22:44–64
90. Greszler SN, Johnson JS (2009) Diastereoselective synthesis of pentasubstituted gamma-butyrolactones from silyl glyoxylates and ketones through a double Reformatsky reaction.. Angew Chem Int Ed 48(20):3689–3691

91. Noack M, Göttlich R (2002) Copper(I) Catalysed cyclisation of unsaturated N-Benzoyloxyamines: An Aminohydroxylation via radicals. Chem Commun 2002(5):536–537
92. Galliford CV, Scheidt CA (2008) An unusual dianion equivalent from acylsilanes for the synthesis of substituted β-Keto esters Chem Commun 2008(16):1926–1928
93. Medson C, Smallridge AJ, Trewhella MA (1997) The stereoselective preparation of β-hydroxy esters using a yeast reduction in an organic solvent. Tetrahedron: Asymmetry 8(7):1049–1054
94. tritzky AR, Wang Z, Wang M, Wilkerson CR, Hall CD, Akhmedov NG (2004) Preparation of β-Keto Esters and β-Diketones by C-Acylation/Deacetylation of Acetoacetic Esters and Acetonyl Ketones with 1-Acylbenzotriazoles. J Org Chem 69(20):6617–6622

Chapter 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 (Fig. 3.1) [1]. Most notably they have been used as herbicides [2, 3] and antibiotics [4, 5]. They have also been used as plant virucides [6–8], anticancer agents [9, 10], and inhibitors of HIV proteases [11–13]. 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 [9, 14–16]. The biological importance of this class of compounds continues to drive efforts toward their efficient and rapid synthesis [17–44]. 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.

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 α-amino phosphonic acids continues to drive efforts toward their efficient and rapid synthesis. Traditionally α-amino phosphonic acids have been

Portions of this chapter have been published: (a) McDonald, S. L.; Wang, Q. "Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives," *Angew. Chem. Int. Ed.* **2014**, *53*, 1867–1871; (b) 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.

S.L. McDonald, *Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds*, Springer Theses, DOI 10.1007/978-3-319-38878-6_3

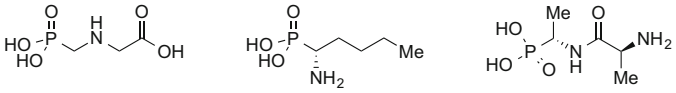
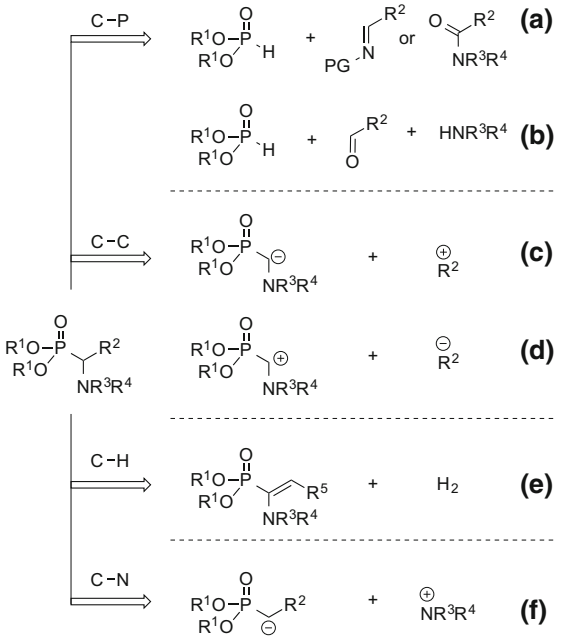


Fig. 3.1 Selected examples of biologically important α-amino phosphonic acids

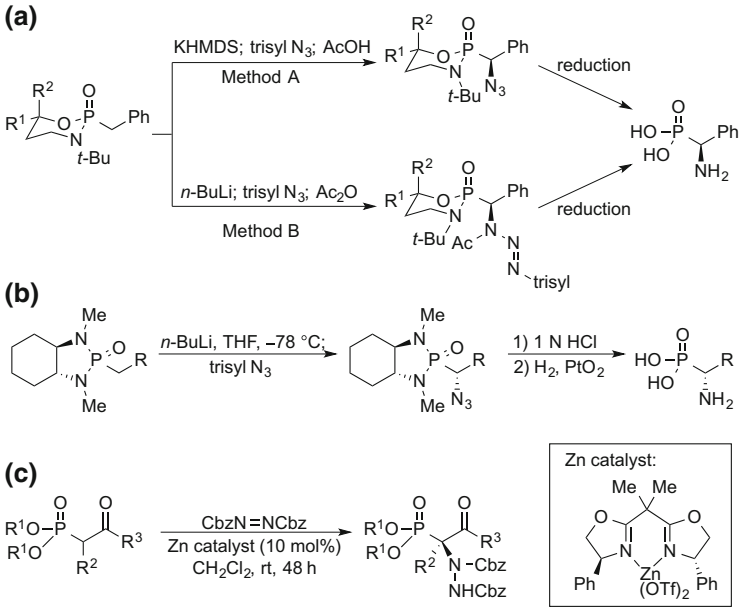


Scheme 3.1 Synthetic approaches toward the preparation of α-amino phosphonic acids

prepared through the formation of C–P bonds, specifically the Pudovik reaction (Scheme 3.1, pathway a) or the Kabachnik-Fields reaction (Scheme 3.1, pathway b). The Pudovik reaction involves the hydrophosphonylation of an imine [20–29] or an amide [30], whereas, the Kabachnik-Fields reaction is a three-component reaction of an amine, an aldehyde, and a dialkyl phosphite [31–33]. Alternatively, C–C bond formation has also been used for the synthesis of α-amino phosphonic acids, either through the addition of an anionic phosphonic analogue of glycine to an electrophilic carbon atom (Scheme 3.1, pathway c) or through the addition of a nucleophile to a cationic phosphoglycine equivalent (Scheme 3.1, pathway d) [34–37]. Additionally, they have also been prepared through formation of C–H bonds through catalytic hydrogenation of enamido phosphonates (Scheme 3.1, pathway e) [38–41].

3.1.1.2 Synthesis of α-Amino Phosphonic Acids Through Formation of C–N Bonds

Complementarily to other approaches (e.g., by C–P, C–C, or C–H bond formation), C–N bond formation using an electrophilic aminating agent represents an attractive approach for a rapid and direct access to α-amino phosphonic acids and their derivatives (Scheme 3.1, pathway f) [17–19, 42–44]. Toward this end, previous studies on α-amination reactions of phosphonic acid derivatives have involved the use of highly reactive azodicarboxylate esters or arylsulfonyl azides. Denmark and co-workers reported the asymmetric amination of chiral oxazaphosphorinanes and phosphonamides with 2,4,6-triisopropylbenzenesulfonyl (trisyl) azide for the synthesis of α-amino phosphonic acids (Scheme 3.2a) [17]. The reaction involved the amination of phosphorus-stabilized α-anions and subsequent trapping of the triazine intermediates with either acetic acid (Method A) or acetic anhydride (Method B). The efficiency of the reaction was contingent on the structure of the auxiliary, the nature of the *P*-alkyl substituent, and the amination method. They were able to achieve up to 93 % amination and >20/1 selectivity; however, yields and selectivity were 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 3.2b) [18]. In 2005, Jørgensen reported a catalytic enantioselective amination of β-keto phosphonates



Scheme 3.2 Previous methods for the electrophilic α-amination of phosphonic acid derivatives

(Scheme 3.2c) [19]. The reactions were catalyzed by a chiral bisoxazolinezinc ditriflate using dibenzyl azodicarboxylate as the aminating reagent. The desired α-amino products were obtained in good isolated yields and high enantiomeric excesses. For all of these methods, the corresponding α-amino phosphonic acids were obtained after the reduction of the N–N bond. Despite the success, they were restricted to the formation of primary amines (the installation of an NH_2 group), the use of highly electrophilic nitrogen atoms, and a narrow scope of phosphonates because they needed to be compatible with the reductive cleavage conditions.

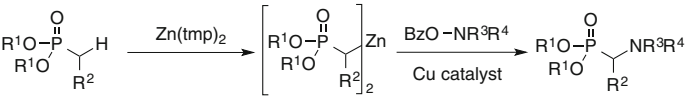
Even with the significant advances in the arsenal of modern synthetic chemistry, the potential of C–N bond formation as a powerful approach to α-amino phosphonic acids remains underexplored. To date, no examples of C–N bond formation have been reported for directly introducing secondary or tertiary amines to the α-position of phosphonates, thus limiting the synthesis and discovery of novel α-amino phosphonic acids of biological importance [16, 45, 46]. 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 [47–50]. 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 $Zn(tmp)_2$, and we examined the reactivity of the α-zincates toward electrophilic amination using *O*-benzoylhydroxylamines (Scheme 3.3). Different from those organozinc reagents typically prepared from their organolithium



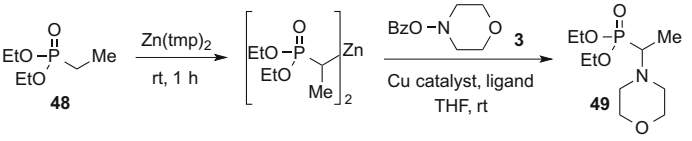
Scheme 3.3 Direct approach to α-amino phosphonates

or Grignard precursors [47–50], the phosphonate α-zincates are proposed to form via an H/Zn exchange [51–53]. 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.

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 3.1). As the α-zincation of substituted phosphonates had not been reported previously, we first confirmed that the corresponding α-zincate of **48** was effectively formed upon the treatment with $Zn(tmp)_2$.

Table 3.1 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 CH_2Br_2 as a quantitative internal standard
[d]**3** recovered in 24 % yield
[e]**3** recovered in 25 % yield

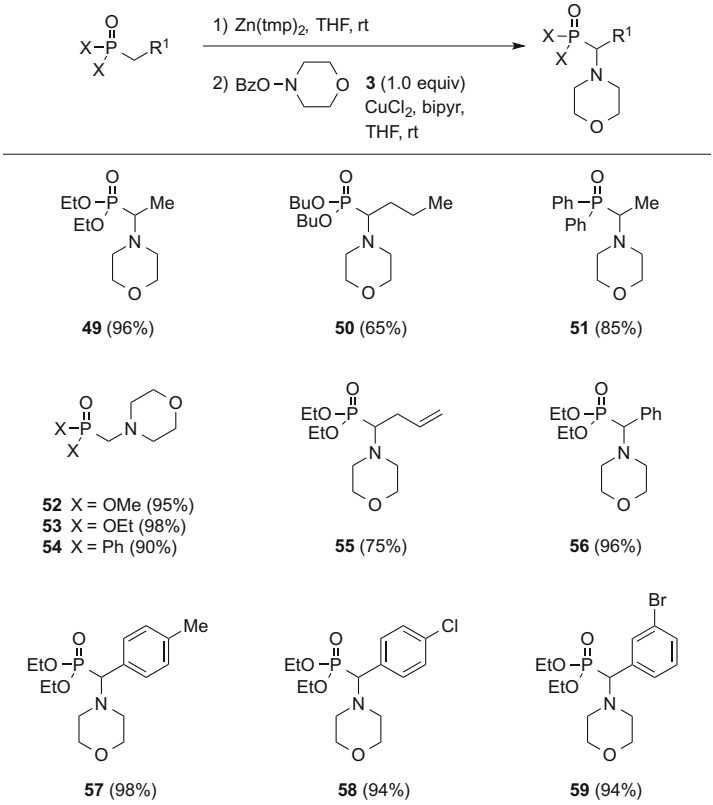
See SI Having successfully obtained the α-zincate through deprotonation of **48** with $Zn(tmp)_2$, we examined the formation of α-aminophosphonate **49** by using different copper salts as catalysts. No amination occurred when the α-zincate was treated with *O*-benzoylhydroxylamine **3** alone (entry 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). We then examined several ligands in order to accelerate the reaction. 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 $CuCl_2$-catalyzed amination (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). With this information, we chose $CuCl_2$/2,2′-bipyridine as the standard catalyst system for the amination step.

With effective α-amination conditions identified, we examined the scope of phosphonates and derivatives using **3** (Table 3.2). 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 provide direct access to a broad array of amines at the α-position of a phosphonate. On this basis, we did an extensive study of aminations using phosphonate **60** (Table 3.3). A diverse range of cyclic amines was successfully installed to form several α-amino phosphonates, including *N*-Boc piperazine **62**, diazepane **63**, tetrahydroisoquinoline **64**, and piperidines **65** and **66**. Various acyclic amines similarly gave the corresponding α-amino phosphonates **67–70** in excellent yields. However, sterically encumbered *N*,*N*-diisopropyl-substituted amine **71** was not formed. Meanwhile, phosphonate **61**, which lacks an α-substituent, gave the desired *N*,*N*-diisopropylamino derivative **72** in 90 % yield. For the synthesis of secondary amines, the amination of phosphonates **60** and **61** was effective, providing **73** and **74**, in 40 and 78 % yield, respectively. This outcome 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.

Finally, we evaluated the efficacy of this transformation on a larger scale with a lower catalyst loading of only 0.5 mol% of $CuCl_2$ and 1 mol% of bipyridine ligand (Scheme 3.4). 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.

Table 3.2 α-Amination of different phosphonates and phosphine oxides[a]

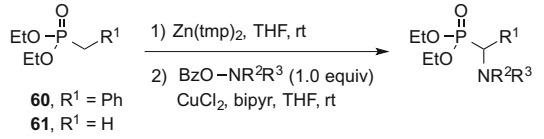


[a]Isolated yields. Standard reaction conditions: phosphonate or phosphine oxide (2.1 equiv), **3** (1.0 equiv), $Zn(tmp)_2$ (1.0 equiv), $CuCl_2$ (10 mol%), bipyr (20 mol%), rt. Reactions typically run on 0.2 mmol scale

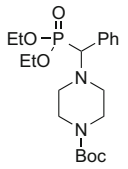
3.2.3 *Mechanism Studies*

To investigate if the copper-catalyzed amination step possibly involved any radical intermediates, we performed the following two control experiments: (1) the reaction of **76**, which contains a cyclopropyl substituent at the α-position, with model *O*-benzoylhydroxylamine **3**, and (2) the amination using *O*-benzoyl-*N*-butyl-*N*-(2-methyl-pent-4-en-1-yl)hydroxylamine **79** with model phosphonate **60** (Scheme 3.5). For the reaction of model *O*-benzoylhydroxylamine **3** with phosphonate **76**, aminated product **77** was exclusively formed in excellent yield, and the ring-opened product **78** was not observed [54]. In the reaction with *O*-benzoylhydroxylamine **79** with phosphonate **60**, we obtained the desired amination product

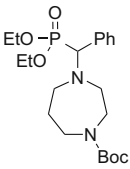
Table 3.3 Amine scope of phosphonate amination[a]



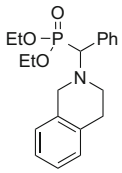
60, R^1 = Ph
61, R^1 = H



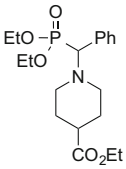
62 (98%)



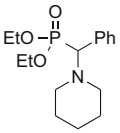
63 (75%)



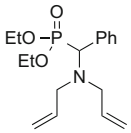
64 (90%)



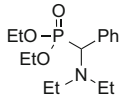
65 (92%)



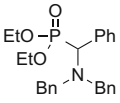
66 (93%)



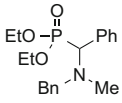
67 (89%)



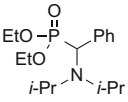
68 (97%)



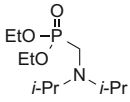
69 (95%)



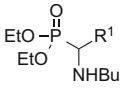
70 (90%)



71 (0%)[b]



72 (90%)

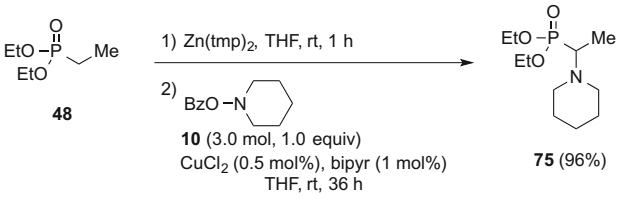


R = Ph **73** (40%)
R = H **74** (78%)

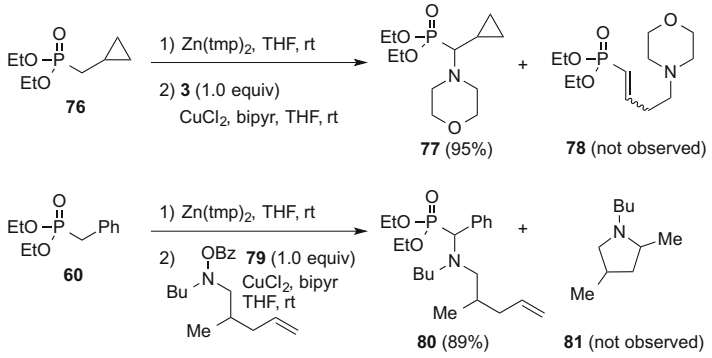
[a]Isolated yields. Standard reaction conditions: **60** or **61** (2.1 equiv), *O*-acylhydroxylamine (1.0 equiv), $Zn(tmp)_2$ (1.0 equiv), $CuCl_2$ (10 mol%), bipyr (20 mol%), rt. Reactions typically run on 0.2 mmol scale

[b]Yields determined by ^1H NMR spectroscopy using CH_2Br_2 as a quantitative internal standard, and confirmed by GC/MS

80 exclusively. The exposure of *O*-benzoylhydroxylamine **79** to the copper catalyst did not give any detectable cyclization product, such as the pyrrolidine-containing structure from the copper-catalyzed 5-*exo* radical cyclization reported previously [55]. The results from both experiments suggests the absence of long-lived aminyl radical species or copper-coordinated radical complex in the amination pathway.

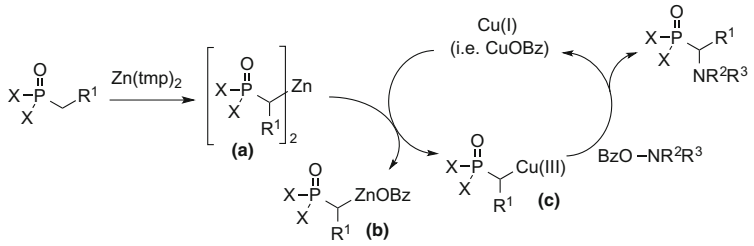


Scheme 3.4 An efficient scale-up amination reaction with 0.5 mol% catalyst loading



Scheme 3.5 Control experiments to probe possible radical intermediates

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 3.6). 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



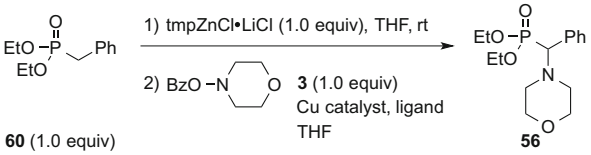
Scheme 3.6 Proposed reaction pathway for the α-amination of phosphonates and phosphine oxides

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.

3.2.4 *Alternative Method for the α-Zincation of Phosphonates*

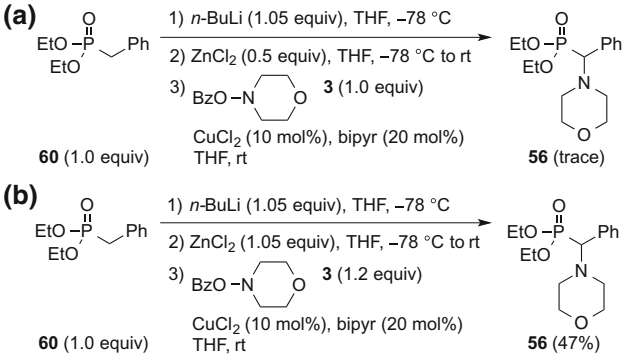
Despite the utility of the amination using $Zn(tmp)_2$ as the base for zincation, it was not without some limitations. Most importantly, the use of $Zn(tmp)_2$ required the sacrifice of an additional equivalent of the phosphonate moiety. To overcome this drawback, we explored the amination of an alternative monozinc intermediate using tmpZnCl•LiCl [56–61] in the C–H metallation step (Table 3.4). 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

Table 3.4 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 CH_2Br_2 as a quantitative internal standard
[c]1.2 equivalents of *O*-benzoylhydroxylamine **3** used
[d]1.5 equivalents of *O*-benzoylhydroxylamine **3** used



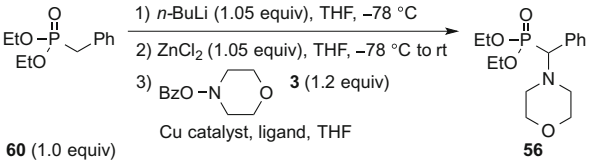
Scheme 3.7 Phosphonate amination using a Li/Zn exchange for α-zincation

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 tmpZnCl•LiCl as the base for the amination of phosphonates seemed promising, the yields were not comparable to those observed using $Zn(tmp)_2$ as the base.

Next, we decided to look into α-zincation that was achieved via *n*-BuLi deprotonation followed by Li/Zn exchange using $ZnCl_2$ (Scheme 3.7). We attempted the amination using either 0.5 or 1.05 equivalents of $ZnCl_2$ for the Li/Zn exchange, which mimicked the bis and mono α-zincates, respectively. When 0.5 equivalents of $ZnCl_2$ was used only trace amount of amination was observed (Scheme 3.7a). On the other hand, when 1.05 equivalents of $ZnCl_2$ was used, α-amino phosphonate **56** was observed in 47 % (Scheme 3.7b). 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 3.7a; therefore, amination was limited.

We attempted to optimize the amination reaction using a Li/Zn exchange for α-zincation (Table 3.5). 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 3.5 Optimization of phosphonate amination using a Li/Zn exchange for α-zincation[a]



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

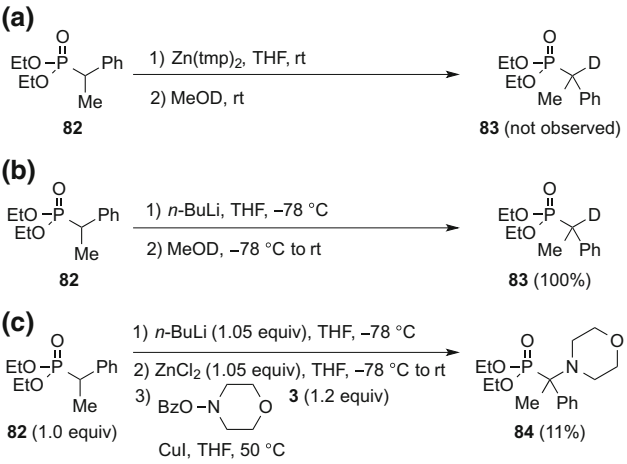
[a]Reactions run on a 0.2 mmol scale
[b]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard

3.2.5 α-Amination of Disubstituted Phosphonates

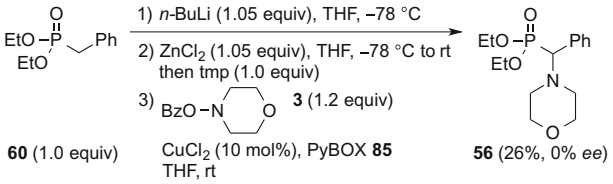
Attempts to aminate disubstituted phosphonates were unsuccessful using $Zn(tmp)_2$ because deprotonation did not provide the required α-zincates (Scheme 3.8a). This is most likely due to the increased steric hindrance. To see if deprotonation of the α-proton was possible, we used *n*-BuLi for deprotonation of phosphonate **82** followed by a deuterium quench. We were pleased to observe full deuterium incorporation at the α-position (Scheme 3.8b). 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 3.9c).

3.2.5.1 Development of an Asymmetric α-Amination

The previous aminations developed by Denmark [17], Hanessian [18], and Jørgensen [19] 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



Scheme 3.8 Deprotonation studies and amination of disubstituted phosphonate **82**



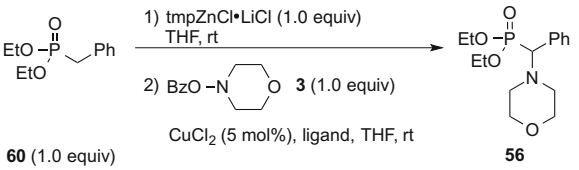
Scheme 3.9 Study of the effect of 2,2,6,6-tetramethylpiperadine on stereoselctivity of the asymmetric α-amination of phosphonates

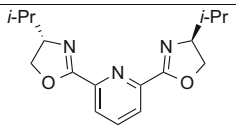
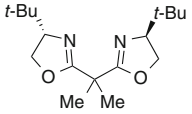
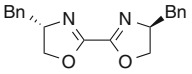
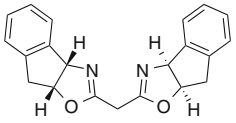
α-amino phosphonates and required the sacrifice of one equivalent of phosphonate. Therefore, an asymmetric electrophilic amination for the synthesis of secondary and tertiary α-amino phosphonic acids and derivatives is needed. Moreover, this would be the first example of an asymmetric α-amination of phosphonates incorporating primary and secondary amines. Towards this we sought to develop an asymmetric amination from two approaches—chiral ligands and chiral auxiliaries.

3.2.5.2 Asymmetric α-Amination of Phosphonates via Chiral Ligands

We started our development of an asymmetric amination by screening $CuCl_2$ with various chiral ligands (Table 3.6). 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

Table 3.6 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]	*ee* (%)
1		**85**	31	0
2		**86**	28	0
3		**87**	28	0
4		**88**	24	0

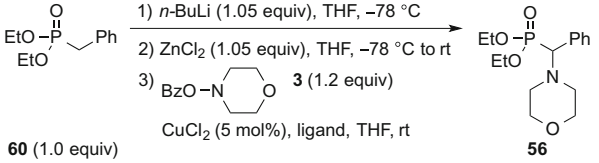
[a]Reactions run on 0.2 mmol scale

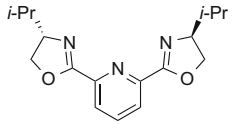
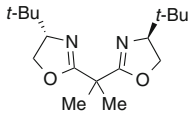
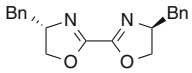
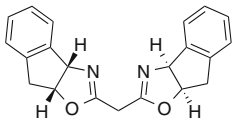
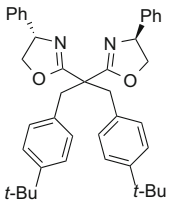
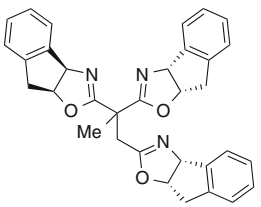
[b]Isolated yields

(entries 2–4). Amination was also observed albeit in low yields. However, the reactions using the PyBOX and BOX ligands were not stereoselective.

Next, we screened chiral ligands for the amination using the Li/Zn exchange for α-zincation (Table 3.7). 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

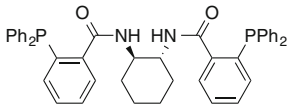
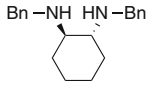
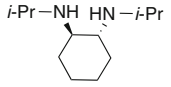
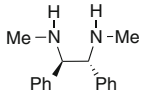
Table 3.7 Chiral ligand screen for the development of an asymmetric α-amination of phosphonates using a Li/Zn exchange for α-zincation[a]



entry	ligand (8 mol%)		yield (%)[b]	*ee* (%)
1		**85**	21	14
2		**86**	40	4
3		**87**	39	10
4		**88**	11	2
5		**89**	26	10
6		**90**	27	0

(continued)

Table 3.7 (continued)

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

was not observed. For reactions using diamine ligands **92–94**, α-amino phosphonate **56** was isolated in low yields; however, enantioselectivity was not observed for the amination reaction.

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 3.9). 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.

3.2.5.3 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

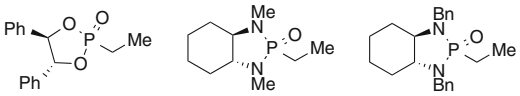
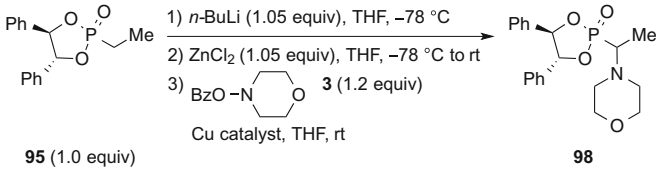


Fig. 3.2 Chiral phosphonates and phosphonamides for asymmetric α-amination

Table 3.8 Screen of copper salts for the amination of chiral phosphonate **95**[a]



Entry	Cu catalyst (10 mol%)	Yield (%)[b]	*dr* (%)
1	CuCl	0	–
2	CuI	0	–
3	$CuCl_2$	0	–
4	$Cu(OAc)_2$	0	–

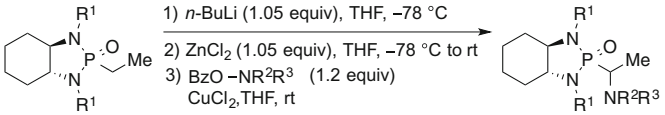
[a]Reactions run on a 0.2 mmol scale
[b]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard

phosphonamides shown in Fig. 3.2. 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.

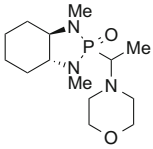
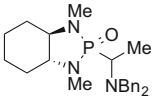
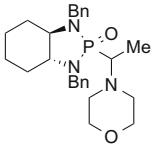
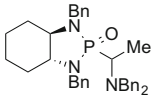
First, we attempted the amination of chiral phosphonate **95** using the Li/Zn exchange method for α-zincation (Table 3.8). Copper(I) and copper(II) salts were screened. Despite consumption of *O*-benzoylhydroxylamine **3** in the reactions, amination was not observed.

Next, we screened chiral phosphonamides **96** and **97** for the amination (Table 3.9). We hoped to achieve amination using *O*-benzoylhydroxylamine **3** or *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine **14** with $CuCl_2$ as the catalyst. In these attempted reactions, the corresponding *O*-benzoylhydroxylamine was consumed; however amination was not observed.

Table 3.9 Asymmetric amination of chiral phosphonamides[a]



R^1 = Me **96**
R^1 = Bn **97**

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 ^{1}H NMR spectroscopy with CH_2Br_2 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

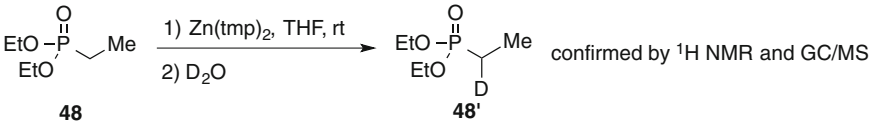
3.4.1 General Information

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 × 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 $KMnO_4$ 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 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 [50].

Instrumentation. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C 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 ($CHCl_3$: 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.

3.4.2 Initial Deprotonation of Phosphonates



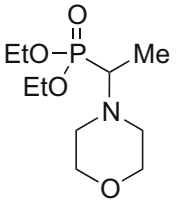
48 **48'**

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 $Zn(tmp)_2$. 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

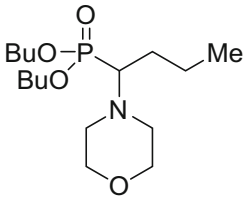
General Experimental Procedure for the Amination Reaction using $Zn(tmp)_2$. A mixture of $Zn(tmp)_2$ (0.5 M solution in toluene, 0.4 mL, 0.2 mmol, 1.0 equiv) and phosphonate or phosphine oxide (0.42 mmol, 2.1 equiv) was stirred at room temperature for 1 h. To the above mixture, was added a mixture of *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

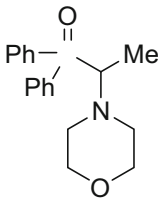


Diethyl-(1-morpholinoethyl)phosphonate (49). Purification by column chromatography (5 % isopropanol–hexanes) gave **49** as a colorless oil (96 %); $R_f = 0.26$ (100 % ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.21–4.08 (m, 4H), 3.68 (t, J = 4.4 Hz, 4H), 2.93 (dq, J = 18.8, 7.2 Hz, 1H), 2.81 (dt, J = 11.6,

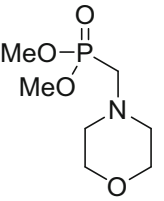
4.4 Hz, 2H), 2.62 (dt, J = 11.6, 4.4 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 67.4, 62.0 (d, J_{C-P} = 157.9 Hz), 58.1, 56.8, 50.3, 50.3, 16.6, 16.5, 9.4; FTIR (thin film): cm^{-1} 2852, 1227, 1019, 959; HRMS-ESI (m/z) Calcd for ($C_{10}H_{23}NO_4P$) ($[M+H]^+$): 252.1359; found: 252.1364.



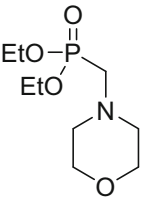
Dibutyl-(1-morpholinobutyl)phosphonate (50). Purification by column chromatography (5 % isopropanol–hexanes) gave **50** as a colorless oil (65 %); R_f = 0.30 (5 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.10–3.97 (m, 4H), 3.68–3.59 (m, 4H), 2.85–2.70 (m, 5H), 1.77–1.5 (m, 7H), 1.42–1.34 (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_{C-P} = 6.9 Hz), 64.8 (d, J_{C-P} = 6.9 Hz), 61.9 (d, J_{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 ($C_{16}H_{35}NO_4P$) ($[M+H]^+$): 336.2298; found: 336.2296.



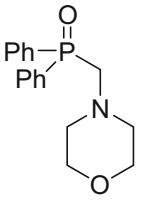
(1-Morpholinoethyl)diphenylphosphine oxide (51). Purification by column chromatography (30 % isopropanol–hexanes) gave **51** as a white solid (85 %); R_f = 0.44 (30 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89–7.79 (m, 4H), 7.52–7.42 (m, 6H), 3.56–3.53 (m, 4H), 3.43 (dt, J = 15.8, 7.2 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 ($C_{18}H_{23}NO_2P$) ($[M+H]^+$): 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); ^{1}H 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 ($C_7H_{17}NO_4P$) ($[M+H]^+$): 210.089; found: 210.0895.

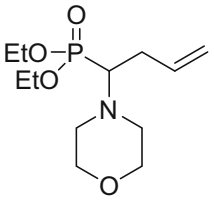


Diethyl-(morpholinomethyl)phosphonate (53). Purification by column chromatography (100 % ethyl acetate pretreated with 2 % Et_3N) gave **53** as a colorless oil (98 %); R_f = 0.08 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.20–4.11 (m, 4H), 3.71 (t, *J* = 4.6 Hz, 4H), 2.77 (d, *J* = 11.6 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_{C-P} = 6.8 Hz), 55.2 (d, J_{C-P} = 10.2 Hz), 53.5, 16.4 (d, J_{C-P} = 5.7 Hz); FTIR (thin film): cm^{-1} 2853, 1218, 1113, 1018, 958; HRMS-ESI (m/z) Calcd for ($C_9H_{21}NO_4P$) ($[M+H]^+$): 238.1203; found: 238.1207.

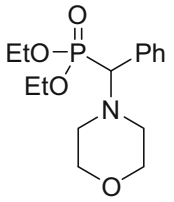


(Morpholinomethyl)diphenylphosphine oxide (54). Purification by column chromatography (30 % isopropanol–hexanes) gave **54** as a white solid (90 %); R_f = 0.23 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82–7.77 (m, 4H), 7.54–7.41 (m, 6H), 3.62 (t, *J* = 4.8 Hz, 4H), 3.22 (d, *J* = 6.4 Hz, 2H), 2.63 (t,

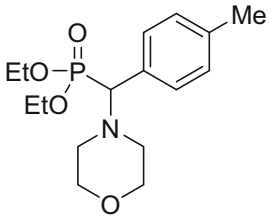
J = 4.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.7, 131.9, 131.8, 131.2 (d, J_{C-P} = 8.7 Hz), 130.7, 138.8, 128.5, 128.4, 66.9, 58.7 (d, J_{C-P} = 87.7 Hz), 55.7, 55.7; FTIR (thin film): cm^{-1} 2920, 2852, 1437, 1180, 1117; HRMS-ESI (m/z) Calcd for ($C_{17}H_{21}NO_2P$) ([M+H]$^+$): 302.1304; found: 302.1312.



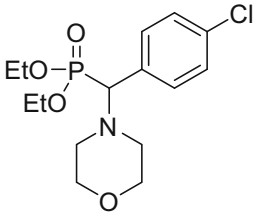
Diethyl-(1-morpholinobut-3-en-1-yl)phosphonate (55). Purification by column chromatography (5 % isopropanol–hexanes) gave **55** as a colorless oil (75 %); R_f = 0.18 (5 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.94–5.84 (m 1H), 5.14–5.03 (m, 2H), 4.20–4.05 (m, 4H), 3.63 (dt, J = 5.6, 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_{C-P} = 13.7 Hz), 116.6, 67.6, 62.5 (d, J_{C-P} = 144.3 Hz), 62.3 (d, J_{C-P} = 6.7 Hz), 61.2 (d, J_{C-P} = 6.7 Hz), 50.5, 50.5, 30.7 (d, J_{C-P} = 6.0 Hz), 16.6 (d, J_{C-P} = 5.3 Hz), 16.5 (d, J_{C-P} = 5.3 Hz); FTIR (thin film): cm^{-1} 2977, 2850, 1639, 1452, 1228, 1115, 1018, 953; HRMS-ESI (m/z) Calcd for ($C_{12}H_{25}NO_4P$) ([M+H]$^+$): 278.1516; found: 278.1519.



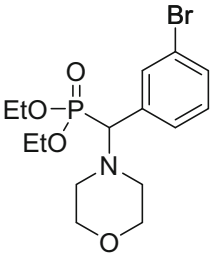
Diethyl-(morpholino(phenyl)methyl)phosphonate (56). Purification by column chromatography (5 % isopropanol–hexanes) gave **56** as a colorless oil (96 %); R_f = 0.30 (5 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47–7.45 (m, 2H), 7.38–7.32 (m, 3H), 4.25–4.17 (m, 2H), 3.93–3.88 (m, 1H), 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_{C-P} = 8.0 Hz), 128.2, 128.1, 68.6 (J_{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 ($C_{15}H_{25}NO_4P$) ([M+H]$^+$): 314.1516; found: 314.1512.



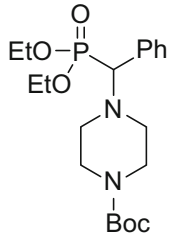
Diethyl-(morpholino(*p*-tolyl)methyl)phosphonate (57). Purification by column chromatography (5 % isopropanol–hexanes) gave **57** as a pale yellow solid (98 %); R_f = 0.25 (5 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.26–4.14 (m, 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 ($CDCl_3$, 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 ($C_{16}H_{27}NO_4P$) ($[M+H]^+$): 328.1672; found: 328.1668.



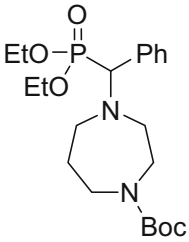
Diethyl-((4-chlorophenyl)(morpholino)methyl)phosphonate (58). Purification by column chromatography (5 % isopropanol–hexanes) gave **58** as a colorless oil (94 %); R_f = 0.20 (5 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J* = 9.6 Hz, 2H), 7.29 (d, *J* = 9.6 Hz, 2H), 4.28–4.13 (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); ^{13}C NMR ($CDCl_3$, 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 ($C_{15}H_{24}ClNO_4P$) ($[M+H]^+$): 348.1126; found: 348.1126.



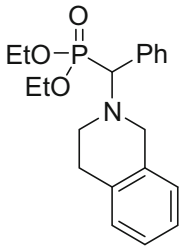
Diethyl-((3-bromophenyl)(morpholino)methyl)phosphonate (59). Purification by column chromatography (5 % isopropanol–hexanes) gave **59** as a colorless oil (94 %); R_f = 0.34 (10 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58–7.56 (m, 1H), 7.47–7.42 (m, 2H), 7.25–7.20 (m, 1H), 4.26–4.15 (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, $J_{C–P}$ = 9.0 Hz), 131.2, 129.8, 128.9 (d, $J_{C–P}$ = 7.5 Hz), 122.3, 68.0 (d, $J_{C–P}$ = 160.1 Hz), 67.2, 63.0, 62.4, 51.9, 51.8, 16.5 (d, $J_{C–P}$ = 5.6 Hz), 16.2 (d, $J_{C–P}$ = 5.6 Hz); FTIR (thin film): cm^{-1} 2977, 2851, 1473, 1238, 1115, 1020, 959, 864; HRMS-ESI (m/z) Calcd for ($C_{15}H_{24}BrNO_4P$) ([M+H]$^+$): 392.0721; found: 392.0727.



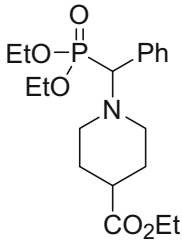
***tert*-Butyl-4-((diethoxyphosphoryl)(phenyl)methyl)piperazine-1-carboxylate (62)**. Purification by column chromatography (50 % ethyl acetate–hexanes) gave **62** as a white solid (98 %); R_f = 0.65 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.41 (m, 2H), 7.35–7.28 (m, 3H), 4.27–4.15 (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, $J_{C–P}$ = 8.5 Hz), 126.9, 79.5, 68.1 (d, $J_{C–P}$ = 160.5 Hz), 62.9 (d, $J_{C–P}$ = 3.9 Hz), 62.2 (d, $J_{C–P}$ = 3.9 Hz), 51.0 (2H), 44.1, 43.5, 28.3, 16.5 (d, $J_{C–P}$ = 5.5 Hz), 16.1 (d, $J_{C–P}$ = 5.5 Hz); FTIR (thin film): cm^{-1} 2976, 2929, 1688, 1420, 1242, 1160, 1020, 955; HRMS-ESI (m/z) Calcd for ($C_{20}H_{34}N_2O_5P$) ([M+H]$^+$): 413.2200; found: 413.2203.



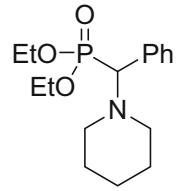
***tert*-Butyl-4-((diethoxyphosphoryl)(phenyl)methyl)-1,4-diazepane-1-carboxylate (63)**. Purification by column chromatography (5 % isopropanol–hexanes) gave **63** as a colorless oil (75 %); R_f = 0.46 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz, 60 °C): δ 7.50–7.47 (m, 2H), 7.35–7.28 (m, 3H), 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, $J_{C–P}$ = 16.9 Hz), 128. 2, 127.9, 79.3, 68.2 (d, $J_{C–P}$ = 157.8 Hz), 62.9 (d, $J_{C–P}$ = 7.0 Hz), 62.2 (d, $J_{C–P}$ = 7.0 Hz), 55.1, 53.9, 47.8, 47.2, 45.3, 28.8, 16.7 (d, $J_{C–P}$ = 5.5 Hz), 16.3 (d, $J_{C–P}$ = 5.5 Hz); FTIR (thin film): cm^{-1} 2976, 2929, 1685, 1411, 1163, 1009, 958; HRMS-ESI (m/z) Calcd for ($C_{21}H_{36}N_2O_5P$) ([M+H]$^+$): 427.2356; found: 427.2357.



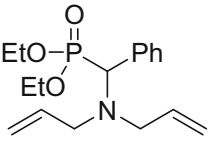
Diethyl-((3,4-dihydroisoquinolin-2(1*H*)-yl)(phenyl)methyl)phosphonate (64). Purification by column chromatography (5 % isopropanol–hexanes) gave **64** as a colorless oil (90 %); R_f = 0.54 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.54 (m, 2H), 7.39–7.30 (m, 3H), 7.09–7.04 (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, $J_{C–P}$ = 8.3 Hz), 128.5, 128.1, 128.0, 126.5, 125.9, 125.4, 67.6 (d, $J_{C–P}$ = 159.7 Hz), 63.0 (d, $J_{C–P}$ = 3.0 Hz), 62.2 (d, $J_{C–P}$ = 3.0 Hz), 54.0 (d, $J_{C–P}$ = 11.3 Hz), 48.4 (d, $J_{C–P}$ = 6.9 Hz) 29.5, 16.5 (d, $J_{C–P}$ = 5.7 Hz), 16.2 (d, $J_{C–P}$ = 5.7 Hz); FTIR (thin film): cm^{-1} 2978, 2904, 1453, 1243, 1012, 959; HRMS-ESI (m/z) Calcd for ($C_{20}H_{27}NO_3P$) ([M+H]$^+$): 360.1723; found: 360.1725.



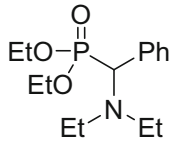
Ethyl-1-((diethoxyphosphoryl)(phenyl)methyl)piperidine-4-carboxylate (65). Purification by column chromatography (100 % ethyl acetate) gave **65** as a colorless oil (92 %); R_f = 0.66 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.43 (m, 2H), 7.35–7.30 (m, 3H), 4.28–4.17 (m, 2H), 4.07 (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_{C-P} = 8.6 Hz), 128.0, 127.9, 68.2 (J_{C-P} = 161 Hz), 63.1, 62.0, 60.2, 52.6 (d, J_{C-P} = 14.3 Hz), 49.3, 40.8, 28.8, 28.7, 16.6 (d, J_{C-P} = 5.6 Hz), 16.1 (d, J_{C-P} = 5.1 Hz), 14.1; FTIR (thin film): cm^{-1} 2980, 1730, 1245, 1027, 962; HRMS-ESI (m/z) Calcd for ($C_{19}H_{31}NO_5P$) ($[M+H]^+$): 384.1934; found: 384.1935.



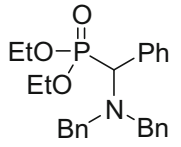
Diethyl-(phenyl(piperidin-1-yl)methyl)phosphonate (66). Purification by column chromatography (30 % ethyl acetate–hexanes) gave **66** as a yellow oil (93 %); R_f = 0.63 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47–7.44 (m, 2H), 7.35–7.29 (m, 3H), 4.32–4.18 (m, 2H), 3.96–3.86 (m, 1H), 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_{C-P} = 8.8 Hz), 127.9, 127.7, 68.6 (d, J_{C-P} = 160.9 Hz), 63.1 (d, J_{C-P} = 6.1 Hz), 61.9 (d, J_{C-P} = 6.1 Hz), 52.5, 52.4, 26.4, 24.0, 16.5 (d, J_{C-P} = 5.6 Hz), 16.1 (d, J_{C-P} = 5.6 Hz); FTIR (thin film): cm^{-1} 2929, 2807, 1451, 1242, 1019, 953; HRMS-ESI (m/z) Calcd for ($C_{16}H_{27}NO_3P$) ($[M+H]^+$): 312.1723; found: 312.1726. (m/z) Calcd for ($C_{15}H_{27}NO_3P$) ($[M+H]^+$): 300.1723; found: 300.1724.



Diethyl-((diallylamino)(phenyl)methyl)phosphonate (67). Purification by column chromatography (30 % ethyl acetate–hexanes) gave **67** as a colorless oil (89 %); R_f = 0.51 (10 % isopropanol–hexanes); ^{1}H 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, $J_{C–P}$ = 5.3 Hz), 130.7 (d, $J_{C–P}$ = 8.9 Hz), 128.1, 127.8, 117.4, 63.1 (d, $J_{C–P}$ = 5.0 Hz), 61.9 (d, $J_{C–P}$ = 5.0 Hz), 60.5 (d, $J_{C–P}$ = 163.0 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 ($C_{17}H_{27}NO_3P$) ([M +H]$^+$): 324.1723; found: 324.1727.

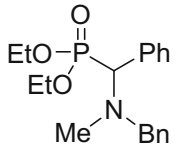


Diethyl-((diethylamino)(phenyl)methyl)phosphonate (68). Purification by column chromatography (5 % isopropanol–hexanes) gave **68** as a colorless oil (97 %); R_f = 0.43 (10 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.45 (m, 2H), 7.34–7.28 (m, 3H), 4.24 (quin, J = 7.2 Hz, 2H), 4.16 (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, $J_{C–P}$ = 8.6 Hz), 128.0, 127.6, 62.8, 62.5 (d, $J_{C–P}$ = 155.6 Hz), 61.5, 44.8, 44.7, 16.5 (d, $J_{C–P}$ = 4.9 Hz), 16.2 (d, $J_{C–P}$ = 4.1 Hz), 13.3; FTIR (thin film): cm^{-1} 2970, 1243, 1023, 958; HRMS-ESI

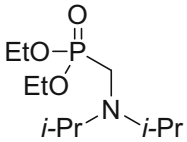


Diethyl-((dibenzylamino)(phenyl)methyl)phosphonate (69). Purification by column chromatography (30 % ethyl acetate–hexanes) gave **69** as a white solid (95 %); R_f = 0.75 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ

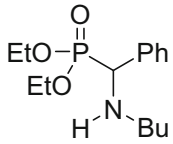
7.50–7.47 (m, 2H), 7.44–7.37 (m, 7H), 7.34–7.30 (m, 4H), 7.27–7.22 (m, 2H), 4.32 (d, J = 13.6 Hz, 2H), 4.26–4.13 (m, 2H), 4.16 (d, J = 25.6 Hz, 1H), 3.92–3.85 (m, 1H), 3.72–3.65 (m, 1H), 3.26 (d, J = 13.6 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.5, 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 ($C_{25}H_{31}NO_3P$) ($[M+H]^+$): 424.2036; found: 424.2043.



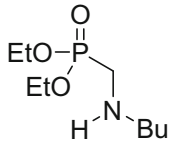
Diethyl-((benzyl(methyl)amino)(phenyl)methyl)phosphonate (70). Purification by column chromatography (30 % ethyl acetate–hexanes) gave **70** as a colorless oil (90 %); R_f = 0.44 (30 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.48 (m, 2H), 7.41–7.30 (m, 7H), 7.27–7.25 (m, 1H), 4.30–4.18 (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_{C-P} = 8.6 Hz), 128.9, 128.2, 128.1, 128.0, 127.0, 64.9 (d, J_{C-P} = 161.0 Hz), 62.5 (d, J_{C-P} = 3.3 Hz), 62.1 (d, J_{C-P} = 3.3 Hz), 59.8, (d, J_{C-P} = 12.6 Hz), 39.8 (d, J_{C-P} = 4.6 Hz), 16.5 (d, J_{C-P} = 6.0 Hz), 16.1 (d, J_{C-P} = 6.0 Hz); FTIR (thin film): cm^{-1} 2979, 2797, 1452, 1242, 1022, 957; HRMS-ESI (m/z) Calcd for ($C_{19}H_{27}NO_3P$) ($[M+H]^+$): 348.1723; found: 348.1728.



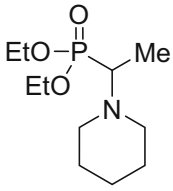
Diethyl-((diisopropylamino)methyl)phosphonate (72). Purification by column chromatography (10 % isopropanol–hexanes) gave **72** as a pale yellow oil (90 %); R_f = 0.46 (10 % isopropanol–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.14 (quin, J = 7.2 Hz, 4H), 3.24–3.14 (m, 2H), 2.85 (d, J = 10 Hz, 2H), 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_{C-P} = 6.5 Hz), 48.7 (d, J_{C-P} = 6.9 Hz), 41.7 (d, J_{C-P} = 173.2 Hz), 20.4, 16.5 (d, J_{C-P} = 5.6 Hz); FTIR (thin film): cm^{-1} 2965, 1262, 1022, 956; HRMS-ESI (m/z) Calcd for ($C_{11}H_{27}NO_3P$) ($[M+H]^+$): 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); ^{1}H 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, $J_{C–P}$ = 6.0 Hz), 128.3, 127.7, 62.8 (d, $J_{C–P}$ = 21.9 Hz), 61.2 (d, $J_{C–P}$ = 151.5 Hz), 47.8 (d, $J_{C–P}$ = 16.6 Hz), 32.0, 29.7, 20.3, 16.4 (d, $J_{C–P}$ = 5.6 Hz), 16.2 (d, $J_{C–P}$ = 5.6 Hz), 13.9; FTIR (thin film): cm^{-1} 3305, 2926, 2857, 1453, 1240, 1022, 962; HRMS-ESI (m/z) Calcd for ($C_{15}H_{27}NO_3P$) ($[M+H]^+$): 300.1729; found: 300.1727.

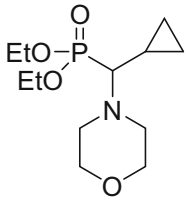


Diethyl-((butylamino)methyl)phosphonate (74). Purification by column chromatography (10 % isopropanol–hexanes) gave **74** as a pale yellow oil (78 %); R_f = 0.34 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.19–4.07 (m, 4H), 2.97 (d, *J* = 12.4 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 1.64 (br 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, $J_{C–P}$ = 5.8 Hz), 51.0 (d, $J_{C–P}$ = 15.0 Hz), 45.2 (d, $J_{C–P}$ = 152.6 Hz), 31.8, 20.2, 16.5 (d, $J_{C–P}$ = 5.5 Hz), 13.9; FTIR (thin film): cm^{-1} 2929, 1229, 1098, 1023, 961; HRMS-ESI (m/z) Calcd for ($C_9H_{23}NO_3P$) ($[M+H]^+$): 224.1410; found: 224.1411.

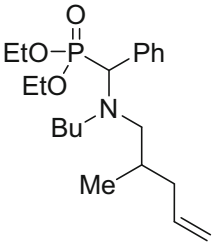


Diethyl-(1-(piperidin-1-yl)ethyl)phosphonate (75). Purification by column chromatography (5 % isopropanol–hexanes) gave **75** as a yellow oil (96 %); R_f = 0.31 (100 % ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.21–4.03 (m, 4H), 2.95 (dq,

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_{C-P} = 6.5 Hz), 61.0 (d, J_{C-P} = 6.5 Hz), 58.0 (d, J_{C-P} = 150.7 Hz), 51.2 51.1, 26.6, 24.4, 16.6 (d, J_{C-P} = 5.3 Hz), 16.5 (d, J_{C-P} = 5.3 Hz), 9.5 (d, J_{C-P} = 2.8 Hz); FTIR (thin film): cm^{-1} 2931, 1232, 1018, 953; HRMS-ESI (m/z) Calcd for ($C_{11}H_{25}NO_3P$) ([M+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); ^{1}H 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_{C-P} = 157.1 Hz), 67.6, 62.8, 61.4, 51.4, 51.4, 16.6, 16.5, 6.4 (d, J_{C-P} = 5.3 Hz), 5.6 (d, J_{C-P} = 16.8 Hz), 3.4; FTIR (thin film): cm^{-1} 2851, 1238, 1021, 951; HRMS-ESI (m/z) Calcd for ($C_{12}H_{25}NO_4P$) ([M+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); ^{1}H 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, $J_{C–P}$ = 7.4 Hz), 136.8 (d, $J_{C–P}$ = 4.7 Hz), 130.7 (d, $J_{C–P}$ = 4.7 Hz), 127.9, 127.7, 62.3 (d, $J_{C–P}$ = 161.2 Hz), 62.1, 62.0, 61.9, 58.1 (d, $J_{C–P}$ = 8.7 Hz), 57.8 (d, $J_{C–P}$ = 8.7 Hz), 51.3 (t, $J_{C–P}$ = 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 ($C_{21}H_{37}NO_3P$) ($[M+H]^+$): 382.2506; found: 382.2505.

References

1. Mucha A, Kafarski P, Berlicki L (2011) Remarkable potential of the α-Aminophosphonate/Phosphinate structural motif in medicinal chemistry. J Med Chem 54(17):5955–5980
2. Forlani G, Berlicki L, Duo M, Dziedziola G, Giberti S, Bertazzini M, Kafarski P (2013) Synthesis and evaluation of effective inhibitors of plant δ^1-Pyrroline-5-Carboxylate reductase. J Agric Food Chem 61(28):6792–6798
3. Forlani G, Occhipinti A, Berlicki L, Dziedziola G, Wieczorek A, Kafarski P (2008) Tailoring the structure of aminobisphosphonates to target plant P5C reductase. J Agric Food Chem 56 (9):3193–3199
4. Allen JG, Atherton FR, Hall MJ, Hassall CH, Holmes SW, Lambert RW, Nisbet LJ, Ringrose PS (1978) Phosphonopeptides, a new class of synthetic antibacterial agents. Nature 272:56–58
5. Atherton FR, Hassall CH, Lambert RW (1986) Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl)phosphonic acid. J Med Chem 29(1):29–40
6. Chen MH, Chen Z, Song BA, Bhadury PS, Yang S, Cai XJ, Hu DY, Xue W, Zeng S (2009) Synthesis and antiviral activities of Chiral Thiourea derivatives containing an α-Aminophosphonate Moiety. J Agric Food Chem 57(4):1383–1388
7. Hu DY, Wan QQ, Yang S, Song BA, Bhadury PS, Jin LH, Yan K, Liu F, Chen Z, Xue W (2008) Synthesis and Antiviral activities of Amide derivatives containing the α-Aminophosphonate Moiety. J Agric Food Chem 56(3):998–1001
8. Long N, Cai X-J, Song BA, Yang S, Chen Z, Bhadury PS, Hu DY, Jin L-H, Xue W (2008) Synthesis and Antiviral Activities of Cyanoacrylate derivatives containing an α-Aminophosphonate Moiety. J Agric Food Chem 56(13):5242–5246
9. Kafarski P, Lejczak B (2001) Aminophosphonic acids of potential medical importance. Curr Med Chem Anticancer Agents 1(3):301–312
10. Lavielle G, Hautefaye P, Schaeffer C, Boutin JA, Cudennec CA, Pierre A (1991) New α-Amino phosphonic acid-derivatives of Vinblastine - chemistry and Antitumor-activity. J Med Chem 34(7):1998–2003
11. Allen MC, Fuhrer W, Tuck B, Wade R, Wood JM (1989) Renin inhibitors. Synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond. J Med Chem 32(7):1652–1661
12. Bird J, Demello RC, Harper GP, Hunter DJ, Karran EH, Markwell RE, Mileswilliams AJ, Rahman SS, Ward RW (1994) Synthesis of novel N-phosphonoalkyl dipeptide inhibitors of human collagenase. J Med Chem 37(1):158–169
13. Smith WW, Bartlett PA (1998) Macrocyclic inhibitors of penicillopepsin. 3. design, synthesis, and evaluation of an inhibitor bridged between P2 and P1'. J Am Chem Soc 120(19): 4622–4628
14. Kafarski P, Lejczak B (1991) Biological activity of aminophosphonic acids. Phosphorus Sulfur 63:193–215

15. Kudzin ZH, Kudzin MH, Drabowicz J, Stevens CV (2011) Aminophosphonic acids - Phosphorus analogues of natural amino acids. Part 1: Syntheses of α-Aminophosphonic acids. Curr Org Synth 15(12):2015–2071
16. Kukhar VP, Soloshonok VA, Solodenko VA (1994) Asymmetric-synthesis of phosphorus analogs of amino-acids. Phosphorus Sulfur 92:239–264
17. Denmark SE, Chatani N, Pansare SV (1992) Asymmetric electrophilic amination of Chiral phosphorus-stabilized Anions. Tetrahedron 489(11):2191–2208
18. Hanessian S, Bennani YL (1994) Electrophilic Amination and Azidation of Chiral α-Alkyl phosphonamides: Asymmetric syntheses of α-Amino α-Alkyl phosphonic acids. Synthesis 1994(12):1272–1274
19. Bernardi L, Zhuang W, Jørgensen KA (2005) An easy approach to optically active α-Amino phosphonic acid derivatives by Chiral Zn(II)-Catalyzed enantioselective amination of phosphonates. J Am Chem Soc 127(16):5772–5773
20. Pudovik AN (1952) Dokl Akad Nauk SSSR 74:1528
21. Pudovik AN, Konovalova I (1979) Addition reactions of Esters of phosphorus(III) acids with unsaturated systems. Synthesis 1979(2):81
22. Sasai H, Arai S, Tahara Y, Shibasaki M (1995) Catalytic asymmetric synthesis of α-Amino phosphonates using Lanthanoid-Potassium-BINOL complexes. J Org Chem 60(21): 6656–6657
23. Smith AB, Yager KM, Taylor CM (1995) Enantioselective synthesis of diverse α-Amino phosphonate diesters. J Am Chem Soc 117(44):10879–10888
24. Lefebvre IM, Evans SA (1997) Studies toward the asymmetric synthesis of α-Amino phosphonic acids via the addition of phosphites to Enantiopure Sulfinimines. J Org Chem 62(22):7532–7533
25. Davis FA, Lee S, Yan H, Titus DD (2001) Asymmetric synthesis of quaternary α-Amino phosphonates using Sulfinimines. Org Lett 3(11):1757–1760
26. Joly GD, Jacobsen EN (2004) Thiourea-Catalyzed Enantioselective Hydrophosphonylation of Imines: Practical access to enantiomerically enriched α-Amino phosphonic acids. J Am Chem Soc 126(13):4102–4103
27. Abell JP, Yamamoto H (2008) Catalytic enantioselective pudovik reaction of Aldehydes and Aldimines with Tethered Bis(8-quinolinato) (TBOx) Aluminum complex. J Am Chem Soc 130(32):10521–10523
28. Nakamura S, Hayashi M, Hiramatsu Y, Shibata N, Funahashi Y, Toru T (2009) Catalytic Enantioselective Hydrophosphonylation of Ketimines using Cinchona Alkaloids. J Am Chem Soc 131(51):18240–1841
29. Ingle GK, Liang YX, Mormino MG, Li GL, Fronczek FR, Antilla JC (2011) Chiral Magnesium BINOL phosphate-catalyzed phosphination of imines: Access to enantioenriched α-Amino phosphine oxides. Org Lett 13(6):2054–2057
30. Gao Y, Huang Z, Zhuang R, Xu J, Zhang P, Tang G, Zhao Y (2013) Direct transformation of Amides into α-Amino phosphonates via a reductive phosphination process. Org Lett 15 (16):4214–4217
31. Fields EK (1952) The synthesis of esters of substituted Amino phosphonic acids. J Am Chem Soc 74(6):1528–1531
32. Kabachnik MI, Medved TY (1953) New method for the synthesis of 1-aminoalkylphosphonic acids. Bull Acad Sci USSR 2(5):769–777
33. Cheng X, Goddard R, Buth G, List B (2008) Direct catalytic asymmetric three-component Kabachnik–fields reaction. Angew Chem Int Ed 47(27):5079–5081
34. Hanessian S, Bennani YL (1990) A versatile asymmetric synthesis of α-Amino α-Alkyl-phosphonic acids of high enantiomeric purity. Tetrahedron Lett 31(45):6465–6468
35. Groth U, Richter L, Schollkopf U (1992) Asymmetric-synthesis of enantiomerically pure phosphonic analogs of Glutamic-acid and proline. Tetrahedron 48(1):117–122
36. Hannour S, Roumestant ML, Viallefont P, Riche C, Martinez J, El Hallaoui A, Ouazzani F (1998) Asymmetric synthesis of (2S,3R,4R)-ethoxycarbonylcyclopropyl phosphonoglycine. Tetrahedron: Asymmetry 9(13):2329–2332

37. Kobayashi S, Kiyohara H, Nakamura Y, Matsubara R (2004) Catalytic asymmetric synthesis of α-Amino phosphonates using enantioselective carbon-carbon bond-forming reactions. J Am Chem Soc 126(21):6558–6559
38. Burk MJ, Stammers TA, Straub JA (1999) Enantioselective synthesis of α-Hydroxy and α-Amino phosphonates via catalytic asymmetric Hydrogenation. Org Lett 1(3):387–390
39. Hammerschmidt F, Hanbauer M (2000) Transformation of Arylmethylamines into α-Aminophosphonic acids via metalated phosphoramidates: rearrangement of partly configurationally stable N-Phosphorylated α-Aminocarbanions. J Org Chem 65(19): 6121–6131
40. Gridnev ID, Yasutake M, Imamoto T, Beletskaya IPP (2004) Asymmetric hydrogenation of α,β-unsaturated phosphonates with Rh-BisP* and Rh-MiniPHOS catalysts: Scope and mechanism of the reaction. Proc Natl Acad Sci USA 101(15):5385–5390
41. Goulioukina NS, Shergold IA, Bondarenko GN, Ilyin MM, Davankov VA, Beletskaya IP (2012) Palladium-Catalyzed Asymmetric Hydrogenation of N-Hydroxy-α-imino Phosphonates using Brønsted acid as activator: The first catalytic Enantioselective approach to Chiral N-Hydroxy-α-Amino phosphonates. Adv Synth Catal 354(14–15):2727–2733
42. Jommi G, Miglierini G, Pagliarin R, Sello G, Sisti M (1992) Studies toward a model for predicting the Diastereoselectivity in the electrophilic amination of Chiral 1,3,2-Oxazaphospholanes. Tetrahedron 48(35):7275–7288
43. Pagliarin R, Papeo G, Sello G, Sisti M, Paleari L (1996) Design of β-amino alcohols as chiral auxiliaries in the electrophilic amination of 1,3,2-oxazaphospholanes. Tetrahedron 52 (43):13783–13794
44. Jiang Q, Ren Y, Feng J (2008) Direct binding with histone deacetylase 6 mediates the reversible recruitment of parkin to the centrosome. J Neurosci 28(48):12993–13002
45. Naydenova ED, Todorov PT, Troev KD (2010) Recent synthesis of aminophosphonic acids as potential biological importance. Amino Acids 38(1):23–30
46. Ordonez M, Rojas-Cabrera H, Cativiela C (2009) An overview of Stereoselective synthesis of α-Aminophosphonic acids and derivatives. Tetrahedron 65(1):17–49
47. Berman AM, Johnson JS (2004) Copper-catalyzed electrophilic amination of diorganozinc reagents. J Am Chem Soc 126(18):5680–5681
48. Berman AM, Johnson JS (2005) Copper-catalyzed electrophilic amination of functionalized Diarylzinc reagents. J Org Chem 70(1):364–366
49. Berman AM, Johnson JS (2005) Nickel-catalyzed electrophilic amination of organozinc halides. Synlett 2005(11):1799–1801
50. Berman AM, Johnson JS (2006) Copper-catalyzed electrophilic amination of organozinc nucleophiles: Documentation of O-Benzoyl Hydroxylamines as broadly useful $R_2N(+)$ and RHN(+) Synthons. J Org Chem 71(1):219–224
51. Hlavinka ML, Hagadorn JR (2006) Structures of Zinc Ketone Enolates. Organometallics 25 (14):3501–3507
52. Hlavinka ML, Hagadorn JR (2007) $Zn(tmp)_2$: A versatile base for the selective functionalization of C−H Bonds. Organometallics 26(17):4105–4108
53. Rees WS, Just O, Schumann H, Weimann R (1998) First structural characterization of a zinc-bis(dialkylamide) compound. Polyhedron 17(5–6):1001–1004
54. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of Arylboronates with N,N-Dialkylhydroxylamines. Angew Chem Int Ed 51(15):3642–3645
55. Noack M, Göttlich R (2002) Copper(I) catalysed cyclisation of unsaturated N-Benzoyloxyamines: An Aminohydroxylation via radicals. Chem Commun 2002(5): 536–537
56. Haas B, Mosrin M, Ila H, Malakhov V, Knochel P (2011) Regio- and chemoselective metalation of Arenes and Heteroarenes using hindered metal Amide bases. Angew Chem Int Ed 50(42):9794–9824
57. Bresser T, Monzon G, Mosrin M, Knochel P (2010) Scaleable preparation of sensitive functionalized Aromatics and Heteroaromatics via directed metalation using tmpZnCl·LiCl. Org Process Res Dev 14(6):1299–1303

58. Bresser T, Mosrin M, Monzon G, Knochel P (2010) Regio- and Chemoselective Zincation of sensitive and moderately activated Aromatics and Heteroaromatics using TMPZnCl·LiCl. J Org Chem 75(14):4686–4695
59. Mosrin M, Bresser T, Knochel P (2009) Regio- and Chemoselective multiple functionalization of Chloropyrazine derivatives. Application to the synthesis of Coelenterazine. Org Lett 11 (15):3406–3409
60. Mosrin M, Knochel P (2009) TMPZnCl·LiCl: A new active selective base for the directed Zincation of sensitive aromatics and Heteroaromatics. Org Lett 11(8):1837–1840
61. Unsinn A, Ford MJ, Knochel P (2013) New preparation of TMPZnCl·LiCl by Zn insertion into TMPCl. Application to the functionalization of dibromodiazines. Org Lett 15(5): 1128–1131

Chapter 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 [1–8]. For example, the 2-piperazinylbenzimidazole derivative lerisetron is currently in clinical trials for the treatment of nausea associated with cancer chemotherapy (Fig. 4.1) [1]. Other classes of heteroaryl amines, such as anti-HIV agent HM13N [2], WRC-0571 [3], and linagliptin [4], are also extensively used in drug discovery. Therefore, efficient methods for the synthesis of these important heteroaryl amines are highly valuable.

4.1.1 Aryl Amination Reactions

Heteroaromatic and aryl amines are functionally and biologically important molecules [1–8]. The importance of nitrogen-containing compounds continues to drive the development of new C–N bond-forming transformations (Scheme 4.1) [9]. 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 $[NR_2]^+$ 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.

Portions of this chapter have been published: (a) McDonald, S. L.; Hendrick, C. E.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes via C–H Zincation," *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670; (b) McDonald, S. L.; Hendrick, C. E.; Bitting K. J.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroaromatic and Aromatic C–H Bonds via TMPZnCl•LiCl Mediated Metalation," *Org. Synth.* **2015**, *92*, 356–372.

S.L. McDonald, *Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds*, Springer Theses, DOI 10.1007/978-3-319-38878-6_4

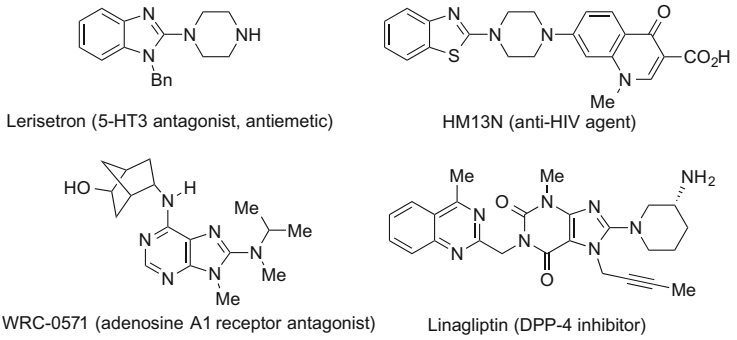
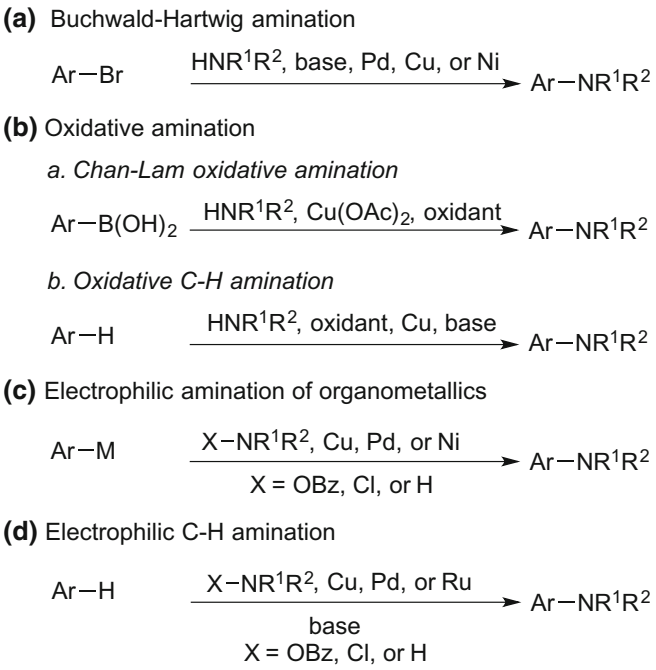


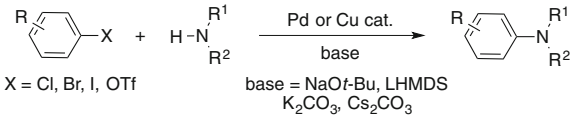
Fig. 4.1 Selected examples of bioactive heteroaromatic amines



Scheme 4.1 Amination strategies to access Ar–NR^1R^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 [10]. More than a decade later Buchwald and



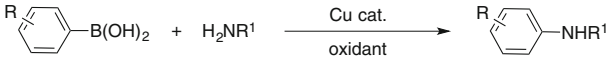
Scheme 4.2 The Buchwald-Hartwig amination for the synthesis of aryl amines

co-workers reported a new catalytic aryl amination procedure based on Migita's amination [11]. 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. NaO*t*-Bu) to replace the need for stoichiometric tributyltin [12, 13]. The resulting Buchwald-Hartwig amination became one of the first practical methods for the synthesis of arylamines (Scheme 4.2).

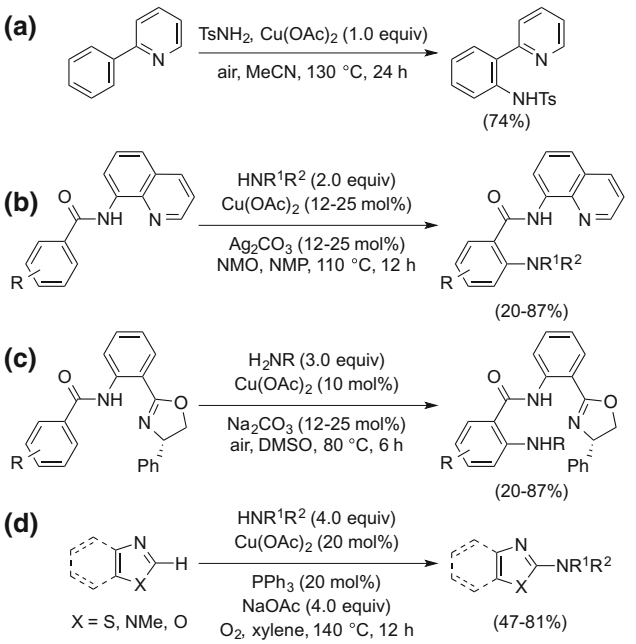
The Buchwald-Hartwig amination is the state-of-the-art method and most powerful tool for the synthesis of aryl amines. It is a transition metal-catalyzed cross-coupling reaction between aryl halides or triflates and amines (Scheme 2.2). The development of the Buchwald-Hartwig amination allowed for a 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 [14, 15]. 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 [14].

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 4.3) [16, 17]. 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 [18–20].



Scheme 4.3 Chan-Lam oxidative coupling for the synthesis of aryl amines



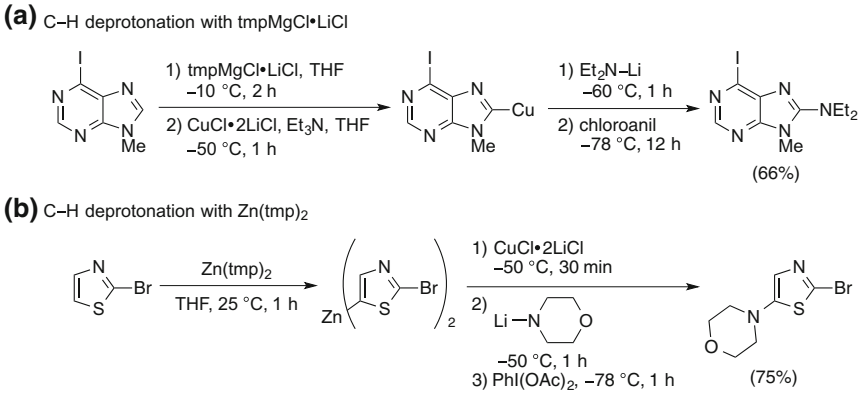
Scheme 4.4 Oxidative C–H amination reactions

In addition to the Chan-Lam coupling, some progress in this area has also been accomplished by oxidative C–H amination reactions (Scheme 4.4) [21–43]. 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 4.4a) [39]. 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 [40–42]. 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 4.4b) [31]. 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 using a wide range of sulfonamides, amides, and anilines as amine donors for their reaction (Scheme 4.4c) [43]. 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 $Cu(OAc)_2$ (Scheme 4.4d) [28]. The reaction conditions were extended to benzothiazole, benzoxazole, *N*-methylbenzimidazole, and

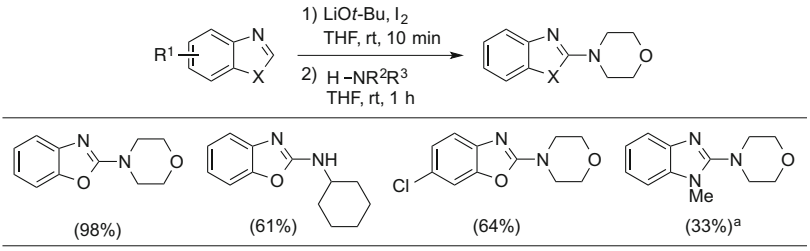
4,5-dimethylbenzimidazole using secondary amines. However, four equivalents of the amine nucleophile were required in order to prevent side reactions of the organocopper intermediate, thus limiting this method to simple and commercially available amines. Additional deprotonative, copper-catalyzed oxidative aminations of thiazoles and oxazoles have since been reported but are still limited by the excess of nucleophile needed [33].

An alternative approach to direct oxidative C–H amination of arenes and heteroarenes was reported by Knochel and co-workers (Scheme 4.5) [22–25]. Knochel's oxidative amination started with the deprotonation of the arene or heteroarene with tmpMgCl•LiCl or $Zn(tmp)_2$ and then treatment of the anion with stoichiometric CuCl•2LiCl. 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.

Several metal-free C–H/N–H coupling methods have also been developed via an oxidative re-aromatization pathway [36–38]. Most recently, Reutrakul and co-workers reported a one-pot synthesis of *N*-substituted 2-aminoazole derivatives (Scheme 4.6) [38]. Using iodine to mediate C–N bond formation, their transformation employed the use of simple azole 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.



Scheme 4.5 Oxidative amination developed by Knochel and co-workers



[a] Requires microwave irradation

Scheme 4.6 Metal-free C–H/N–H coupling

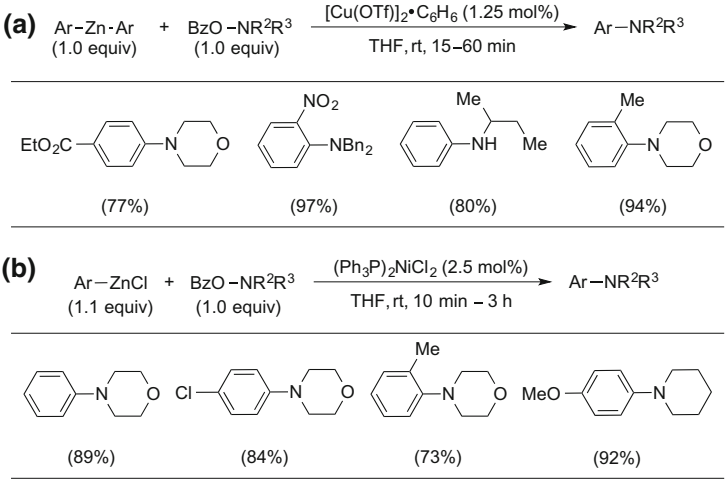
4.2 Electrophilic Amination for the Synthesis of Aryl Amines

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 [44–53]. To date, most electrophilic aminations have been achieved using various carbanions with $[NR_2]^+$ synthons. Many of these amination reactions leverage the use of transition metals.

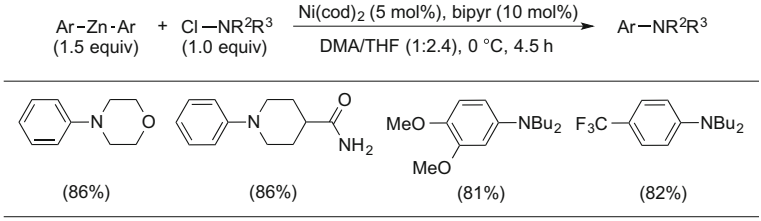
4.2.1 Electrophilic Amination of Organometallics

The electrophilic amination of carbanions is well known with a large number of organometallic reagents used, including organozincs [54–58]. Grignard reagents [44, 59–61] organoboron reagents [62, 63], organosilicon reagents [64] and aryl and heteroaryl lithiums [65]. In 2004, Berman and Johnson reported their pioneering work on the copper-catalyzed electrophilic amination of diorganozincs using *O*-acylhydroxylamines (Scheme 4.7a) [54]. 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 [55]. Later they were able to extend their method to organozinc halides using a nickel catalyst (Scheme 4.7b) [56]. However, despite mild reaction conditions and good yields, the nickel-catalyzed amination lacked the generality of their previous copper-catalyzed system.

Following the work of the Johnson group, Barker and Jarvo reported a nickel-catalyzed coupling of diorganozincs with *N*-chloramines in good yield (Scheme 4.8) [58]. The use of *N*-chloramines added a significant advance to the



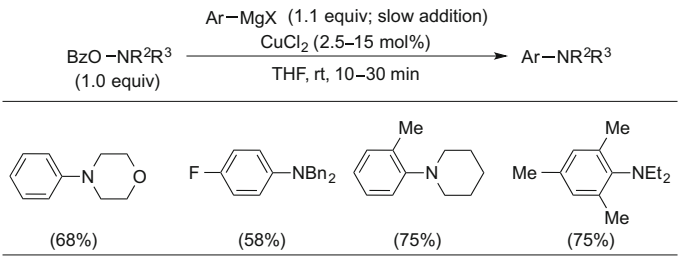
Scheme 4.7 Electrophilic amination of organozincs using *O*-benzoylhydroxylamines



Scheme 4.8 Electrophilic amination of organozincs using *N*-chloramines

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.

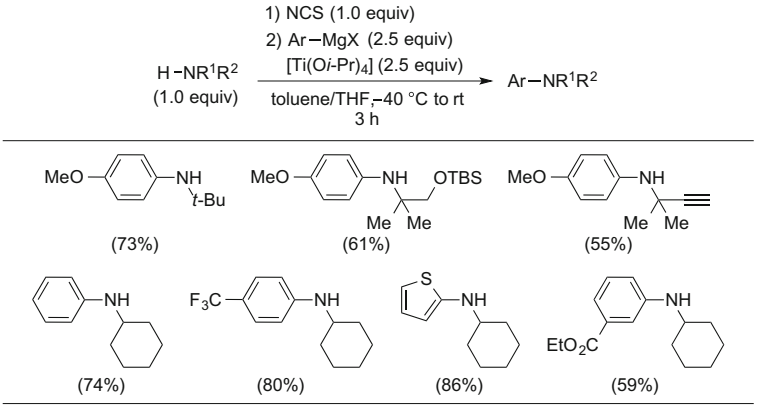
Electrophilic amination of Grignard reagents using primary *O*-alkylhydroxylamines and haloamines has been broadly used to synthesize primary amines [44]; however the use of *N*-substituted hydroxylamines and haloamines has been more limited due to side reactions such as *C*-acylation and halogenation. Following their reports on the electrophilic amination of organozincs [54–57], Johnson and co-workers reported a copper-catalyzed amination of Grignard reagent with *O*-acylhydroxylamines (Scheme 4.9) [59]. Aryl amines were synthesized in



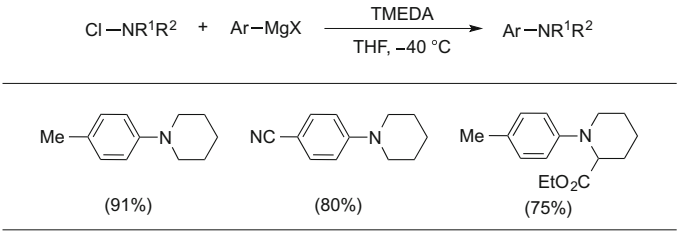
Scheme 4.9 Copper-catalyzed electrophilic amination of Grignard reagents via *O*-benzoylhydroxylamines

moderate to excellent yield, and the slow 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 [54–57], 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 4.10) [60]. 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 4.10 Titanium-mediated amination of aryl Grignard reagents



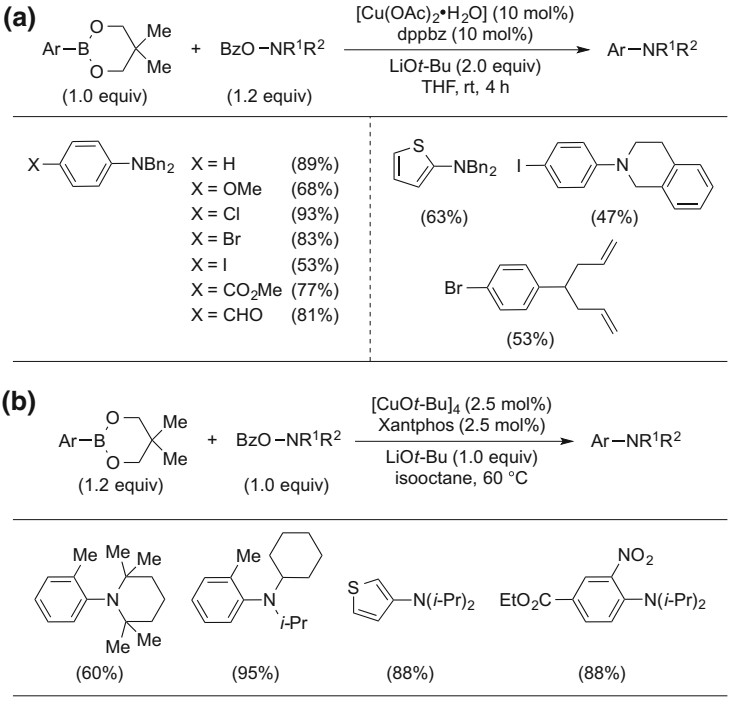
Scheme 4.11 Metal-free amination of aryl Grignard reagents

In 2010, Nakamura and co-workers reported a metal-free electrophilic amination of aryl Grignard reagents with *N*-chloramines (Scheme 4.11) [61]. 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.

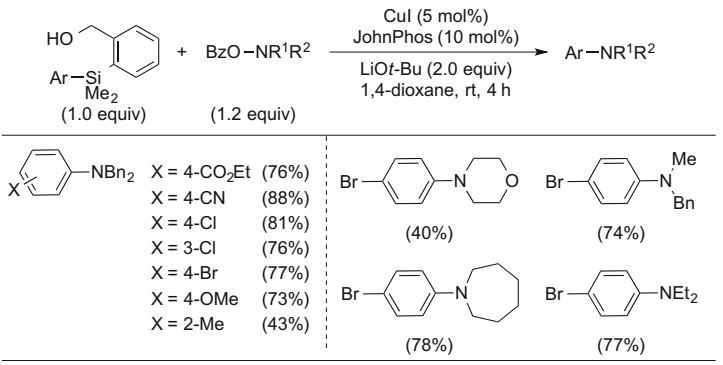
Recently organoboron reagents have been used for the synthesis of aryl amines. In 2012, Miura and Lalic concurrently disclosed copper-catalyzed electrophilic aminations of aryl boronic esters [62, 63]. In the work by Miura and co-workers, a wide variety of anilines were obtained in moderate to good yields by coupling aryl boronates with *O*-benzoylhydroxylamines using $Cu(OAc)_2•H_2O$ as the catalyst (Scheme 4.12a) [62]. Meanwhile, Lalic and co-workers focused on a copper-catalyzed electrophilic amination of aryl boronic esters for the synthesis of sterically hindered anilines (Scheme 4.12b) [63]. They found that boronic esters derived from neopentyl glycol were crucial for the reaction. Using a catalyst formed in situ from $[CuO\textit{t}\text{-}Bu]_4$ 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.

Organosilicon reagents can also undergo direct electrophilic amination. Miura and co-workers reported a copper-catalyzed amination of aryl silanes (Scheme 4.13) [64]. 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.

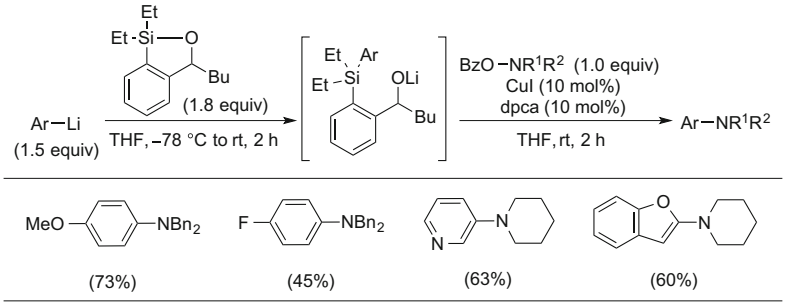
Although organolithium reagents are commercially available or readily available through lithium–halogen exchange, their use for electrophilic amination has been limited due to low yields and often limited substrate scope. Therefore, organolithiums are often converted to other organometallic reagents [44]. Amos Smith and co-workers developed a copper-catalyzed amination of organolithiums using *O*-benzoylhydroxylamines as the electrophilic nitrogen source (Scheme 4.14) [65]. 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



Scheme 4.12 Copper-catalyzed electrophilic aminations of aryl boronic esters



Scheme 4.13 Copper-catalyzed electrophilic amination of arylsilanes

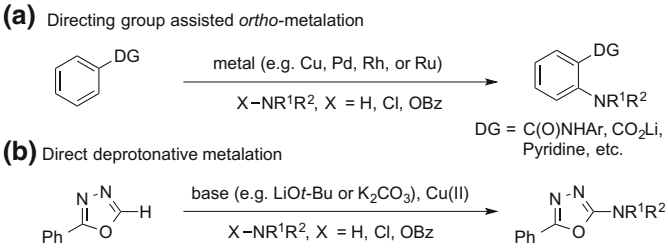


Scheme 4.14 Electrophilic amination of organolithiums mediated by siloxane transfer agents

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.

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 [66–71]. 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 4.15). The first approach (Scheme 4.15a), involving directing group-assisted metallation, has proven to be powerful for the

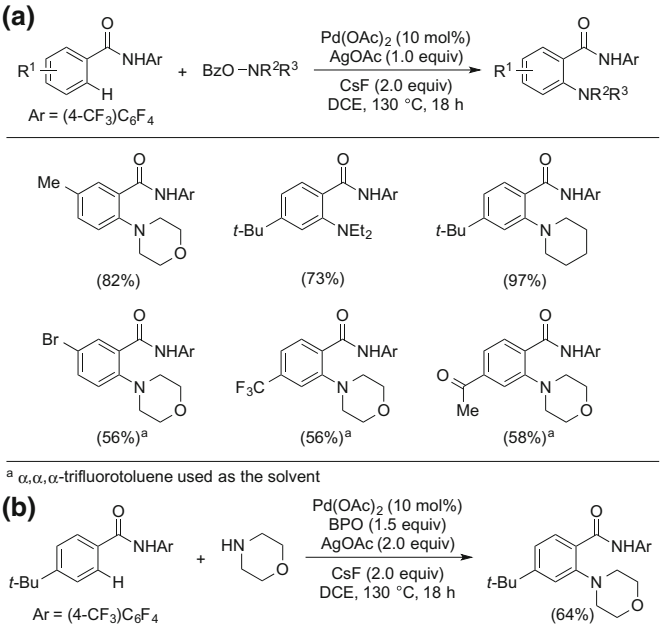


Scheme 4.15 Metal-catalyzed direct C–H aminations

synthesis of *ortho*-substituted arylamines [66–69]. The second approach (Scheme 4.15b), via direct deprotonative metallation, is particularly useful for the amination of electron-deficient arenes, such as 1,3,4-oxadiazoles and polyfluoroarenes [70, 71].

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 4.16) [66]. 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 4.16b).

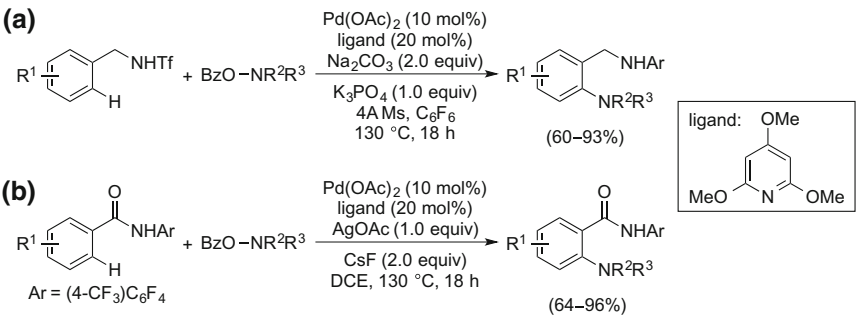


Scheme 4.16 Palladium-catalyzed C–H amination of *N*-aryl benzamides

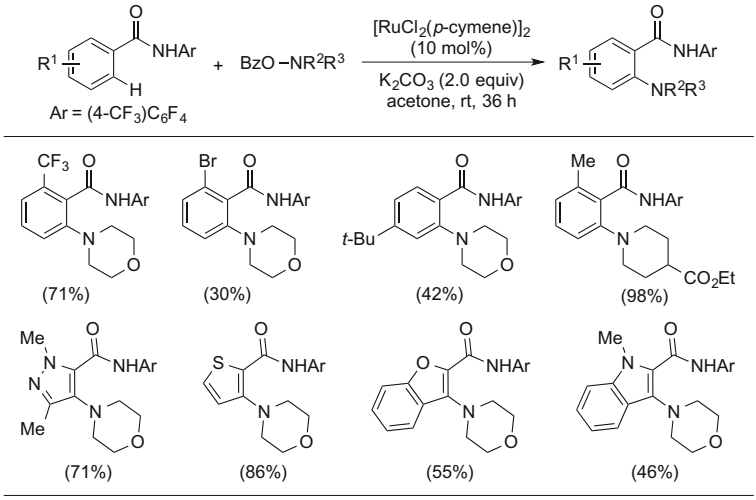
Despite the utility of the initial palladium-catalyzed C–H amination reported by Yu and co-workers, it was limited in substrate scope and had poor efficiency for electron-withdrawn benzamides. Recently, Yu and co-workers disclosed a palladium-catalyzed *ortho* C–H amination in which pyridine and quinoline-based ligands promoted the amination of these more difficult substrates (Scheme 4.17) [67]. 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.

In addition to palladium, ruthenium and rhodium have been shown to be effective catalysts for direct *ortho* C–H amination [68, 69]. Following their initial palladium-catalyzed *ortho* C–H amination [66], Yu and co-workers disclosed a ruthenium-catalyzed *ortho* C–H amination of benzamides (Scheme 4.18) [68]. 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.

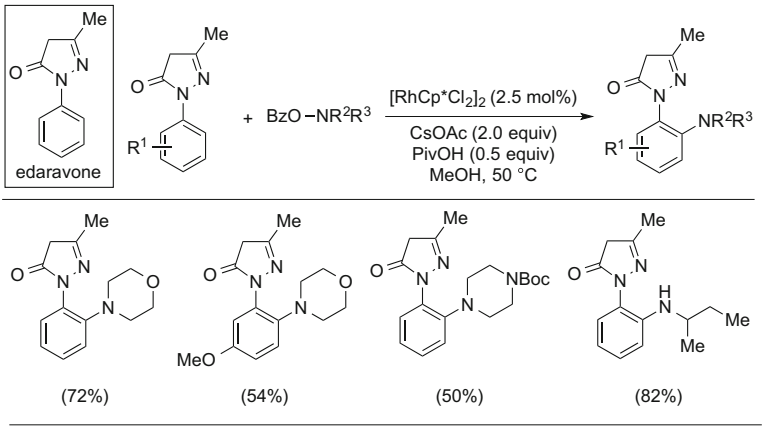
Zhang and Yao reported a rhodium-catalyzed aryl C–H amination using a pyrazolone moiety as an *ortho* directing group (Scheme 4.19) [69]. Their amination method is notable because they were able to introduce primary and secondary amines under mild conditions to make novel analogues of the neuroprotection drug edaravone [72–75].



Scheme 4.17 Ligand-promoted palladium-catalyzed C–H amination



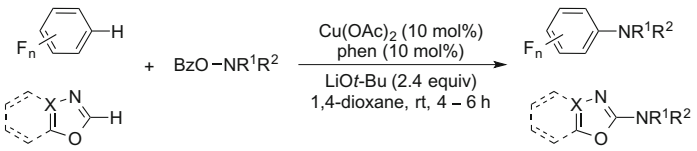
Scheme 4.18 Ruthenium-catalyzed *ortho* C–H amination of arenes and heteroarenes



Scheme 4.19 Rhodium-catalyzed *ortho* C–H amination

4.2.2.2 Direct Deprotonative Metallation for C–H Amination

Direct deprotonative metallation/amination 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



Scheme 4.20 Copper-catalyzed direct C–H amination of polyfluoroarenes and azoles

amination of polyfluoroarenes and azoles (Scheme 4.20) [70]. Using *O*-benzoylhydroxylamines as the nitrogen source, they were able to synthesize the corresponding anilines and aminoazoles in moderate to good yields under mild reaction conditions.

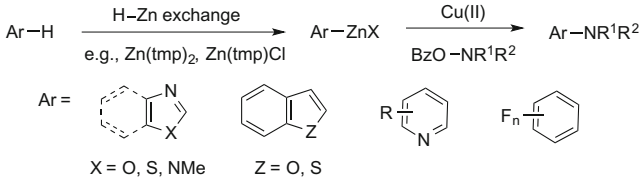
4.2.3 Limitations of Current Methods

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 [76]. 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 [76].

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 organozinc reagents with *O*-benzoylhydroxylamines reported by Johnson and co-workers [54–57], 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 4.21). Our approach was



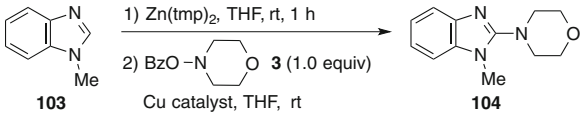
Scheme 4.21 C–H zincation and copper-catalyzed electrophilic amination heteroarenes and arenes

built on the use of strong and non-nucleophilic zinc bases [77–90], such as Zn $(tmp)_2$ (pKa of the conjugate acid = 37), [87–90] 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 [54, 91], 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 [92–95]. 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 [22–35, 70, 71].

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 4.1). We focused on *O*-benzoylhydroxylamines as the electrophilic nitrogen source because of their easy availability and previous use in the electrophilic amination of different aryl organometallic reagents [54–57, 59, 62–65]. 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).

Table 4.1 Optimization studies for copper-catalyzed amination of *N*-methylbenzimidazole (**103**) and *O*-benzoylhydroxylamine **3**[a]



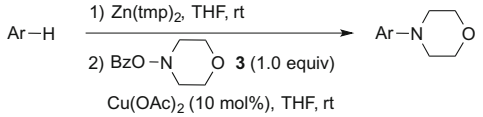
Entry	103 (equiv)	$Zn(tmp)_2$ (equiv)	Copper (10 mol %)	Time (h)[b]	104 (%)[c]
1	2.1	1.0	–	72[d]	0
2	2.1	1.0	CuI	4	82
3	2.1	1.0	CuBr	19	80
4	2.1	1.0	CuCl	4	88
5	2.1	1.0	CuCN	19	81
6	2.1	1.0	$[CuOTf]_2$•tol	4	71
7	2.1	1.0	$CuCl_2$	3.5	89
8	2.1	1.0	$Cu(acac)_2$	3.5	82
9	2.1	1.0	$Cu(OTf)_2$	5	76
10	2.1	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

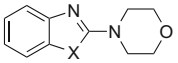
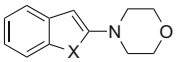
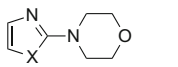
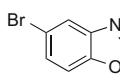
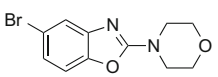
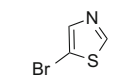
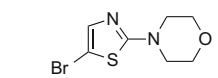
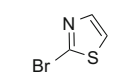
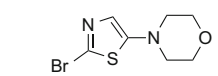
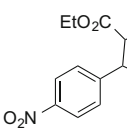
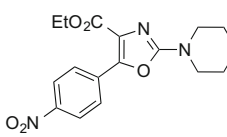
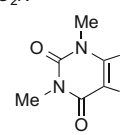
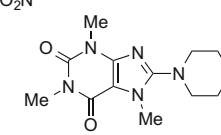
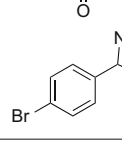
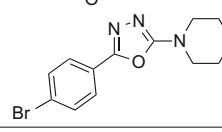
[a]Reactions run on a 0.2 mmol scale
[b]Time required for complete consumption of **3** in step 2
[c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard
[d]**3** not fully consumed after 72 h

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 [22–35, 70, 71]. Toward this end, we first examined the amination reactions of different azoles using *O*-benzoylhydroxylamine **3** (Table 4.2). 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•$MgCl_2$ 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.

We next wanted to expand the heteroarene and arene scope beyond azole compounds (Table 4.3). 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

Table 4.2 Amination of azole compounds[a]



entry	Ar–H	time (h)[b]	product	yield (%)
1	 **103** X = NMe	1; 5	 **104** X = NMe	96
2	**105** X = S	1; 5	**106** X = S	93
3	**107** X = O	1; 5	**108** X = O	95
4	 **109** X = O	1;[c] 5	 **110** X = O	71
5	**111** X = S	1;[c] 5	**112** X = S	70
6	 **113** X = NMe	1; 12	 **114** X = NMe	82
7	**115** X = O	1; 12	**116** X = O	92
8	**117** X = S	1; 12	**118** X = S	95
9	 **119**	1; 24	 **120**	96
10	 **121**	1; 5	 **122**	85
11	 **123**	1; 5	 **124**	90
12	 **125**	1; 4	 **126**	89
13	 **127**	1;[d] 24	 **128**	82
14	 **129**	1; 4	 **130**	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)

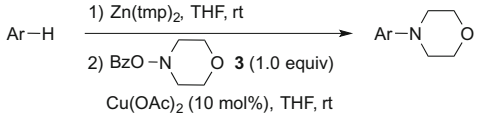
[b]Reaction time for deprotonation and amination step respectively

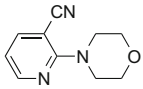
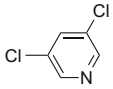
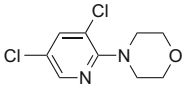
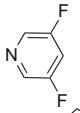
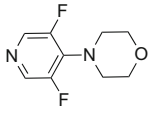
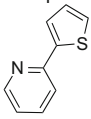
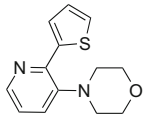
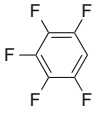
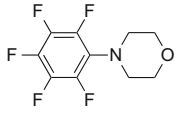
[c]$Zn(tmp)_2$•LiCl•$MgCl_2$[25] was used as base

[d]Deprotonation step run in CH_2Cl_2 because of the poor solubility of **127** in THF

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 4.3 Amination of pyridines and arenes[a]



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)

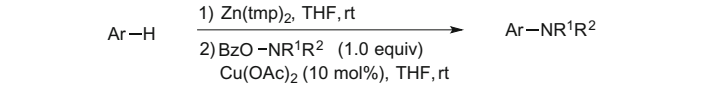
[b]Reaction time for deprotonation and amination step respectively

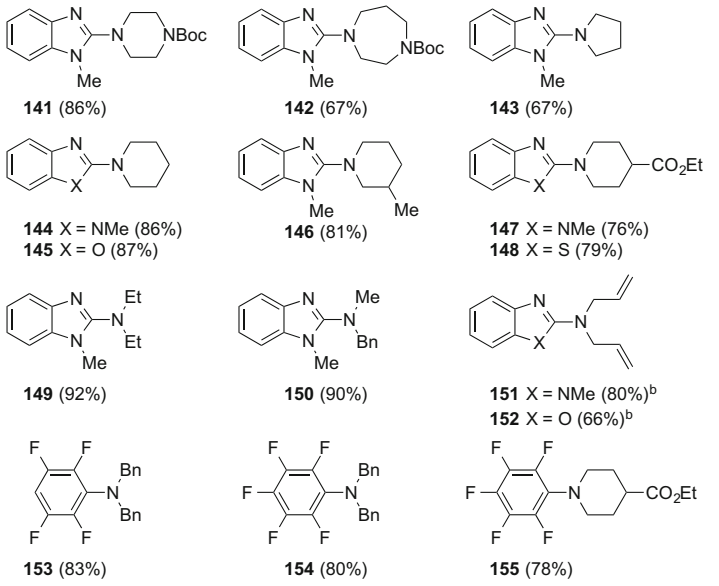
[c]Amination step run at 50 °C

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 4.4). 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

Table 4.4 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; $BzONR^1R^2$ (1.0 equiv, 0.08M), $Cu(OAc)_2$ (10 mol %), rt, 5 h

[b]Amination step run for 24 h

benzyl group or allyl group can additionally afford either a secondary amine or a primary amine (e.g., **150**–**154**).

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•LiCl [81–86] in the C–H metallation (Table 4.5). 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.

With amination conditions identified, we next examined the generality of the transformation (Table 4.6). 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 chlorides were equally effective as diarylzincs 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.

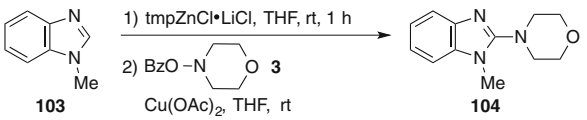
Given the broad generality and operational simplicity of this amination reaction, its utility for the synthesis of medicinally valuable agents was demonstrated by the rapid synthesis of lerisetron **167** (Scheme 4.22). This 5-HT3 receptor antagonist was readily prepared from the simple benzimidazole **165** by using the standard amination conditions.

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 4.23) because of the increasing presence of amine-substituted pyridines in pharmaceutical sciences [96–98]. 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.

4.3.3.1 Proposed Mechanism for the Amination

Based on current experimental observations and related mechanistic studies [59, 70], a possible mechanism is proposed for this copper-catalyzed amination reaction (Scheme 4.24). It involves (1) the transmetallation 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

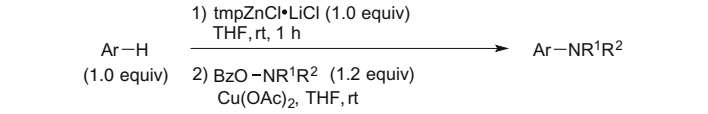
Table 4.5 Condition optimization using tmpZnCl•LiCl for C–H zincation

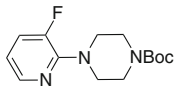


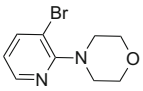
Entry	103 (equiv)	3 (equiv)	tmpZnCl•LiCl (equiv)	Time (h)[a]	104 (%)[b]
1	1.1	1	1	4	79
2	1.05	1.2	1	4	88
3	1	1.2	1	3	89

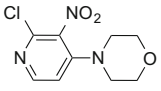
[a]Time required for complete consumption of **3** in step 2
[b]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard

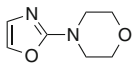
Table 4.6 Direct amination using a tmpZnCl•LiCl-mediated metallation[a]

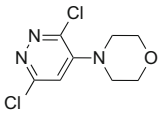


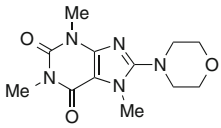

156 (65%)[b]

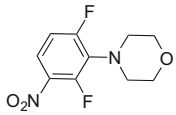

157 (60%)[b]

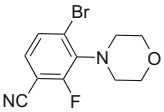

158 (81%)

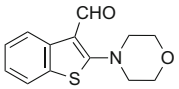

116 (76%)

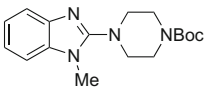

159 (90%)

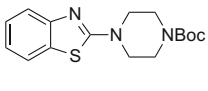

128 (65%)[c]

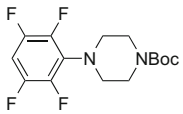

160 (98%)

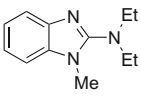

161 (90%)[d]

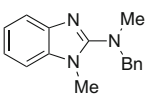

162 (86%)

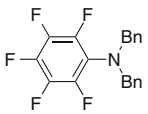

141 (94%)


163 (86%)


164 (89%)


149 (52%)


150 (61%)


154 (71%)[e]

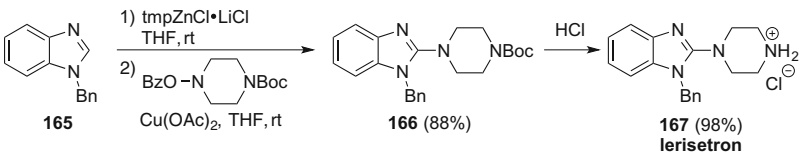
[a]Isolated yields. Reactions run on 0.2 mmol scale and 10 mol% $Cu(OAc)_2$ used

[b]Amination step run at 50 °C

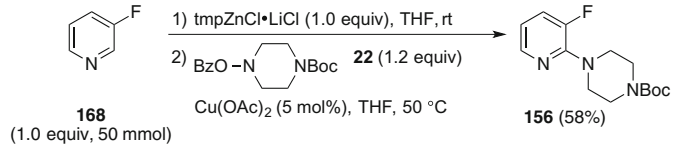
[c]Deprotonation step run in CH_2Cl_2 because of the poor solubility of **127** in THF

[d]Deprotonation step run at 65 °C

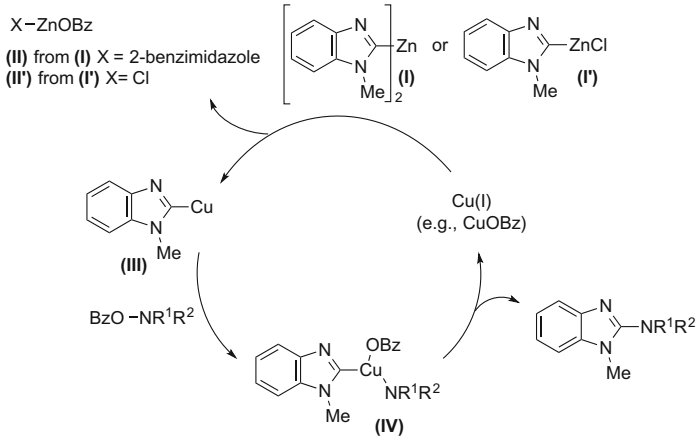
[e]Deprotonation run for 1.5 h



Scheme 4.22 A rapid synthesis of lerisetron via C–H zincation and amination



Scheme 4.23 Large-scale amination of 3-fluoropyridine **168**



Scheme 4.24 Proposed reaction pathway for heteroarenes and arenes

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 4.2, 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.

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 × 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.).

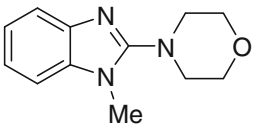
Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich or Strem and used as received. Dry THF and toluene were obtained using an Innovative Technologies solvent purification system. tmpZnCl•LiCl was prepared according to literature procedure [86]. *O*-acylhydroxylamine derivatives were prepared according to literature procedure [57].

Instrumentation. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}CNMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 or 125 MHz respectively) spectrometer at ambient temperature. Chemical shifts for ^{1}H 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.

4.5.1.1 Experimental Procedures

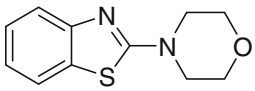
Typical Procedure 1 (TP1): General Experimental Procedure for C–H Amination via $Zn(tmp)_2$ Mediated Metallation.
To an 8 mL microwave tube charged with heteroaryl compound (0.420 mmol, 2.1 equiv) was added THF (1 mL) followed by dropwise addition of $Zn(tmp)_2$ (0.5 M solution in tol, 0.40 mL, 0.200 mmol, 1.0 equiv) under N_2. 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 Et_2O. 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 N_2. 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 N_2. 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 $NaHCO_3$ and extracted into EtOAc), the reaction was quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (1 mL). The reaction mixture was subsequently basified with saturated aqueous solution of Na_2CO_3 (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash-column chromatography.

4.5.2 Characterization of Compounds

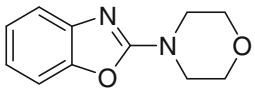


4-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)morpholine (104). Compound prepared according to TP1. Purification by flash-column chromatography (100 % ethyl acetate) gave **104** as a white solid (41.6 mg, 96 %); R_f = 0.32 (100 % ethyl

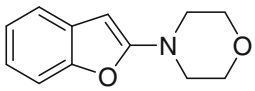
acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63–7.60 (m, 1H), 7.22–7.17 (m, 3H), 3.90 (t, J = 4.6 Hz, 4H), 3.62 (s, 3H), 3.32 (t, J = 4.6 Hz, 4H); Spectroscopic data was identical to that reported previously [99].



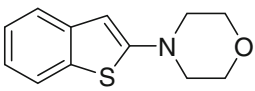
4-(Benzo[*d*]thiazol-2-yl)morpholine (106). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **106** as a pale yellow solid (40.6 mg, 93 %); R_f = 0.57 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 7.6 Hz, 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 [99].



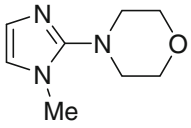
2-Morpholinobenzo[*d*]oxazole (108). Compound prepared according to TP1. Purification by flash-column chromatography (50 % ethyl acetate–hexanes) gave **108** as a yellow solid (38.9 mg, 95 %); R_f = 0.64 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (dd, J = 8.0, 0.8 Hz, 1H), 7.27 (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 [99].



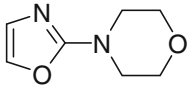
4-(Benzofuran-2-yl)morpholine (110). Compound prepared according to TP1. Deprotonation of **109** achieved with $Zn(tmp)_2$•LiCl•$MgCl_2$ at room temperature for 24 h. Purification by flash-column chromatography (10 % ethyl acetate–hexanes) gave **110** as a white solid (28.9 mg, 71 %); R_f = 0.64 (50 % ethyl acetate–hexanes); ^{1}H 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 [24].



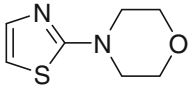
4-(Benzo[*b*]thiophen-2-yl)morpholine (112). Compound prepared according to TP1. Deprotonation of **111** achieved with $Zn(tmp)_2$•LiCl•$MgCl_2$ at room temperature for 24 h. Purification by flash-column chromatography (10 % ethyl acetate–hexanes) gave **112** as a white solid (30.7 mg, 70 %); R_f = 0.66 (50 % ethyl acetate–hexanes); ^{1}H 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 [25].



4-(1-Methyl-1*H*-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); ^{1}H 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 ($C_8H_{14}N_3O$) ($[M+H]^+$): 168.1131; found 168.1133.

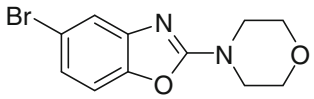


4-(Oxazol-2-yl)morpholine (116). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **116** as a white solid (28.3 mg, 92 %); R_f = 0.27 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 1H), 6.83 (s, 1H), 3.78 (t, *J* = 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 ($C_7H_{11}N_2O_2$) ($[M+H]^+$): 155.0815; found 155.0811.

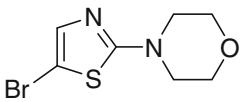


4-(Thiazol-2-yl)morpholine (118). Compound prepared according to TP1. Purification by flash-column chromatography (50 % ethyl acetate–hexanes) gave **118** as a colorless oil (32.3 mg, 95 %); R_f = 0.49 (50 % ethyl acetate–hexanes); ^{1}H

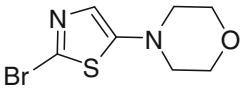
NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 3.81 (t, J = 5.0 Hz, 4H), 3.46 (t, J = 5.0 Hz, 4H); Spectroscopic data was identical to that reported previously [99].



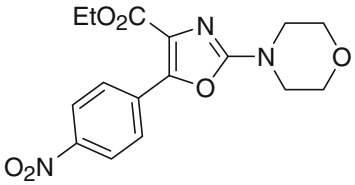
5-Bromo-2-morpholinobenzo[*d*]oxazole (120). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **120** as a white solid (54.3 mg, 96 %); R_f = 0.52 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (dd, J = 2.0, 0.8 Hz, 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 ($C_{11}H_{12}BrN_2O_2$) ([M+H]$^+$): 283.0077; found 283.0080.



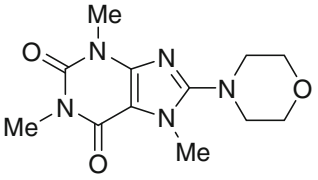
4-(5-Bromothiazol-2-yl)morpholine (122). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **122** as a pale yellow solid (42.3 mg, 85 %); R_f = 0.71 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09 (s, 1H), 3.80 (t, J = 5.0 Hz, 4H), 3.40 (t, J = 5.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 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 ($C_7H_{10}BrN_2OS$) ([M+H]$^+$): 248.9692; found 248.9691.



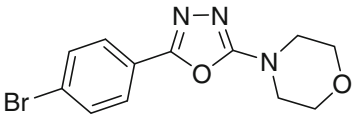
4-(2-Bromothiazol-5-yl)morpholine (124). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **124** as a white solid (44.7 mg, 90 %); R_f = 0.65 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 1H), 3.82 (t, J = 4.8 Hz, 4H), 3.05 (t, J = 4.8 Hz, 4H); Spectroscopic data was identical to that reported previously [24].



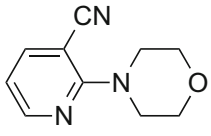
Ethyl-2-morpholino-5-(4-nitrophenyl)oxazole-4-carboxylate (126). Compound prepared according to TP1. Purification by flash-column chromatography (60 % ethyl acetate–hexanes) gave **126** as a neon yellow solid (61.8 mg, 89 %); R_f = 0.18 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 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); ^{13}C NMR ($CDCl_3$, 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 ($C_{17}H_{18}N_3O_6$) ($[M+H]^+$): 348.1190; found 348.1193.



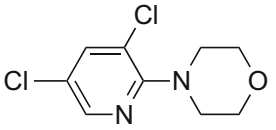
1,3,7-Trimethyl-8-morpholino-3,7-dihydro-1*H*-purine-2,6-dione (128). Compound prepared according to TP1. Deprotonation of **127** was done in CH_2Cl_2 due to low solubility in THF. Purification by flash-column chromatography (80 % ethyl acetate–hexanes) gave **128** as a white solid (45.8 mg, 82 %); R_f = 0.24 (100 % ethyl acetate); ^{1}H 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 ($C_{12}H_{18}N_5O_3$) ($[M+H]^+$): 280.1404; found 280.1405.



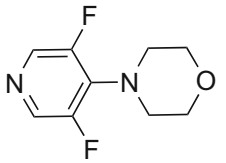
4-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)morpholine (130). Compound prepared according to TP1. Purification by flash-column chromatography (50 % ethyl acetate–hexanes) gave **130** as a white solid (56.4 mg, 91 %); R_f = 0.08 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, *J* = 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 ($C_{12}H_{13}BrN_3O_2$) ($[M+H]^+$): 310.0186; found 310.0188.



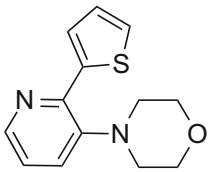
2-Morpholinonicotinonitrile (132). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (20 % ethyl acetate–hexanes) gave **132** as a pale yellow solid (30.6 mg, 81 %); R_f = 0.50 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (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 ($C_{10}H_{12}N_3O$) ([M +H]$^+$): 190.0975; found: 190.0975.



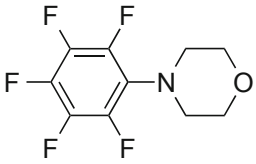
4-(3,5-Dichloropyridin-2-yl)morpholine (134). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (20 % ethyl acetate–hexanes) gave **134** as a pale yellow solid (36.8 mg, 91 %); R_f = 0.82 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 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 ($C_9H_{11}C_{l2}N_2O$) ([M+H]$^+$): 233.0243; found: 233.0243.



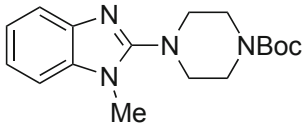
4-(3,5-Difluoropyridin-4-yl)morpholine (136). Compound prepared according to TP1. Amination step run at 50 °C. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **136** as a pale yellow solid (36.2 mg, 91 %); R_f = 0.48 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 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 ($C_9H_{11}F_2N_2O$) ([M+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); ^{1}H 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 ($C_{13}H_{15}N_2OS$) ($[M+H]^+$): 247.0900; found: 247.0909.

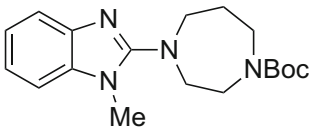


4-(Perfluorophenyl)morpholine (140). Compound prepared according to TP1. Purification by kugelröhr distillation gave **140** as a yellow oil (37.9 mg, 75 %); R_f = 0.88 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (t, *J* = 4.6 H, 4H), 3.20 (t, *J* = 4.6 Hz, 4H); Spectroscopic data was identical to that reported previously [100].

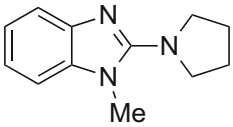


***tert*-Butyl-4-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)piperazine-1-carboxylate (141)**. Compound prepared according to TP1. Purification by flash-column chromatography (50 % ethyl acetate–hexanes) gave **141** as a white solid (54.1 mg, 86 %); R_f = 0.36 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 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),

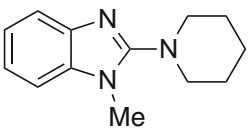
1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, 60 °C): δ 157.5, 154.7, 141.4, 135.7, 121.6, 121.2, 118.1, 108.3, 79.9, 50.2, 43.4, 30.2, 28.3; FTIR (thin film): cm^{-1} 2935, 1634, 1575, 1459, 739; HRMS-ESI (m/z) Calcd for ($C_{17}H_{25}N_4O_2$) ([M+H]$^+$): 317.1972; found: 317.1974.



***tert*-Butyl-4-(1-methyl-1*H*-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); ^{1}H 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 ($C_{18}H_{27}N_4O_2$) ([M+H]$^+$): 331.2129; found: 331.2129.

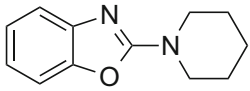


1-Methyl-2-(pyrrolidin-1-yl)-1*H*-benzo[*d*]imidazole (143). Compound prepared according to TP1. Purification by flash-column chromatography (100 % ethyl acetate) gave **143** as a white solid (27.1 mg, 67 %); R_f = 0.31 (100 % ethyl acetate); ^{1}H NMR (CDCl3, 400 MHz): δ 7.48 (dt, J = 7.6, 1.0 Hz, 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 ($C_{12}H_{16}N_3$) ([M+H]$^+$): 202.1339; found: 202.1341.

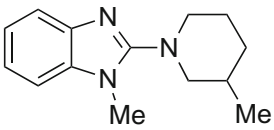


1-Methyl-2-(piperidin-1-yl)-1*H*-benzo[*d*]imidazole (144). Compound prepared according to TP1. Purification by flash-column chromatography (30 % ethyl

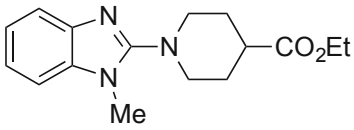
acetate–hexanes) gave **144** as white solid (36.9 mg, 86 %); R_f = 0.45 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.58 (m, 1H), 7.19–7.14 (m, 3H), 3.59 (s, 3H), 3.25 (t, *J* = 5.2 Hz, 4H), 1.79–1.73 (m, 4H), 1.68–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 141.5, 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 ($C_{12}H_{18}N_3$) ([M+H]$^+$): 214.1495; found: 214.1497.



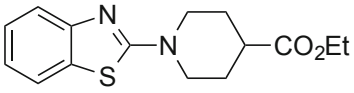
2-(Piperidin-1-yl)benzo[*d*]oxazole (145). Compound prepared according to TP1. Purification by kugelröhr distillation followed by flash-column chromatography (15 % ethyl acetate–hexanes) gave **145** as a white solid (35.0 mg, 87 %); R_f = 0.28 (15 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): 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 ($C_{12}H_{15}N_2O$) ([M+H]$^+$): 203.1179; found: 203.1181.



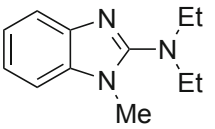
1-Methyl-2-(3-methylpiperidin-1-yl)-1*H*-benzo[*d*]imidazole (146). Compound prepared according to TP1. Purification by flash-column chromatography (10 % ethyl acetate–hexanes) gave **146** as a white solid (37.0 mg, 81 %); R_f = 0.26 (30 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59–7.57 (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 ($C_{14}H_{20}N_3$) ([M+H]$^+$): 230.1652; found: 230.1555.



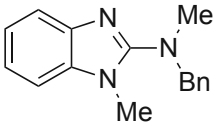
Ethyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)piperidine-4-carboxylate (147). Compound prepared according to TP1. Purification by flash-column chromatography (40 % ethyl acetate–hexanes) gave **147** as a yellow oil (43.9 mg, 76 %); R_f = 0.36 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): 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 ($C_{16}H_{22}N_3O_2$) ([M+H]$^+$): 288.1707; found: 288.1707.



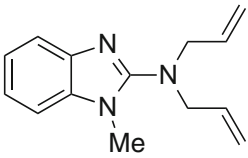
Ethyl-1-(benzo[*d*]thiazol-2-yl)piperidine-4-carboxylate (148). Compound prepared according to TP1. Purification by flash-column chromatography (gradient from 5 % ethyl acetate–hexanes to 15 % ethyl acetate–hexanes) gave **148** as a yellow powder (46.1 mg, 79 %); R_f = 0.20 (15 % ethyl acetate–hexanes); ^{1}H 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 ($C_{15}H_{19}N_2O_2S$) ([M+H]$^+$): 291.1162; found: 291.1164.



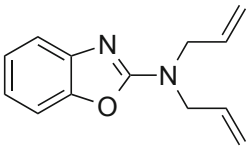
***N,N*-Diethyl-1-methyl-1*H*-benzo[*d*]imidazol-2-amine (149)**. Compound prepared according to TP1. Purification by flash-column chromatography (50 % ethyl acetate–hexanes) gave **149** as a clear oil (37.3 mg, 92 %); R_f = 0.35 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.58 (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 ($C_{12}H_{18}N_3$) ([M+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); ^{1}H 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 ($C_{16}H_{18}N_3$) ([M+H]$^+$): 252.1495; found: 252.1504.

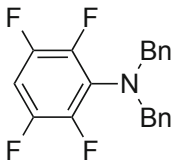


***N,N*-Diallyl-1-methyl-1*H*-benzo[*d*]imidazol-2-amine (151)**. Compound prepared according to TP1. Purification by flash-column chromatography (5 % ethyl acetate–dichloromethane) gave **151** as a clear oil (36.5 mg, 80 %); R_f = 0.17 (15 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 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): δ157.8, 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 ($C_{14}H_{18}N_3$) ([M+H]$^+$): 228.1495; found: 228.1494.

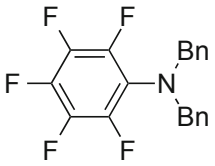


***N,N*-Diallylbenzo[*d*]oxazol-2-amine (152)**. Compound prepared according to TP1. Purification by kugelröhr distillation followed by flash-column chromatography (15 % ethyl acetate–hexanes) gave **152** as a clear oil (28.1 mg, 66 %); R_f = 0.51 (15 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 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),

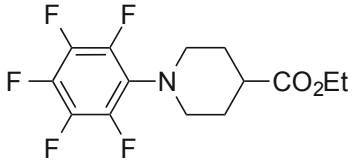
4.16 (d, J = 5.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 148.9, 143.3, 132.5, 123.9, 120.3, 117.8, 116.1, 108.7, 49.9; FTIR (thin film): cm^{-1} 2923, 1631, 1577, 1459, 1243, 740; HRMS-ESI (m/z) Calcd for ($C_{13}H_{15}N_2O$) ([M+H]$^+$): 215.1178; found: 215.1178.



***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); ^{1}H 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 [70].

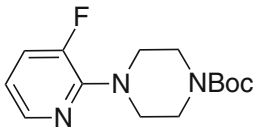


***N*,*N*-Dibenzyl-2,3,4,5,6-pentafluoroaniline (154)**. Compound prepared according to TP1. Purification by flash-column chromatography (5 % dichloromethane–hexanes) gave **154** as a clear oil (58.1 mg, 80 %); R_f = 0.39 (5 % dichloromethane–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.22 (m, 10H), 4.23 (s, 4H); Spectroscopic data was identical to that reported previously [70].

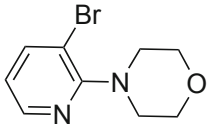


Ethyl-1-(perfluorophenyl)piperidine-4-carboxylate (155). Compound prepared according to TP1. Purification by flash-column chromatography (gradient of 100 % hexanes to 20 % ethyl acetate–hexanes) gave **155** as a yellow oil (50.6 mg, 78 %); R_f = 0.35 (5 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 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,

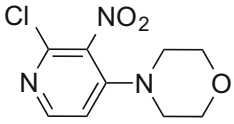
4.0 Hz, 1H), 2.00–1.96 (m, 2H), 1.89–1.81 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3 (dd, J_{C-F} = 246.3, 5.5 Hz), 139.0–135.9 (m, 2C), 126.5 (t, J_{C-F} = 11.3 Hz); FTIR (thin film): cm^{-1} 2959, 1730, 1516, 1498, 985; HRMS-ESI (m/z) Calcd for ($C_{14}H_{15}F_5NO_2$) ([M+H]$^+$): 324.1017; found: 324.1014.



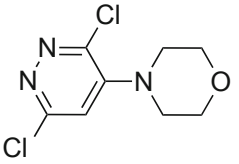
***tert*-Butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate (156)**. Compound prepared according to TP2. Amination step run at 50 °C. Purification by flash-column chromatography (20 % ethyl acetate–hexanes) gave **156** as a yellow solid (37.0 mg, 65 %); R_f = 0.55 (20 % ethyl acetate–hexanes); ^{1}H 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_{C-F} = 255.0 Hz), 149.6 (J_{C-F} = 6.2 Hz), 142.6 (J_{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 $C_{14}H_{21}FN_3O_2$: 282.1612; found 282.1612.



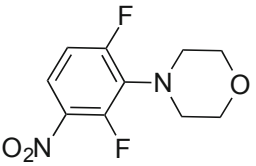
4-(3-Bromopyridin-2-yl)morpholine (157). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Amination step run at 50 °C. Purification by flash-column chromatography (20 % ethyl acetate–hexanes) gave **157** as a yellow oil (50.6 mg, 90 %); R_f = 0.74 (50 % ethyl acetate–hexanes); ^{1}H 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 ($C_9H_{12}BrN_2O$) ([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); ^{1}H 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 ($CDCl_3$, 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 ($C_9H_{11}ClN_3O_3$) ([M+H]+): 244.0483; found: 244.0485.

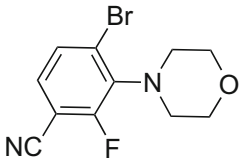


4-(3,6-Dichloropyridazin-4-yl)morpholine (159). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Purification by flash-column chromatography (40 % ethyl acetate–hexanes) gave **159** as a yellow solid (84.1 mg, 90 %); R_f = 0.40 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.30 (t, J = 4.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 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 ($C_8H_{10}Cl_2N_3O$) ([M +H]$^+$): 234.0195; found: 234.0195.

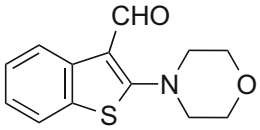


4-(2,6-Difluoro-3-nitrophenyl)morpholine (160). Compound prepared according to TP2. Reaction run on a 0.400 mmol scale. Purification by flash-column chromatography (10 % ethyl acetate–hexanes) gave **160** as a yellow solid (95.5 mg, 98 %); R_f = 0.83 (50 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 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); ^{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} 3062, 2971, 2861, 1578, 1528,

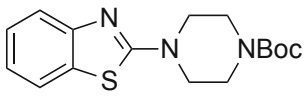
1380, 1068, 1019; HRMS-ESI (m/z) Calcd for ($C_{10}H_{11}F_2N_2O_2$) ([M+H]$^+$): 245.0732; found: 245.0736.



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); ^{1}H 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 ($C_{11}H_{11}BrFN_2O$) ([M+H]$^+$): 285.0033; found: 285.0029.

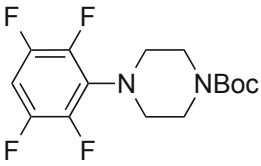


2-Morpholinobenzo[*b*]thiophene-3-carbaldehyde (162). Compound prepared according to TP2. Purification by flash-column chromatography (30 % ethyl acetate–hexanes) gave **162** as a white solid (35.6 mg, 72 %); R_f = 0.25 (30 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.18 (s, 1H), 8.31 (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 ($C_{13}H_{14}NO_2S$) ([M+H]$^+$): 248.0740; found: 248.0734.

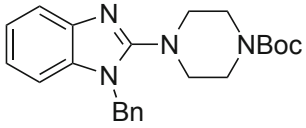


***tert*-Butyl-4-(benzo[*d*]thiazol-2-yl)piperazine-1-carboxylate (163)**. Compound prepared according to TP2. Purification by flash-column chromatography (gradient from 5 % ethyl acetate–hexanes to 20 % ethyl acetate–hexanes) gave **163** as a

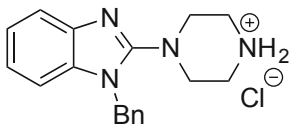
white solid (55.0 mg, 86 %); R_f = 0.28 (20 % ethyl acetate–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.59 (m, 1H), 7.57–7.55 (m, 1H), 7.33–7.28 (m, 1H), 7.11–7.07 (m, 1H), 3.63–3.54 (m, 8H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 154.6, 152.7, 130.9, 126.0, 121.6, 120.7, 119.4, 80.3, 48.3, 43.2, 28.4; FTIR (thin film): cm^{-1} 2974, 1696, 1536, 1444, 1167; HRMS-ESI (m/z) Calcd for ($C_{16}H_{22}N_3O_2S$) ([M+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); ^{1}H 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 ($C_{15}H_{19}F_4N_2O_2$) ([M+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); ^{1}H 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 ($C_{23}H_{29}N_4O_2$) ([M+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 Et_2O. 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 %). ^{1}H NMR (D_2O, 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); ^{13}C NMR (D_2O, 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 ($C_{18}H_{21}N_4$) ([M-HCl]$^+$): 293.1761; found: 293.1763.

References

1. Orjales A, Mosquera R, Labeaga L, Rodes R (1997) New 2-piperazinylbenzimidazole derivatives as 5-HT_3 antagonists. Synthesis and pharmacological evaluation. J Med Chem 40 (4):586–593
2. Massari S, Daelemans D, Barreca ML, Knezevich A, Sabatini S, Cecchetti V, Marcello A, Pannecouque C, Tabarrini O (2010) A 1,8-naphthyridone derivative targets the HIV-1 Tat-mediated transcription and potently inhibits the HIV-1 replication. J Med Chem 53 (2):641–648
3. Jin CY, Burgess JP, Rehder KS, Brine GA (2007) Synthesis of N^6-[endo-2'-(endo-5'-hydroxy)norbornyl]-8-(N-methylisopropyl-amino)-9-methyladenine (WRC-0571): a potent and selective adenosine A1 receptor antagonist. Synthesis 2007(2):219–224
4. Eckhardt M, Langkopf E, Mark M, Tadayyon M, Thomas L, Nar H, Pfrengle W, Guth B, Lotz R, Sieger P, Fuchs H, Himmelsbach F (2007) 8-(3-(R)-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 Inhibitor for the treatment of type 2 diabetes. J Med Chem 50(26):6450–6453
5. Bansal Y, Silakari O (2012) The therapeutic journey of benzimidazoles: a review. Bioorgan Med Chem 20(21):6208–6236
6. Gallardo-Godoy A, Gever J, Fife KL, Silber BM, Prusiner SB, Renslo AR (2011) 2-Aminothiazoles as therapeutic leads for prion diseases. J Med Chem 54(4):1010–1021
7. Zhang TZ, Yan ZH, Sromek A, Knapp BI, Scrimale T, Bidlack JM, Neumeyer JL (2011) Aminothiazolomorphinans with mixed κ and μ opioid activity. J Med Chem 54(6): 1903–1913
8. Zimmermann G, Papke B, Ismail S, Vartak N, Chandra A, Hoffmann M, Hahn SA, Triola G, Wittinghofer A, Bastiaens PI, Waldmann H (2013) Small molecule inhibition of the KRAS-PDEδ interaction impairs oncogenic KRAS signalling. Nature 497(7451):638–642
9. Hili R, Yudin AK (2006) Making carbon-nitrogen bonds in biological and chemical synthesis. Nat Chem Biol 2(6):284–287
10. Kosugi M, Kameyama M, Migita T (1983) Palladium-catalyzed aromatic aminaiton of aryl bromides with N,N-diethylamino-tributyltin. Chem Lett 12(6):927–928
11. Guram AS, Buchwald SL (1994) Palladium-catalyzed aromatic aminations with in situ generated aminostannanes. J Am Chem Soc 116(17):7901–7902

12. Guram AS, Rennels RA, Buchwald SL (1995) A simple catalytic method for the conversion of aryl bromides to arylamines. Angew Chem Int Ed 34(12):1348–1350
13. Louie J, Hartwig JF (1995) Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. Tetrahedron Lett 36(21):3609–3612
14. Hartwig JF (1998) Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: scope and mechanism. Angew Chem Int Ed 37(15):2046–2067
15. Wolfe JP, Buchwald SL (1997) Nickel-catalyzed amination of aryl chlorides. J Am Chem Soc 119(26):6054–6058
16. Chan DMT, Monaco KL, Wang RP, Winters MP (1998) New nand O-arylations with phenylboronic acids and cupric acetate. Tetrahedron Lett 39(19):2933–2936
17. Lam PYS, Clark CG, Saubern S, Adams J, Winters MP, Chan DMT, Combs A (1998) New aryl/heteroaryl C–N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. Tetrahedron Lett 39(19):2941–2944
18. Quach TD, Batey RA (2003) Ligand- and base-free copper(II)-catalyzed C−N bond formation: cross-coupling reactions of organoboron compounds with aliphatic amines and anilines. Org Lett 5(23):4397–4400
19. Rossi SA, Shimkin KW, Xu Q, Mori-Quiroz LM, Watson DA (2013) Selective formation of secondary amides via the copper-catalyzed cross-coupling of alkylboronic acids with primary amides. Org Lett 15(9):2314–2317
20. Sueki S, Kuninobu Y (2013) Copper-catalyzed N- and O-alkylation of amines and phenols using alkylborane reagents. Org Lett 15(7):1544–1547
21. Cho SH, Kim JY, Lee SY, Chang S (2009) Silver-mediated direct amination of benzoxazoles: tuning the amino group source from formamides to parent amines. Angew Chem Int Ed 48(48):9127–9130
22. Boudet N, Dubbaka SR, Knochel P (2008) Oxidative amination of cuprated pyrimidine and purine derivatives. Org Lett 10(9):1715–1718
23. del Amo V, Dubbaka SR, Krasovskiy A, Knochel P (2006) General preparation of primary, secondary, and tertiary aryl amines by the oxidative coupling of polyfunctional aryl and heteroaryl amidocuprates. Angew Chem Int Ed 45(46):7838–7842
24. Kienle M, Dunst C, Knochel P (2009) Oxidative amination of heteroaromatic zinc reagents mediated by PhI(OAc). Org Lett 11(22):5158–5161
25. Kienle M, Wagner AJ, Dunst C, Knochel P (2011) Preparation of heterocyclic amines by an oxidative amination of zinc organometallics mediated by Cu(I): a new oxidative cycloamination for the preparation of annulated Indole derivatives. Chem Asian J 6(2):517–523
26. Li Y, Xie Y, Zhang R, Jin K, Wang X, Duan C (2011) Copper- catalyzed direct oxidative C–H amination of benzoxazoles with formamides or secondary amines under mild conditions. J Org Chem 76(13):5444–5449
27. Mitsuda S, Fujiwara T, Kimigafukuro K, Monguchi D, Mori A (2012) Copper-catalyzed oxidative C–H, N–H coupling of azoles and thiophenes. Tetrahedron 68(16):3585–3590
28. Monguchi D, Fujiwara T, Furukawa H, Mori A (2009) Direct amination of azoles via catalytic C−H, N−H coupling. Org Lett 11(7):1607–1610
29. Sun K, Li Y, Xiong T, Zhang JP, Zhang QA (2011) Palladium-catalyzed C–H aminations of anilides with N-fluorobenzenesulfonimide. J Am Chem Soc 133(6):1694–1697
30. Thu HY, Yu WY, Che CM (2006) Intermolecular amidation of unactivated sp and sp C–H bonds via palladium-catalyzed cascade C–H activation/nitrene insertion. J Am Chem Soc 128(28):9048–9049
31. Tran LD, Roane J, Daugulis O (2013) Directed amination of non-acidic arene C–H bonds by a copper-silver catalytic system. Angew Chem Int Ed 52(23):6043–6046
32. Wagh YS, Bhanage BM (2012) $Cu(acac)_2$ Catalyzed oxidative C–H bond amination of azoles with amines under base-free conditions. Tetrahedron Lett 53(48):6500–6503
33. Wang Q, Schreiber SL (2009) Copper-mediated amidation of heterocyclic and aromatic C−H bonds. Org Lett 11(22):5178–5180

34. Xiao B, Gong TJ, Xu J, Liu ZJ, Liu L (2011) Palladium-catalyzed intermolecular directed C–H amidation of aromatic ketones. J Am Chem Soc 133(5):1466–1474
35. Xu J, Li JR, Wei Z, Zhang Q, Shi DX (2013) Direct amination of azoles using $CuCl_2$ complexes of amines under mild conditions. RSC Adv 3(25):9622–9624
36. Lamani M, Prabhu KR (2011) Iodine-catalyzed amination of benzoxazoles: A metal-free route to 2-aminobenzoxazoles under mild conditions. J Org Chem 76(22):7938–7944
37. Wertz S, Kodama S, Studer A (2011) Amination of benzoxazoles and 1,3,4-oxadiazoles Using 2,2,6,6-tetramethylpiperidine-N-oxoammonium tetrafluoroborate as an organic oxidant. Angew Chem Int Ed 50(48):11511–11515
38. Yotphan S, Beukeaw D, Reutrakul V (2013) A convenient one-pot synthesis of N-substituted 2-Aminoazole derivatives. Synthesis 45(7):936–9425:936
39. Chen X, Hao X-S, Goodhue CE, Yu J-Q (2006) Cu(II)-catalyzed functionalizations of aryl C −H bonds using O2 as an oxidant. J Am Chem Soc 128(21):6790–6791
40. John A, Nicholas KM (2011) Copper-catalyzed amidation of 2-phenylpyridine with oxygen as the terminal oxidant. J Org Chem 76(10):4158–4162
41. Shuai Q, Deng G, Chua Z, Bohle DS, Li C-J (2010) Copper-catalyzed highly regioselective oxidative C–H bond amidation of 2-arylpyridine derivatives and 1-methylindoles. Adv Synth Catal 352(4):632–636
42. Uemura T, Imoto S, Chatani N (2006) Amination of the ortho C–H bonds by the $Cu(OAc)_2$-mediated reaction of 2-phenylpyridines with anilines. Chem Lett 35(8):842–843
43. Shang M, Sun S-Z, Dai H-X, Yu J-Q (2014) Cu(II)-mediated C–H amidation and amination of arenes: exceptional compatibility with heterocycles. J Am Chem Soc 136(9):3354–3357
44. Erdik E, Ay M (1989) Electrophilic amination of carbanions. Chem Rev 89(8):1947–1980
45. Greck C, Genet JP (1997) Electrophilic amination: new synthetic applications. Synlett 1997 (7):741–748
46. Dembech P, Seconi G, Ricci A (2000) The electrophilic amination of carbanions: an unconventional new entry to C–N bond formation. Chem Eur J 6(8):1281–1286
47. Erdik E (2004) Electrophilic α-Amination of carbonyl compounds. Tetrahedron 60(40): 8747–8782
48. Greck C, Drouillat B, Thomassigny C (2004) Asymmetric electrophilic α-Amination of carbonyl groups. Eur J Org Chem 2004(7):1377–1385
49. Ciganek E (2009) Electrophilic amination of carbanions, enolates, and their surrogates. Wiley
50. Seebach D (1979) Methods of reactivity umpolung. Angew Chem Int Ed 18(4):239–258
51. Barker TJ, Jarvo ER (2011) Developments in transition-metal-catalyzed reactions using electrophilic nitrogen sources. Synthesis 2011(24):3954–3964
52. Lalic G, Rucker RP (2013) Copper-catalyzed electrophilic amination of organoboron compounds. Synlett 24(3):269–275
53. Yan X, Yang X, Xi C (2014) Recent progress in copper-catalyzed electrophilic amination. Catal Sci Technol 4(12):4169–4177
54. Berman AM, Johnson JS (2004) Copper-catalyzed electrophilic amination of diorganozinc reagents. J Am Chem Soc 126(18):5680–5681
55. Berman AM, Johnson JS (2005) Copper-catalyzed electrophilic amination of functionalized diarylzinc reagents. J Org Chem 70(1):364–366
56. Berman AM, Johnson JS (2005) Nickel-catalyzed electrophilic amination of organozinc halides. Synlett 2005(11):1799–1801
57. Berman AM, Johnson JS (2006) Copper-catalyzed electrophilic amination of organozinc nucleophiles: documentation of O-benzoyl hydroxylamines as broadly useful $R_2N(+)$ and RHN(+) synthons. J Org Chem 71(1):219–224
58. Barker TJ, Jarvo ER (2009) Umpolung amination: nickel-catalyzed coupling reactions of N, N-dialkyl-N-chloroamines with diorganozinc reagents. J Am Chem Soc 131(43): 15598–15599

59. Campbell MJ, Johnson JS (2007) Mechanistic studies of the copper-catalyzed electrophilic amination of diorganozinc reagents and development of a zinc-free protocol. Org Lett 9 (8):1521–1524
60. Barker TJ, Jarvo ER (2011) Titanium-mediated amination of grignard reagents using primary and secondary amines. Angew Chem Int Ed 50(36):8325–8328
61. Hatakeyama T, Yoshimoto Y, Ghorai SK, Nakamura M (2010) Transition-metal-free electrophilic amination between aryl grignard reagents and N-chloroamines. Org Lett 12(7):1516–1519
62. Matsuda N, Hirano K, Satoh T, Miura M (2012) Copper-catalyzed amination of arylboronates with N,N-dialkylhydroxylamines. Angew Chem Int Ed 51(15):3642–3645
63. Rucker RP, Whittaker AM, Dang H, Lalic G (2012) Synthesis of hindered anilines: copper-catalyzed electrophilic amination of aryl boronic esters. Angew Chem Int Ed 51 (16):3953–3956
64. Miki Y, Hirano K, Satoh T, Miura M (2013) Copper-catalyzed electrophilic amination of arylsilanes with hydroxylamines. Org Lett 15(1):172–175
65. Nguyen MH, Smith AB (2013) Copper-catalyzed electrophilic amination of organolithiums mediated by recoverable siloxane transfer agents. Org Lett 15(18):4872–4875
66. Yoo EJ, Ma S, Mei T-S, Chan KSL, Yu J-Q (2011) Pd-catalyzed intermolecular C–H amination with alkylamines. J Am Chem Soc 133(20):7652–7655
67. Zhu D, Yang G, He J, Chu L, Chen G, Gong W, Chen K, Eastgate MD, Yu J-Q (2015) Ligand-promoted ortho-C-H amination with Pd catalysts. Angew Chem Int Ed 54(8): 2497–2500
68. Shang M, Zeng S-H, Sun S-Z, Dai H-X, Yu J-Q (2013) Ru(II)-catalyzed ortho-C−H amination of arenes and heteroarenes at room temperature. Org Lett 15(20):5286–5289
69. Wu K, Fan Z, Xue Y, Yao Q, Zhang A (2014) Rh(III)-catalyzed intermolecular C−H amination of 1-aryl-1H-pyrazol-5(4H)-ones with alkylamines. Org Lett 16(1):42–45
70. Matsuda N, Hirano K, Satoh T, Miura M (2011) Copper-catalyzed direct amination of electron-deficient arenes with hydroxylamines. Org Lett 13(11):2860–2863
71. Kawano T, Hirano K, Satoh T, Miura M (2010) A new entry of amination reagents for heteroaromatic C–H bonds: copper-catalyzed direct amination of azoles with chloroamines at room temperature. J Am Chem Soc 132(20):6900–6901
72. Watanabe T, Tahara M, Todo S (2008) The novel antioxidant edaravone: from bench to bedside. Cardiovasc Ther 26(2):101–114
73. Abe K, Yuki S, Kogure K (1988) Strong attenuation of ischemic and postischemic brain edema in rats by a novel free radical scavenger. Stroke 19:480–485
74. Tabrizch R (2000) Edaravone mitsubishi-tokyo. Curr Opin Invest Drugs 1(3):347–354
75. Jin Y-J, Mima T, Raicu V, Park KC, Shimizu K (2002) Combined argatroban and edaravone caused additive neuroprotection against 15 min of forebrain ischemia in gerbils. Neurosci Res 43(1):75–79
76. Wencel-Delord J, Droge T, Liu F, Glorius F (2011) Towards mild metal-catalyzed C–H bond activation. Chem Soc Rev 40(9):4740–4761
77. Clegg W, Dale SH, Harrington RW, Hevia E, Honeyman GW, Mulvey RE (2006) Post-metalation structural insights into the use of alkali-metal-mediated zincation for directed ortho-metalation of a tertiary aromatic amide. Angew Chem Int Ed 45(15):2374–2377
78. Clegg W, Dale SH, Hevia E, Honeyman GW, Mulvey RE (2006) Pre-metalation structural insights into the use of alkali-metal-mediated zincation for directed ortho-metalation of a tertiary aromatic amide. Angew Chem Int Ed 45(15):2370–2374
79. Kondo Y, Shilai M, Uchiyama M, Sakamoto T (1999) TMP−zincate as highly chemoselective base for directed ortho metalation. J Am Chem Soc 121(14):3539–3540
80. Nguyen TT, Marquise N, Chevallier F, Mongin F (2011) Deprotonative metalation of aromatic compounds by using an amino-based lithium cuprate. Chem Eur J 17(37): 10405–10416

81. Haas B, Mosrin M, Ila H, Malakhov V, Knochel P (2011) Regio- and chemoselective metalation of arenes and heteroarenes using hindered metal amide bases. Angew Chem Int Ed 50(42):9794–9824
82. Bresser T, Monzon G, Mosrin M, Knochel P (2010) Scaleable preparation of sensitive functionalized aromatics and heteroaromatics via directed metalation using tmpZnCl·LiCl. Org Process Res Dev 14(6):1299–1303
83. Bresser T, Mosrin M, Monzon G, Knochel P (2010) Regio- and chemoselective zincation of sensitive and moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl. J Org Chem 75(14):4686–4695
84. Mosrin M, Bresser T, Knochel P (2009) Regio- and chemoselective multiple functionalization of chloropyrazine derivatives. Application to the synthesis of coelenterazine. Org Lett 11(15):3406–3409
85. Mosrin M, Knochel P (2009) TMPZnCl·LiCl: A new active selective base for the directed zincation of sensitive aromatics and heteroaromatics. Org Lett 11(8):1837–1840
86. Unsinn A, Ford MJ, Knochel P (2013) New preparation of TMPZnCl·LiCl by Zn insertion into TMPCl. Application to the functionalization of dibromodiazines. Org Lett 15(5):1128–1131
87. Hlavinka ML, Hagadorn JR (2006) Structures of zinc ketone enolates. Organometallics 25 (14):3501–3507
88. Hlavinka ML, Hagadorn JR (2007) Zn(tmp) : A versatile base for the selective functionalization of C−H bonds. Organometallics 26(17):4105–4108
89. Wunderlich SH, Knochel P (2007) $(tmp)_2Zn{\cdot}2\ MgCl_2{\cdot}2$ LiCl: a chemoselective base for the directed zincation of sensitive arenes and heteroarenes. Angew Chem Int Ed 46(40): 7685–7688
90. Balloch L, Kennedy AR, Mulvey RE, Rantanen T, Robertson SD, Snieckus V (2011) Concerning the structures of alkali-metal-mediated ortho zincation of benzamides and phenyl O-carbamate. Organometallics 30(1):145–152
91. Iwao M, Reed JN, Snieckus V (1982) Directed metalation of tertiary benzamides: ortho N-aryl amination and synthesis of acridones. J Am Chem Soc 104(20):5531–5533
92. Knochel P, Singer RD (1993) Preparation and reactions of polyfunctional organozinc reagents in organic synthesis. Chem Rev 93(6):2117–2188
93. Knochel P, Perea JJA, Jones P (1998) Organozinc mediated reactions. Tetrahedron 54(29):8275–8319
94. Jana R, Pathak TP, Sigman MS (2011) Advances in transition metal (Pd,Ni,Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. Chem Rev 111 (3):1417–1492
95. Netherton MR, Fu GC (2004) Nickel-catalyzed cross-couplings of unactivated alkyl halides and pseudohalides with organometallic compounds. Adv Synth Catal 346(13–15): 1525–1532
96. Cui J, Tran-Dube M, Shen H, Nambu M, Kung P, Pairish M, Jia L, Meng J, Funk L, Botrouis I, McTique M, Grodsky N, Pyan K, Padrique E, Alton G, Timofeevski S, Yamazaki S, Li Q, Zou H, Christensen J, Mroxzkowski B, Bender S, Kania R, Edwards M (2011) Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem 54(18):6342–6363
97. May B, Zorn J, Witkop J, Sherrill J, Wallace G, Prusiner S, Cohen F (2007) Structure−ctivity relationship study of prion inhibition by 2-aminopyridine-3,5-dicarbonitrile-based compounds: parallel synthesis, bioactivity, and in vitro pharmacokinetics. J Med Chem 50(1):65–73
98. Zhang D, Ai J, Liang Z, Li C, Peng X, Ji Y, Jiang H, Geng M, Luo C, Liu H (2012) Discovery of novel 2-aminopyridine-3-carboxamides as c-Met kinase inhibitors. Bioorg Med Chem 20(17):5169–5180

99. Hooper MW, Utsunomiya M, Hartwig JF (2003) Scope and mechanism of palladium-catalyzed amination of five-membered heterocyclic halides. J Org Chem 68(7):2861–2873
100. Ge W, Wu B, Huang W (1985) Nucleophilic substitution reaction in polyfluoroaromatics. Reactions with secondary amine nucleophiles. Huaxue Xuebao 43(9):859–864

Curriculum Vitae

Stacey L. McDonald is the daughter of Michael and Carolyn Turner. She was born 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 the Department of Chemistry at Duke University to pursue her Ph.D in organic synthesis.

Education

Duke University
Durham, NC
Doctorate of Philosophy, Organic Chemistry
May 2015

Wofford College
Spartanburg, SC
Bachelor of Science, Chemistry
May 2009

Honors and Awards

Graduate School Conference Travel Fellowship, Duke University; Burroughs Welcome Fellowship, Duke University; Paul Thomas Scholarship, Wofford College; Phi Beta Kappa, Wofford College; Western Carolinas American Chemical Society Outstanding Senior, Wofford College; Dean's List, Wofford College; 1854 Scholarship, Wofford College; Palmetto Fellowship

S.L. McDonald, *Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C–H Bonds*, Springer Theses, DOI 10.1007/978-3-319-38878-6

Publications

McDonald, S. L.; Hendrick, C. E.; Bitting K. J.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroaromatic and Aromatic C−H Bonds via TMPZnCl•LiCl Mediated Metalation," *Org. Synth.* **2015**, *92*, 356−372.

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)

McDonald, S. L.; Hendrick, C. E.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes via C−H Zincation," *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670. (highlighted in Synfacts)

Wang, B.; Rao, Y.; Inoue, M.; Hao, R.; Lai, C.; McDonald, S. L.; Choi, M.; Wang, Q.; Shinohara, M.; Yao, T. "Microtubule acetylation amplifies p38 kinase signaling and anti-inflammatory IL-10 production," *Nature Communication* **2014**, *5*, 3479 doi:10.1038/ncomms4479.

McDonald, S. L.; Wang, Q. "Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives," *Angew. Chem. Int. Ed.* **2014**, *53*, 1867–1871. (highlighted in Synfacts)

McDonald, S. L.; Wang, Q. "Selective α-amination and α-acylation of esters and amides *via* dual reactivity of *O*-acylhydroxylamines toward zinc enolates," *Chem. Commun.* **2014**, *50*, 2535−2538.

Hendrick, C. E.; McDonald, S. L.; Wang, Q. "Insertion of Arynes into *N*-Halo Bonds: A Direct Approach to *Ortho*-Halo aminoarenes," *Org. Lett.* **2013**, *15*, 3444−3447.